05-117761

Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

06-117761

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPUESTOS PARA EL TRATAMIENTO DE TRANSTORNOS INFLAMATORIOS

SOLICITANTE: SCHERING CORPORATION

DIRECCIÓN: 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530, E.U.A.

APODERADO: J. IAN RAISBECK

BOGOTÁ 20 de Noviembre de 2006

P20060009259

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-117761- -00000-0000
Fec: 2006-11-21 17:13:20 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEIYII
Eve: 378 FASENACIONALII
Act 411 PRESENTACION
Folios: 1881

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

(1)

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[ ] Capítulo I. [X] Capítulo II.

(2)

SOLICITANTE (71)

Nombre: SCHERING CORPORATION

Dirección: 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530, E.U.A.

Nacionalidad o Domicilio: ESTADOUNIDENSE

Lugar de Constitución: ESTADOS UNIDOS DE AMERICA

Teléfono: _____ **Fax:** _____

E-mail: _____

IDENTIFICACIÓN

C.C. [ ] **NIT** [ ]

C.E. [ ] **Otro** [ ]

Cual _____

Número _____

REPRESENTANTE O APODERADO

Nombre: J. IAN RAISBECK

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IDENTIFICACIÓN

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Cual _____

Número 79.376.996

TP 135.799

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2005/019131 Fecha Junio 1, 2005

Publicación Internacional No. WO 2005/121130 Fecha Diciembre 22, 2005

(6) **Título (54)** COMPUESTOS PARA EL TRATAMIENTO DE TRASTORNOS INFLAMATORIOS

Clasificación Internacional (51) C07D 409/12, 333/20, 295/18, 471/10, 409/14, 207/26, 417/14, 417/12, C07C 233/18, C07D 307/52, 405/12, 209/44, 217/06, 207/20, 403/12, 401/12, 413/14, 401/14, 413/12, 263/32, 215/14, 513/04, 487/04, 498/04, 471/04, A61K 31/40, 31/4025, 31/403, 31/4427, 31/47, 31/495, 31/496, A61P 19/02.

Prioridad SI [X] N [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Junio 2, 2004	60/576.153

(9) **Comprobante de pago No.** 06-86.188 **Fecha** Noviembre 8, 2006

(10) **ANEX S**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple, ver Exp. No. 06-057.472, sustitución
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(12) Solicito la concesión de la patente,

NOMBRE: J. IAN RAISBECK FIRMA:

C.C. 79.376.996 Btá T.P. 135.799

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6

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-117761- -00000-0000
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Tra. 11 PATENTEIYII
Eve: 379 FASENACIONALII
Act 411 PRESENTACION Folios: 1001

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 86,188
FECHA : NOVIEMBRE 8 DE 2006

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARTE RAISBEGR	CONSIGNACION	BANCO POPULAR	050-00110-6	52198849	07/11/2006	3,704,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL : $	463,000.00

: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Ref.: Nueva soliciud de Patente de Invenciôn titulada " COMPUESTOS PARA EL TRATAMIENTO DE TRASTORNOS INFLAMATORIOS".
Solicitante : SCHERING CORPORATION

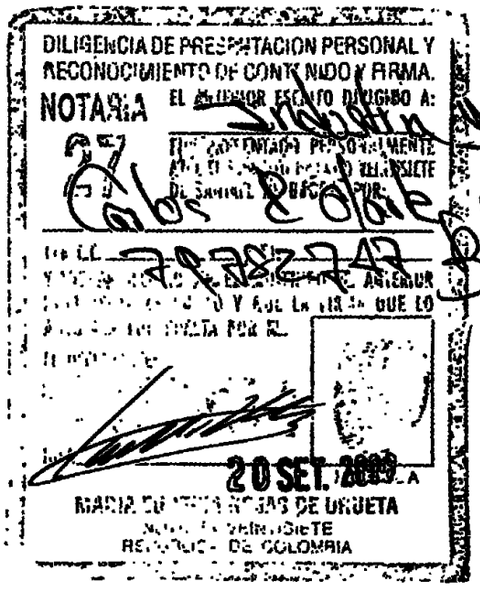
SUSTITUCIÓN DE PODER

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá D.C., identificado como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad, en el doctor **J. IAN RAISBECK LLINAS**, mayor de edad, domiciliado en Bogotá D.C., identificado con la Cédula de Ciudadanía No. 79.376.996 de Bogotá y portador de la Tarjeta Profesional No. 135.799 del Consejo Superior de la Judicatura, para que sea él quien en adelante asuma el trámite de la presente acción.

El apoderado sustituto conserva las mismas facultades del principal.

Atentamente,

CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295 del C. S. de la J.


DILIGENCIA DE PRESENTACION PERSONAL Y
RECONOCIMIENTO DE CONTENIDO Y FIRMA.
NOTARIA
20 SET. 2009
MARIA
REPUBLICA DE COLOMBIA

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SCHERING CORPORATION

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Estados Unidos de América
   - Este documento Público
2. ha sido firmado por Marguerite La Corte
3. Quien ejerce funciones de Notario público de Nueva Jersey
4. Lleva el sello de Marguertie La Corte Notario

CERTIFICADO

5. En Trenton, Nueva Jersey
6. El 29 de agosto 2003
7. Por John E. McCormac Contador Publico- Tesorero de Nueva Jersey 8. No. A 180345
9. Gran Sello del Estado de Nueva Jersey
10. Firma legible de John M.

PODER DE REPRESENTACIÓN

Bilingüe inglés- español otorgado en Kenilworth, Nueva Jersey, Estados Unidos, el 7 de agosto de 2003 y firmado por Edward H. Mazer - Director Juridico senior.

CERTIFICADO NOTARIAL

Bilingüe inglés- español, fechado el 7 de agosto, 2003 certificando las funciones de Edward H. Mazer - Director Juridico senior, de Schering Corporation.

Las certificaciones anteriores se basan en el Poder de representación fechado el 4 noviembre de 2002.

Sello: Marguerite La Corte- Notario público,
Estado de Nueva Jersey
Su comisión vence el 7 de octubre de 2003.
Sello en alto relieve del Notario Público

Es traducción fiel del inglés, con copia archivo, para confrontación. Bogotá 5 septiembre, 2003.

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MARGUERITE LA CORTE

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
MARGUERITE LA CORTE, NOTARY

CERTIFIED

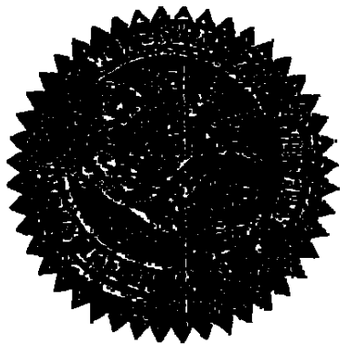
5. AT TRENTON, NEW JERSEY

6. THE 29TH DAY OF AUGUST 2003

7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A180345

9. SEAL/STAMP:



10. SIGNATURE

OLARTERAISBECK
OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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FAX: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,
SCHERING CORPORATION

domiciled in
2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0532, U.S.A.

by means of these presents hereby grants to **Carlos R. Olarte and/or Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

domiciliado en
2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0532, U.S.A.

por medio del presente otorga a **Carlos R. Olarte y/o Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: _____
Edward H. Mazer, Senior Legal Director

Date/Fecha: August 7, 2003

City,Country/Ciudad,Pais: Kenilworth, New Jersey, U.S.A.

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
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www.olarteraisbeck.com

Notarial Certification

On this date, August 7, 2003

The undersigned Notary Public certifies:

1. That Edward H. Mazer

of legal age and domiciled in 149 Greenwood Drive, Millburn, New Jersey 07041, U.S.A.
signed the foregoing document.

2. That the grantor has executed the foregoing document as Senior Legal Director of SCHERING CORPORATION

3. That SCHERING CORPORATION having its principal place of business located in 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530, U.SA.. is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):
Power of Attorney, dated November 4, 2002.

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado
suscribió el documento que antecede.

2. Que el otorgante ha suscrito el referido documento en su carácter de
de

4. Que
con sede principal ubicada en
está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature):

Marguerite LaCorte
Marguerite La Corte
Notary Public of New Jersey
My Commission Expires October 7, 2003

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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22 December 2005 (22.12.2005)

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/576,153 2 June 2004 (02.06.2004) US

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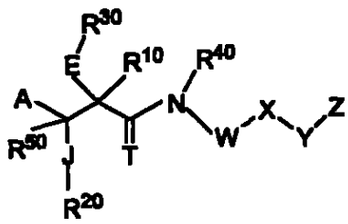
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),

[Continued on next page]

(54) Title: COMPOUNDS FOR THE TREATMENT OF INFLAMMATORY DISORDERS



(I)

(57) Abstract: This invention relates to compounds of the Formula (I) or a pharmaceutically acceptable salt, solvate or isomer thereof, which can be useful for the treatment of diseases or conditions mediated by MMPs, ADAMs, TACE, TNF-α or combinations thereof.

WO 2005/121130 A2

European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

— *without international search report and to be republished upon receipt of that report*

COMPOUNDS FOR THE TREATMENT OF INFLAMMATORY DISORDERS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates generally to tartaric acid functional compounds that can inhibit matrix metalloproteinases (MMPs), a disintegrin and metalloproteases (ADAMs) and/or tumor necrosis factor alpha - converting enzyme (TACE) and in so doing prevent the release of tumor necrosis factor alpha (TNF-*α*), pharmaceutical compositions comprising such compounds, and methods of treatment using such compounds.

Description

Osteo- and rheumatoid arthritis (OA and RA, respectively) are destructive diseases of articular cartilage characterized by localized erosion of the cartilage surface. Findings have shown that articular cartilage from the femoral heads of patients with OA, for example, had a reduced incorporation of radiolabeled sulfate over controls, suggesting that there must be an enhanced rate of cartilage degradation in OA (Mankin et al. J. Bone Joint Surg. 52A (1970) 424-434). There are four classes of protein degradative enzymes in mammalian cells: serine, cysteine, aspartic and metalloproteases. The available evidence supports the belief that it is the metalloproteases that are responsible for the degradation of the extracellular matrix of articullar cartilage in OA and RA. Increased activities of collagenases and stromelysin have been found in OA cartilage and the activity correlates with severity of the lesion (Mankin et al. Arthritis Rheum. 21, 1978, 761-766, Woessner et al. Arthritis Rheum. 26, 1983, 63-68 and Ibid. 27, 1984, 305-312). In addition, aggrecanase (a newly identified metalloprotease) has been identified that provides the specific cleavage product of proteoglycan, found in RA and OA patients (Lohmander L. S. et al. Arthritis Rheum. 36, 1993, 1214-22).

Metalloproteases (MPs) have been implicated as the key enzymes in the destruction of mammalian cartilage and bone. It can be expected that the pathogenesis of such diseases can be modified in a beneficial manner by the administration of MP inhibitors (see Wahl et al. Ann. Rep. Med. Chem. 25, 175-184, AP, San Diego, 1990).

MMPs are a family of over 20 different enzymes that are involved in a variety of biological processes important in the uncontrolled breakdown of connective tissue, including proteoglycan and collagen, leading to resorption of the extracellular matrix. This is a feature of many pathological conditions, such as RA and OA, corneal, epidermal or gastric ulceration; tumor metastasis or invasion; periodontal disease and bone disease. Normally these catabolic enzymes are tightly regulated at the level of their synthesis as well as at their level of extracellular activity through the action of specific inhibitors, such as alpha-2-macroglobulins and TIMPs (tissue inhibitor of MPs), which form inactive complexes with the MMP's.

Tumor necrosis factor alpha (TNF-α) is a cell-associated cytokine that is processed from a 26 kDa precursor form to a 17 kd active form. *See* Black R.A. "Tumor necrosis factor-alpha converting enzyme" Int J Biochem Cell Biol. 2002 Jan;34(1):1-5 and Moss ML, White JM, Lambert MH, Andrews RC."TACE and other ADAM proteases as targets for drug discovery" Drug Discov Today. 2001 Apr 1;6(8):417-426, each of which is incorporated by reference herein.

TNF-α has been shown to play a pivotal role in immune and inflammatory responses. Inappropriate or over-expression of TNF-α is a hallmark of a number of diseases, including RA, Crohn's disease, multiple sclerosis, psoriasis and sepsis. Inhibition of TNF-α production has been shown to be beneficial in many preclinical models of inflammatory disease, making inhibition of TNF-α production or signaling an appealing target for the development of novel anti-inflammatory drugs.

TNF-α is a primary mediator in humans and animals of inflammation, fever and acute phase responses, similar to those observed during acute infection and shock. Excess TNF-α has been shown to be lethal. Blocking the effects of TNF-α with specific antibodies can be beneficial in a variety of conditions, including autoimmune diseases such as RA (Feldman et al, Lancet, (1994) 344, 1105), non-insulin dependent diabetes mellitus (Lohmander L. S. et al., Arthritis Rheum. 36 (1993) 1214-22) and Crohn's disease (Macdonald T. et al., Clin. Exp. Immunol. 81 (1990) 301).

Compounds that inhibit the production of TNF-α are therefore of therapeutic importance for the treatment of inflammatory disorders. Recently it has been shown that metalloproteases, such as TACE, are capable of converting TNF-α from its inactive to active form (Gearing et al Nature, 1994, 370, 555). Since excessive TNF-α production has been noted in several disease conditions also characterized by MMP-mediated tissue degradation, compounds which inhibit both MMPs and TNF-α production may also have a particular advantage in diseases where both mechanisms are involved.

One approach to inhibiting the harmful effects of TNF-α is to inhibit the enzyme, TACE before it can process TNF-α to its soluble form. TACE is a member of the ADAM family of type I membrane proteins and mediates the ectodomain shedding of various membrane-anchored signaling and adhesion proteins. TACE has become increasingly important in the study of several diseases, including inflammatory disease, because of its role in cleaving TNF-α from its "stalk" sequence and thus releasing the soluble form of the TNF-α protein (Black R.A. Int J Biochem Cell Biol. 2002 34,1-5).

There are several patents which disclose hydroxamate, carboxylate and/or lactam based MMP inhibitors.

US 6,677,355 and US 6,534,491(B2), describe compounds that are hydroxamic acid derivatives and MMP inhibitors.

US 6,495,565 discloses lactam derivatives that are potential inhibitors of matrix metalloproteases and/or TNF-α.

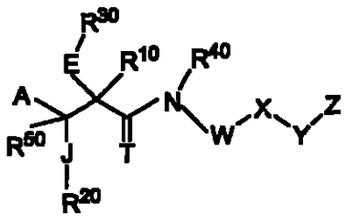
There is a need in the art for inhibitors of MMPs, ADAMs, TACE, and TNF-α, which can be useful as anti-inflammatory compounds and cartilage protecting therapeutics. The inhibition of TNF-α, TACE and or other MMPs can prevent the degradation of cartilage by these enzymes, thereby alleviating the pathological conditions of OA and RA as well as many other auto-immune diseases.

SUMMARY OF THE INVENTION

In its many embodiments, the present invention provides a novel class of compounds as inhibitors of TACE, the production of TNF-α, MMPs, ADAMs

or any combination thereof, methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition or amelioration of one or more diseases associated with TACE, TNF-α, MMPs, ADAMs or any combination thereof using such compounds or pharmaceutical compositions.

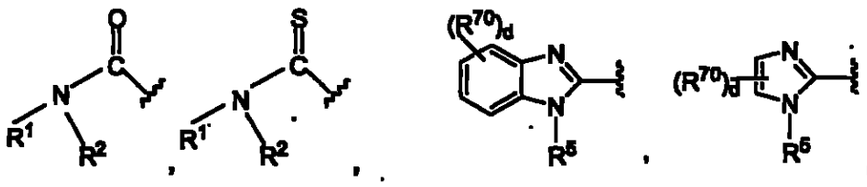
In one embodiment, the present application discloses a compound, or pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in formula (I):



formula (I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

A is selected from the group consisting of:



, and

$-CO_2R^1$;

d is 0 to 4;

J is selected from the group consisting of: O, S, and NR^5;

E is selected from the group consisting of: O, S, and NR^5;

T is O or S;

R^1 and R^2 are the same or different, each being independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; or alternatively R^1 and R^2, taken together with

the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl; wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, heteroaryl and 4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^{10} is selected from the group consisting of H, alkyl, and fluoroalkyl;

R^{20} is selected from the group consisting of H, alkyl, and fluoroalkyl;

R^{30} is H or alkyl, or alternatively R^{30} and R^{40} taken together with the N to which R^{40} is shown attached to in Formula I, are joined to form a 4-7 membered heterocylic ring, wherein said heterocylic ring is unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^{40} is H or alkyl;

R^{50} is H or alkyl;

W is $-(CR^{13}_2)_n-$, wherein n is 0 to 5 or a covalent bond, or alternatively two R^{13} groups can fuse to form a 3-8 membered cycloalkyl, wherein said 3-8 membered cycloalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^6 moieties below;

X is absent or present, and if present X is selected from the group consisting of a covalent bond, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

Y is absent or present, and if present Y is selected from the group consisting of a covalent bond, $-[C(R^6)_2]_n-$ wherein n is 1 to 2, -O-, -S-, $-NR^1-$, $-SO_v-$ wherein v is 1 to 2, $-SO_n(CR^6_2)_p-$ wherein n is 1 or 2 and p is 1 to 4,

$-O(CR^6{}_2)_q-$ or $-(CR^6{}_2)_qO-$ wherein q is 1 to 4, $-N(R^7)S(O)_n-$ or $-S(O)_nN(R^7)-$ wherein n is 1 or 2, and $-N(R^7)C(O)-$ or $-C(O)N(R^7)-$;

Z is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, said cycloalkyl, heterocyclyl, aryl, and heteroaryl being optionally fused with aryl, heterocyclyl, heteroaryl or cycloalky; wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^5 is selected from the group consisting of hydrogen, alkyl, and alkylaryl;

each R^6 is the same or different and is independently selected from the group consisting of hydrogen, halogen, $-SR^{15}$, $-S(O)_qR^{15}$ wherein q is 1 to 2, alkyl, cycloalkyl, heterocyclyl, alkoxyl, hydroxy, nitro, cyano, amino, alkenyl, alkynyl, arylalkyl, aminocarbonyl, alkylcarbonyl, and alkoxycarbonyl;

each R^7 is the same or different and is independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, alkenyl, alkynyl, arylalkyl, alkylcarbonyl, and alkoxycarbonyl, wherein each of the aryl, heteroaryl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^{13} is the same or different and is independently selected from the group consisting of hydrogen, halogen, -OH, $-OR^{14}$, alkyl, cycloalkyl, heterocyclyl, alkenyl, alkynyl, alkylaryl, alkylamino, and alkylcarbonyl;

R^{14} is alkyl;

each R^{70} is a substituent for H where indicated and is the same or different and is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, $-CF_3$, $-OCF_3$, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)_qN(R^{15})(R^{16})$ wherein q is 1 to 2, $-C(=NOR^{15})R^{16}$, $-N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, -

CH_2-N(R^{15})C(O)R^{16}, -N(R^{15})S(O)R^{16}, -N(R^{15})S(O)$_2R^{16}$, -CH_2-N(R^{15})S(O)$_2R^{16}$, -N(R^{17})S(O)$_2$N(R^{16})(R^{15}), -N(R^{17})S(O)N(R^{16})(R^{15}), -N(R^{17})C(O)N(R^{16})(R^{15}), -CH_2-N(R^{17})C(O)N(R^{16})(R^{15}), -N(R^{15})C(O)OR^{16}, -CH_2-N(R^{15})C(O)OR^{16}, and -S(O)$_q R^{15}$ wherein q is 1 to 2; and wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl are independently unsubstituted or substituted by 1 to 5 groups independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, -CF_3, -CN, -OR^{15}, -N(R^{15})(R^{16}), -C(O)OR^{15}, -C(O)N(R^{15})(R^{16}), and -N(R^{15})S(O)R^{16};

each R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, or alternatively R^{15} and R^{16} taken together with the N to which they are shown attached, are joined to form a 4-8 membered heterocylic ring, wherein said 4-8 membered cycloalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{75} moieties below;

each R^{75} is independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl, and wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl are independently unsubstituted or substituted by 1 to 5 groups independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, -CF_3, -CN, -OR^{19}, -N(R^{19})$_2$, -C(O)OR^{19}, -C(O)N(R^{19})$_2$, and -N(R^{19})S(O)R^{19}; and

each R^{19} is independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl.

The compounds of Formula I can be useful as inhibitors and may be useful in the treatment and prevention of diseases associated with TACE, TNF-α, MMPs, ADAMs or any combination thereof.

DETAILED DESCRIPTION OF THE INVENTION

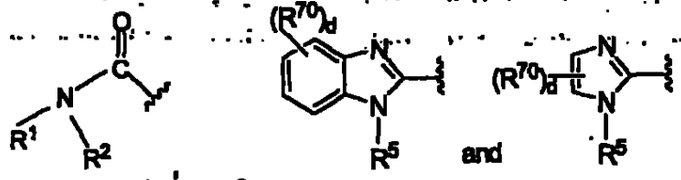
In its several embodiments, the present invention provides a novel class of inhibitors of TACE, the production of TNF-α, MMPs, ADAMs or any combination thereof, pharmaceutical compositions containing one or more of the compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention or amelioration of one or more of the symptoms of inflammation.

In one embodiment, the present invention provides compounds which are represented by structural Formula (I) above or a pharmaceutically acceptable salt, solvate or isomer thereof, wherein the various moieties are as described above.

In one embodiment, R^1 and R^2 are the same or different, each being independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; or alternatively R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, heteroaryl and 4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70}.

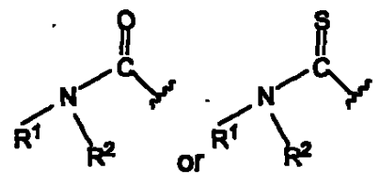
In one embodiment, R^1 and R^2 are the same or different, each being independently selected from the group consisting of H, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; or alternatively R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, heteroaryl and 4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70}.

In one embodiment, A is selected from the group consisting of:



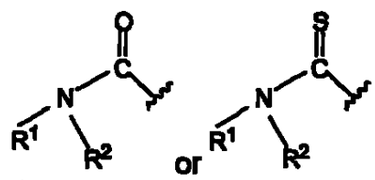
wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

In another embodiment, A is



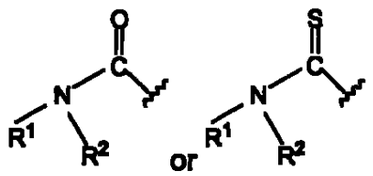
wherein R^1 and R^2 are the same or different, each being independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; wherein said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

In another embodiment, A is



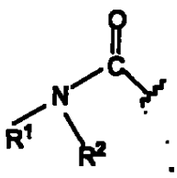
wherein R^1 and R^2 are the same or different, each being independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; wherein said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

In another embodiment, A is

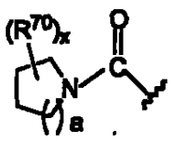


wherein R^1 and R^2 are the same or different, each being independently selected from the group consisting of H, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; wherein said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

In another embodiment, A is

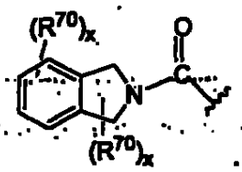


In another embodiment, A is



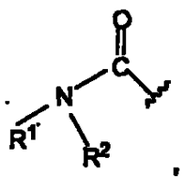
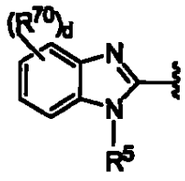
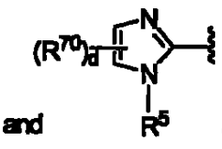
wherein a is 0 to 4 and x is 0 to 4.

In another embodiment, A is



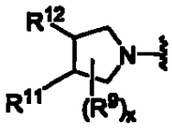
wherein each x idependently is 0 to 4.

In another embodiment, A is selected from the group consisting of:



and


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

wherein a ring is formed from $-NR^1R^2$ and said ring is



wherein

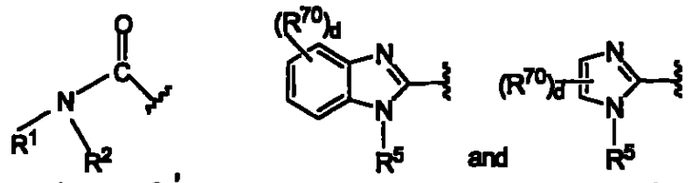
each R^9 is a substituent for H where indicated and can be the same or different, each being independently selected from the group consisting of -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

$R^{11}$and R^{12} taken together with the carbon to which each $R^{11}$and R^{12} are shown attached are fused heteroaryl or fused cycloalkyl, wherein said fused heteroaryl and fused cycloalkyl can be unsubstituted or optionally

independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; and

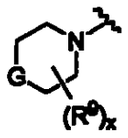
x is 0 to 4, and when x is greater than 1, each R^9 moiety can be the same or different, each moiety being independently selected from the group of R^9 moieties.

In another embodiment, A is selected from the group consisting of:



wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

wherein a ring is formed from $-NR^1R^2$ and said ring is



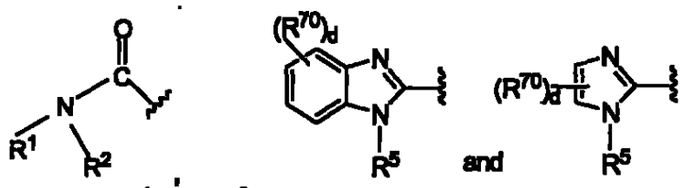
wherein

each R^9 is a substituent for H where indicated and can be the same or different, each being independently selected from the group consisting of -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

x is 0 to 4, and when x is greater than 1, each R^9 moiety can be the same or different, each moiety being independently selected from the group of R^9 moieties; and

G is selected from the group consisting of CH_2, NR^7, O, S, or SO_2.

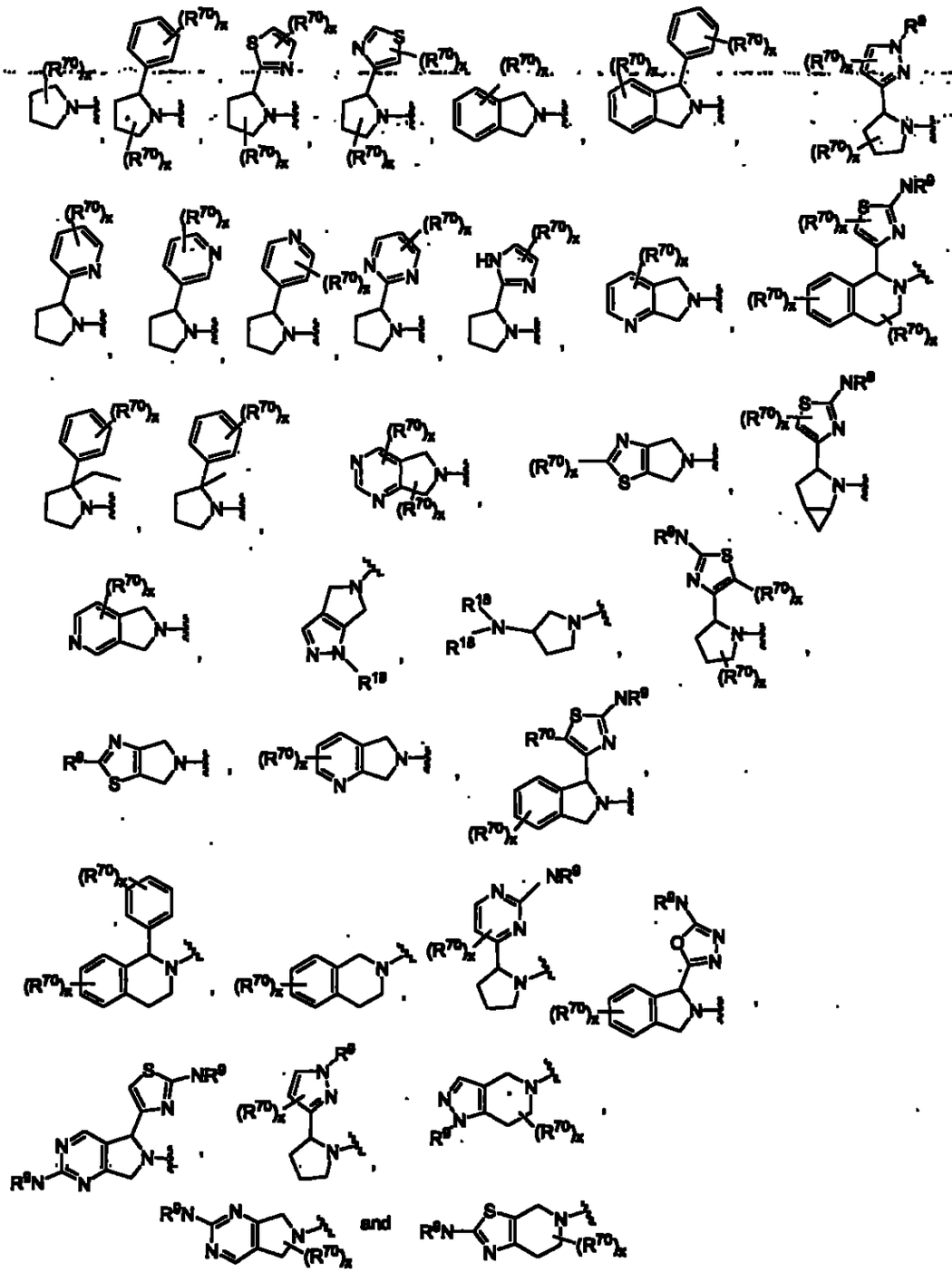
In another embodiment, A is selected from the group consisting of:



and

wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

a ring is formed from $-NR^1R^2$ and said ring is selected from the group consisting of

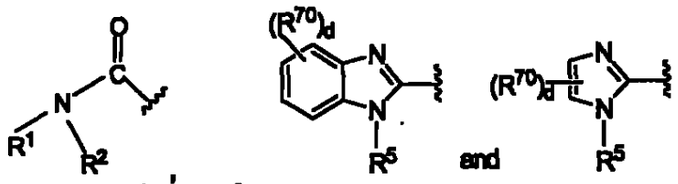


wherein

x is 0 to 4, and when x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties; and

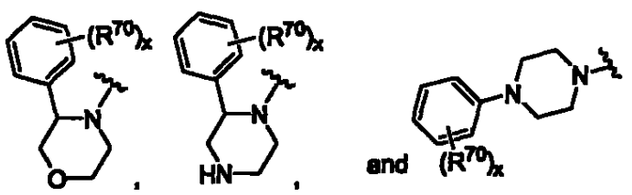
each R^{18} is the same or different and is independently H or alkyl.

In another embodiment, A is selected from the group consisting of:



wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

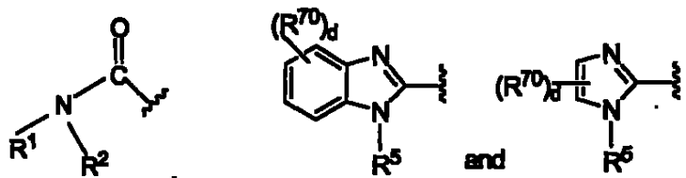
a ring is formed from $-NR^1R^2$ and said ring is selected from the group consisting of



wherein

x is 0 to 4, and when x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

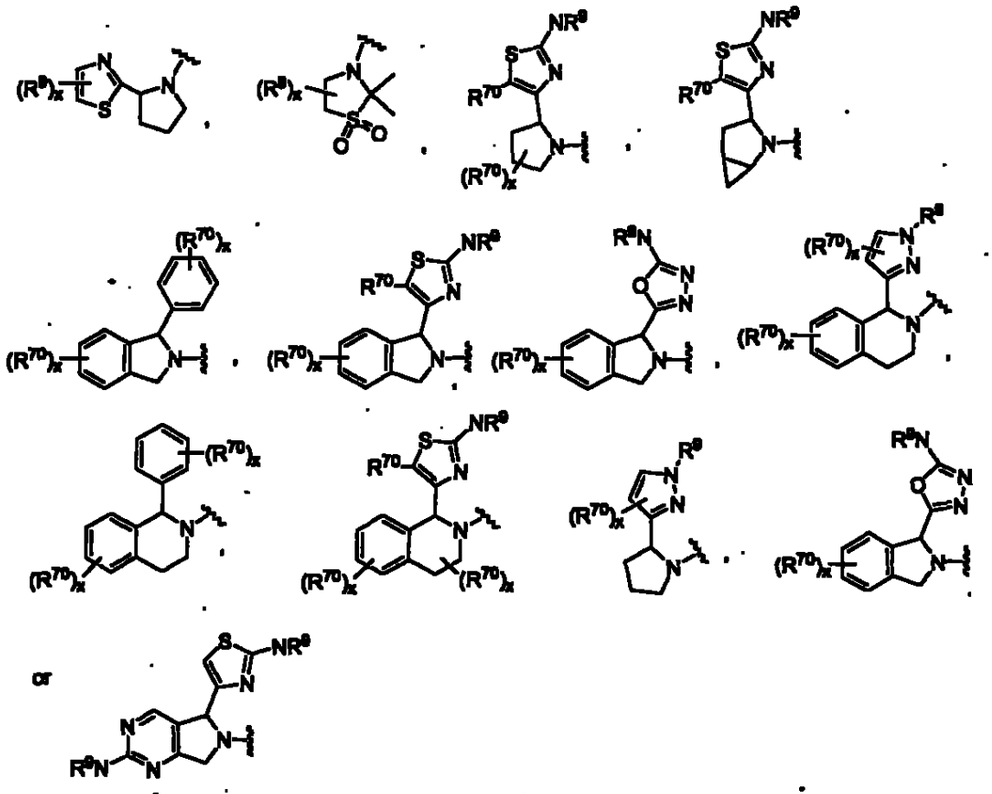
In another embodiment, A is selected from the group consisting of:



wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3

heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

a ring is formed from $-NR^1R^2$ and said ring is



wherein

each R^9 is a substituent for H where indicated and can be the same or different, each being independently selected from the group consisting of -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; and

x is 0 to 4, and when x is greater than 1, each R^9 moiety can be the same or different, each moiety being independently selected from the group of R^9 moieties.

In another embodiment, J is O.

In another embodiment, E is O.

In another embodiment, R^{10} is H or alkyl.

In another embodiment, R^{20}, R^{30}, R^{40}, and R^{50} are all the same and are H.

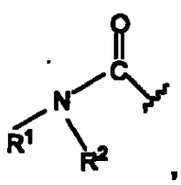
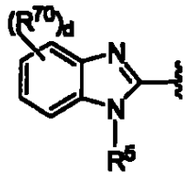
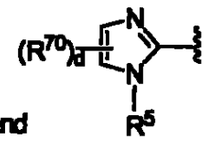
In another embodiment, R^6 is H or alkyl.

In another embodiment, R^6 is H.

In another embodiment, R^{13} is H or alkyl.

In another embodiment, R^{13} is H or $-CH_3$.

In another embodiment, A is selected from the group consisting of



and


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-6 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, wherein R^{70} is aryl.

In another embodiment, Y is a covalent bond or $-[C(R^6)_2]_n-$ wherein n is 1 to 2, $-CH_2-$.

In another embodiment, Y is selected from the group consisting of a covalent bond, $-CH_2-$, -C(H)(OH)-, -C(O)- and –O-.

In another embodiment, Y is a covalent bond or $-CH_2-$.

In another embodiment, Y is a covalent bond.

In another embodiment, W is $-(CR^{13}{}_2)_n-$, in which n is 0-5.

In another embodiment, W is $-(CR^{13}{}_2)_n-$, in which n is 1-5 and each R^{13} is H or alkyl.

In another embodiment, W is selected from the group consisting of -CH_2-, -C(H)(CH_3)-, -C(CH_3)$_2$- and -CH_2CH_2-.

In another embodiment, W is -CH_2-.

In another embodiment, W is -C(H)(CH_3)-.

In another embodiment, X is selected from the group consisting of alkyl, aryl, heterocyclyl and heteroaryl.

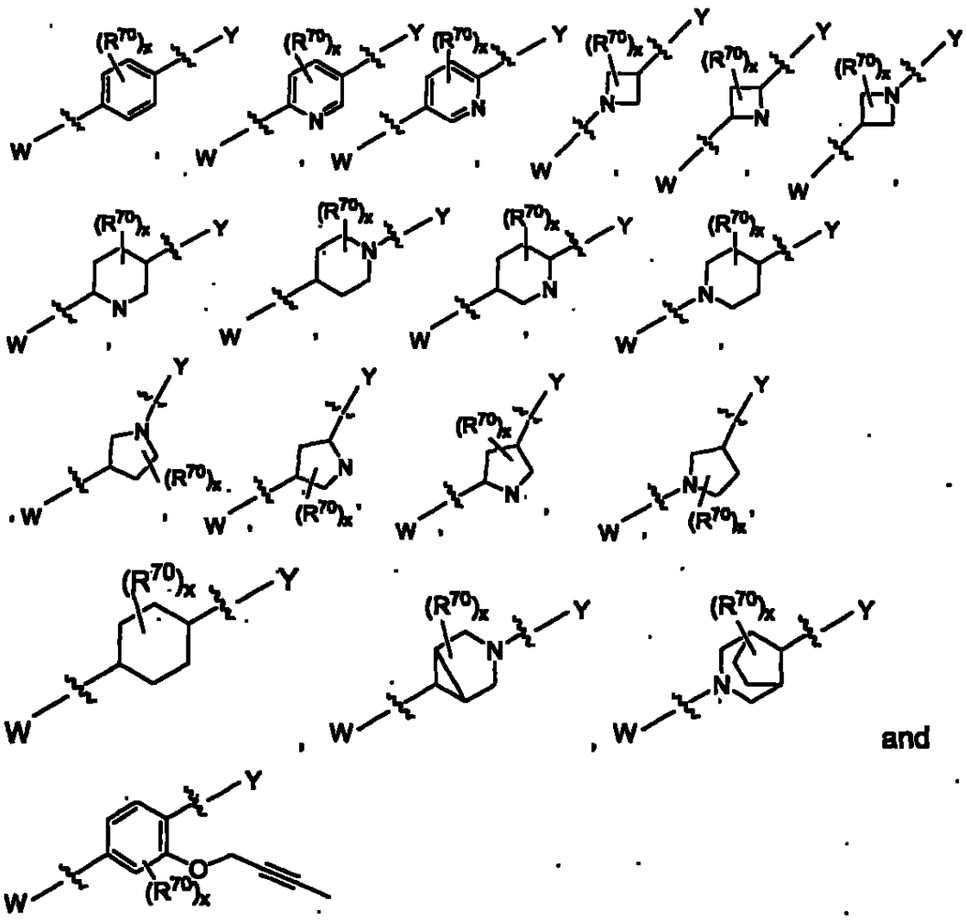
In another embodiment, X is aryl.

In another embodiment, X is heteroaryl.

In another embodiment, X is selected from the group consisting of phenyl, azetidinyl, pyrrolidinyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl.

In another embodiment, X is selected from the group consisting of phenyl, pyridinyl and piperidinyl.

In another embodiment, X is selected from the group consisting of



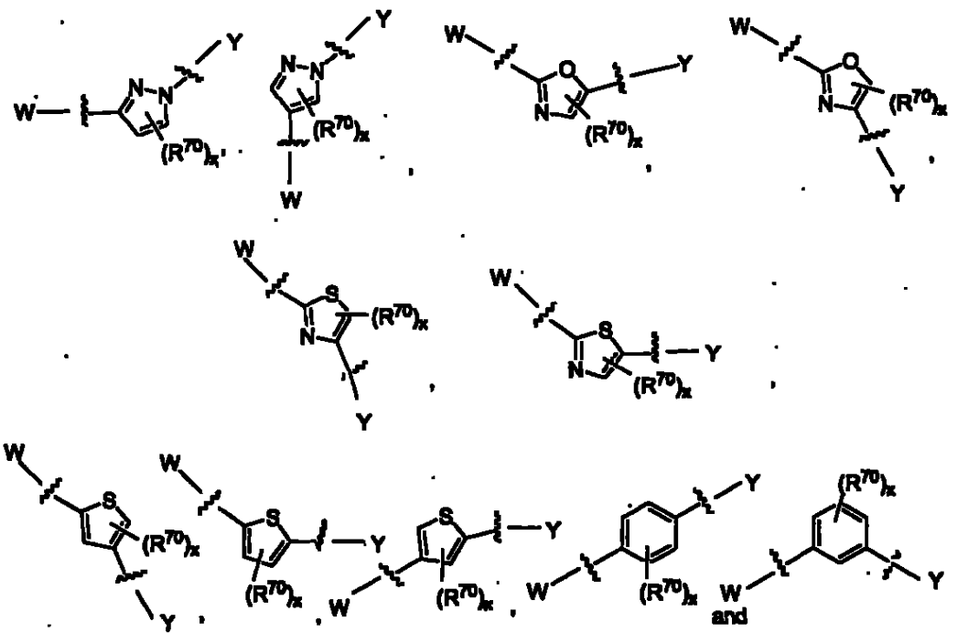
and

wherein

x is 0 to 4, and wherein x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

In the above shown moieties for X, X is the moiety enclosed by ⟨—⟩ and W and Y are shown only to indicate which end of the X is attached to W and which end to Y. Similar depictions occur throughout this application with similar connotations.

In another embodiment X is selected from the group consisting of



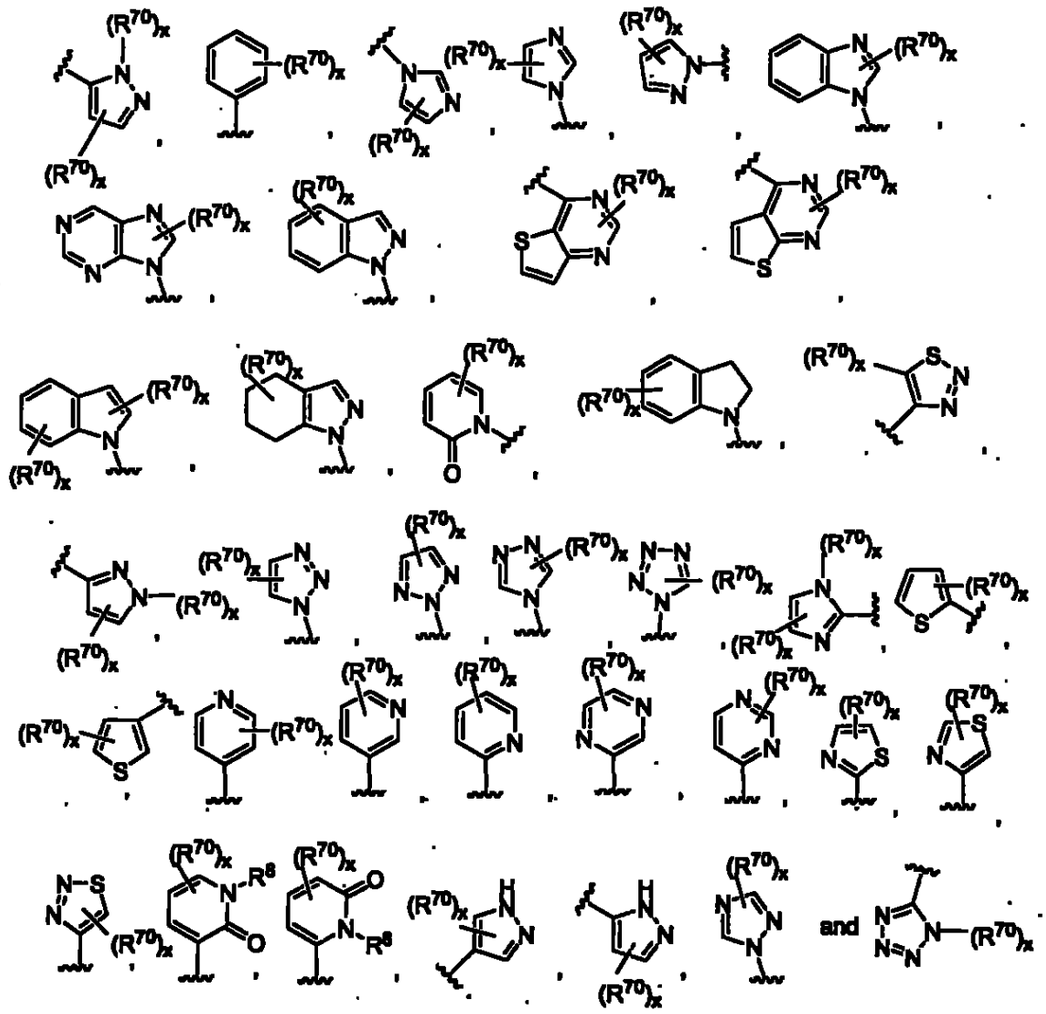
wherein x is 0 to 4, and when x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

In another embodiment, Z is selected from the group consisting of H, aryl and heteroaryl.

In another embodiment, Z is selected from the group consisting of H, phenyl, indolyl, benzimidazolyl, pyrazolyl, thienyl, pyridinyl, thiazolyl, thiadiazolyl, imidazolyl, pyrrolidinyl, pyrazinyl, triazolyl, tetrazolyl and tetrazinyl, wherein said phenyl, indolyl, benzimidazolyl, pyrazolyl, thienyl, pyridinyl, thiazolyl, thiadiazolyl, imidazolyl, pyrrolidinyl, pyrazinyl, triazolyl, tetrazolyl and tetrazinyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different,

each moiety being independently selected from the group consisting of R^{70} moieties.

In another embodiment; Z is selected from the group consisting of



wherein x is 0 to 4, and when x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

In another embodiment, Z is phenyl.

In another embodiment, Z is a phenyl substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

In another embodiment, Z is thienyl.

In another embodiment, Z is a thienyl substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

In another embodiment, Z is pyrazolyl.

In another embodiment, Z is a pyrazolyl substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

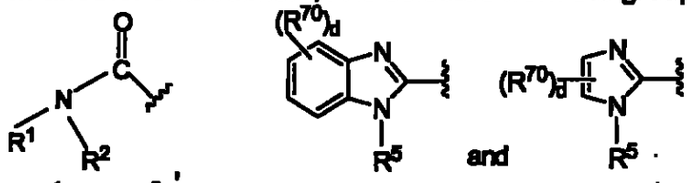
In another embodiment, Z is pyridinyl.

In another embodiment, Z is a pyridinyl substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

In another embodiment, Z is imidazolyl.

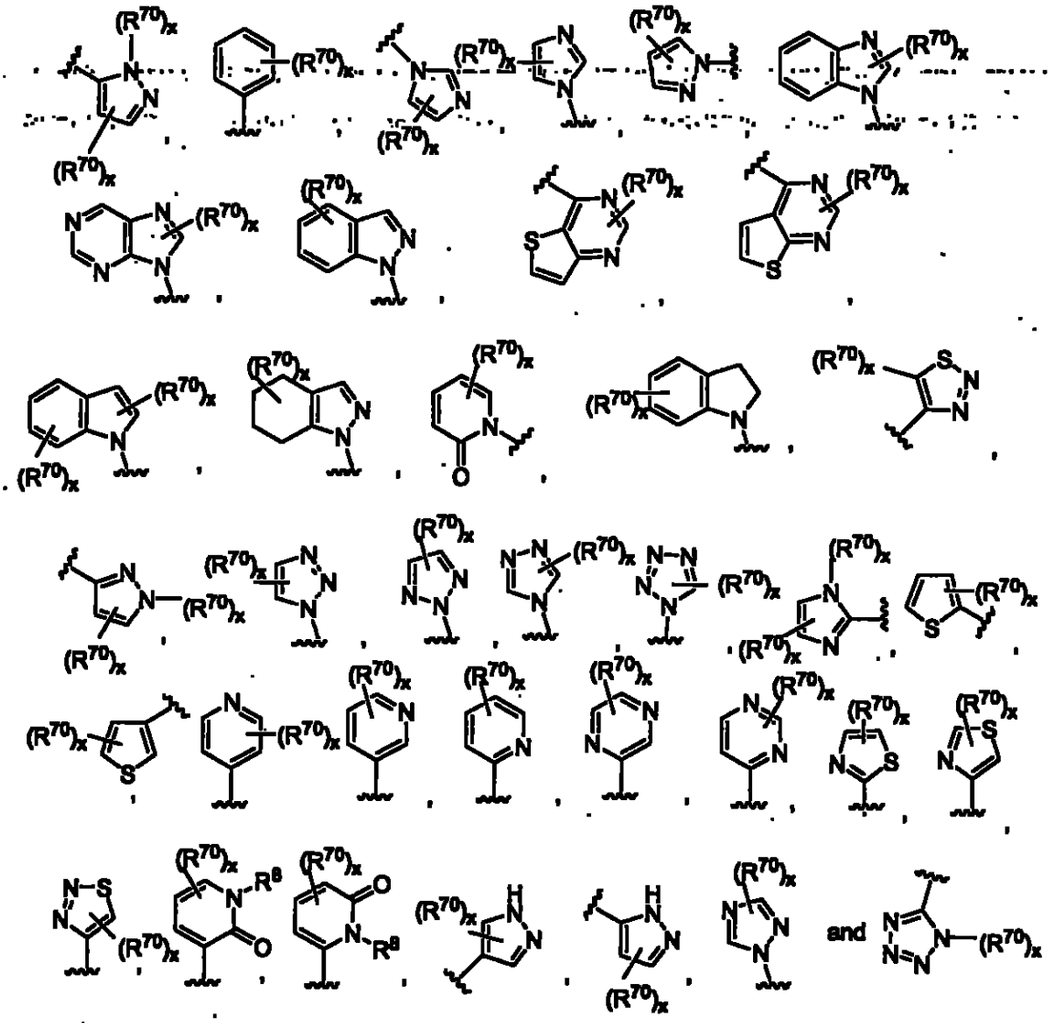
In another embodiment, Z is an imidazolyl substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

In another embodiment, A is selected from the group consisting of:

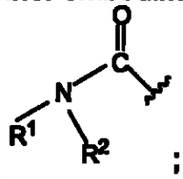


and

wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^{13}_2)_n-$, wherein n is 0 to 5; X is selected from the group consisting of aryl, heteroaryl and heterocyclyl; Y is selected from the group consisting of a covalent bond, $-[C(R^6)_2]_n-$ wherein n is 1 to 2, -O-, -S-, and $-NR^1-$; and Z is selected from the group consisting of



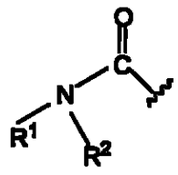
In another embodiment, A is:



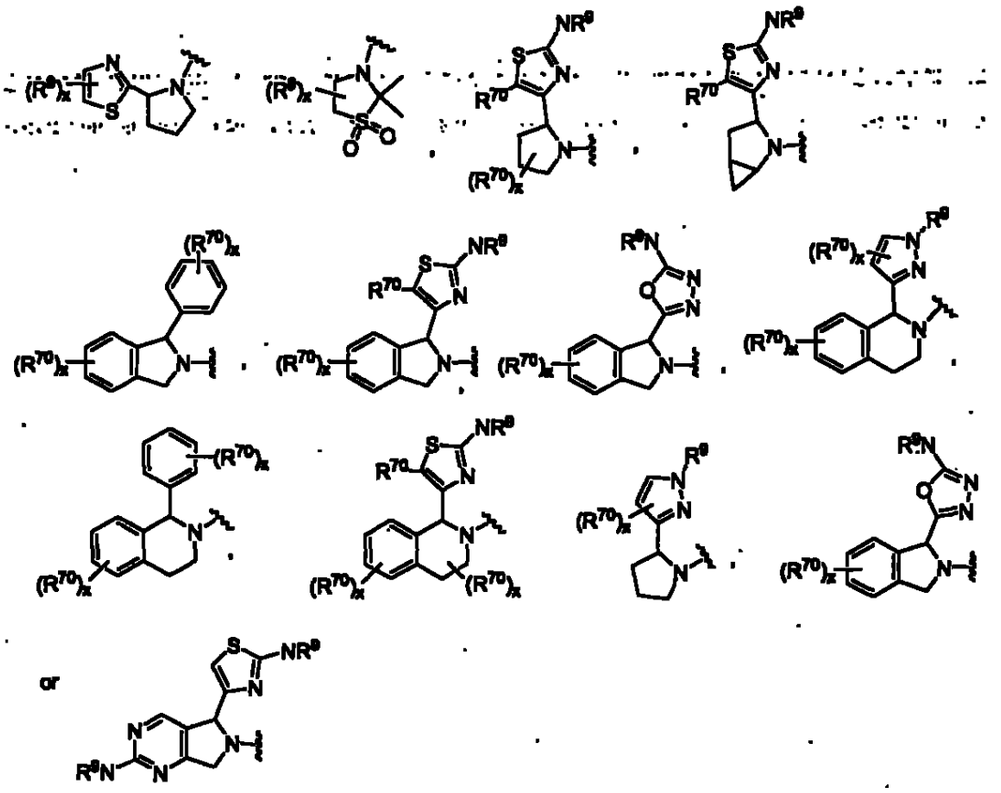
;

wherein;

the $-NR^1R^2$ of



is

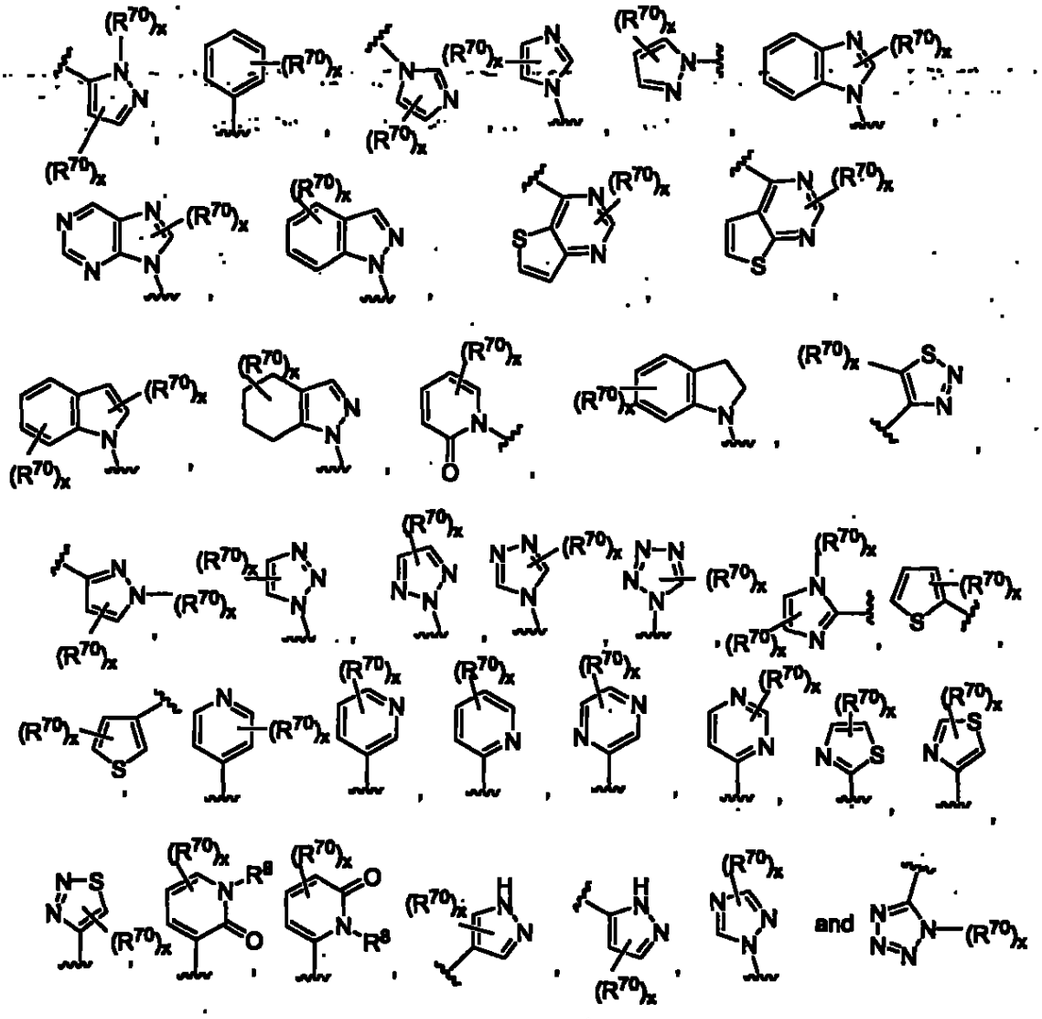


wherein

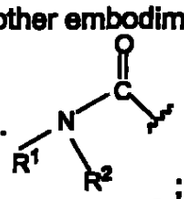
each R^9 is a substituent for H where indicated and can be the same or different, each being independently selected from the group consisting of -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; and

x is 0 to 4, and when x is greater than 1, each R^9 moiety can be the same or different, each moiety being independently selected from the group of R^9 moieties;

E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^{13}_2)_n-$, wherein n is 0 to 5; X is selected from the group consisting of aryl, heteroaryl and heterocyclyl; Y is selected from the group consisting of a covalent bond, $-[C(R^6)_2]_n-$ wherein n is 1 to 2, -O-, -S-, and $-NR^1-$; and Z is selected from the group consisting of

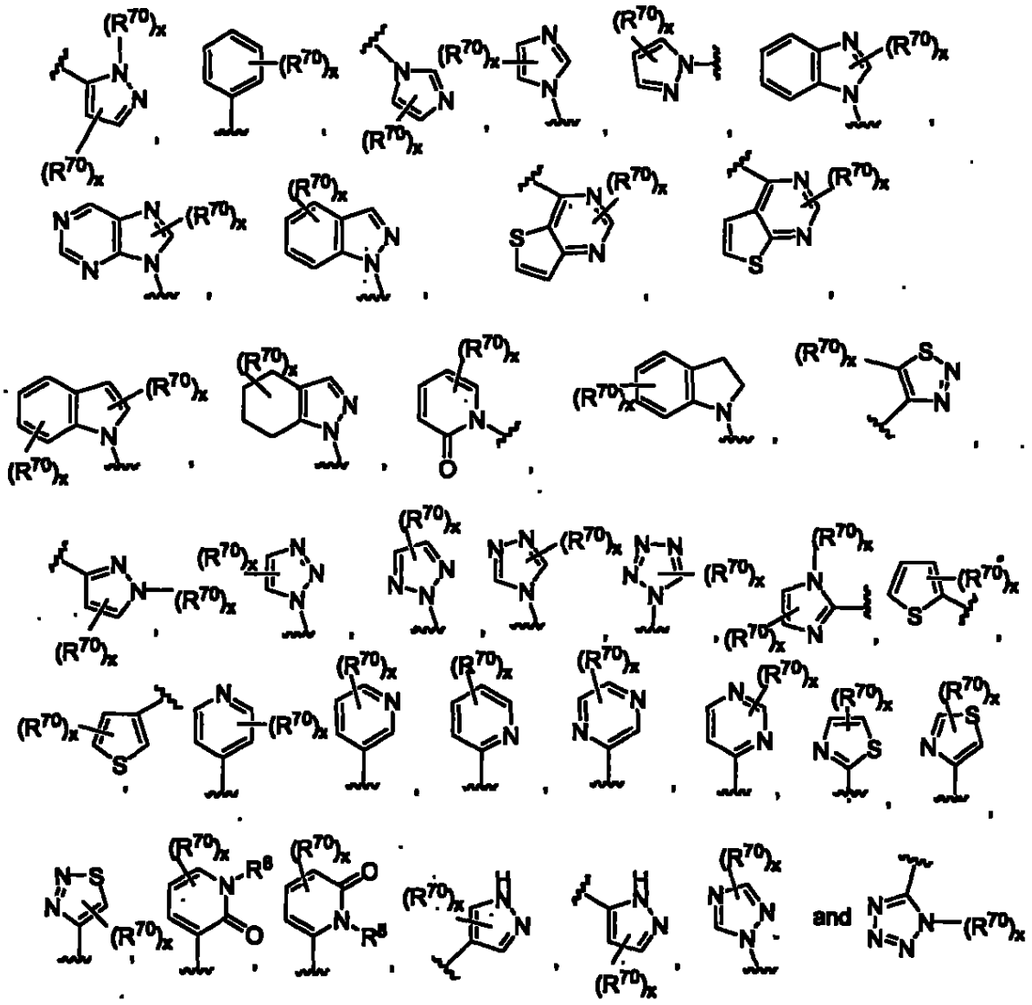


In another embodiment, A is:

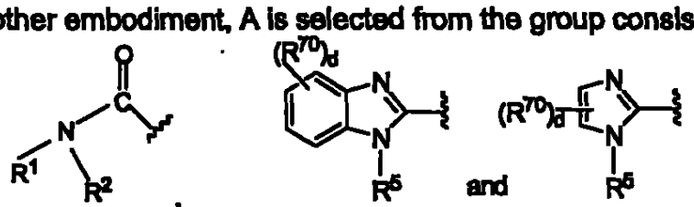


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; E, J and T are the same and are O; R^{10} is H or alkyl;

R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^{13}_2)_n-$, wherein n is 0 to 5; X is selected from the group consisting of aryl, heteroaryl and heterocyclyl; Y is selected from the group consisting of a covalent bond; $[C(R^6)_2]_n-$ wherein n is 1 to 2, -O-, -S-, and $-NR^1-$; and Z is selected from the group consisting of



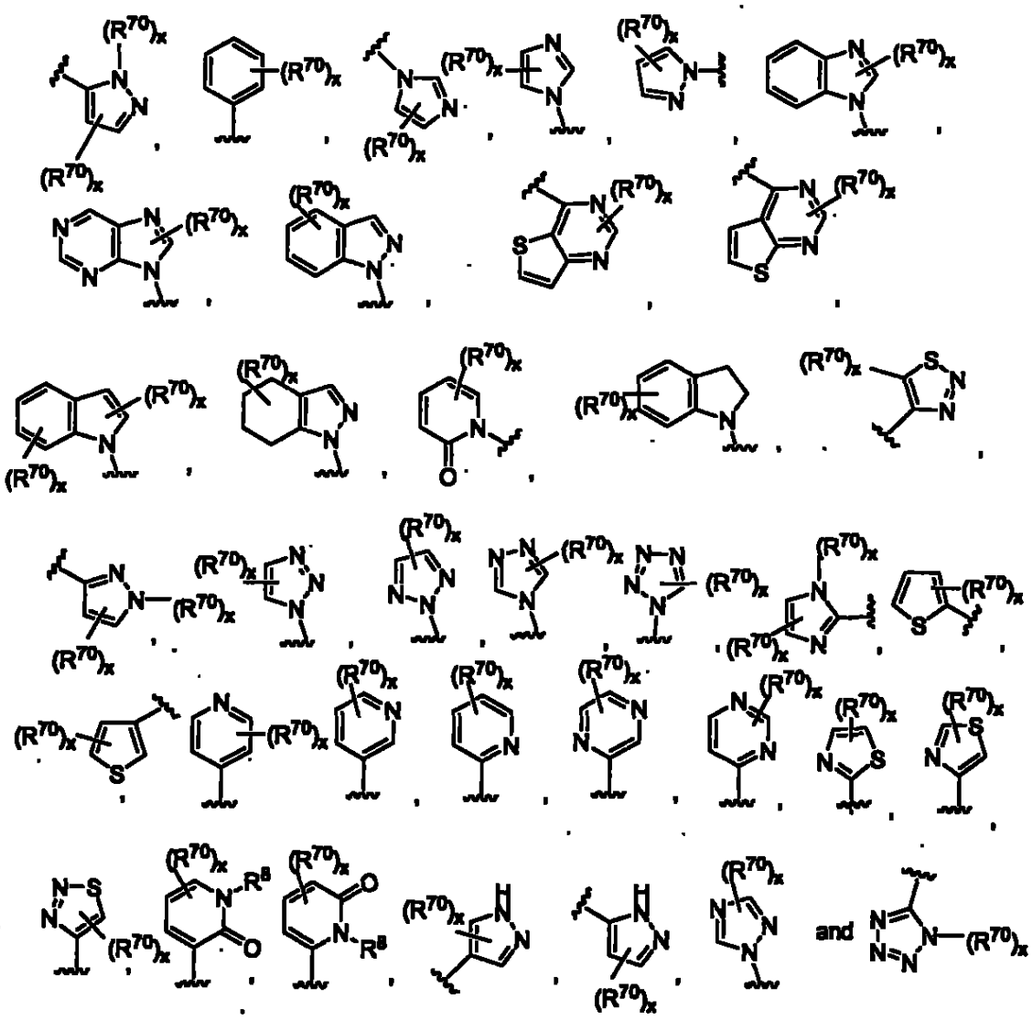
In another embodiment, A is selected from the group consisting of:



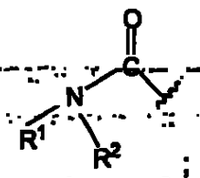
wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms

including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

wherein E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^6_2)_n-$, wherein n is 0 to 5; X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is $-[C(R^6)_2]_n-$ wherein n is 1 to 2; and Z is selected from the group consisting of

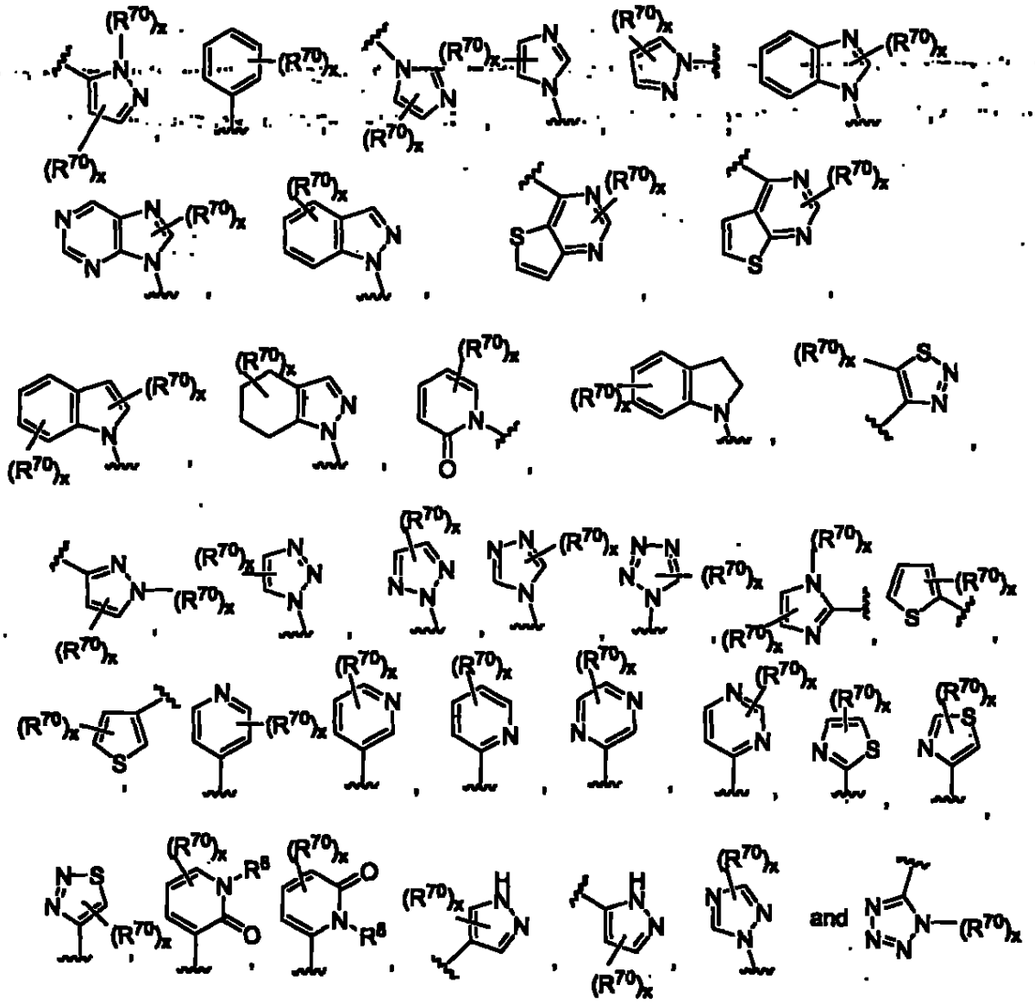


In another embodiment, A is:

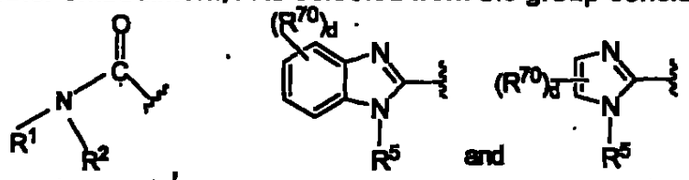


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

wherein E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^6_2)_n-$, wherein n is 0 to 5; X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is $-[C(R^6)_2]_n-$ wherein n is 1 to 2; and Z is selected from the group consisting of



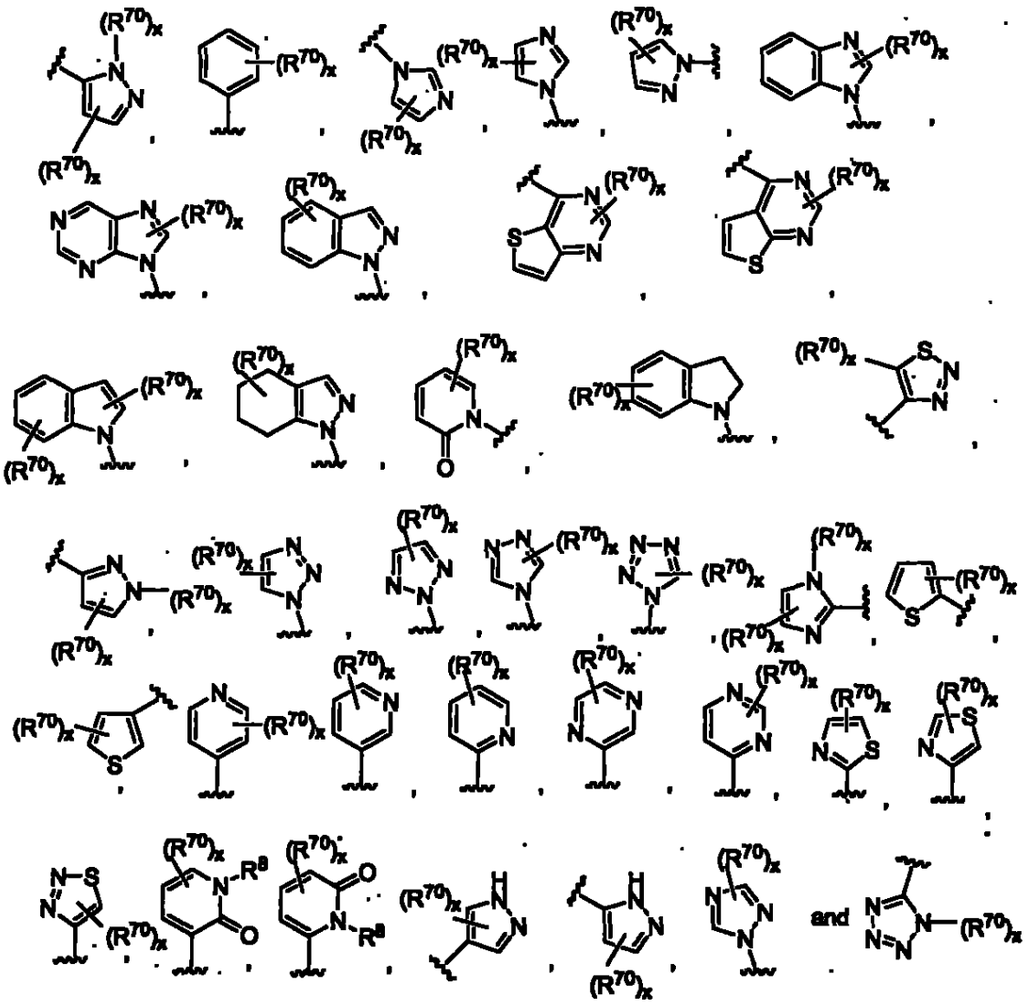
In another embodiment, A is selected from the group consisting of:



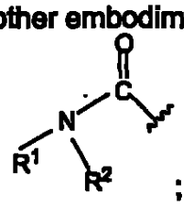
wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be

the same or different, each moiety being independently selected from the group of R^{70} moieties;

E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^8_2)_n-$, wherein n is 0 to 5; X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is selected from the group consisting of O-, -S-, and $-NR^1-$; and Z is selected from the group consisting of

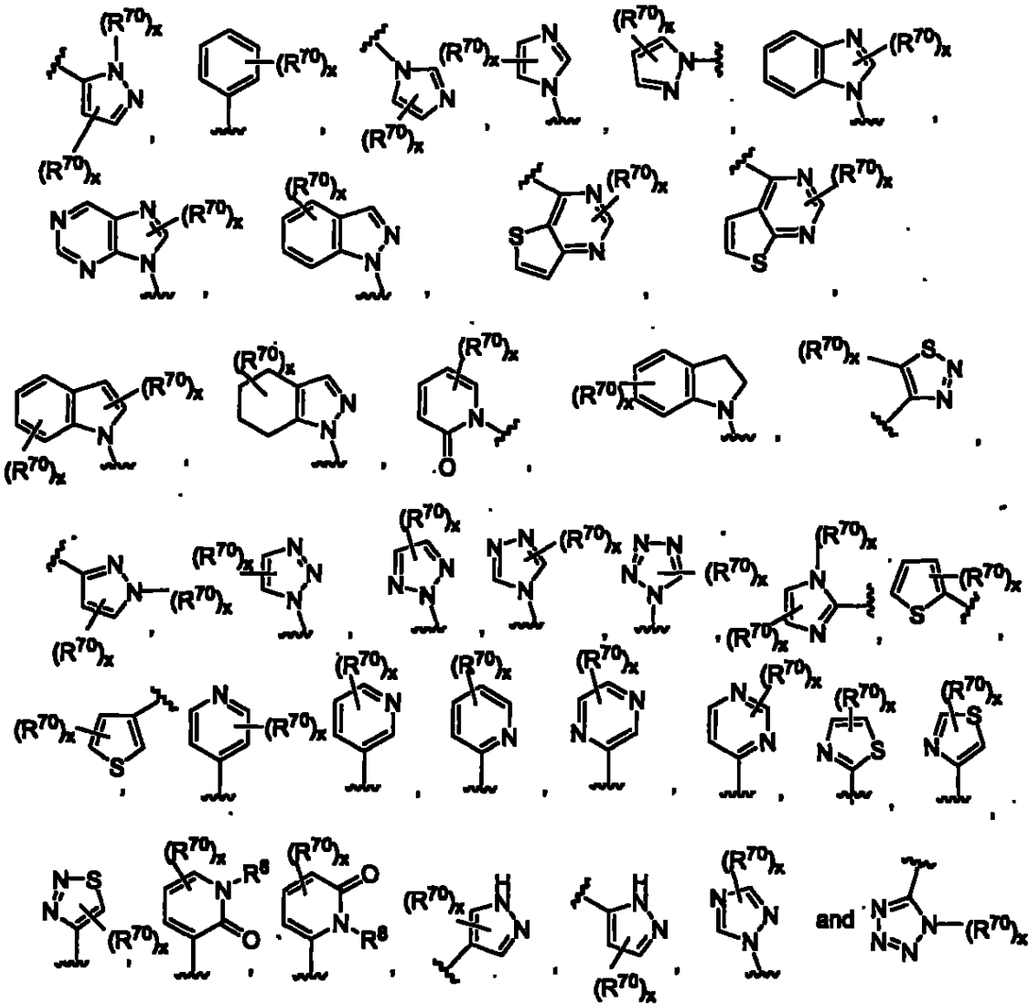


In another embodiment, A is

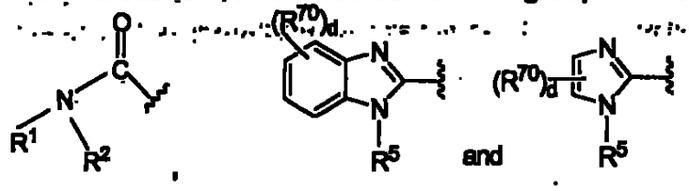


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

wherein E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^6_2)_n-$, wherein n is 0 to 5; X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is selected from the group consisting of O-, -S-, and $-NR^1-$; and Z is selected from the group consisting of

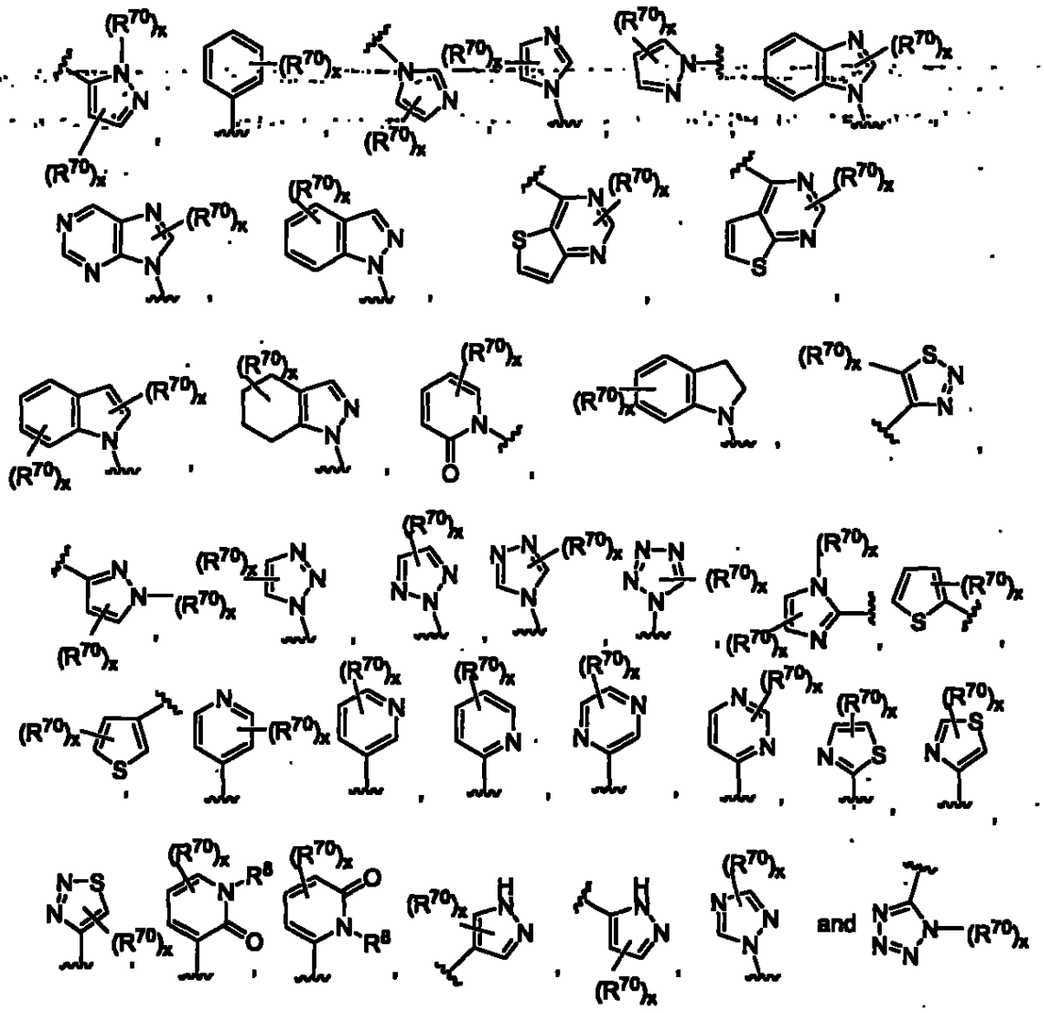


In another embodiment, A is selected from the group consisting of:

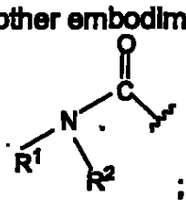


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

wherein E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^{13}_2)_n-$ wherein n is 1 or 2; X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is a covalent bond and Z is selected from the group consisting of

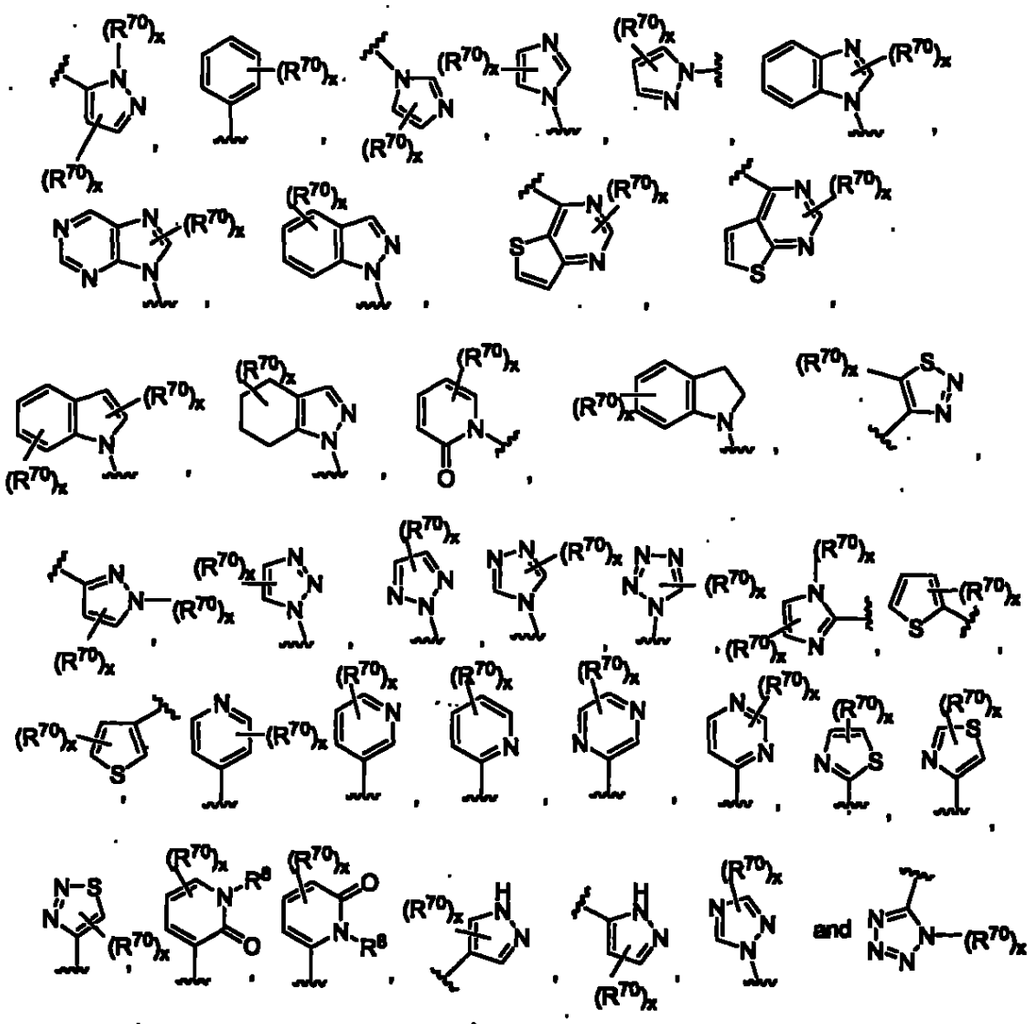


In another embodiment, A is



wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; wherein E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is -

$(CR^{13}_2)_n$- wherein n is 1 or 2; X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is a covalent bond and Z is selected from the group consisting of



In another embodiment, X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl, and pyrazolyl.

In another embodiment, X is selected from the group consisting of phenyl, piperidinyl, thienyl, and pyridinyl and Y is selected from the group consisting of a covalent bond, $-[C(R^6)_2]_n$- wherein n is 1 to 2 and -O-.

In another embodiment, X is phenyl and Y is selected from the group consisting of a covalent bond, $-CH_2$- and -O-.

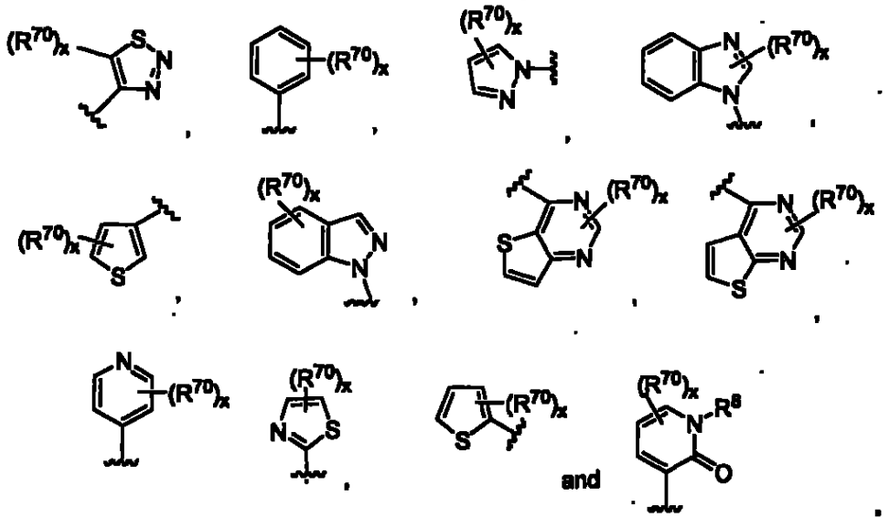
In another embodiment, X is piperidinyl, Y is a covalent bond, and Z is aryl or heteroaryl having two substituents which can be the same or different,

each moiety being independently selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy and amine.

In another embodiment, W is selected from the group consisting of CH_2-, $-C(H)CH_3$-, $-C(CH_3)_2$- and Y is a covalent bond.

In another embodiment, W is $-CH_2$- and Y is $-CH_2$-.

In another embodiment, Z is selected from the group consisting of



Another embodiment of the invention discloses the compounds shown in Table 1 below.

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. The term "substituted alkyl" means that the alkyl group may be substituted by one or more substituents which may be the same or

different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl. The term "Fluoroalkyl" means an alkyl group in which alkyl is as previously described wherein one or more hydrogens are replaced with fluorine atoms.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as

defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

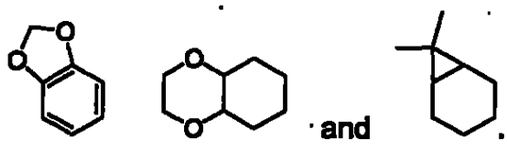
"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring

atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like, as well as partially saturated species such as, for example, indanyl, tetrahydronaphthyl and the like.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

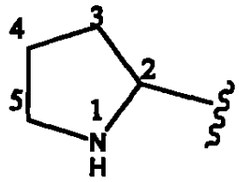
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- and $-SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, $-C(CH_3)_2-$ and the like which form moieties such as, for example:

 and

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or

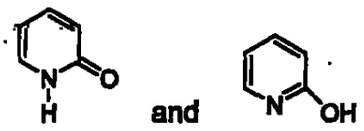
sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:



are considered equivalent in certain embodiments of this invention.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. Th bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups

include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O_2)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-S(O_2)- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By 'stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "isolated" or "in isolated form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. The term "purified" or "in purified form" for a compound refers to the physical state of said compound after

being obtained from a purification process or processes described herein or well known to the skilled artisan; in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula I or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves

varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the CDK(s) and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula I may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical

compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts: Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of Formula I, and salts, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl).

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

Polymorphic forms of the compounds of Formula I, and of the salts, solvates and prodrugs of the compounds of Formula I, are intended to be included in the present invention.

The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula I can be inhibitors of TACE, TNF-α, ADAM and/or MMP activity.

In one aspect, the invention provides a pharmaceutical composition comprising as an active ingredient at least one compound of formula 1.

In another aspect, the invention provides a pharmaceutical composition of formula 1 additionally comprising at least one pharmaceutically acceptable carrier.

In another aspect, the invention provides a method of treating disorders associated with TACE, TNF-*α*, MMPs, ADAMs or any combination thereof or any combination thereof, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound of formula 1.

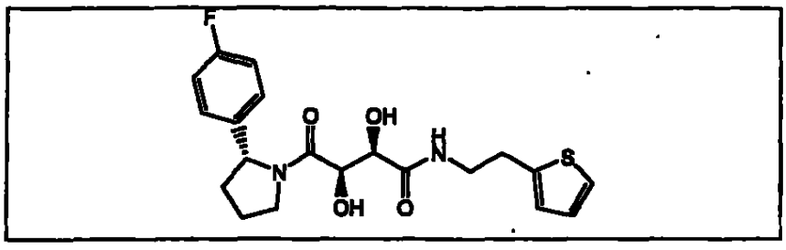
In another aspect, the invention provides a use of a compound of formula 1 for the manufacture of a medicament to treat disorders associated with TACE, TNF-*α*, MMPs, ADAMs or any combination thereof.

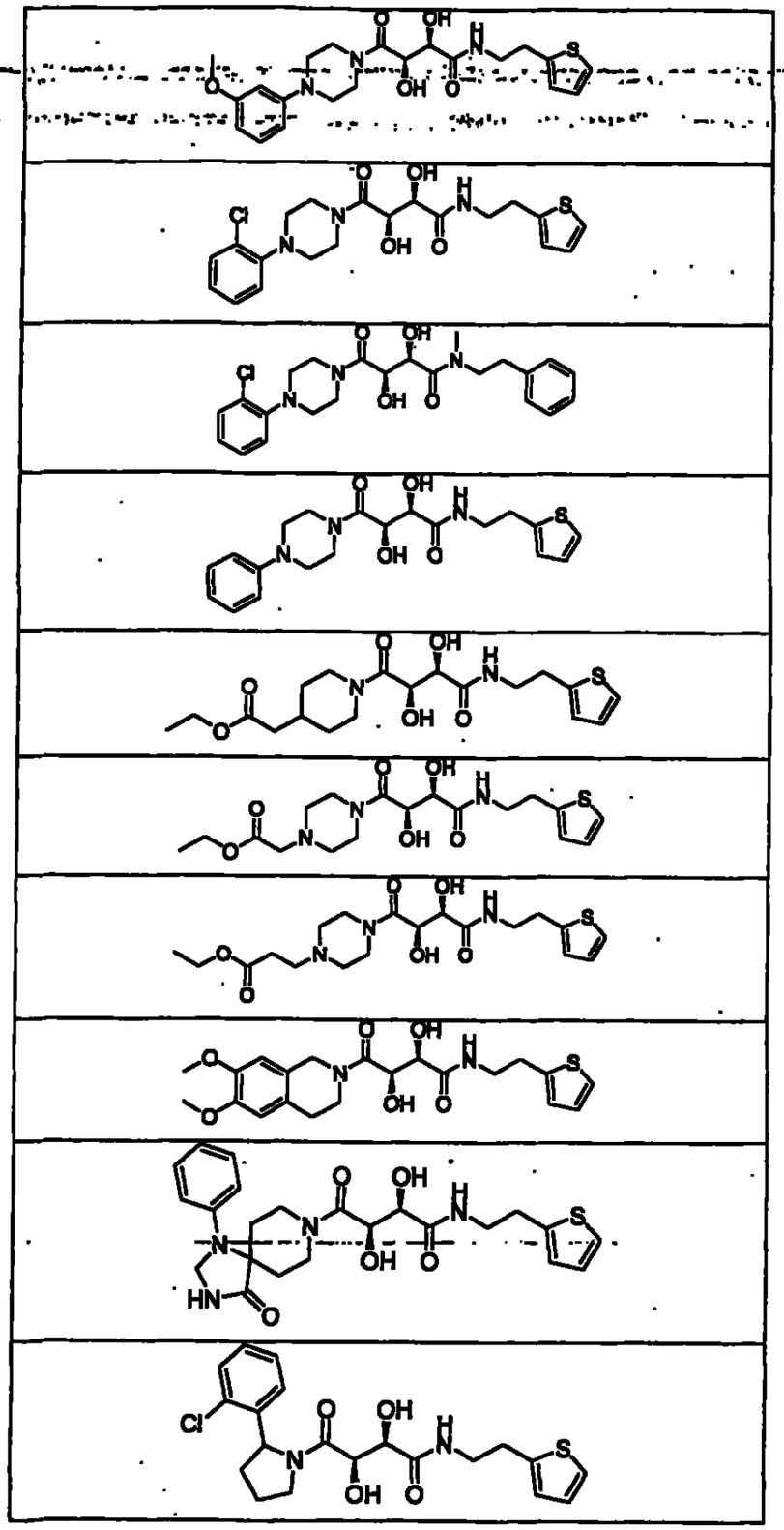
The compounds of Formula I can have anti-inflammatory activity and/or immunomodulatory activity and can be useful in the treatment of diseases including but not limited to septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases

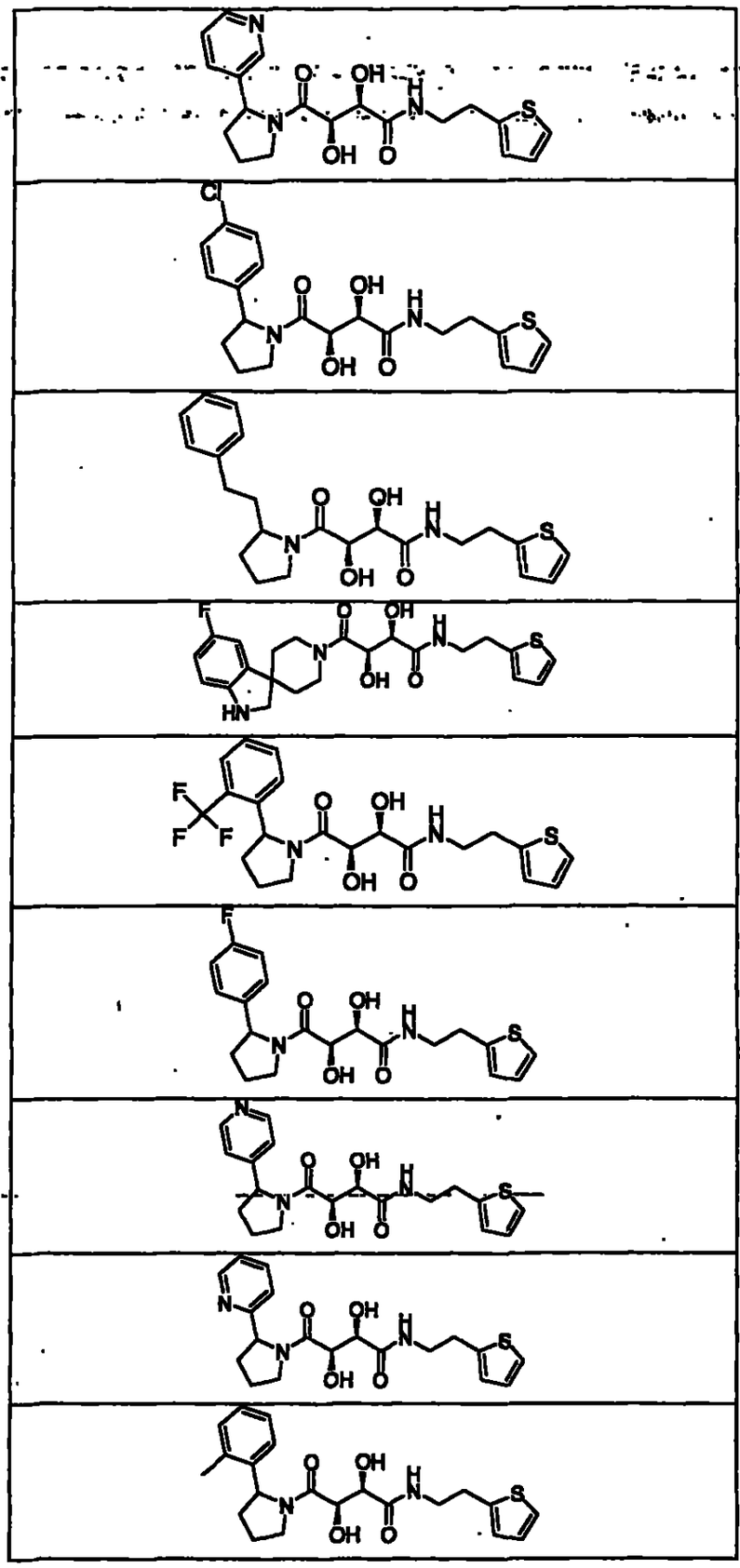
involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, OA and RA, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, uveitis, Wegener's granulomatosis, Behcehe disease, Sjogren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, transplant rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and/or bronchitis. It is contemplated that a compound of this invention may be useful in treating one or more of the diseases listed.

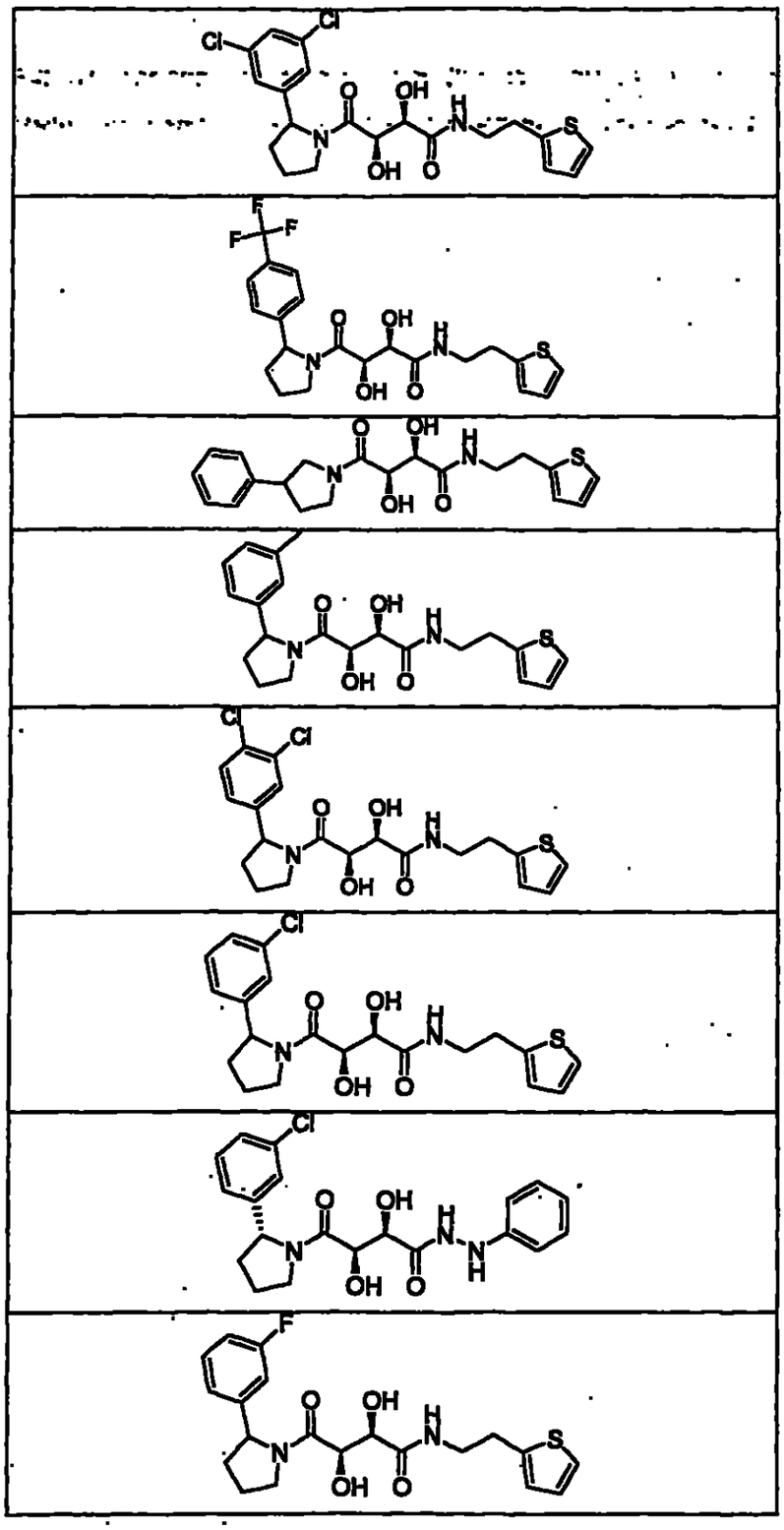
In another aspect, the invention provides a method of preparing a pharmaceutical composition for treating the disorders associated with TACE, TNF-α, MMPs, ADAMs or any combination thereof, said method comprising bringing into intimate contact at least one compound of formula 1 and at least one pharmaceutically acceptable carrier.

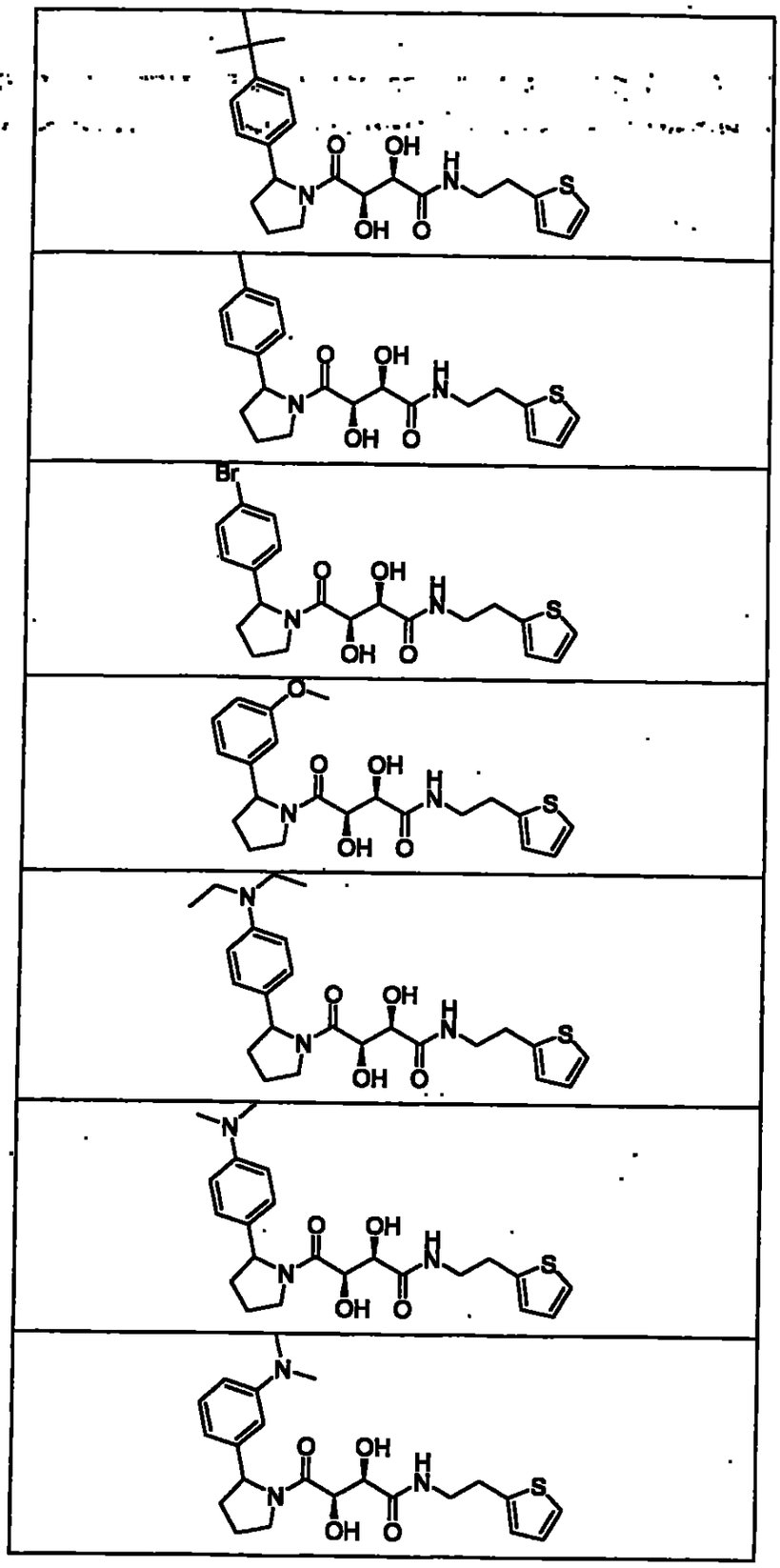
In another aspect, the invention provides a compound of formula (I) exhibiting TACE, TNF-α, MMPs, ADAMs or any combination thereof inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the compounds of structures listed below:



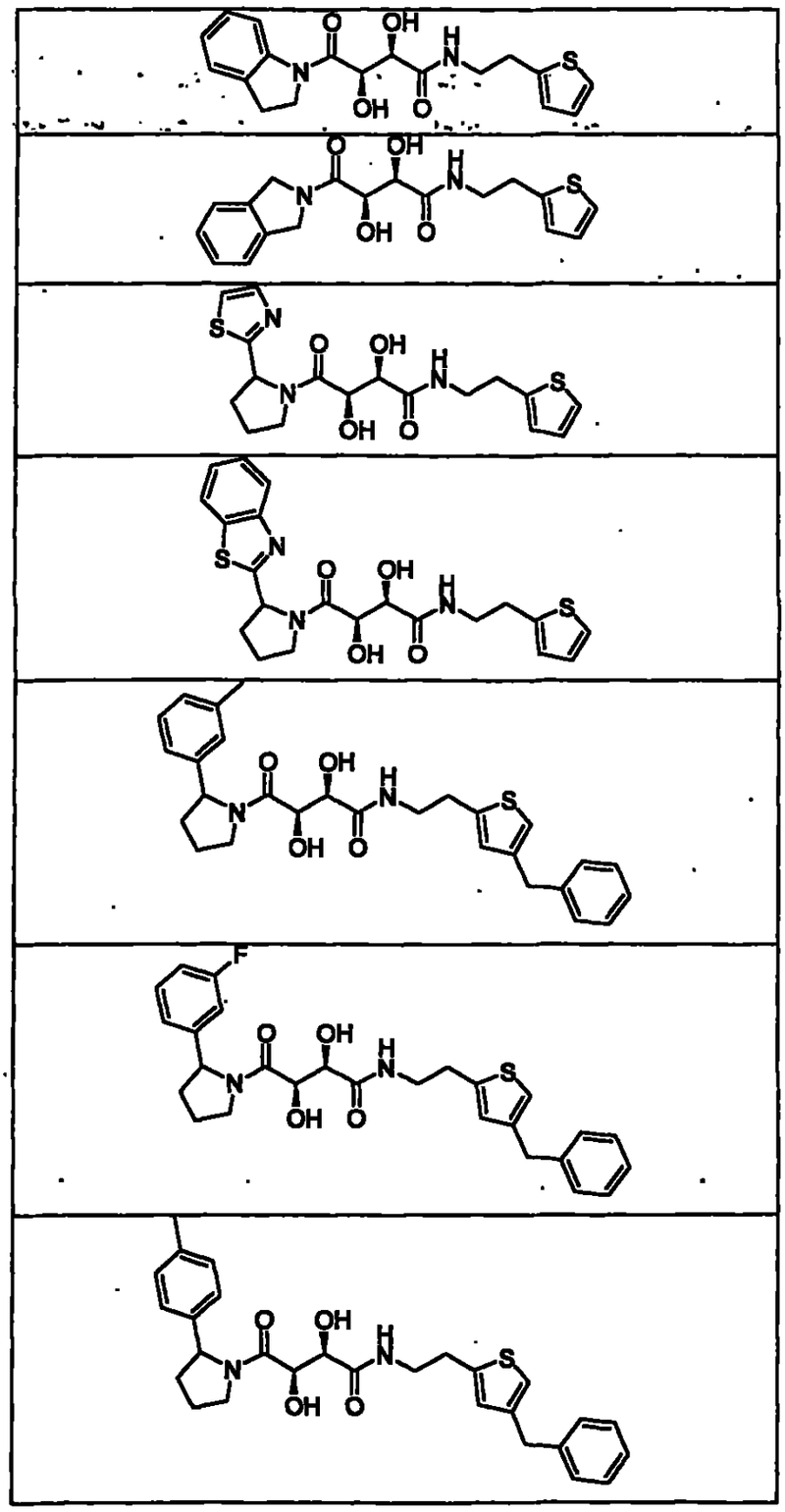


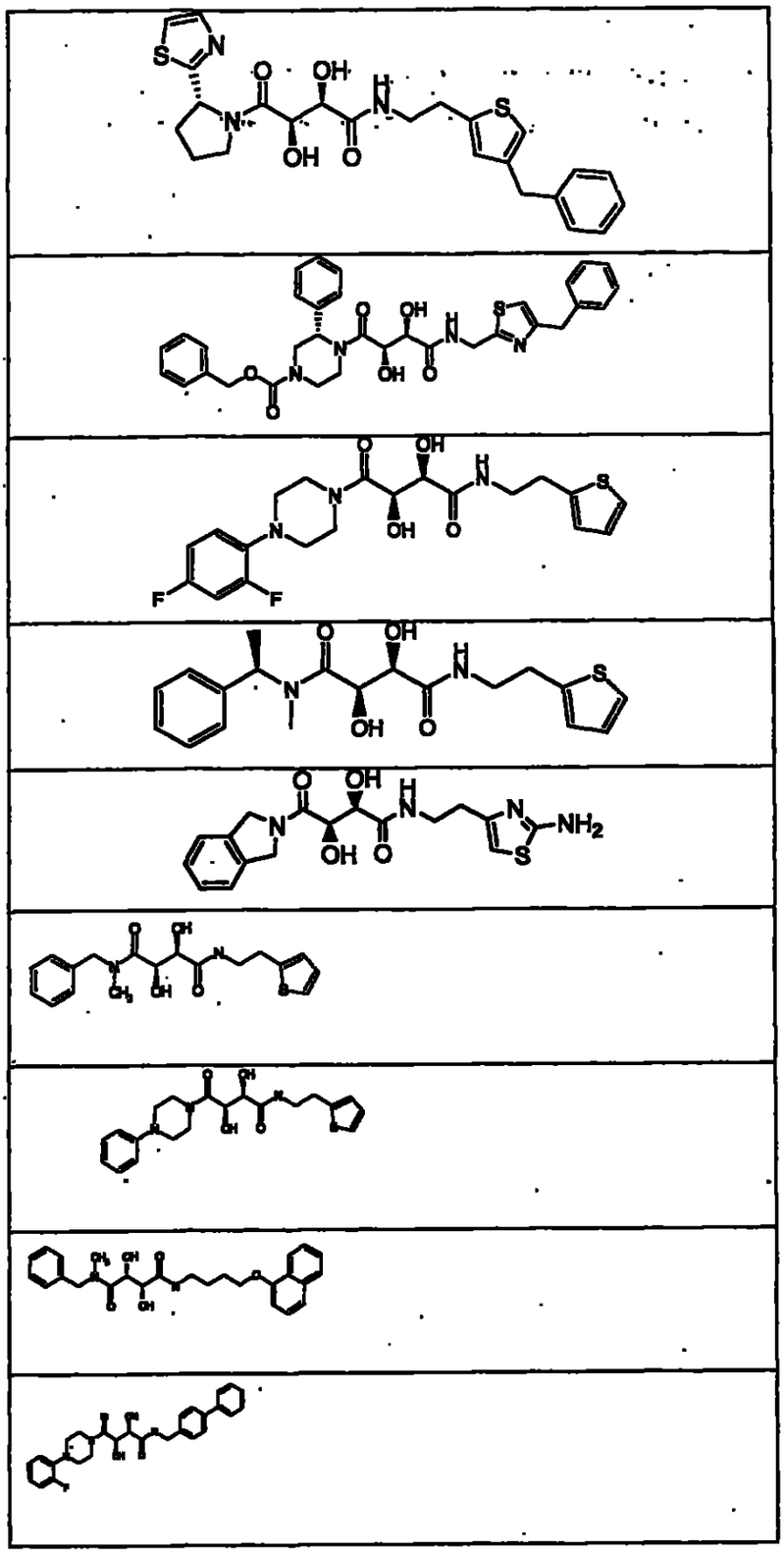


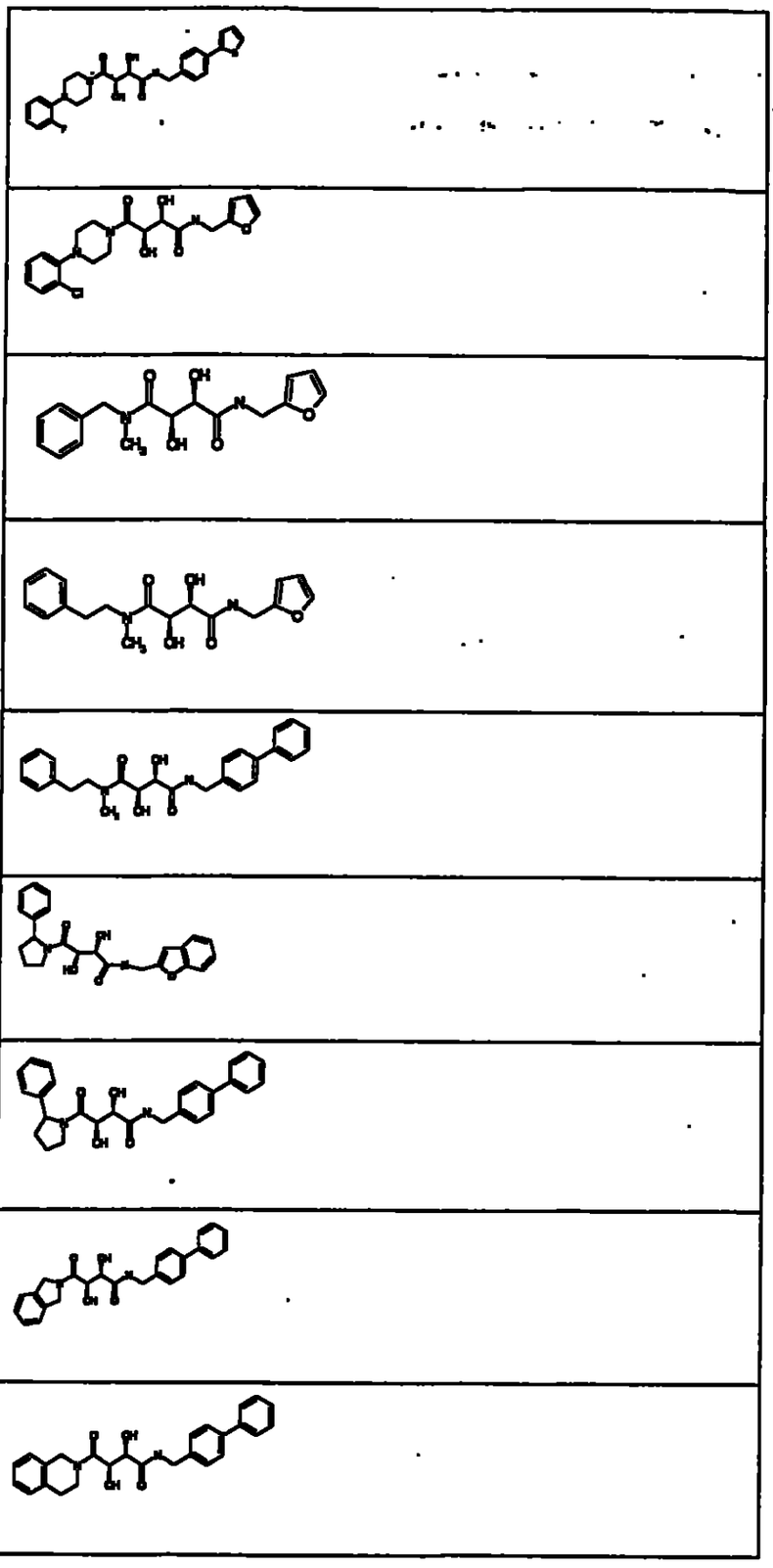


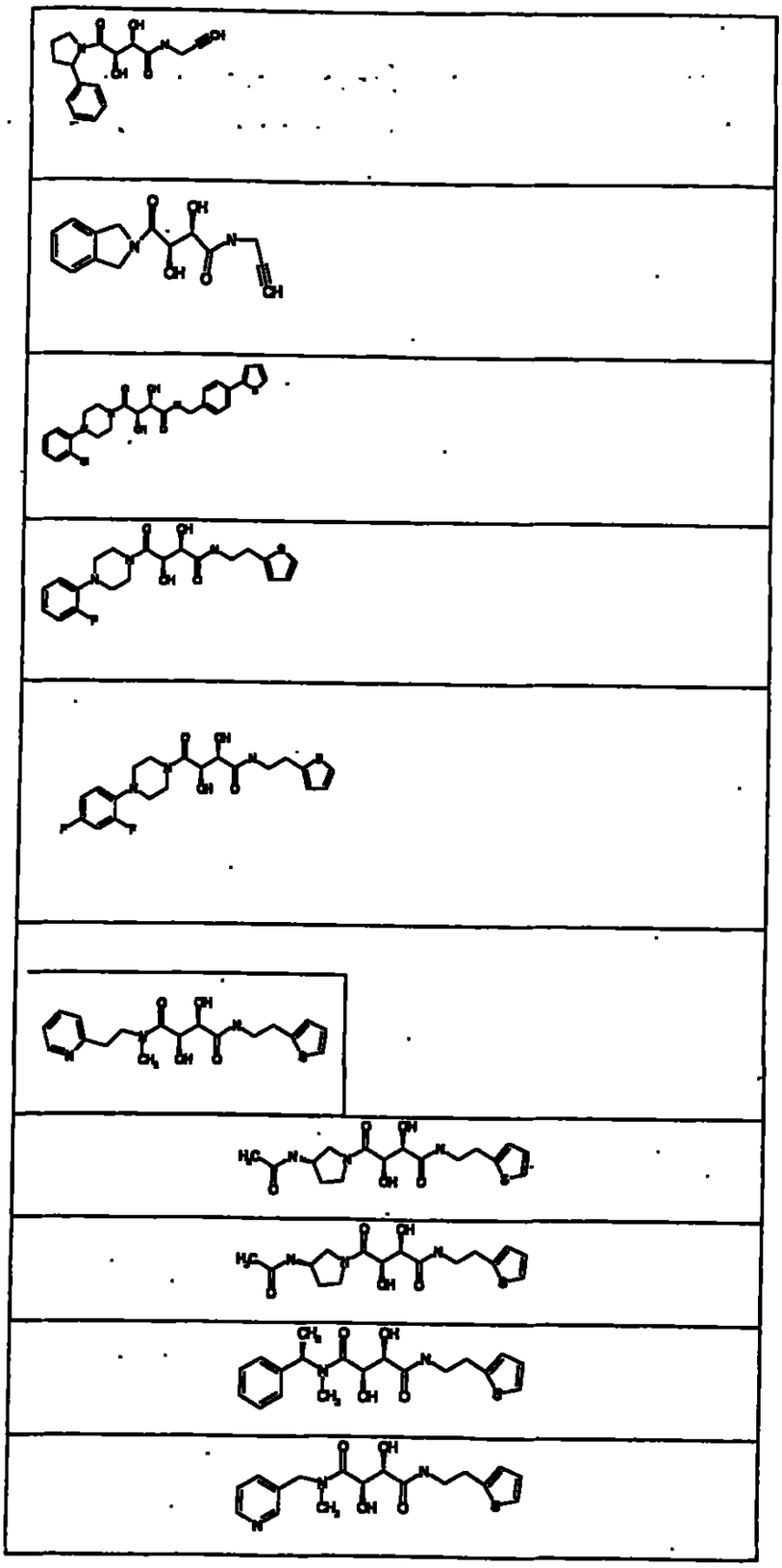


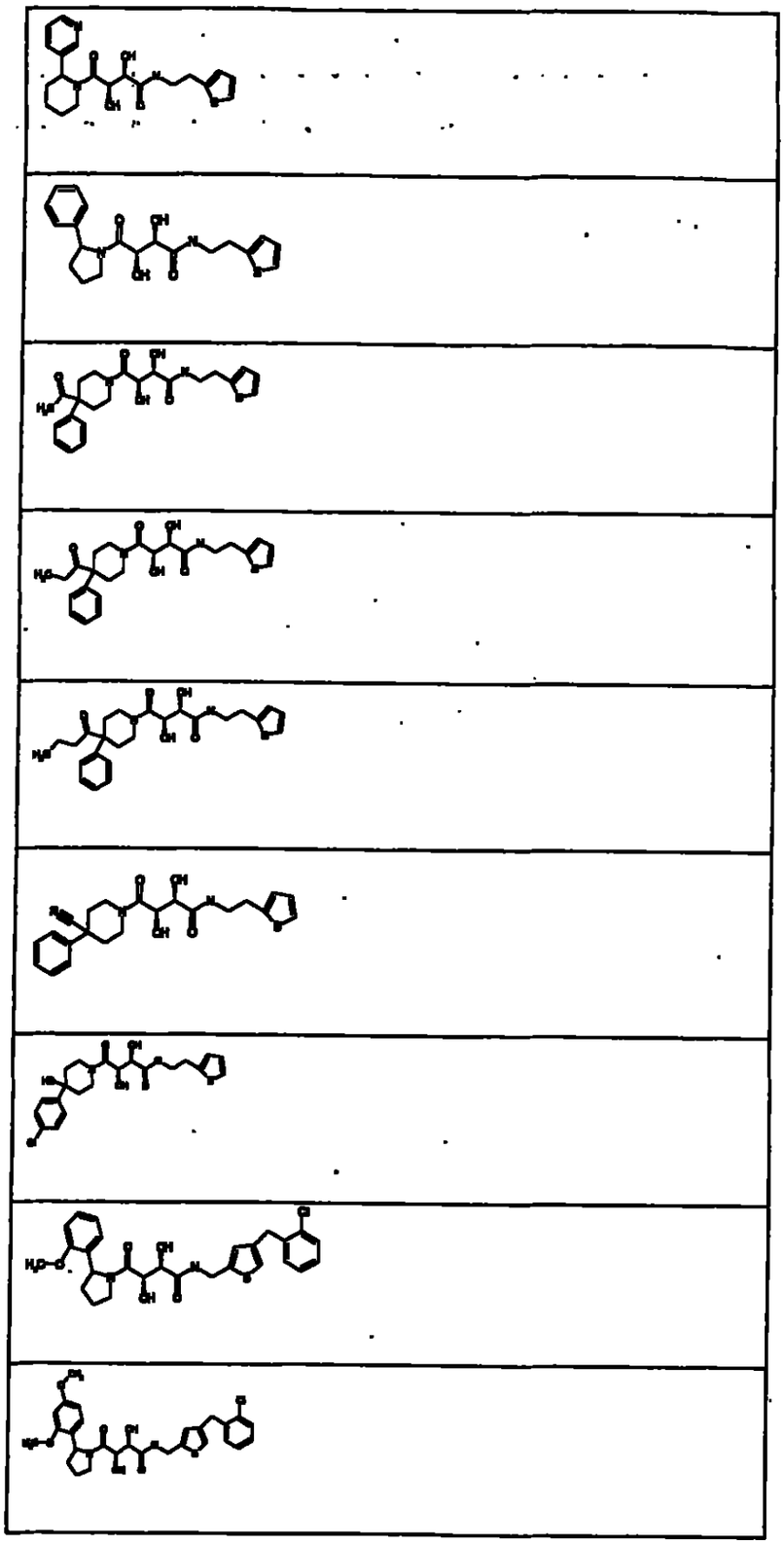
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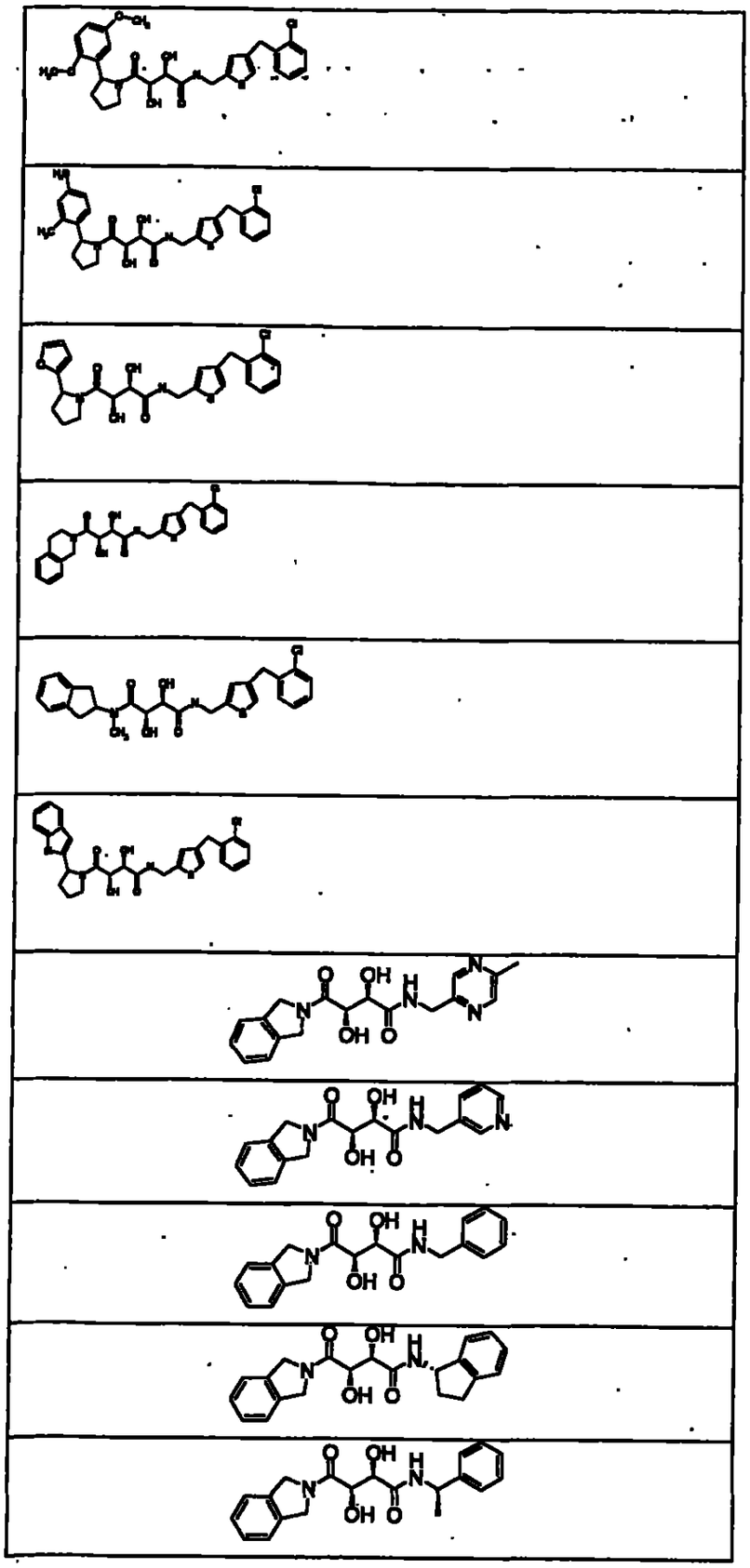


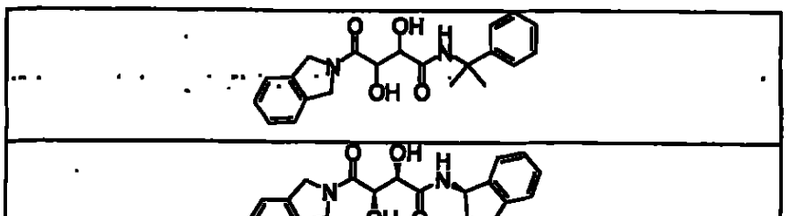


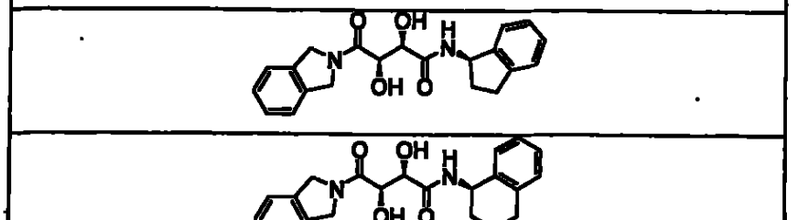


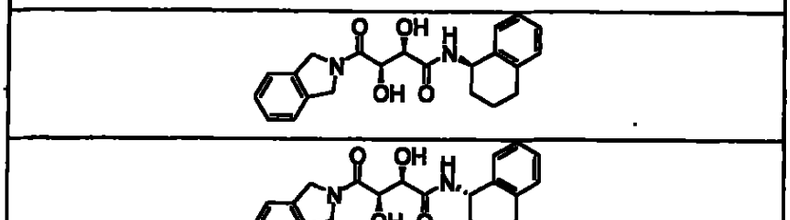


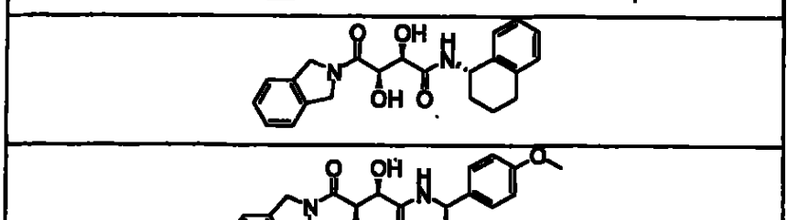


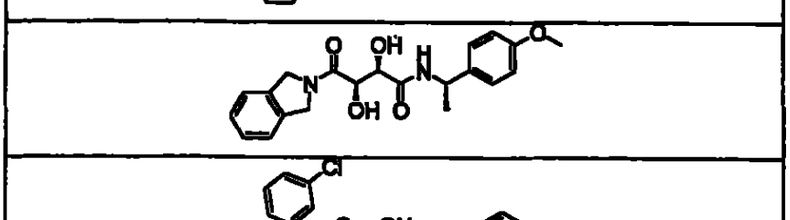


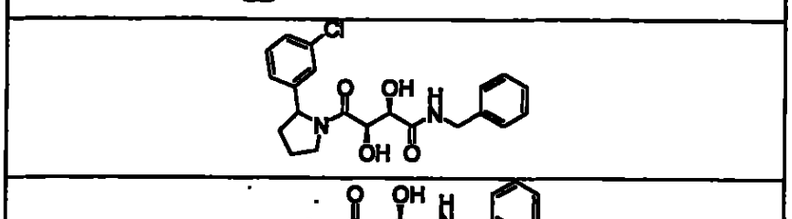


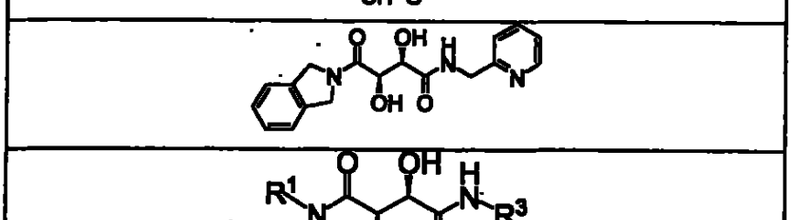


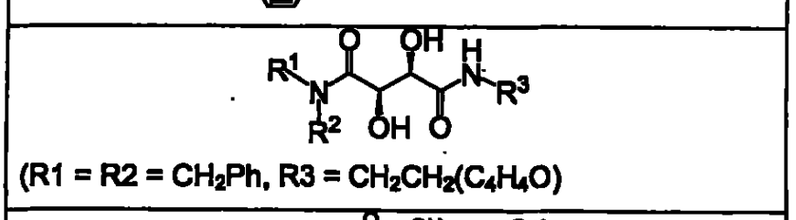




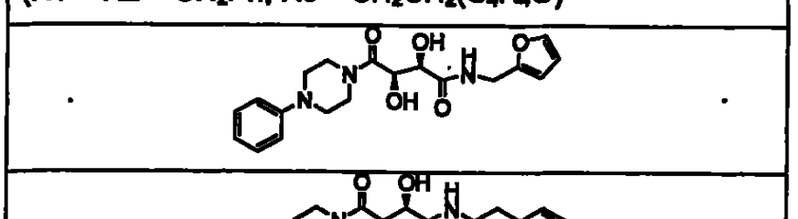


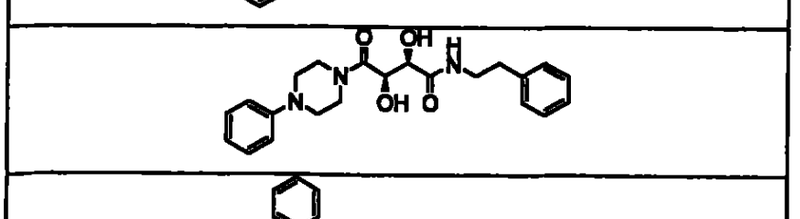


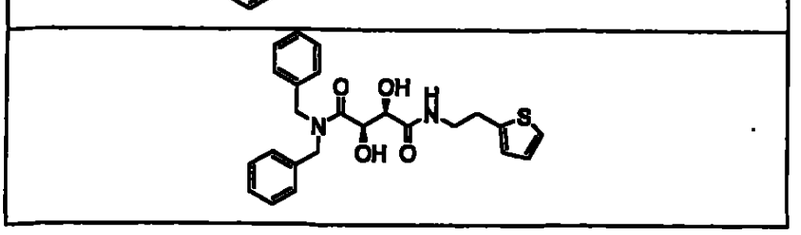


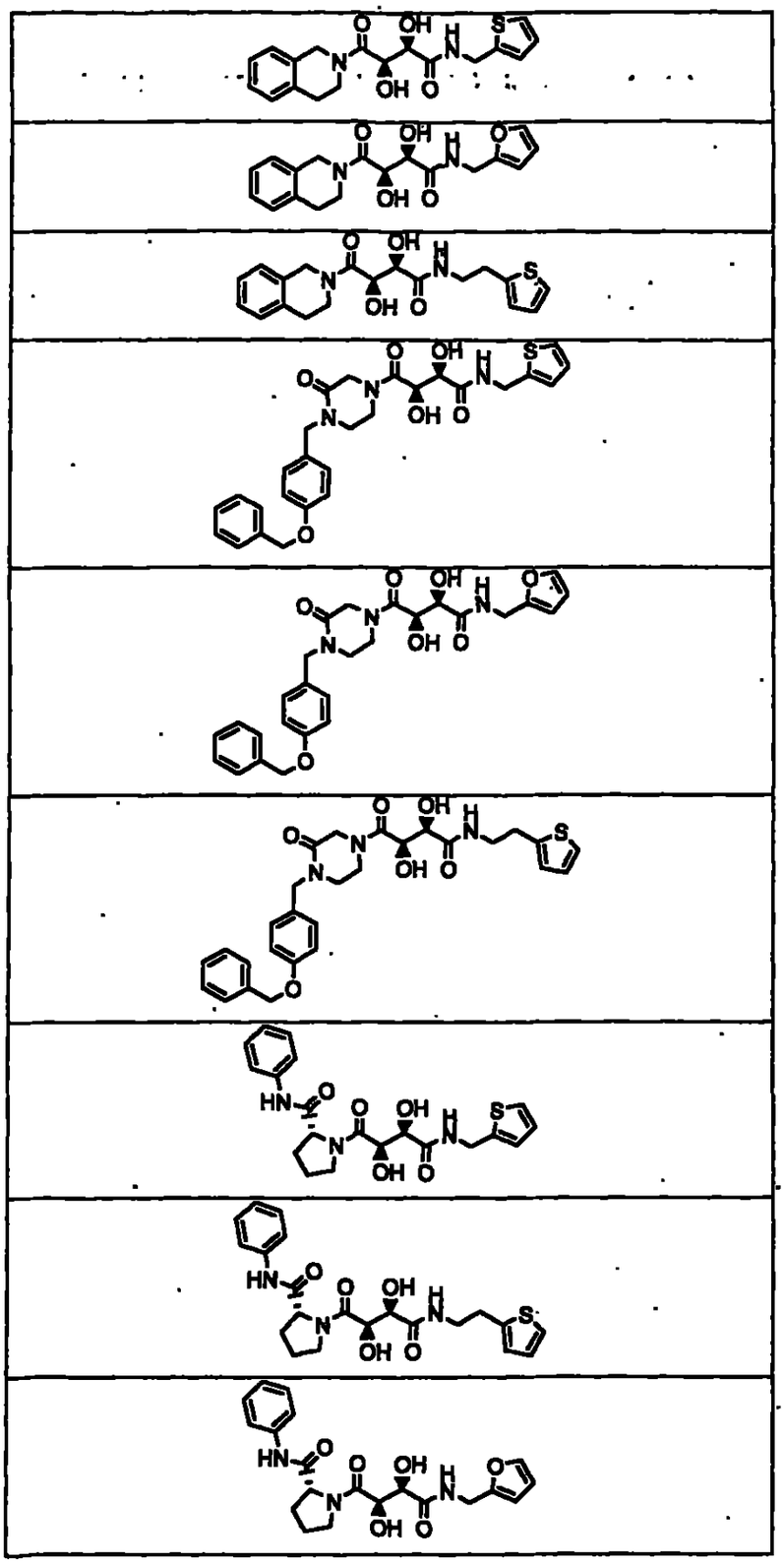


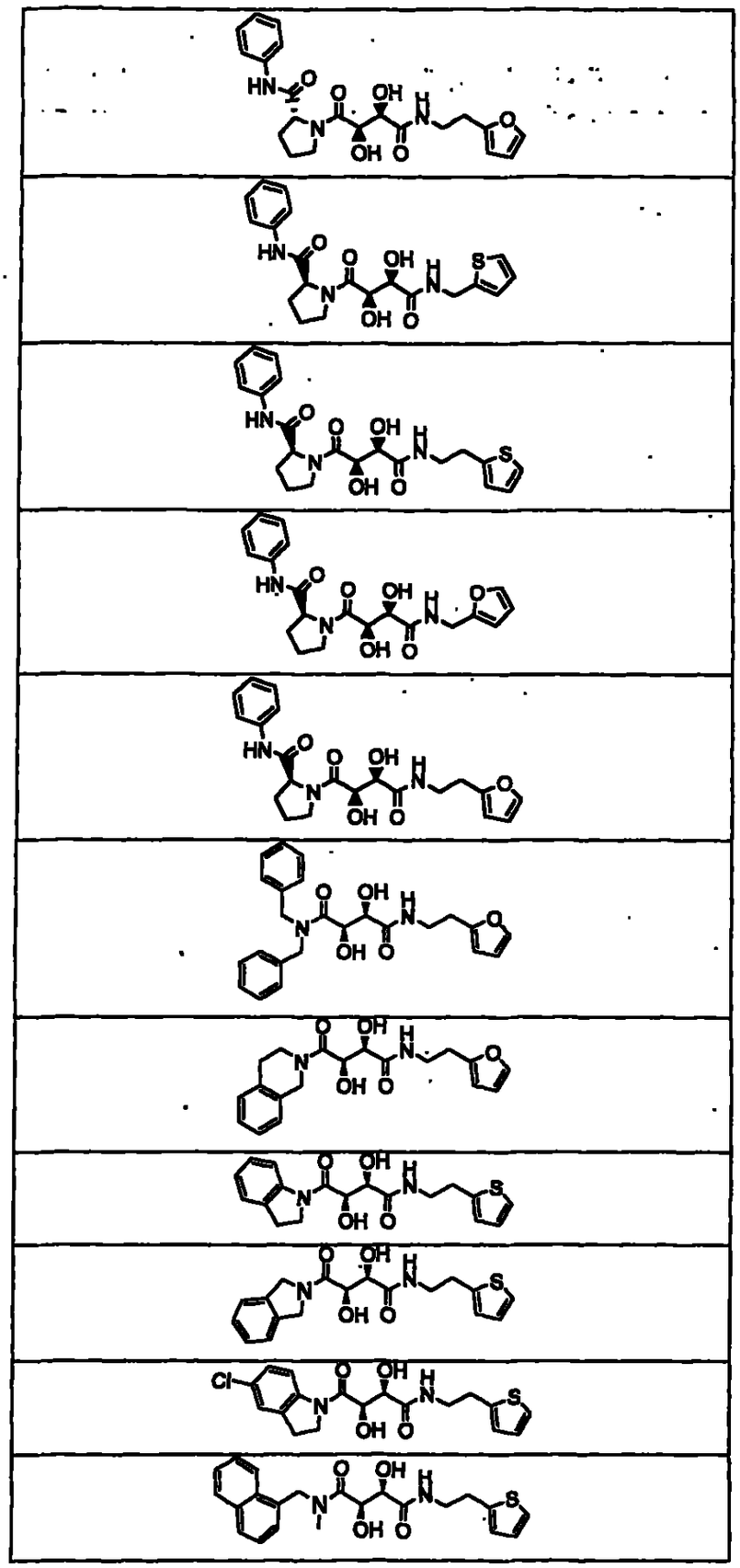
(R1 = R2 = CH_2Ph, R3 = $CH_2CH_2(C_4H_4O)$)

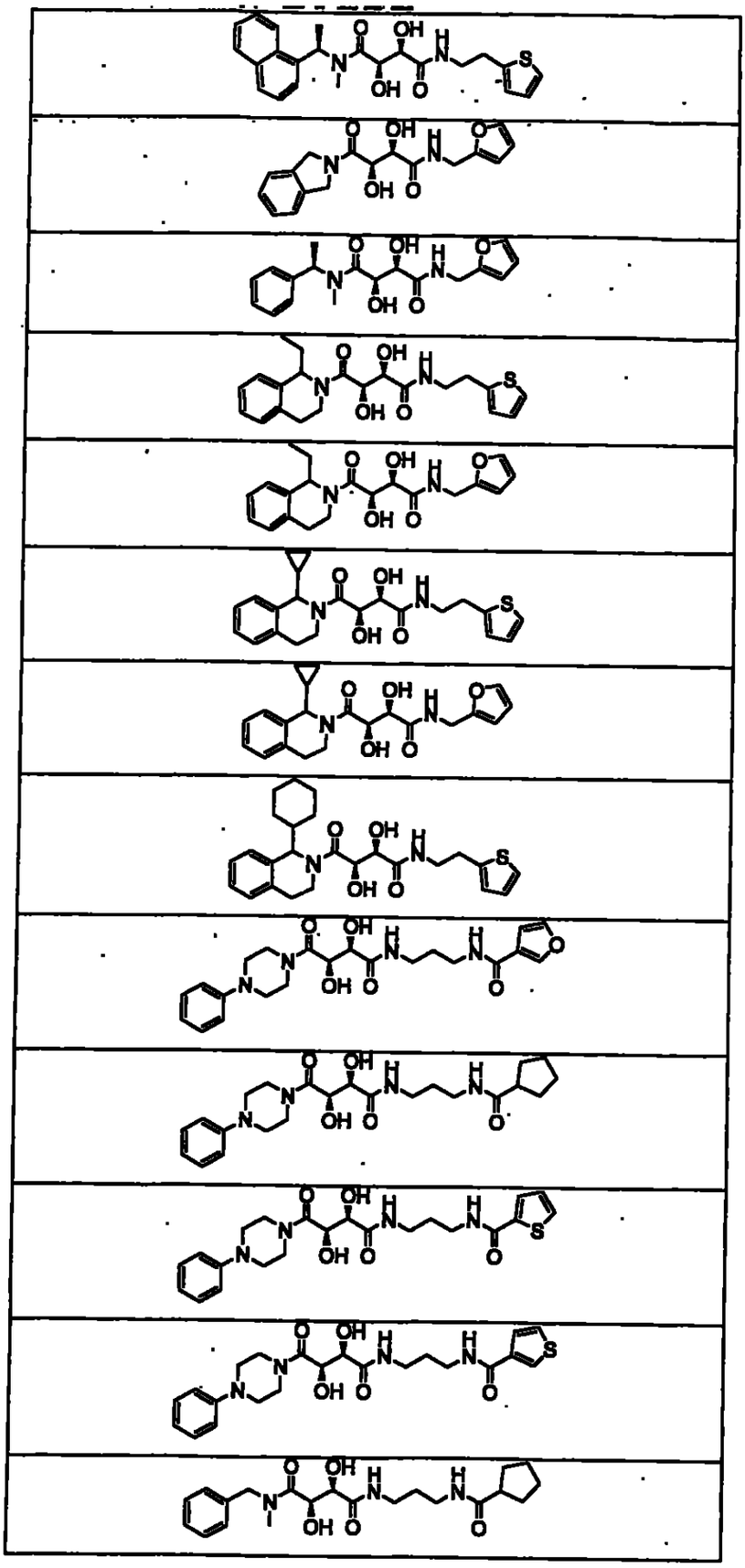


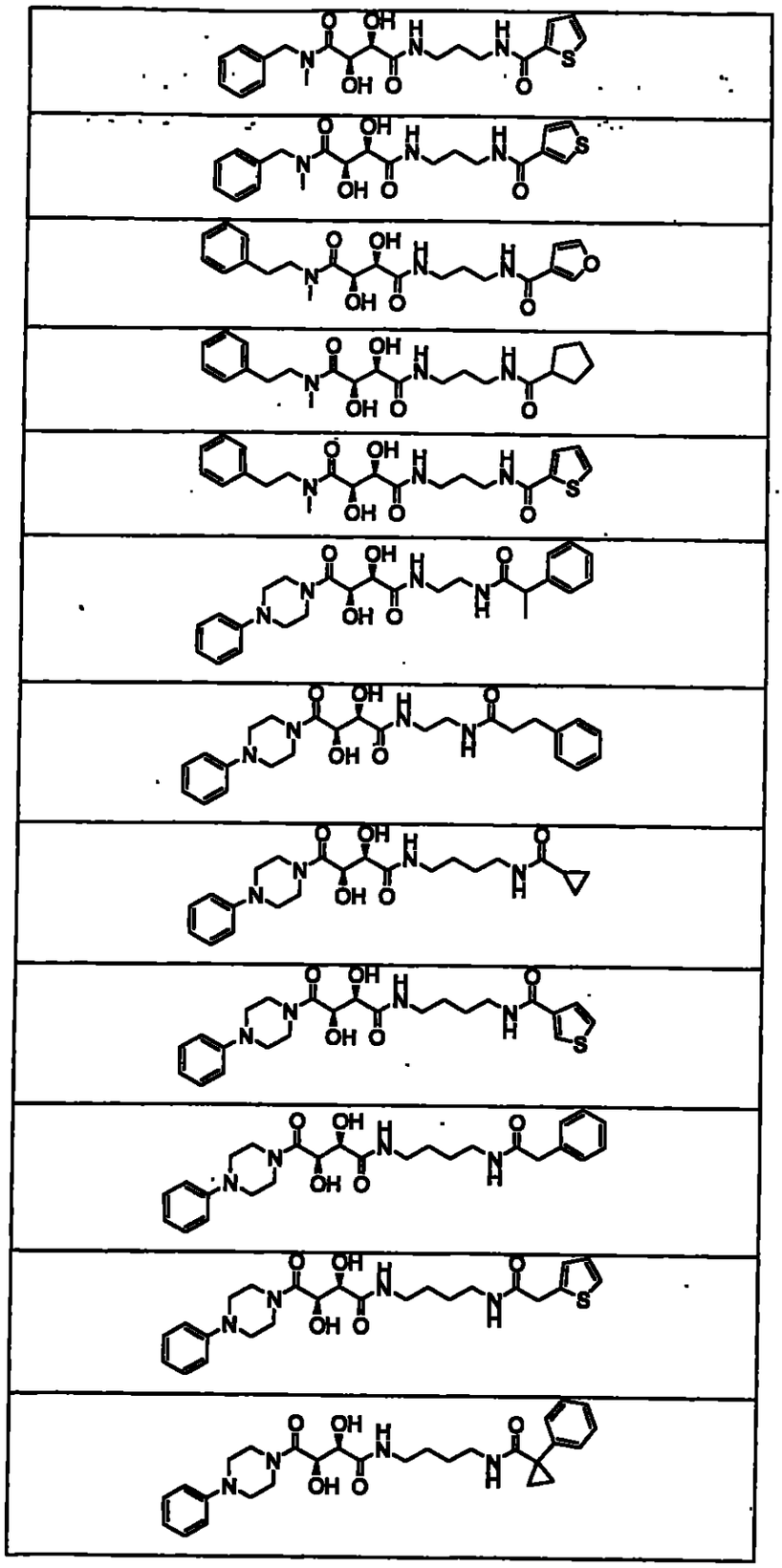


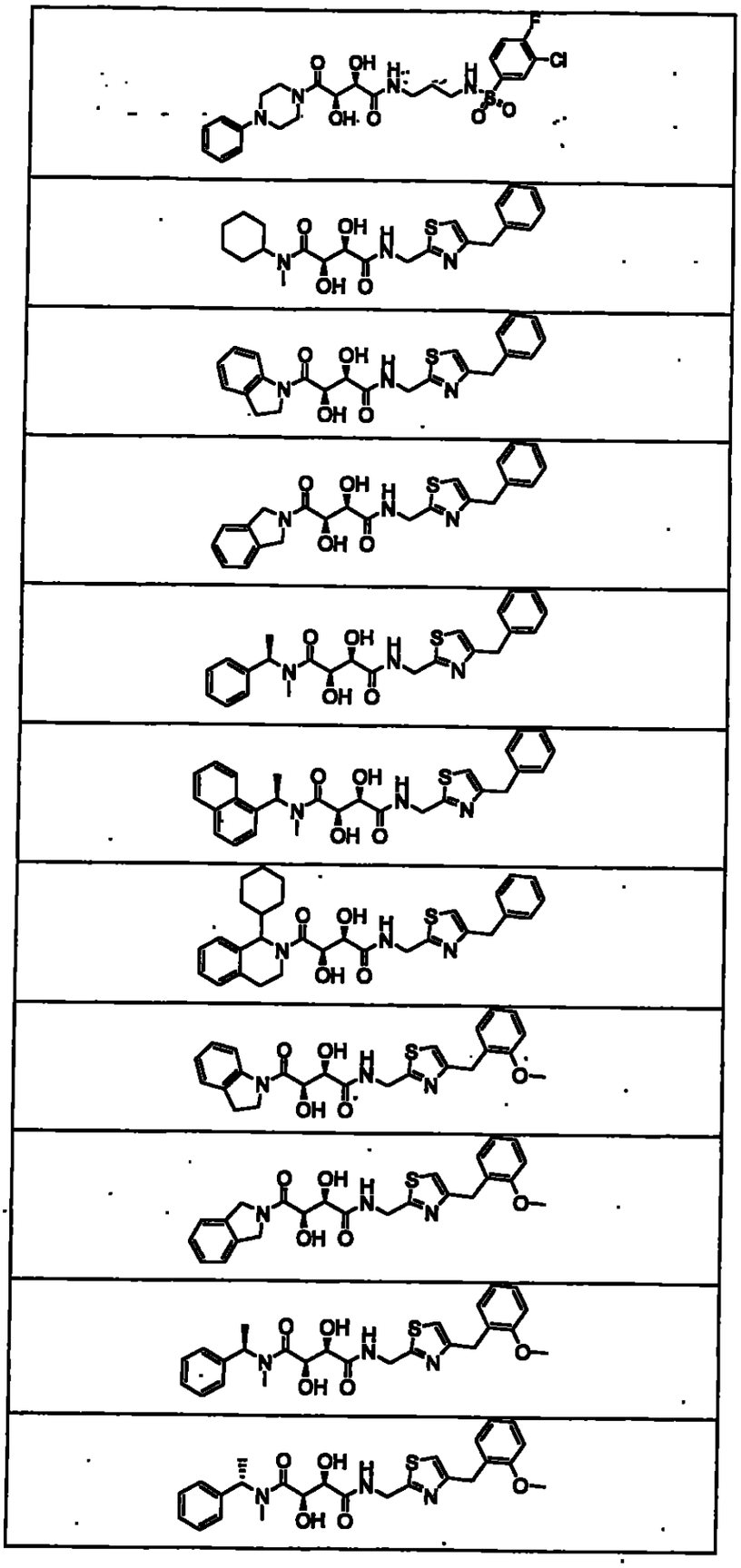


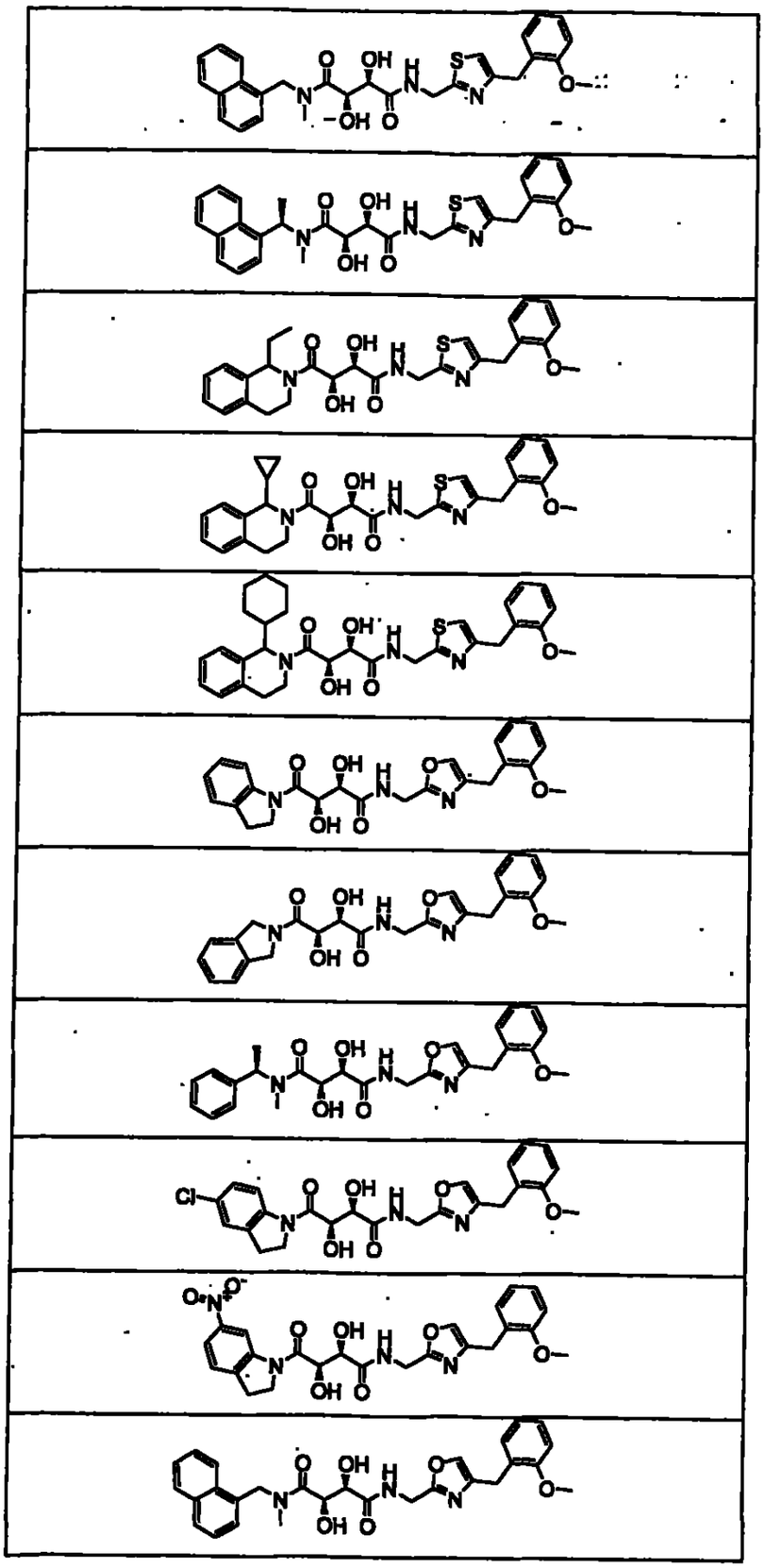


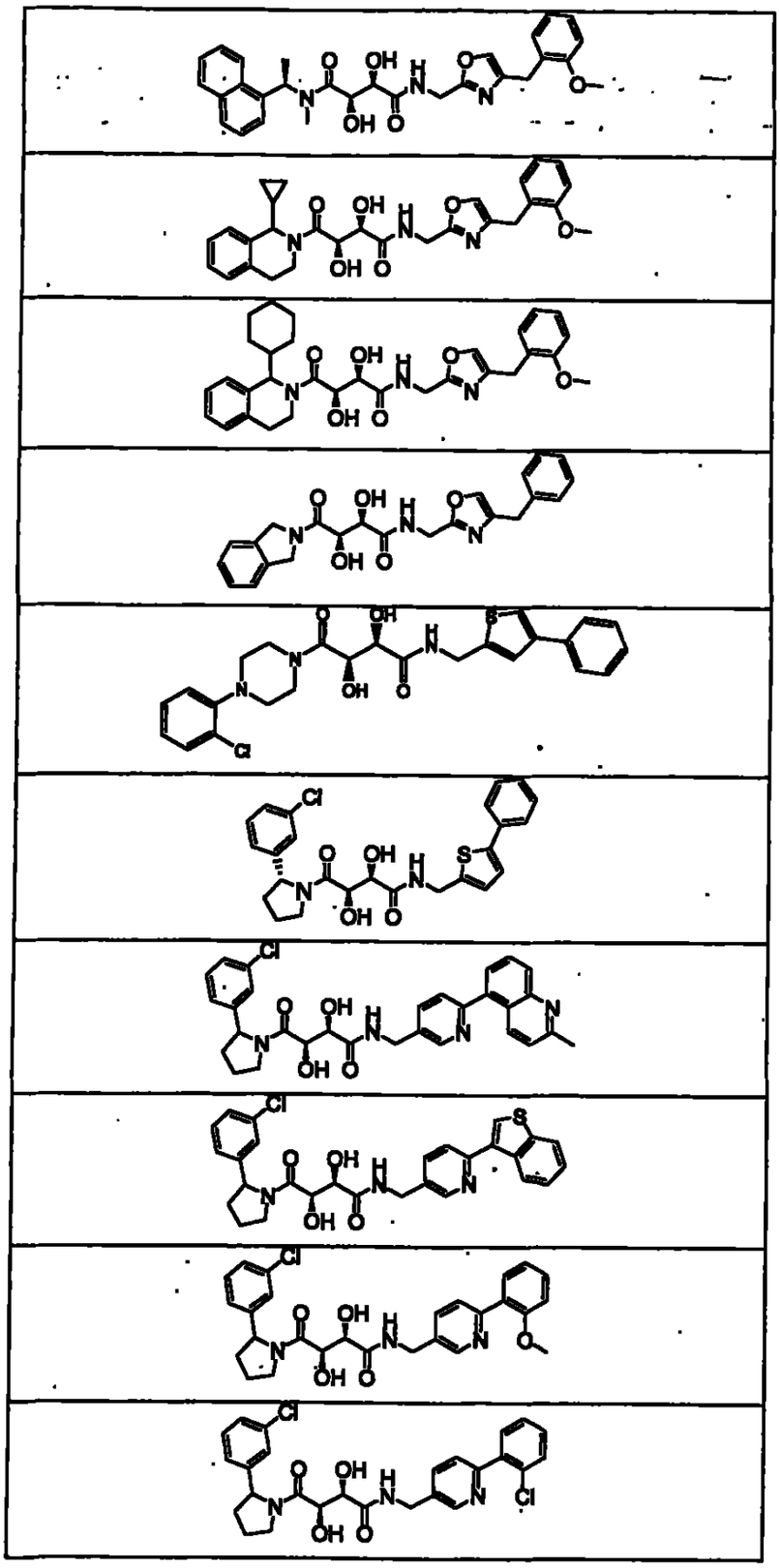


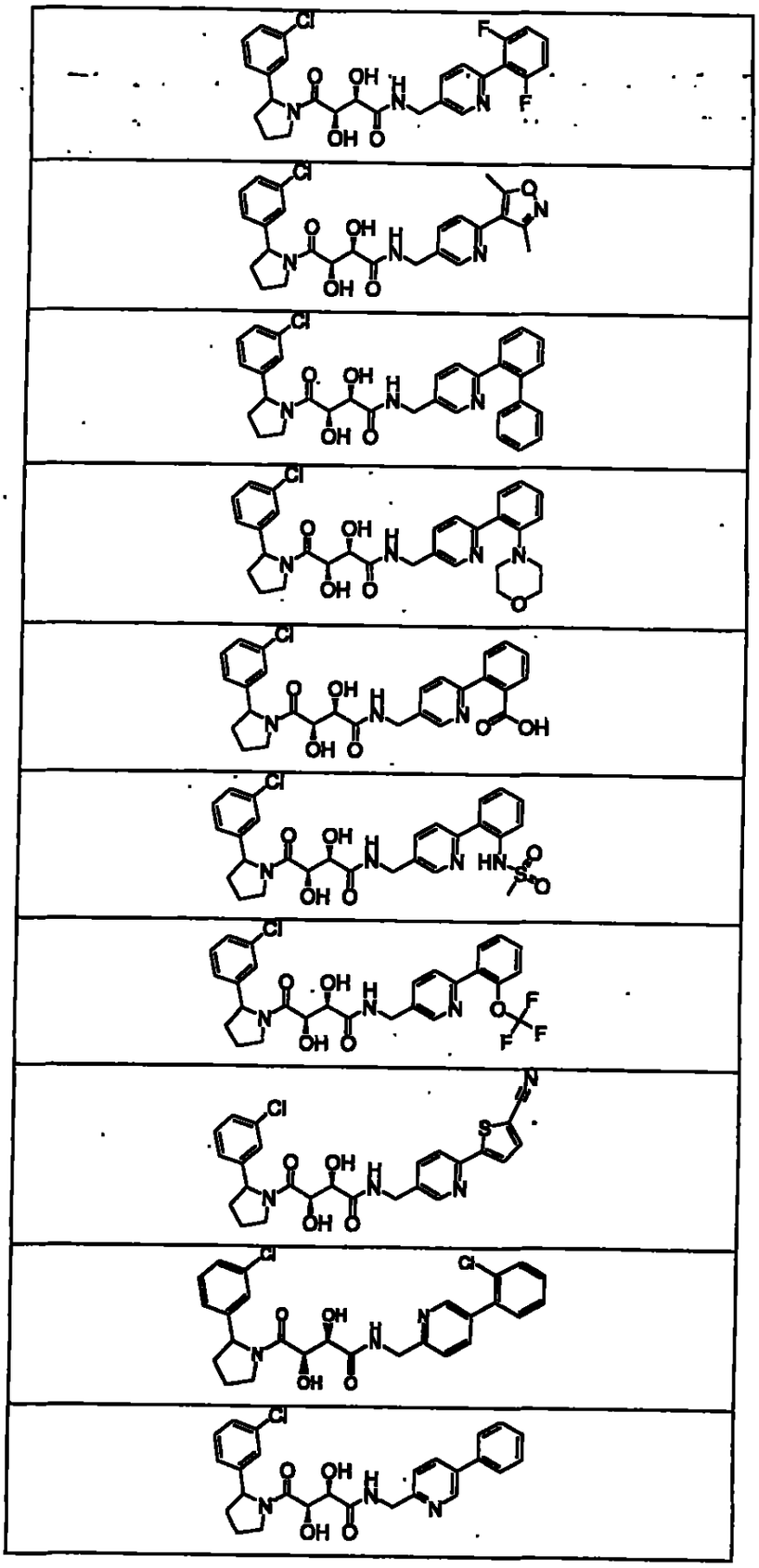


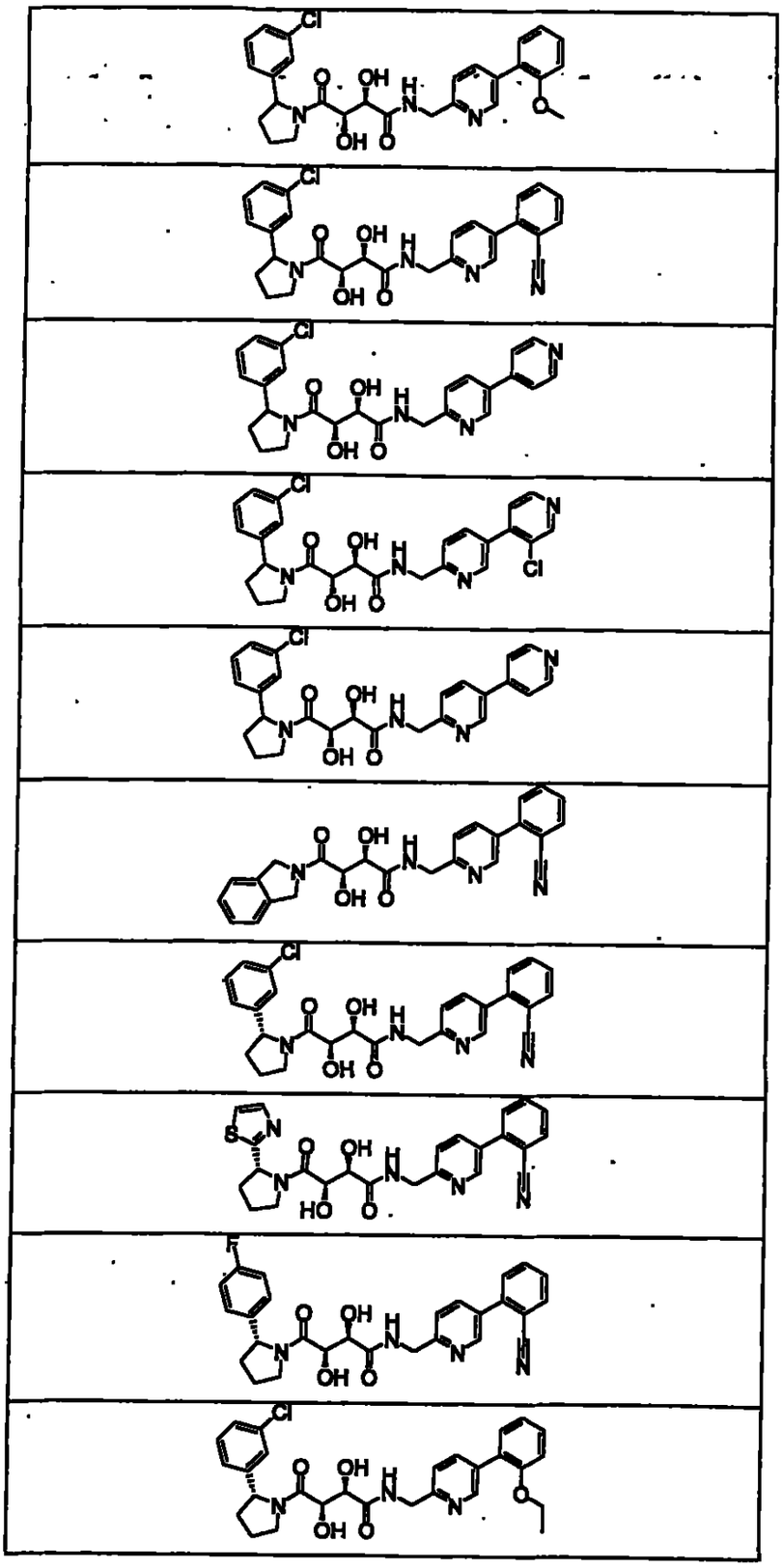


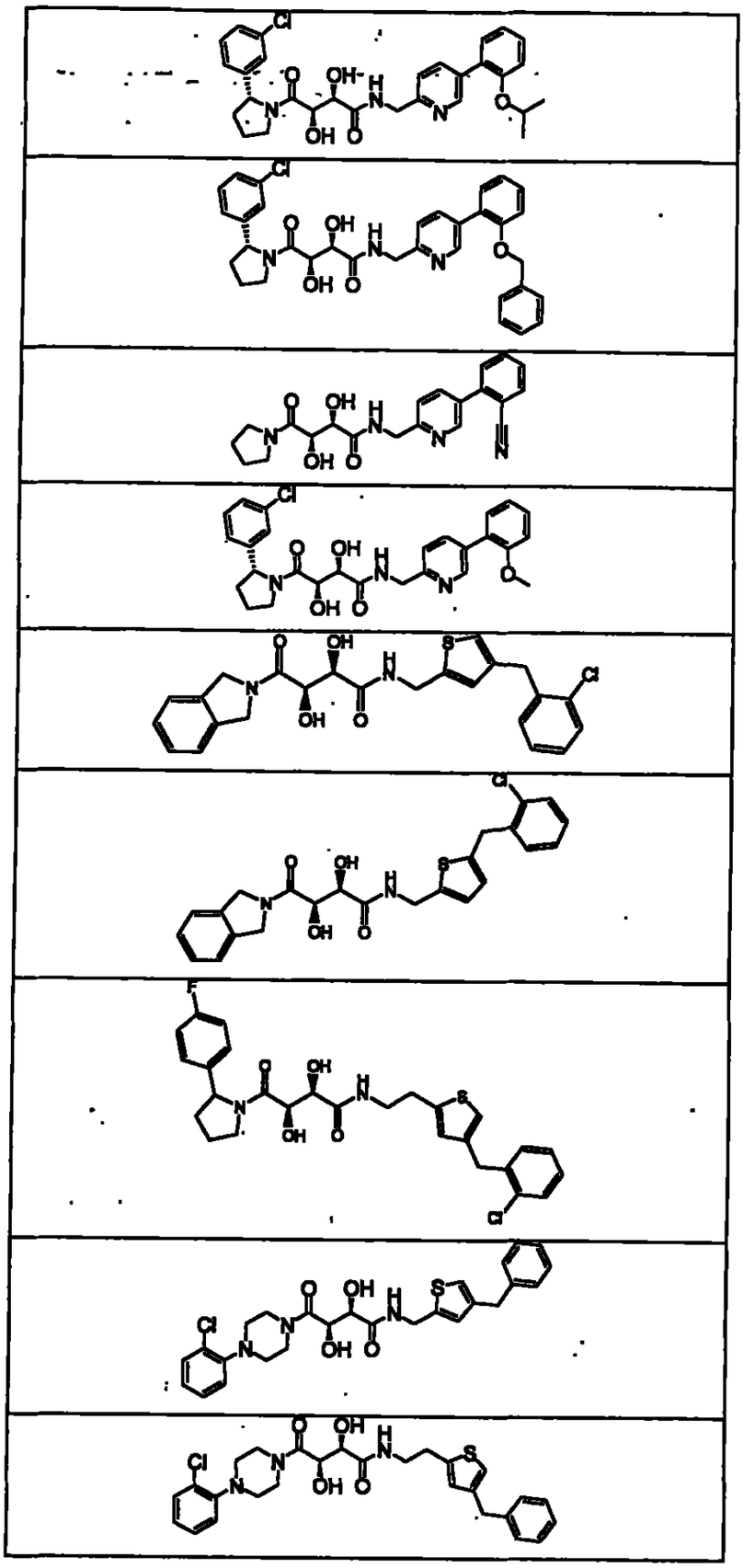


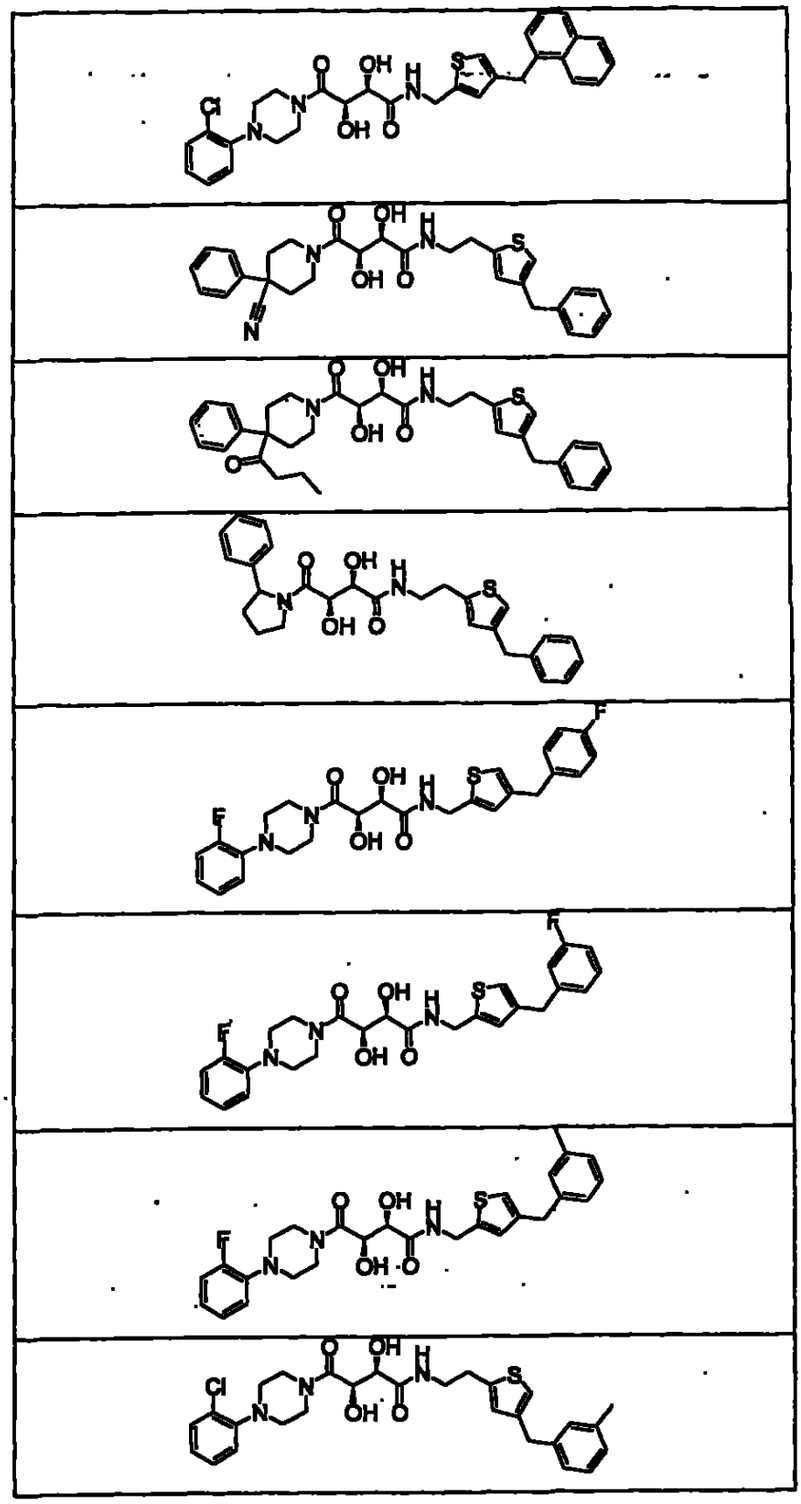


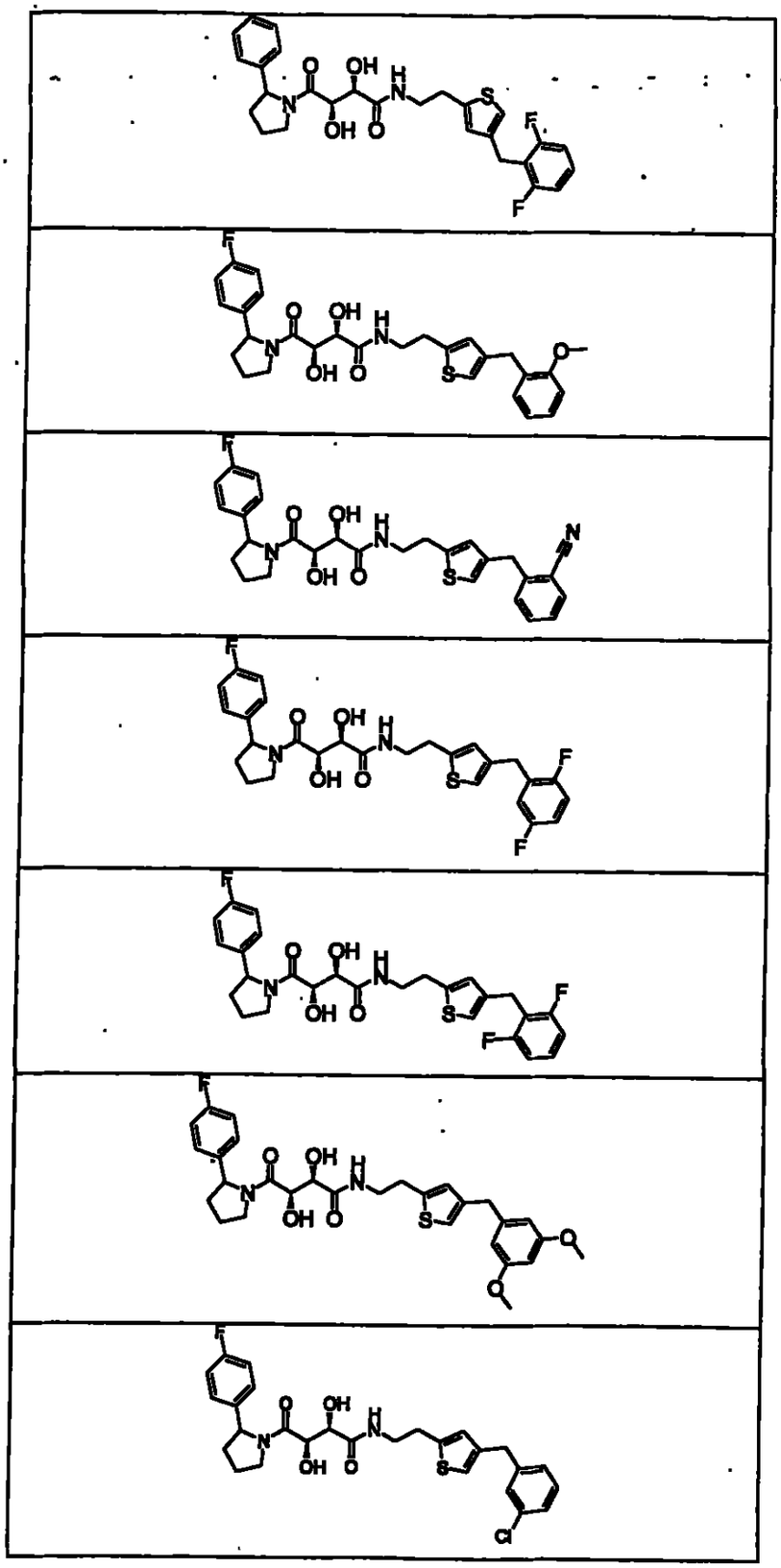


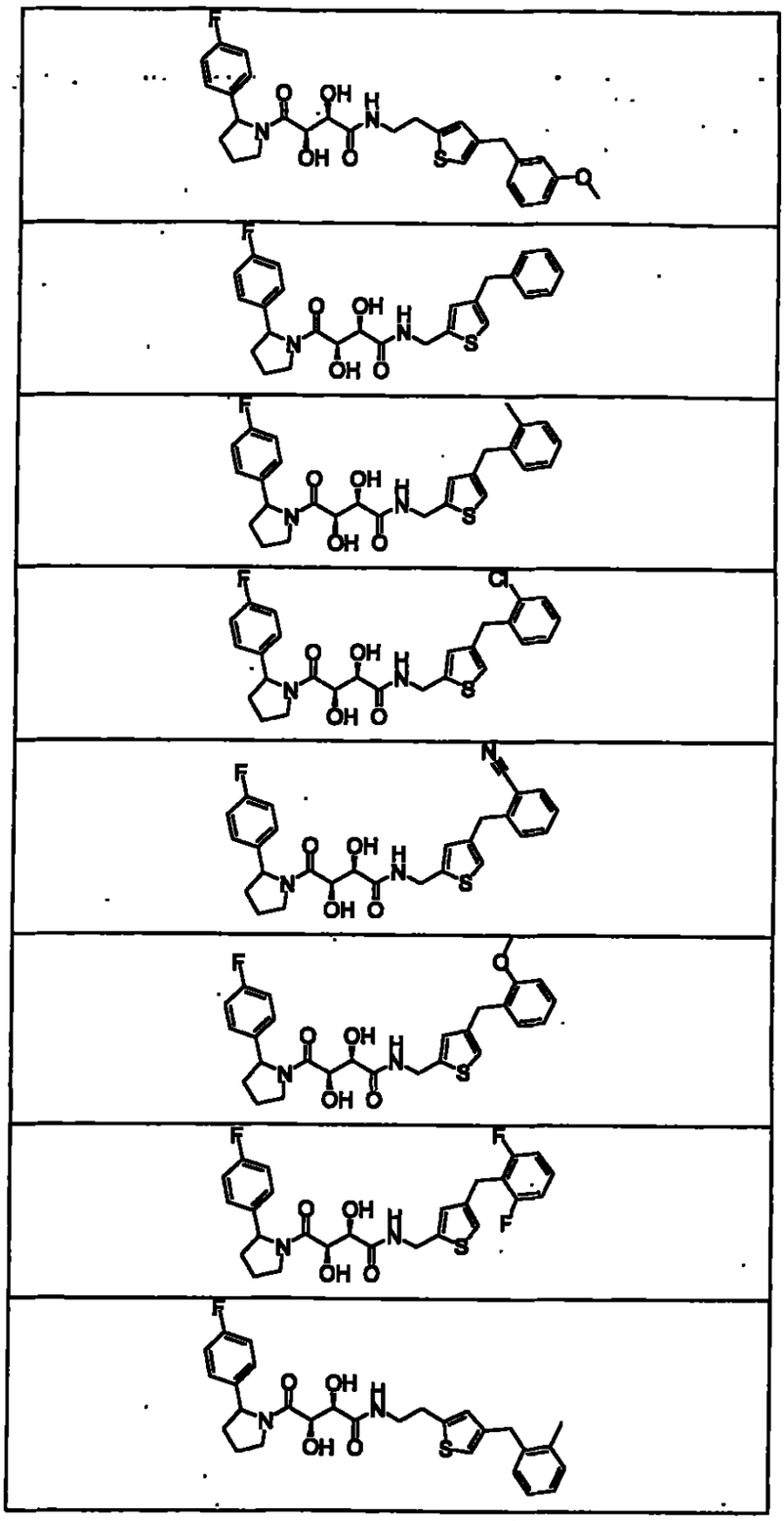


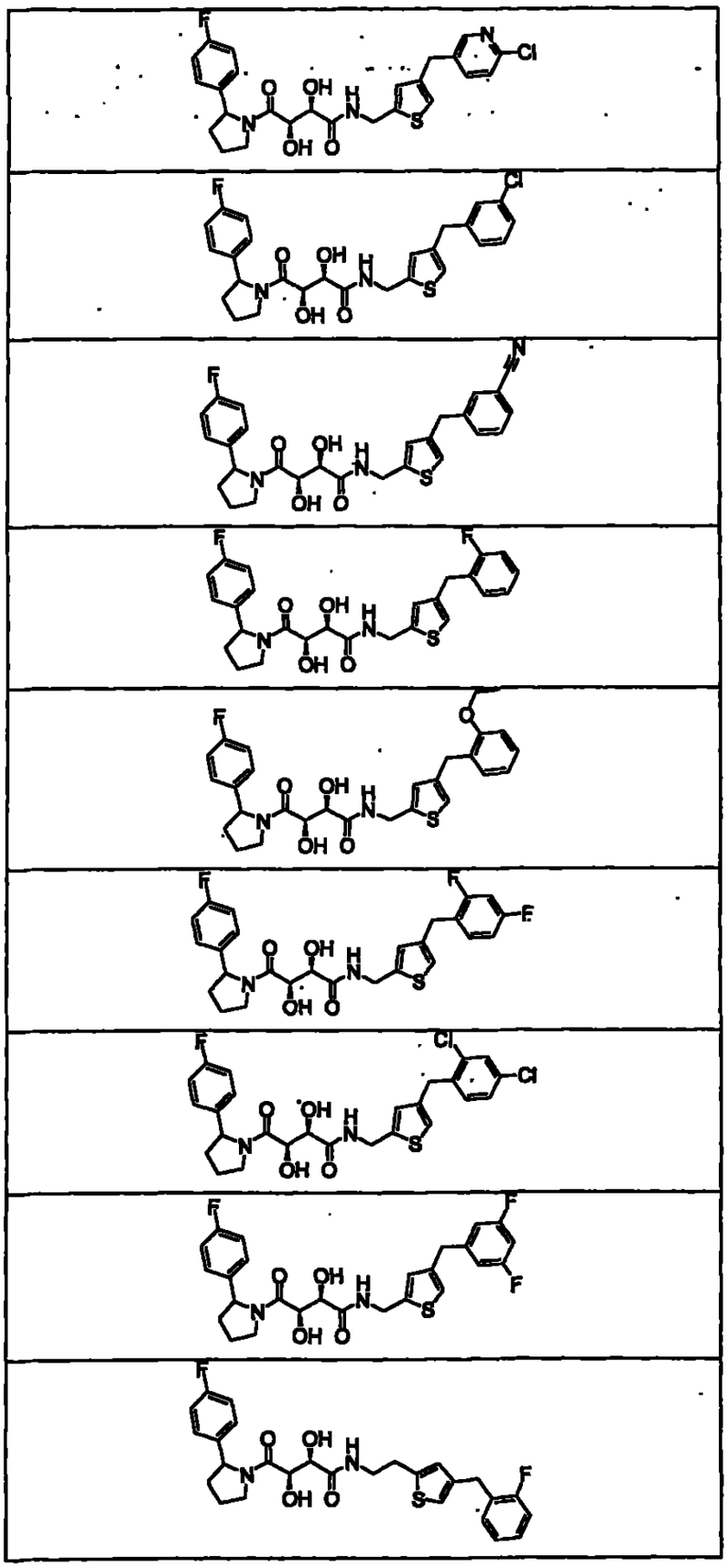


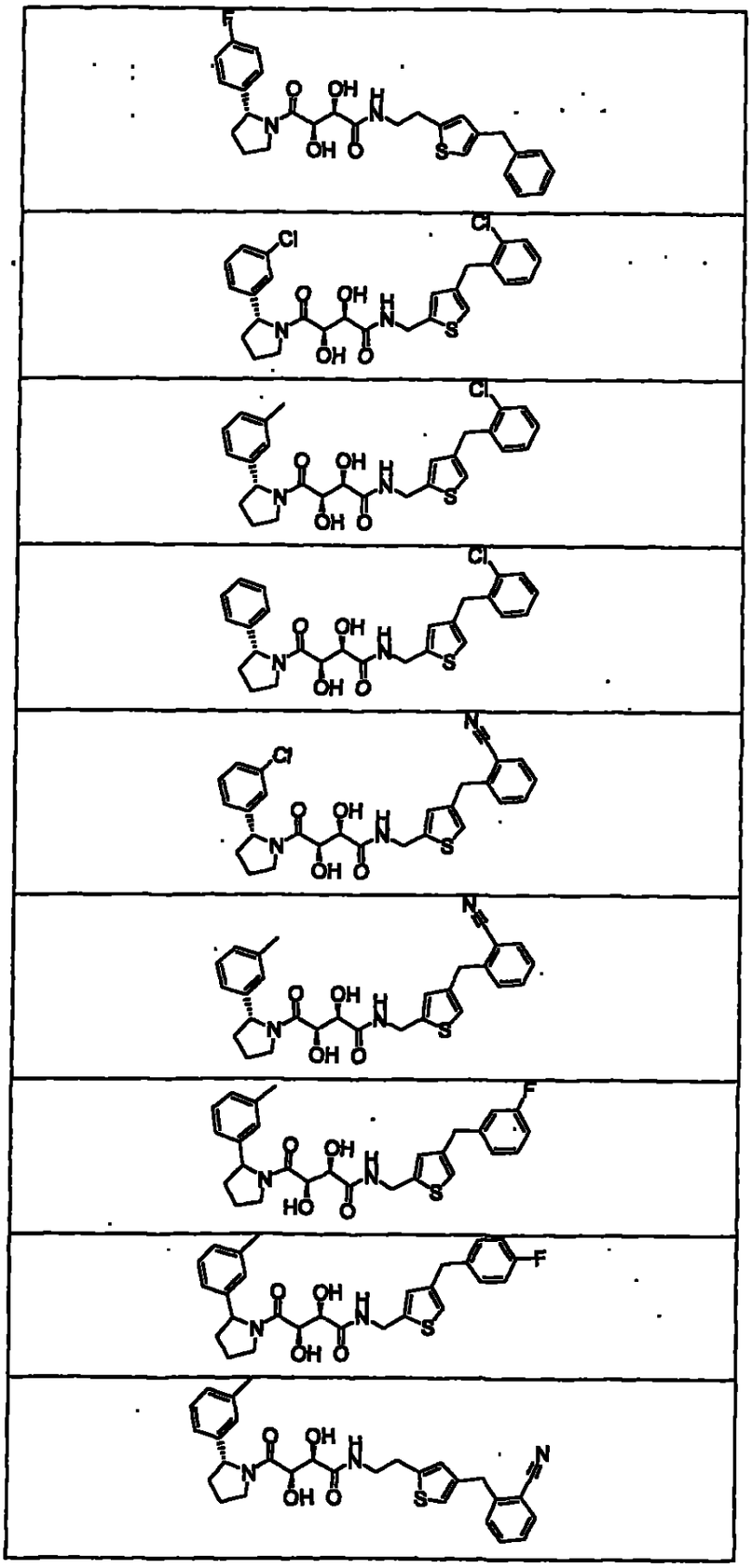


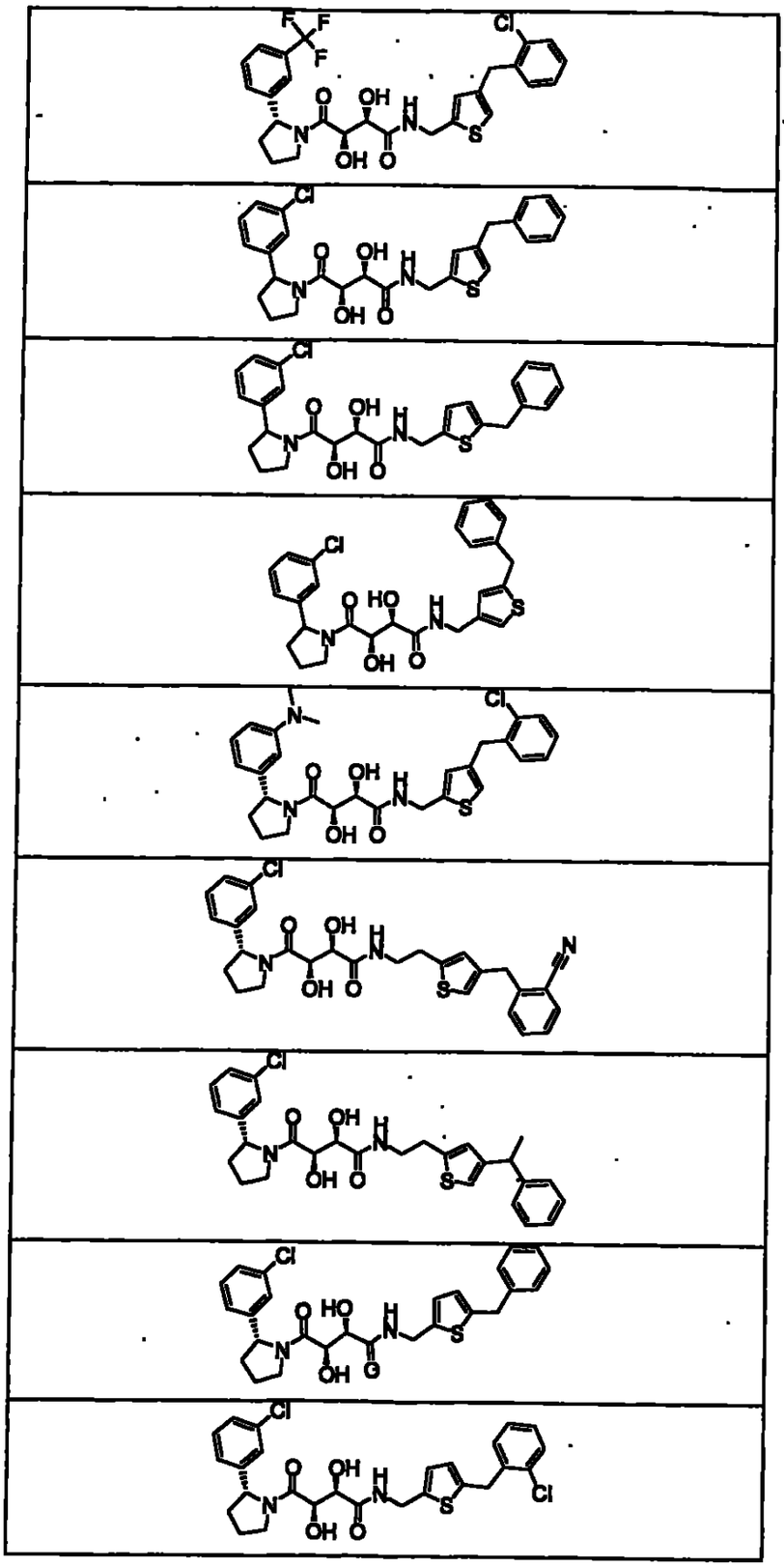


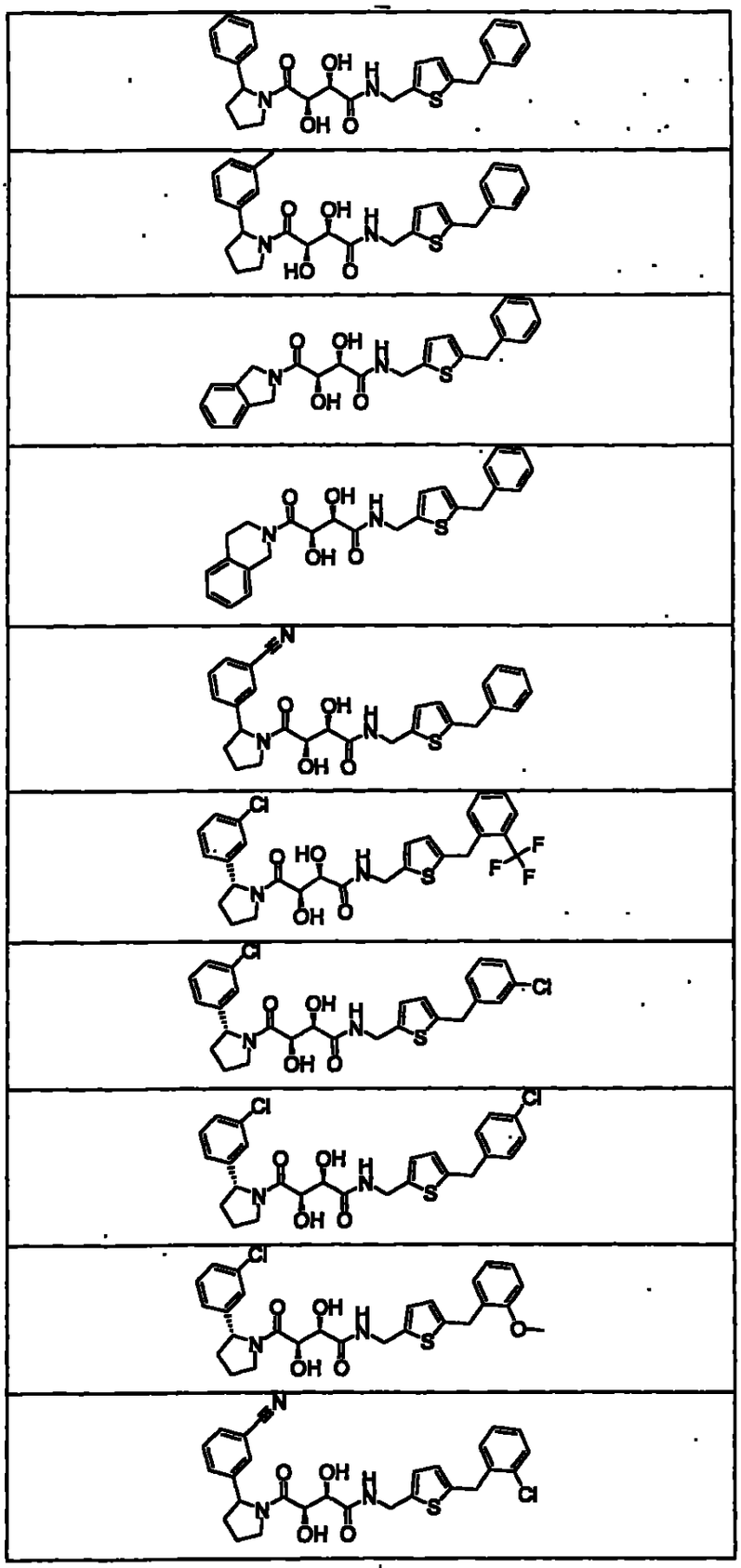


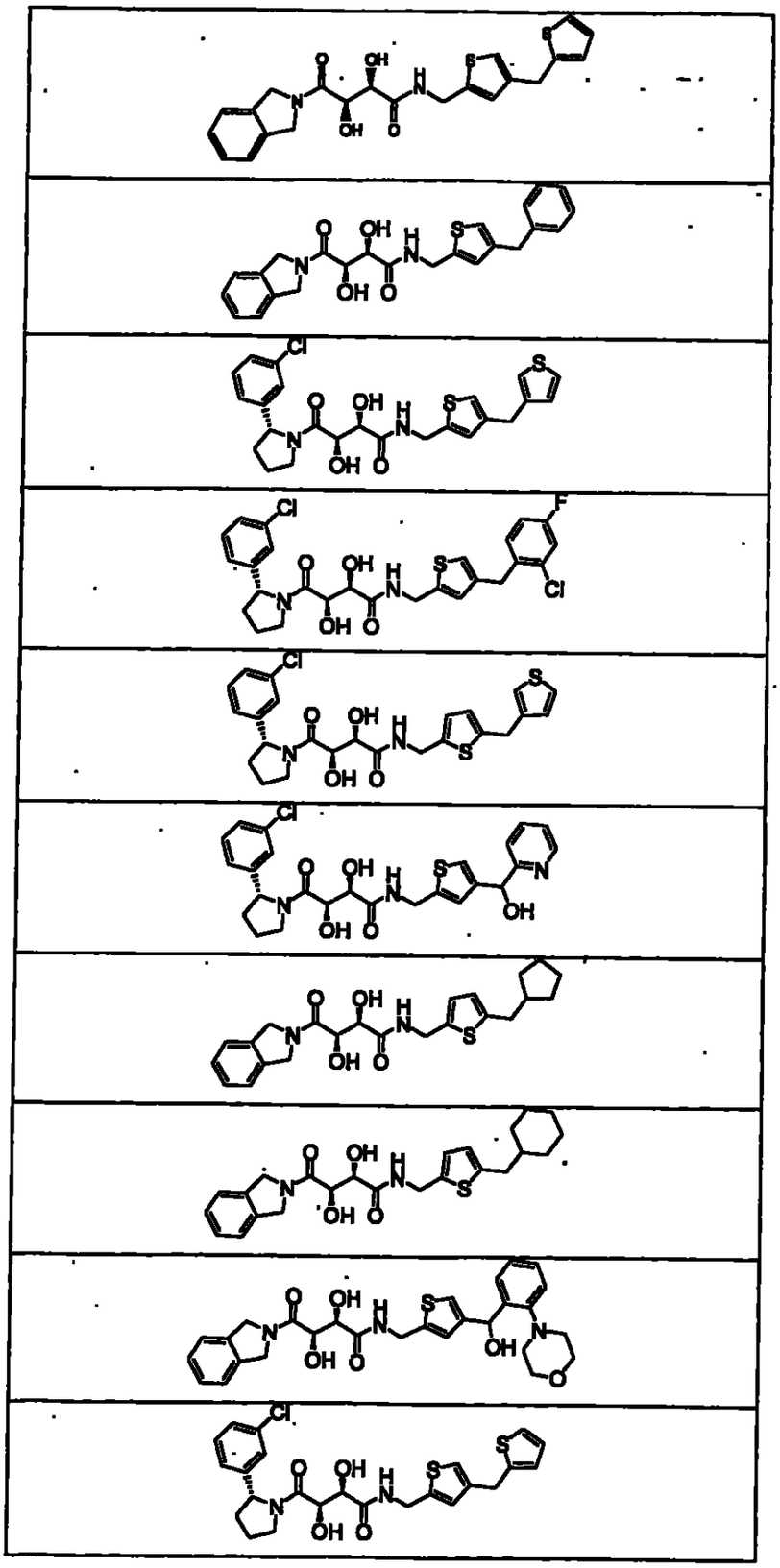


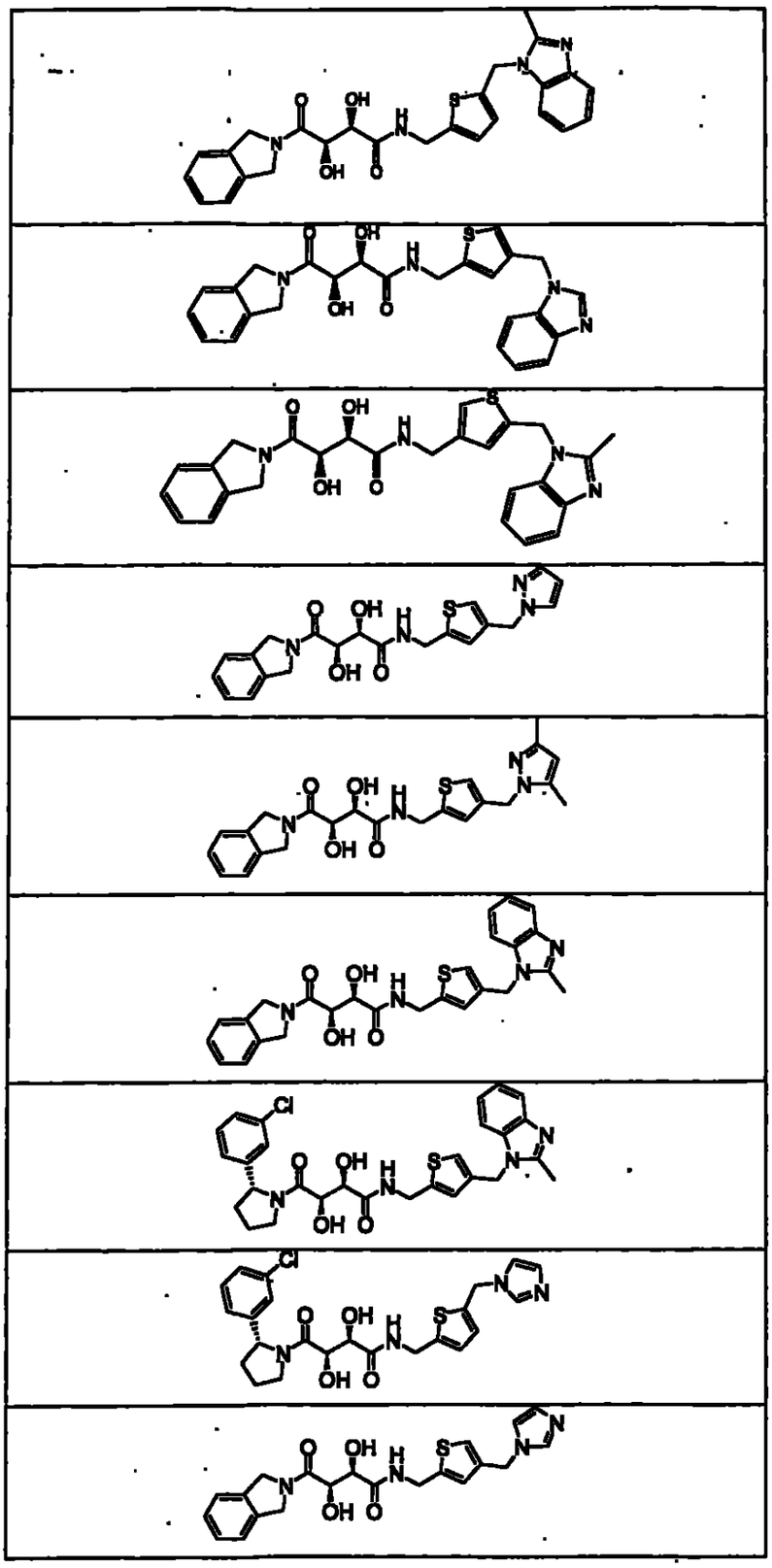


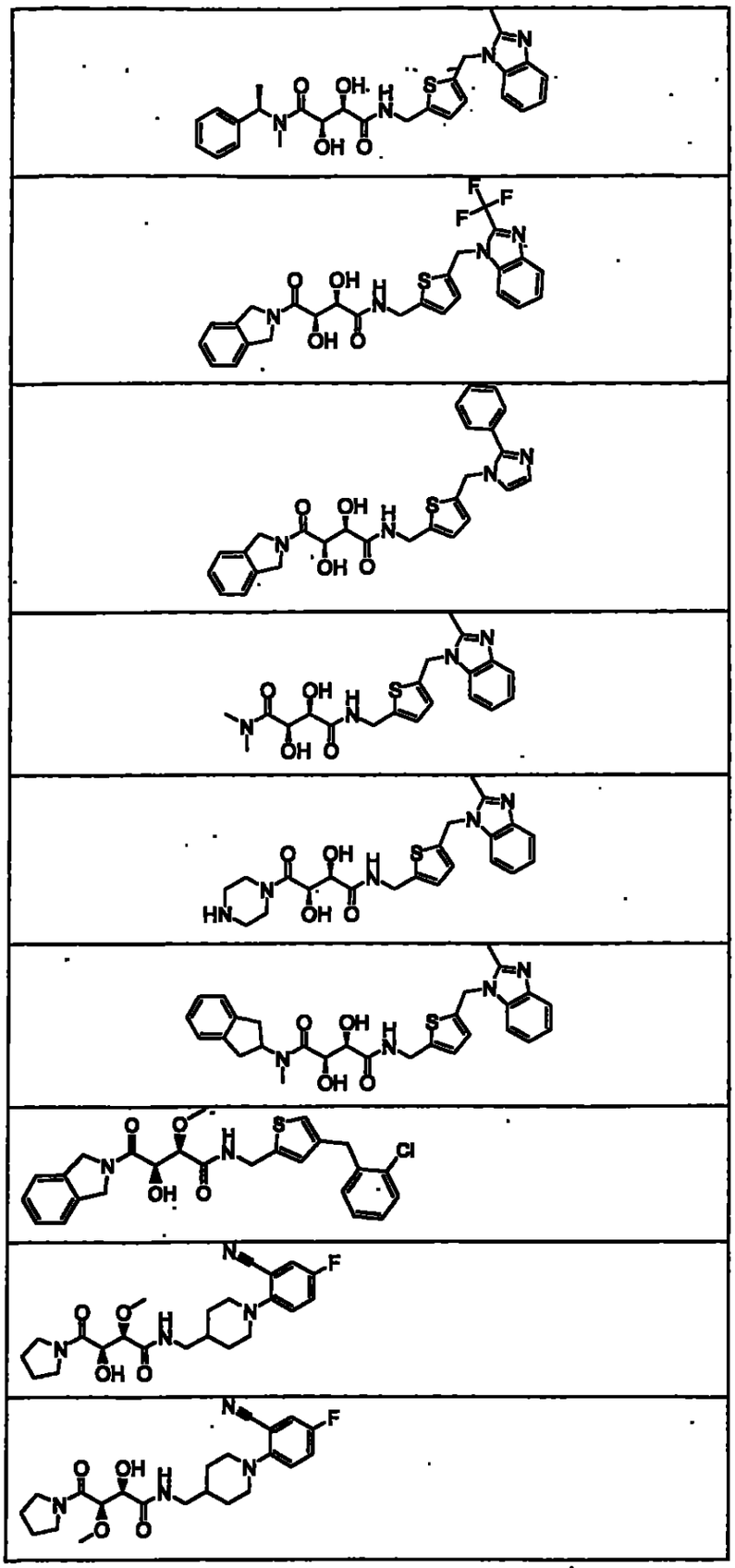


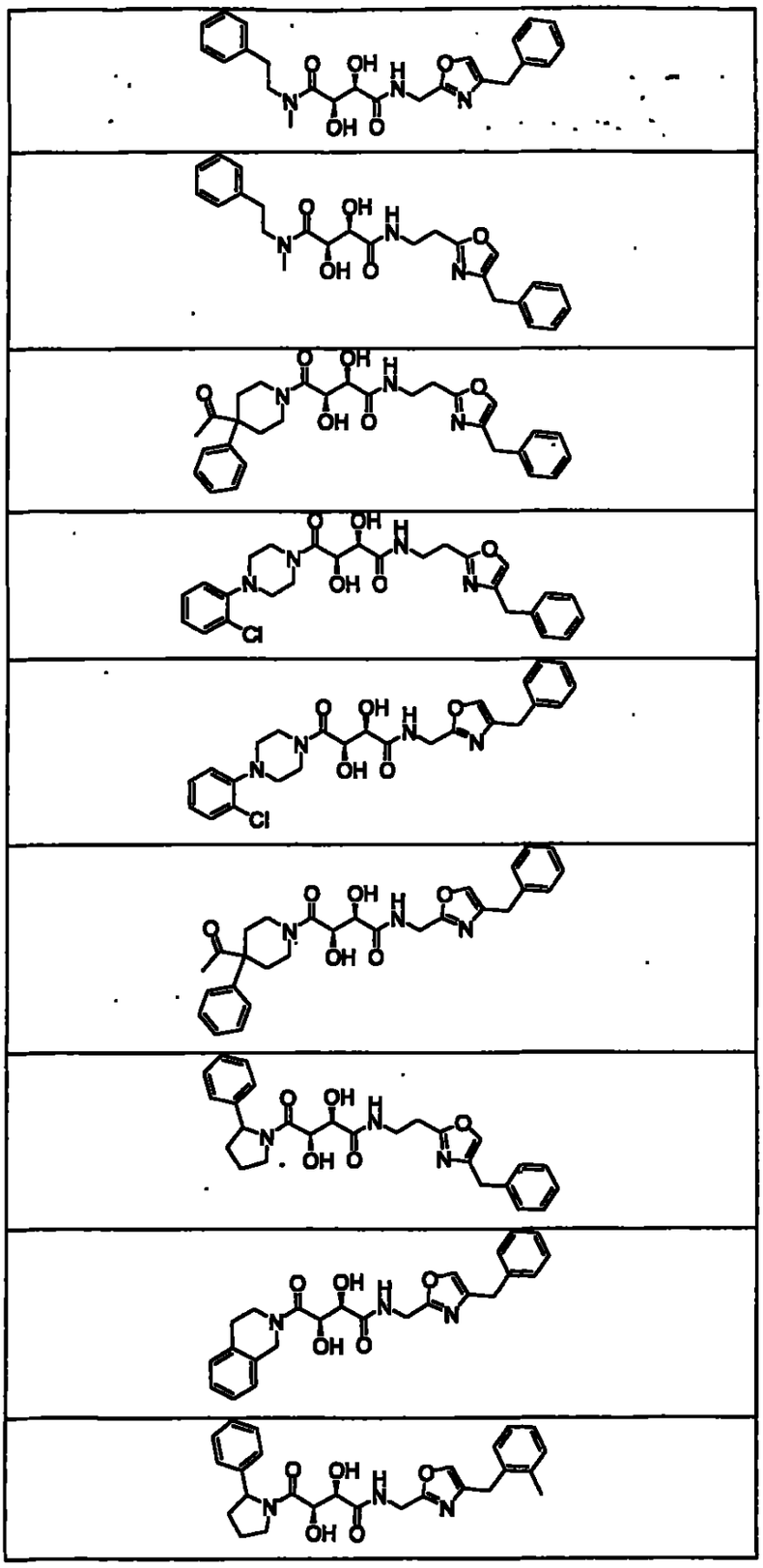


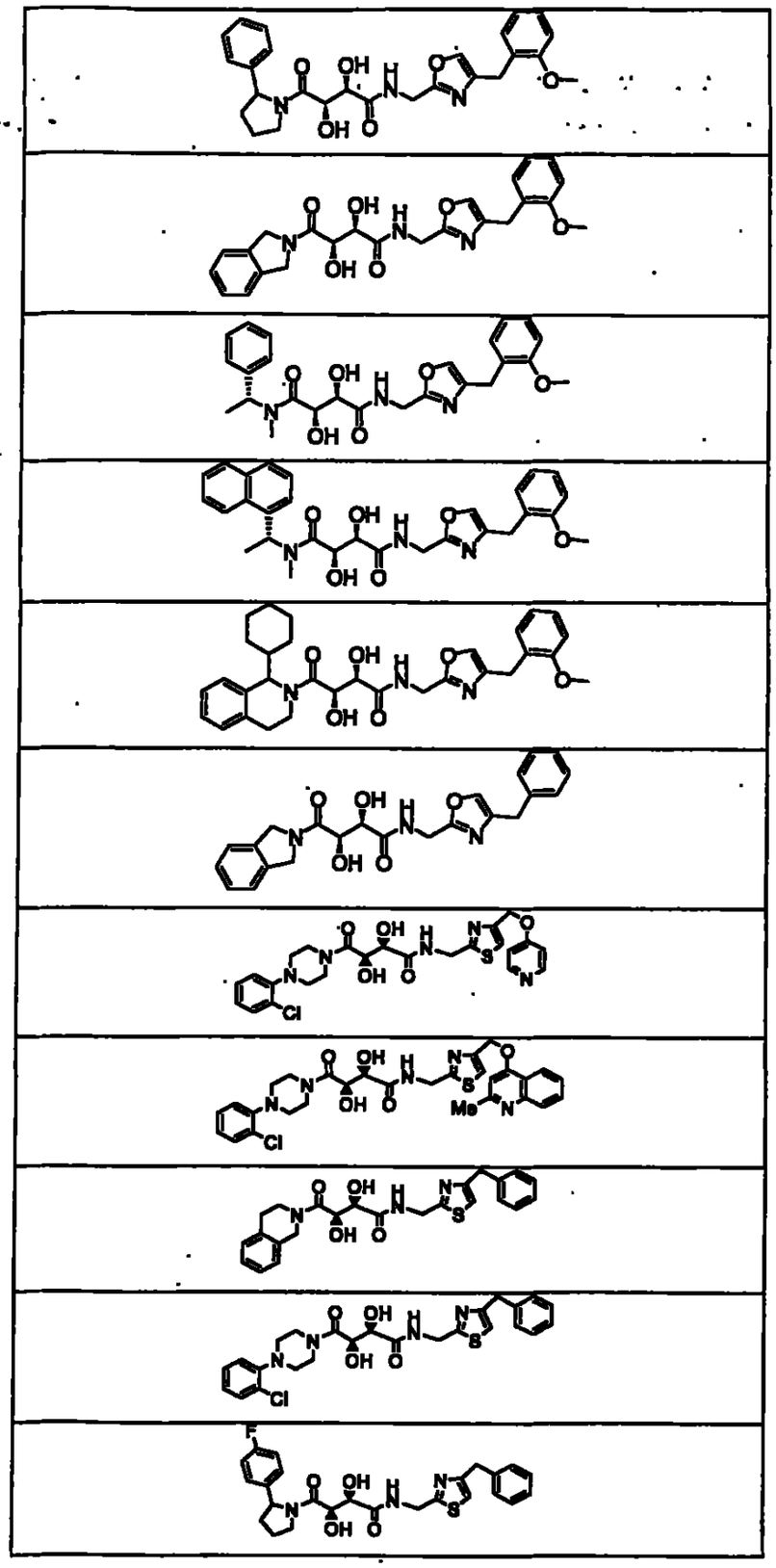


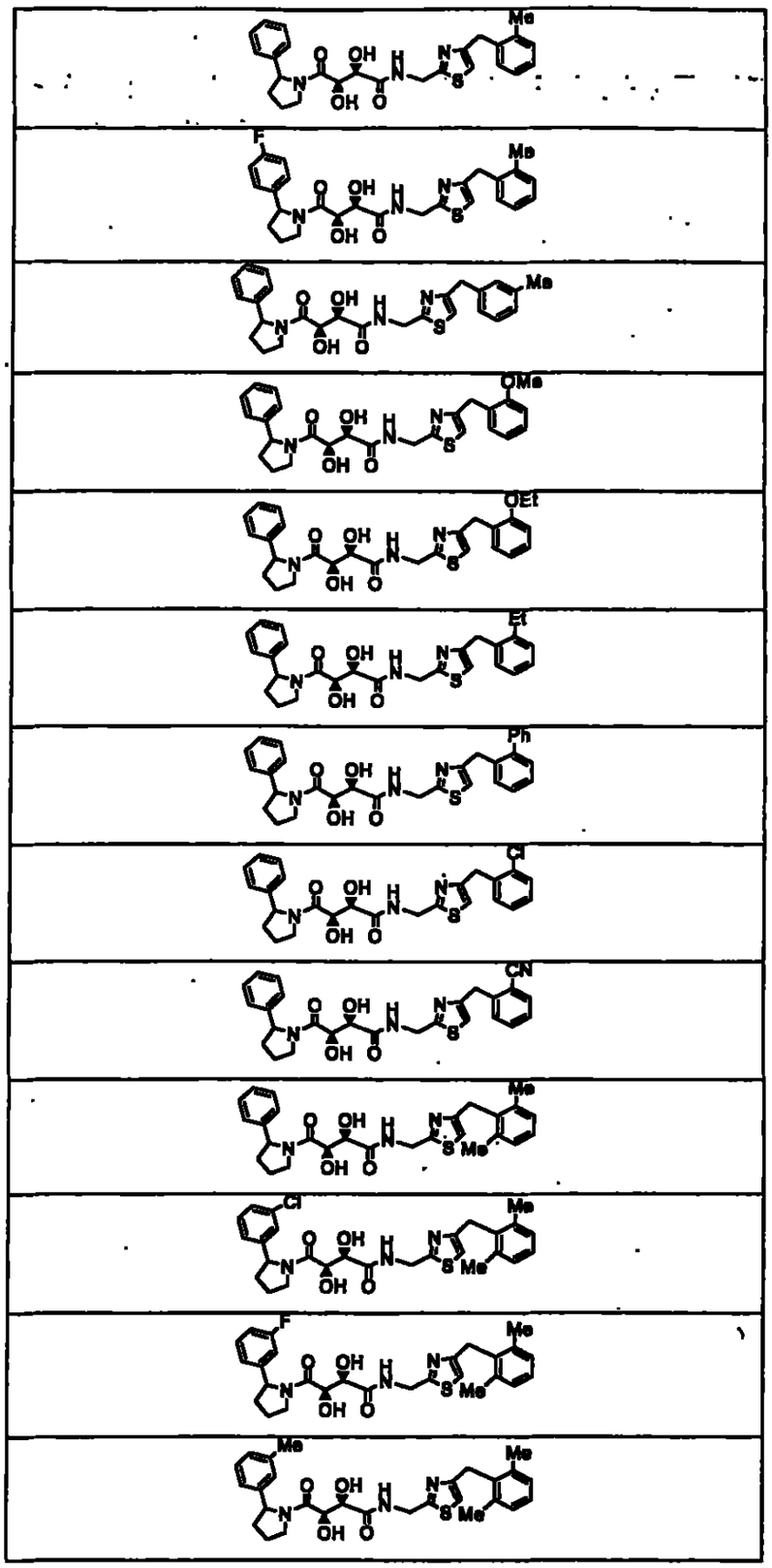


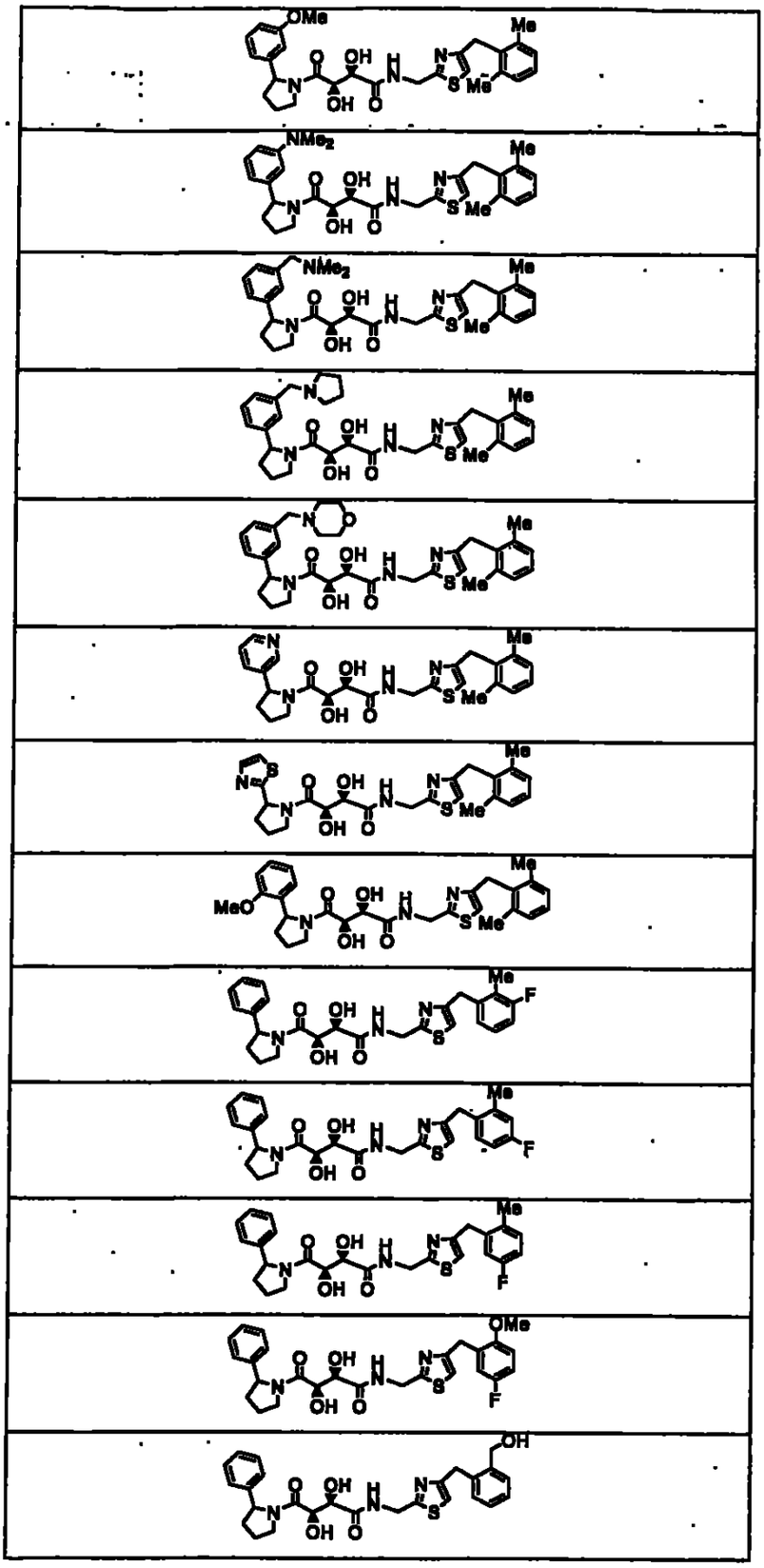


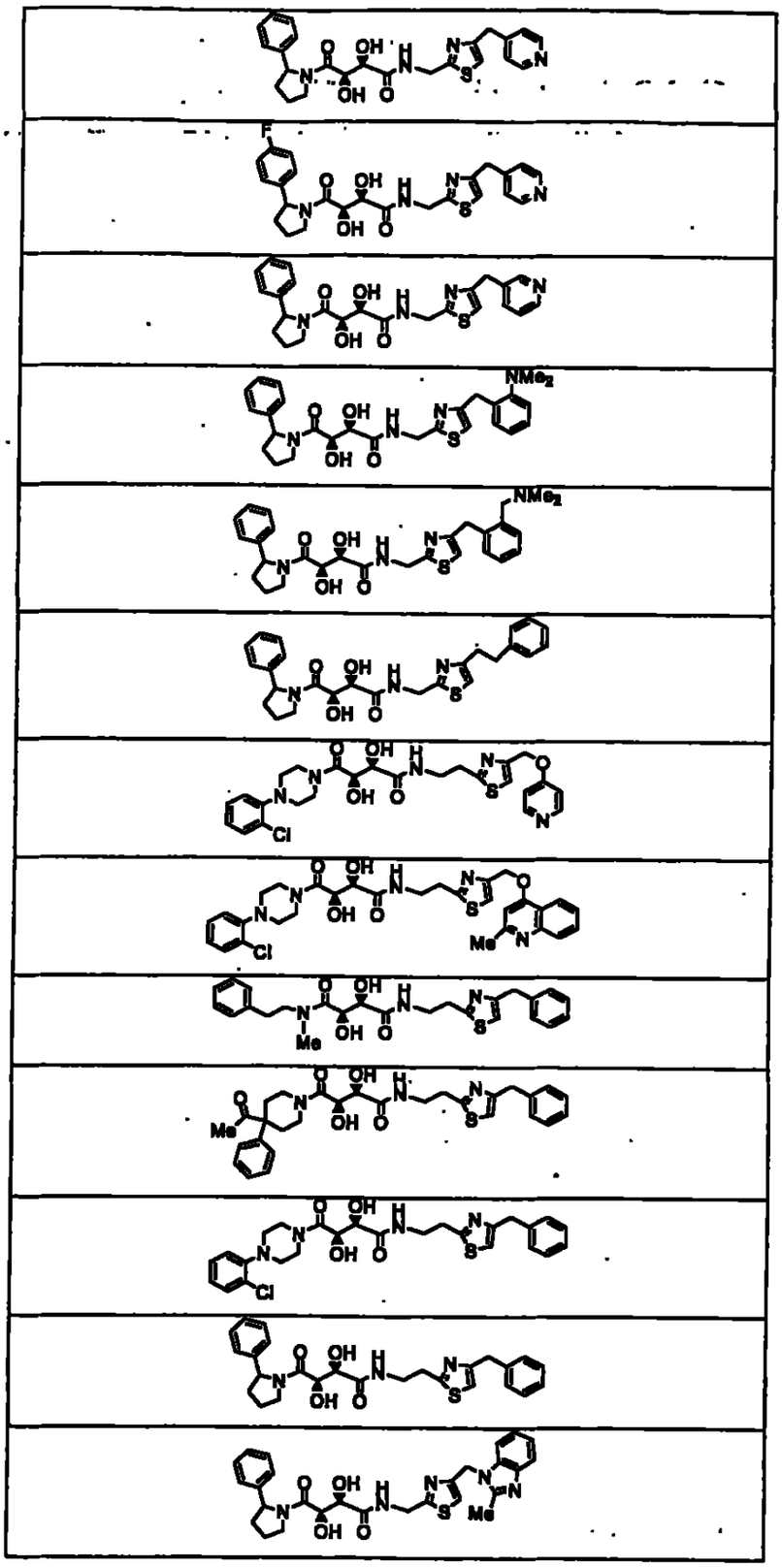


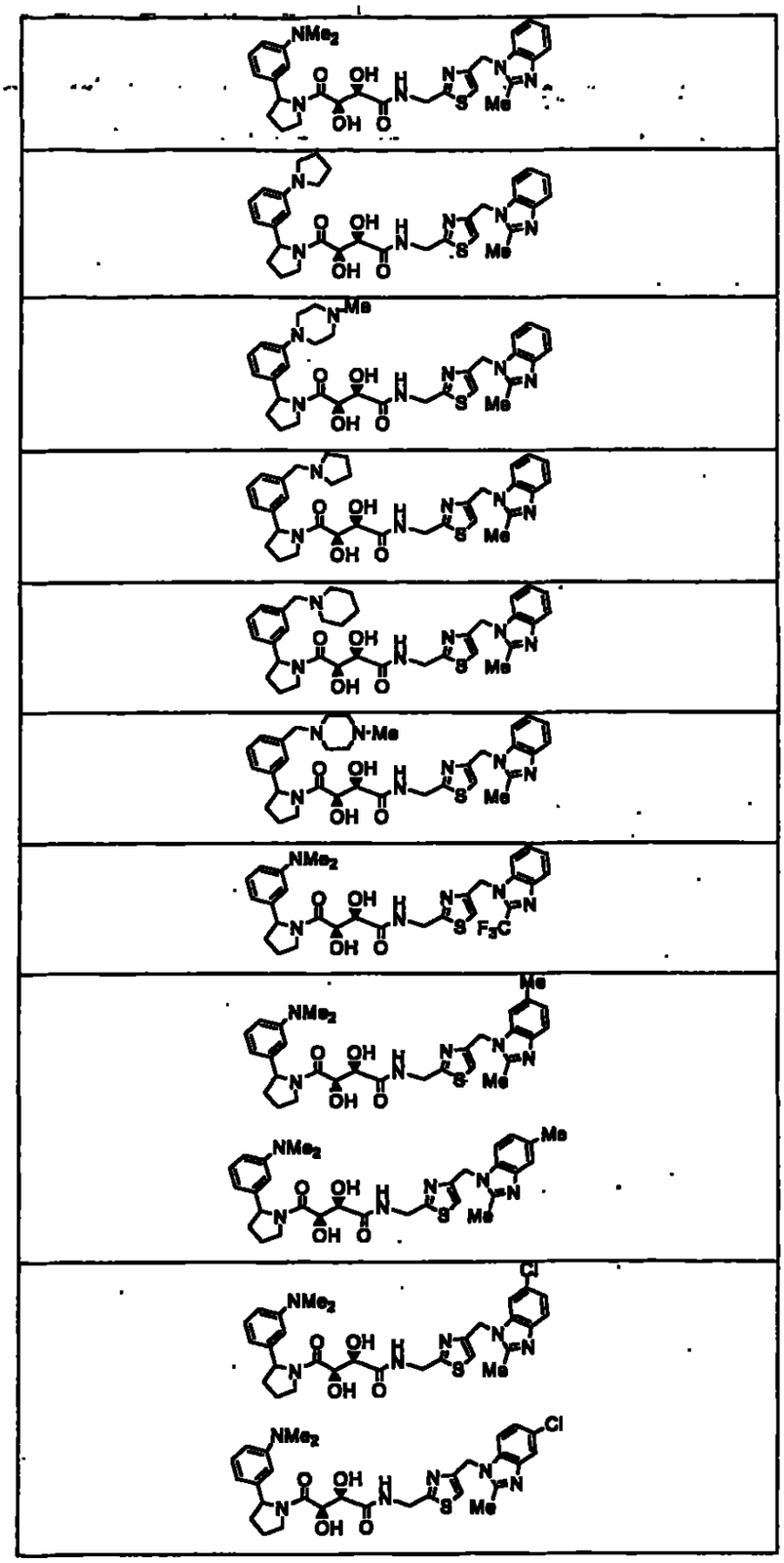


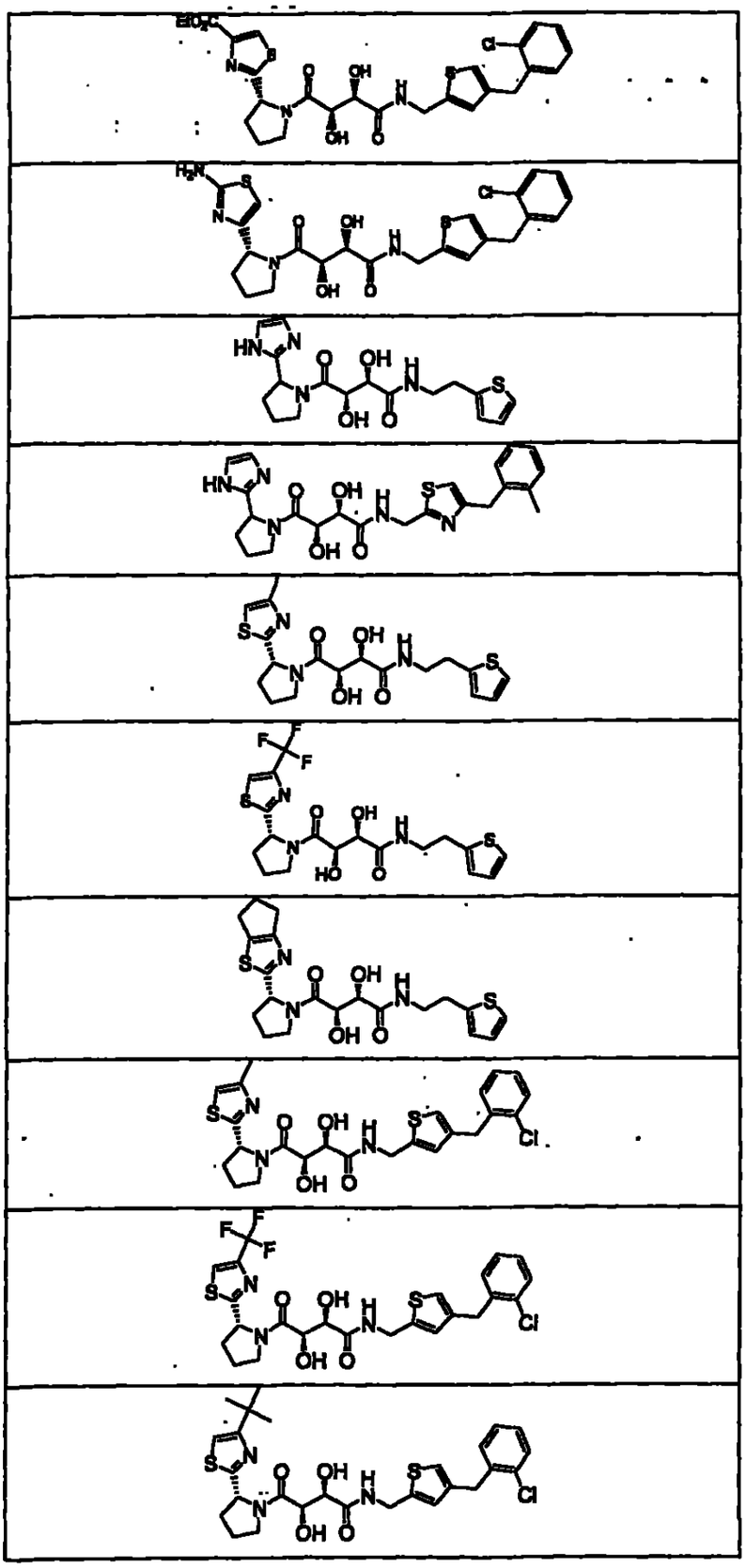


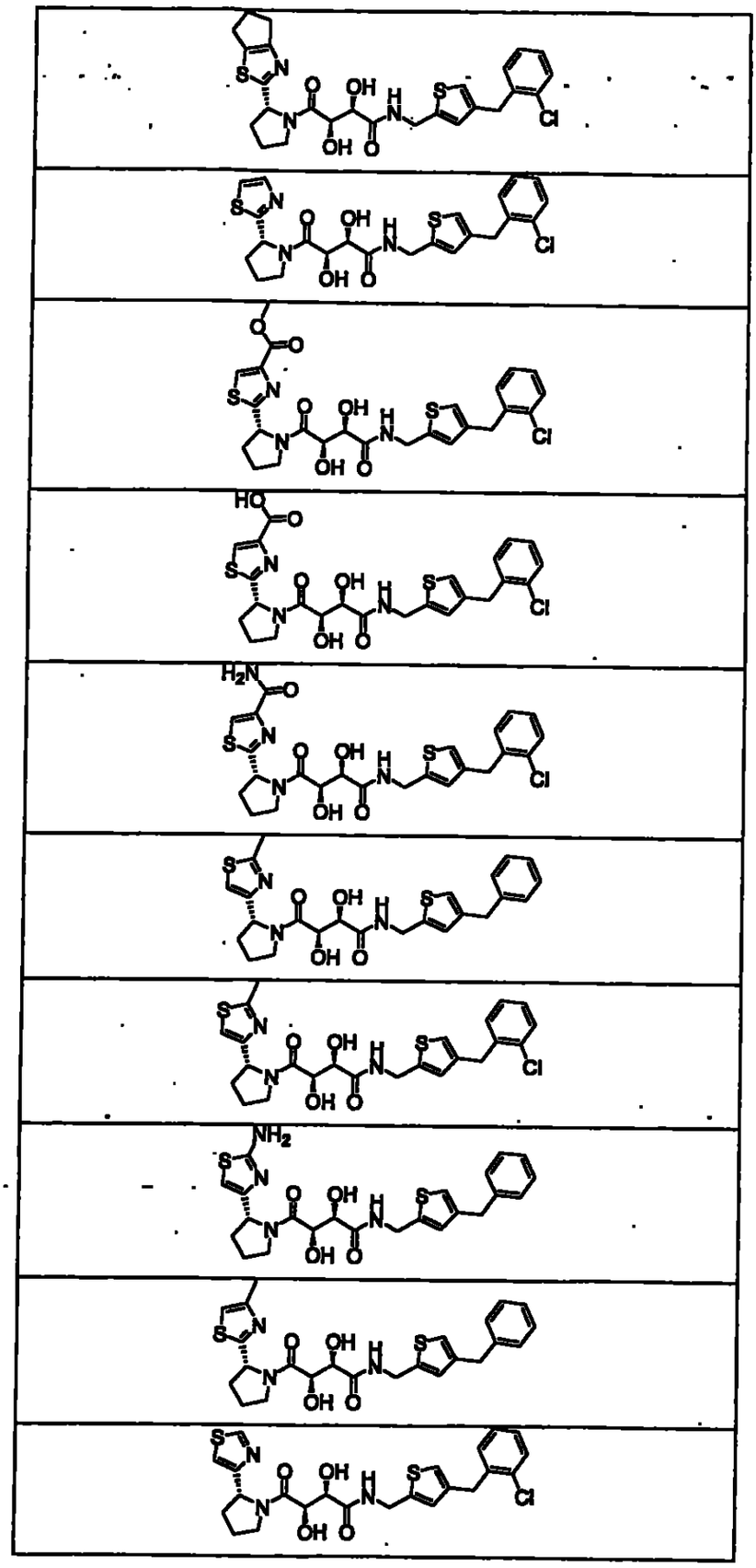


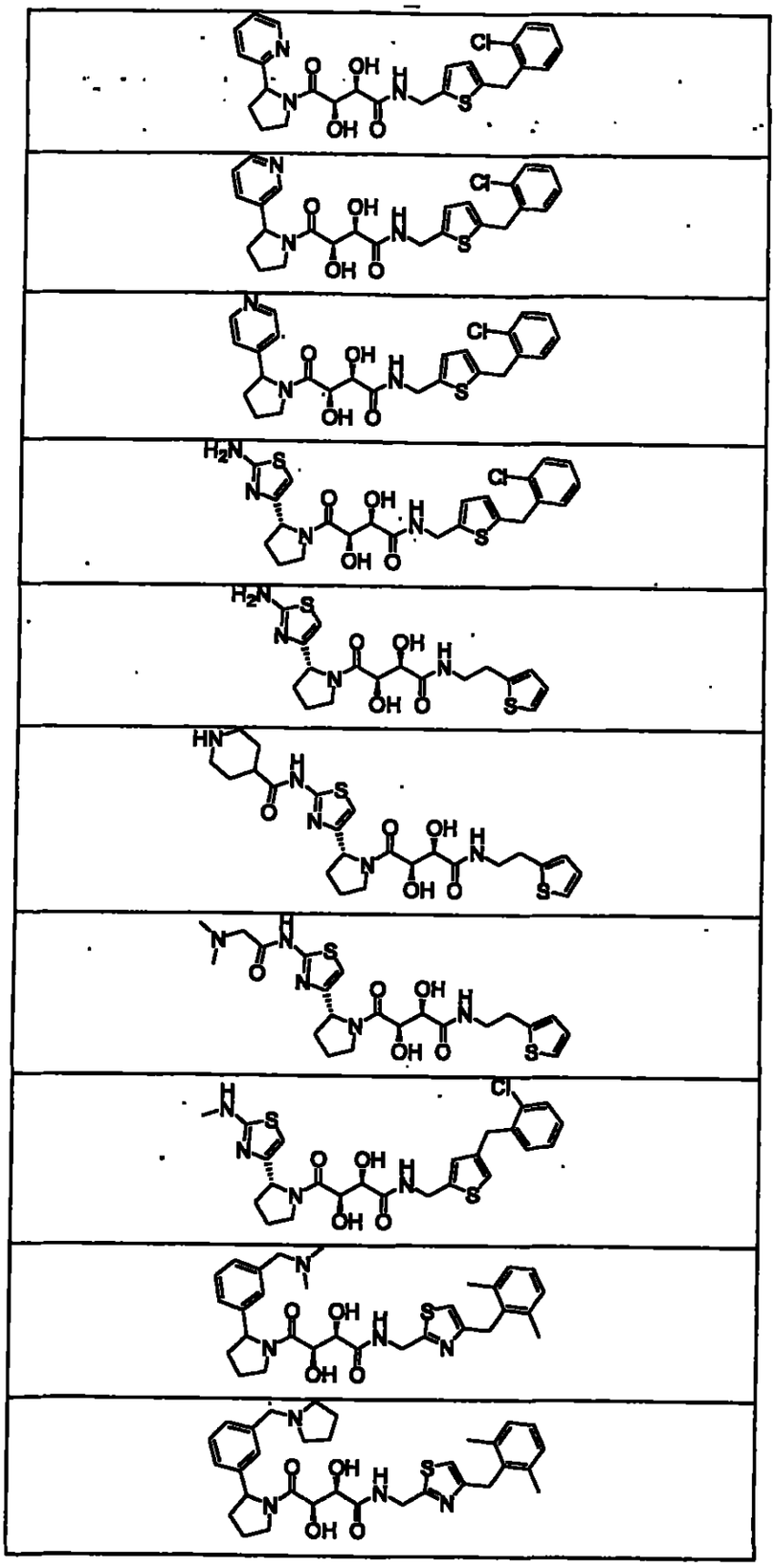


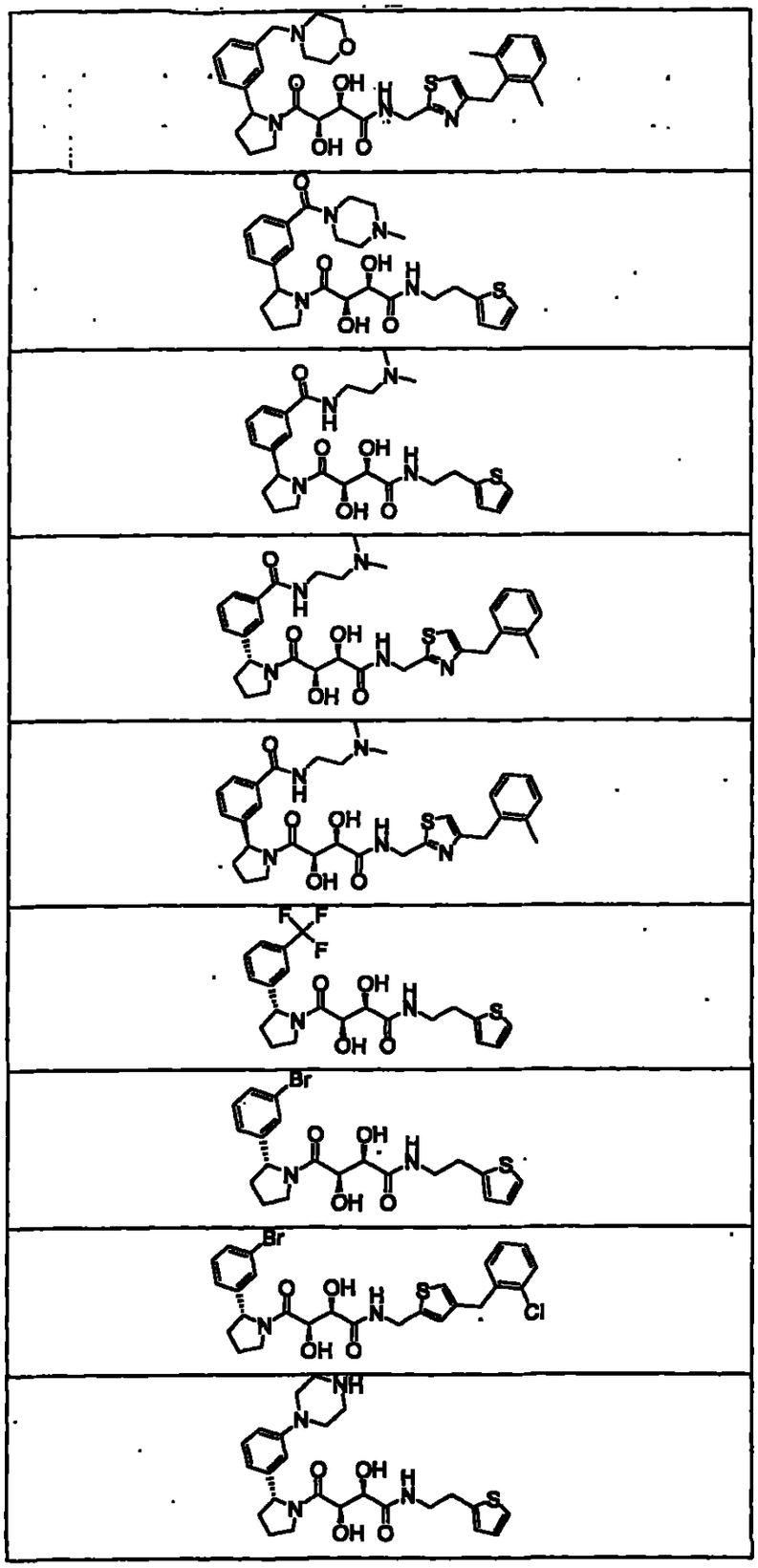


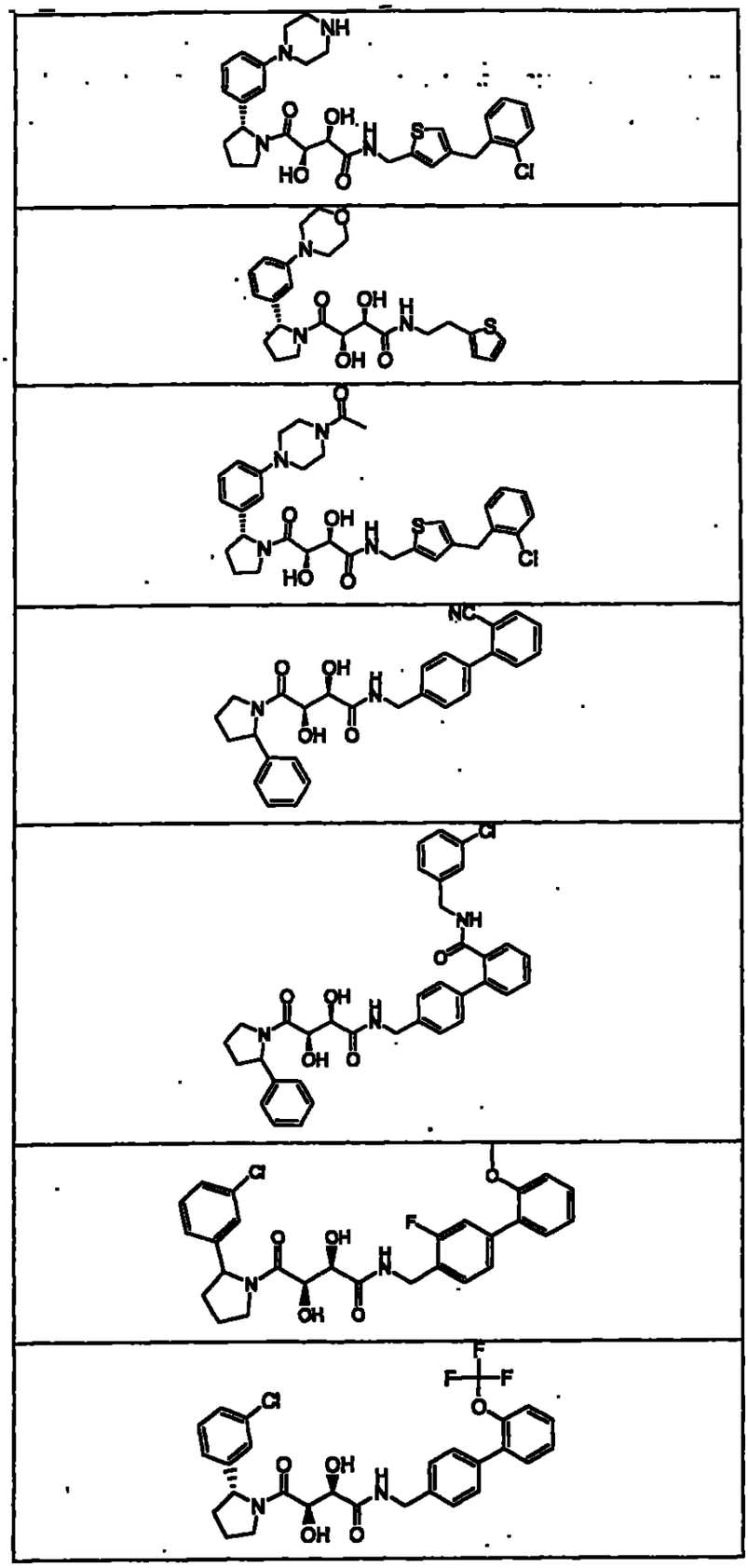


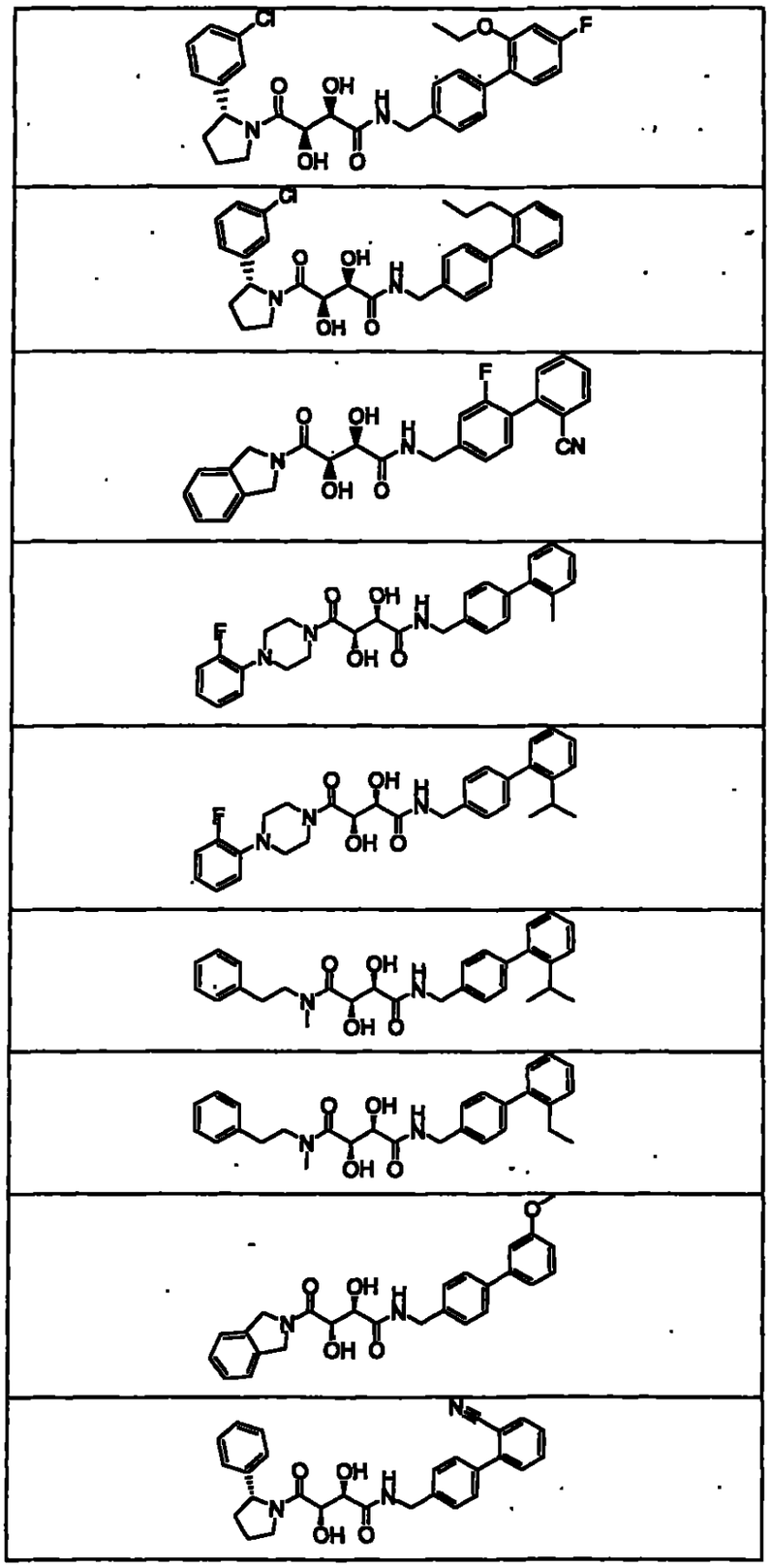


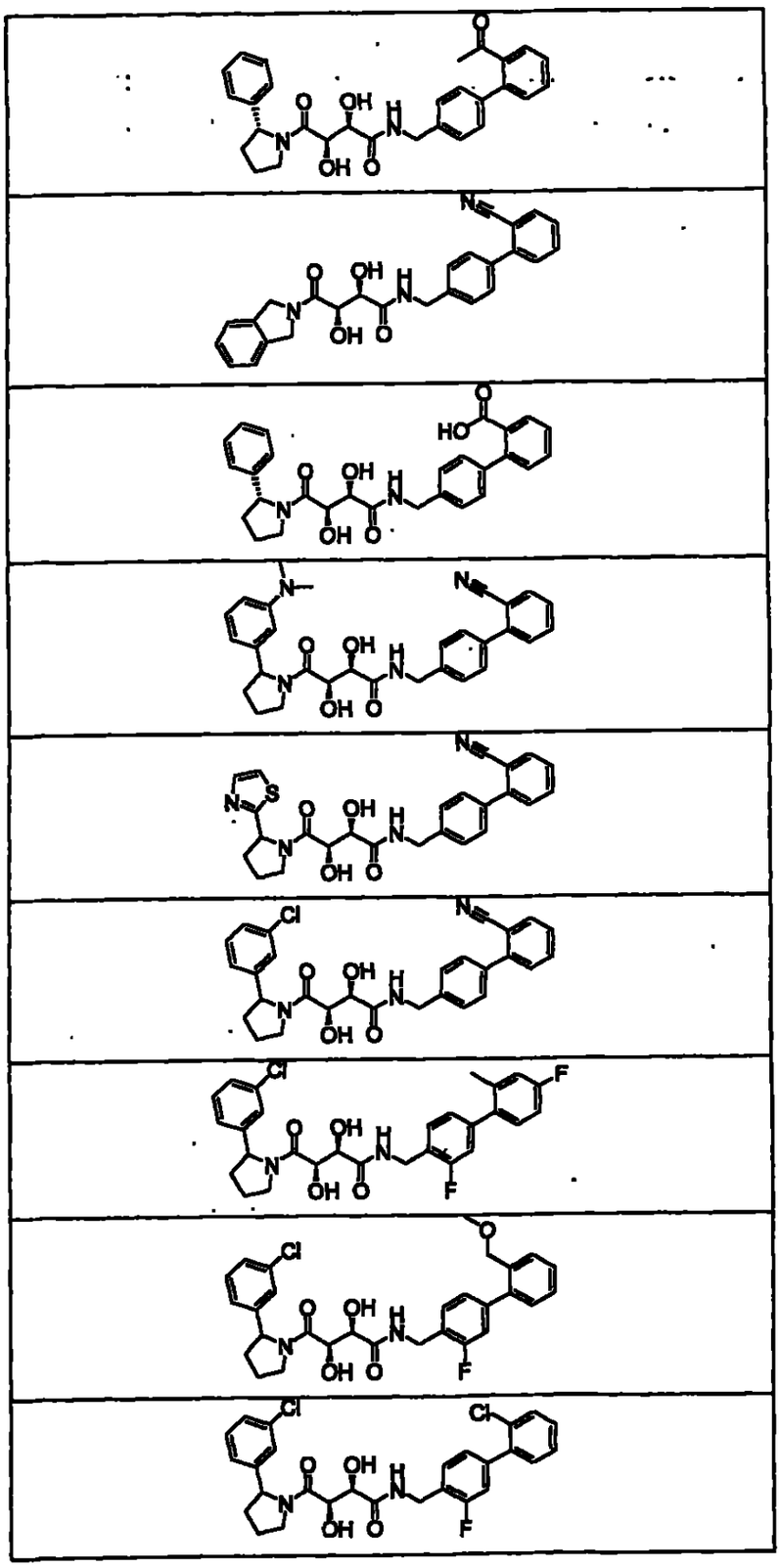


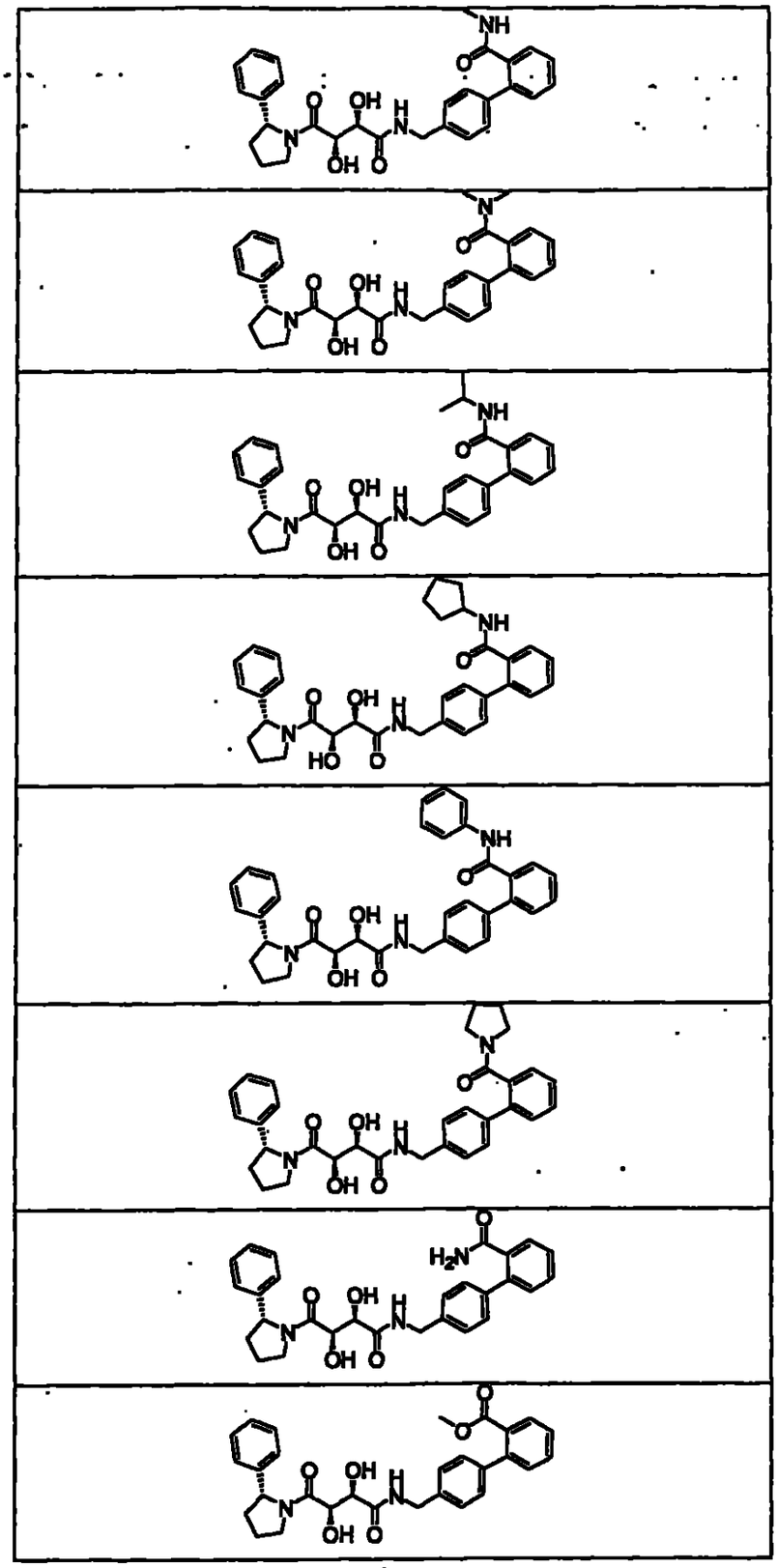


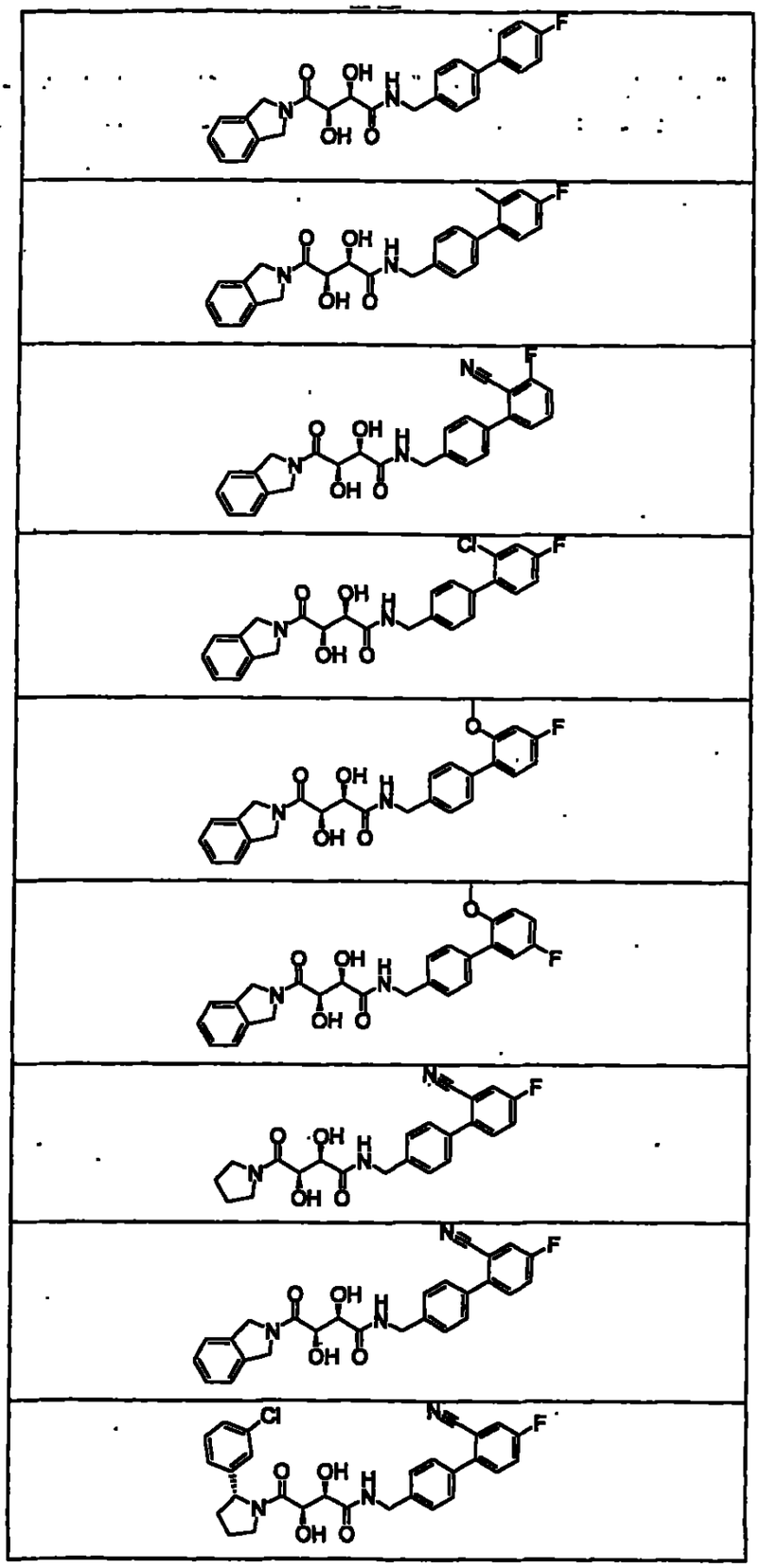


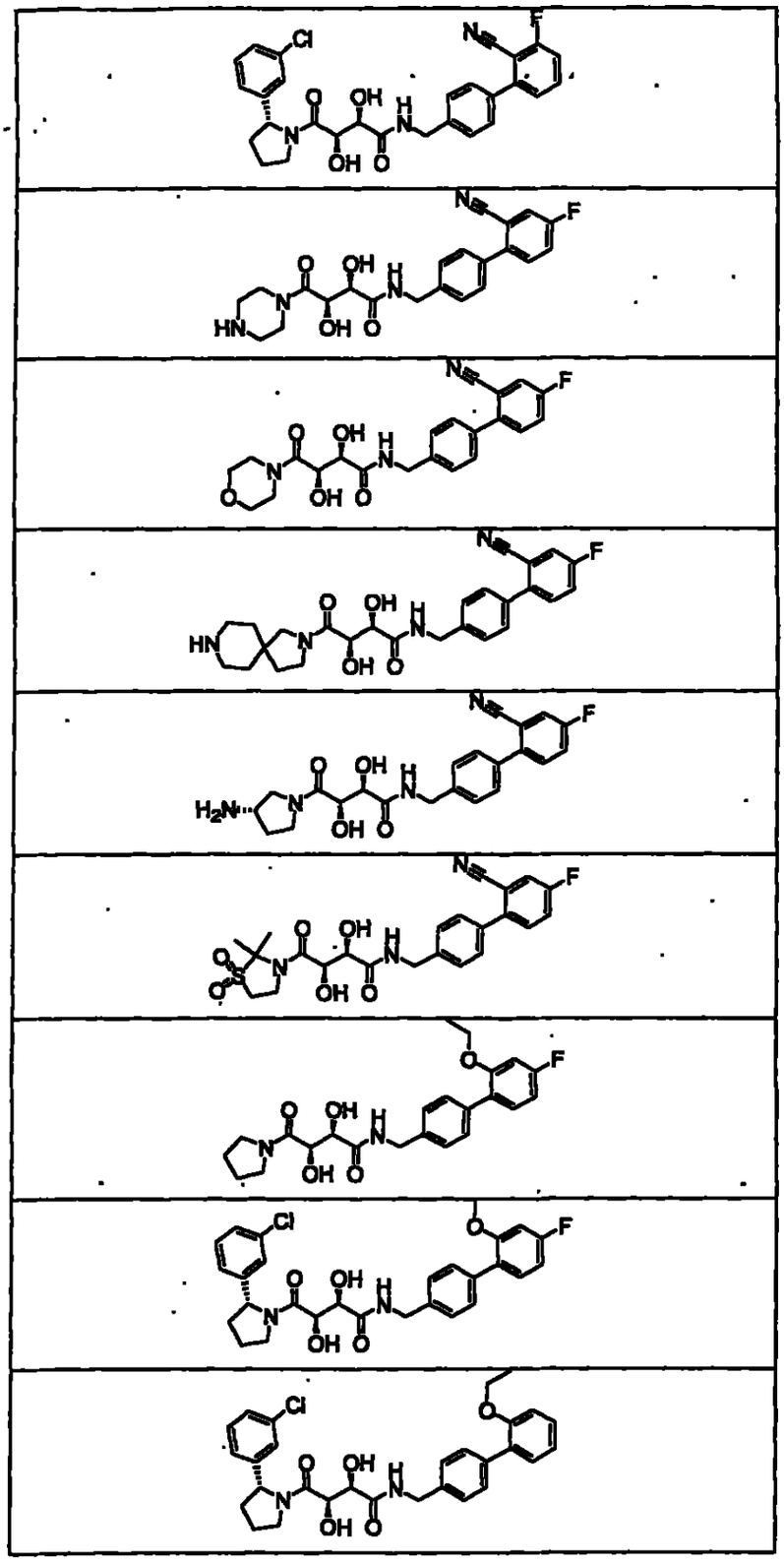


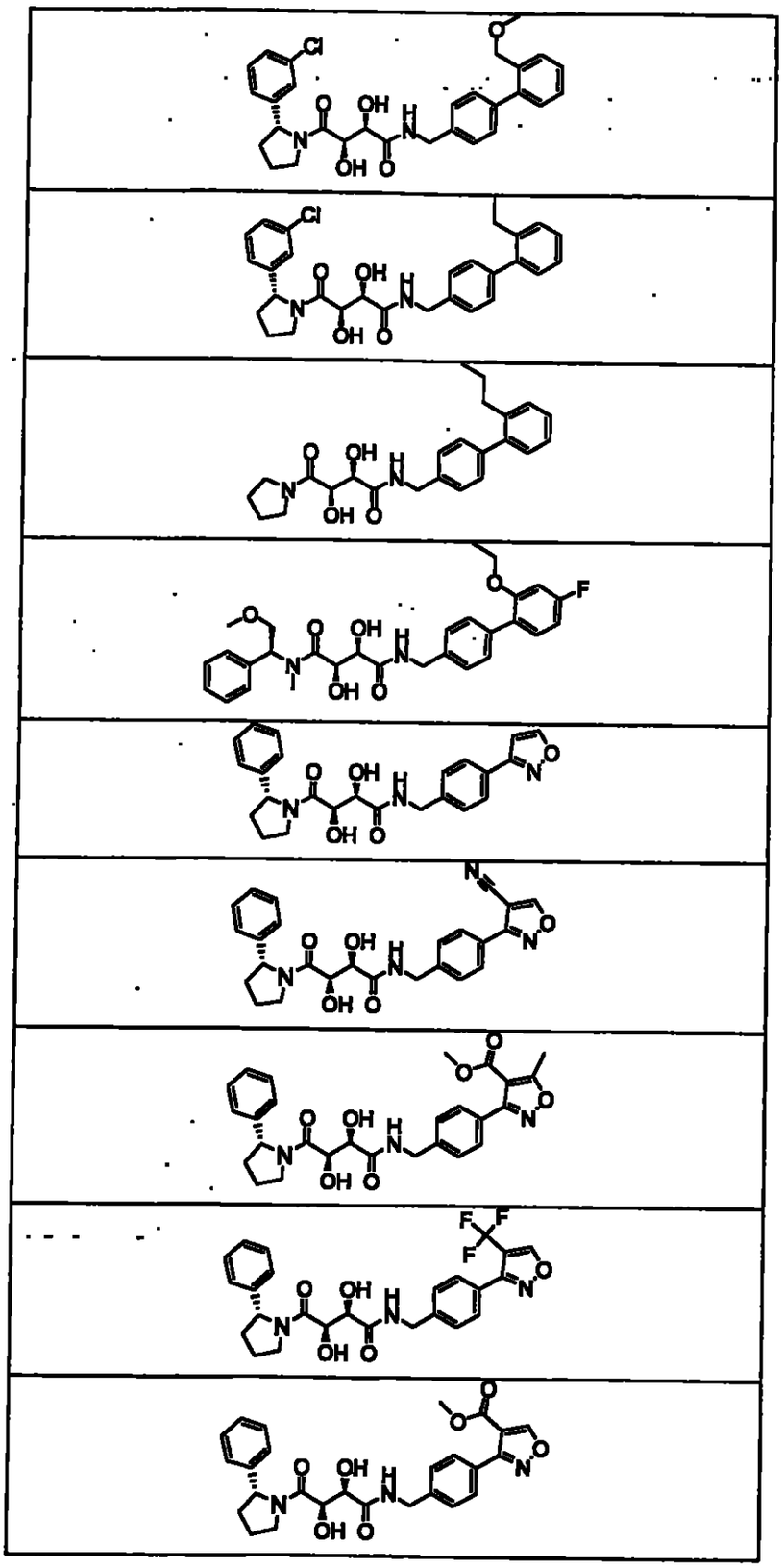


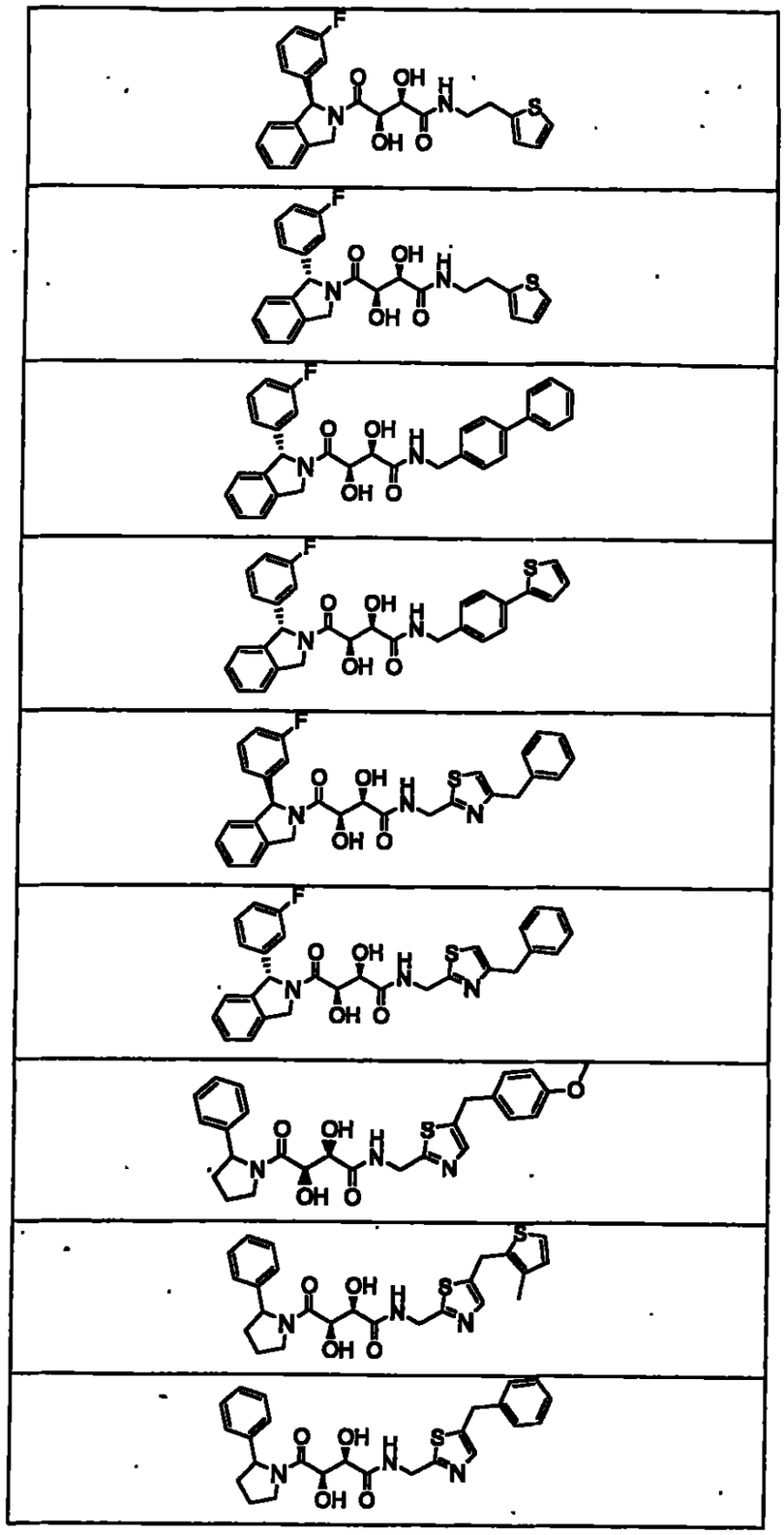


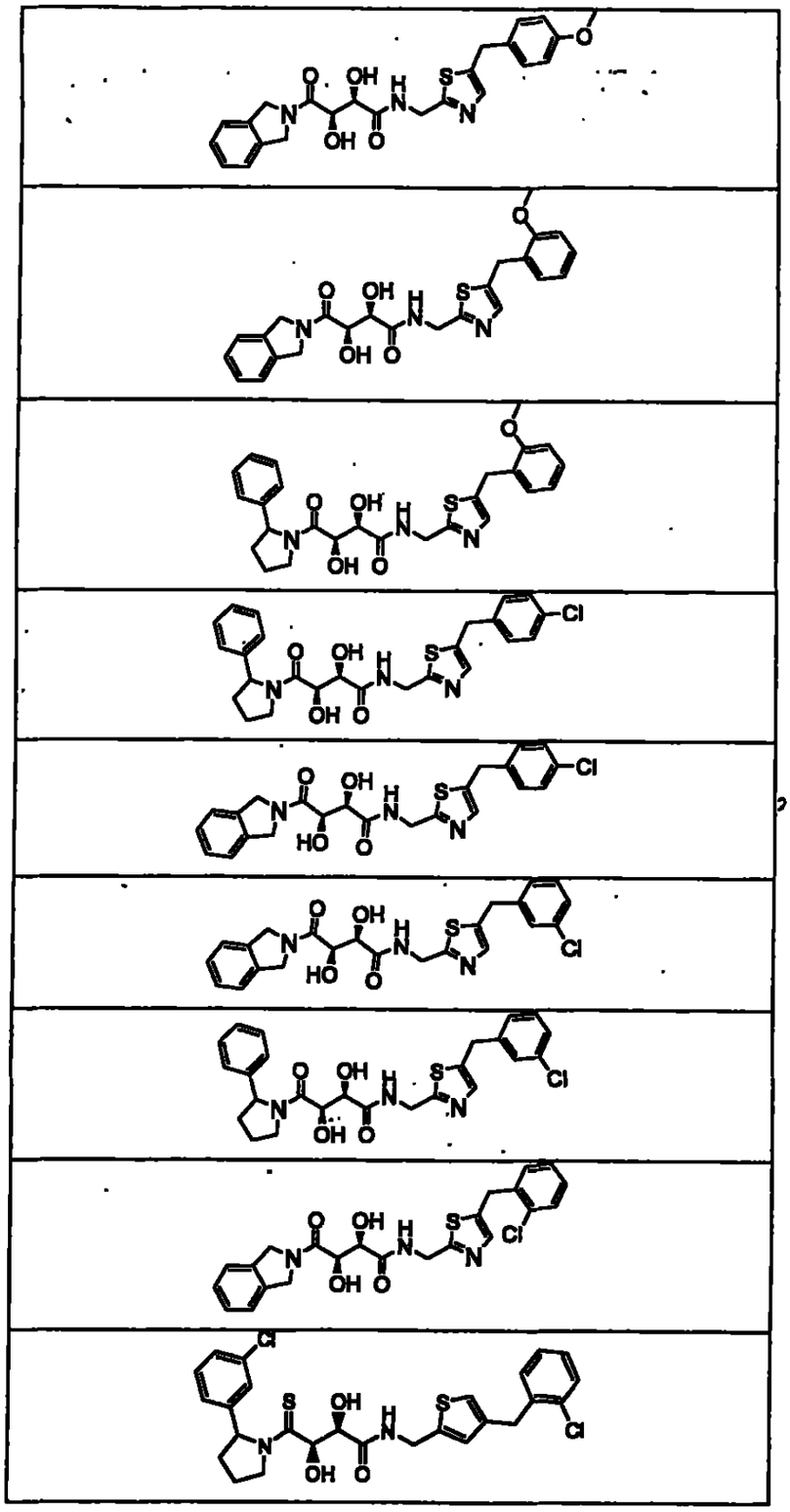


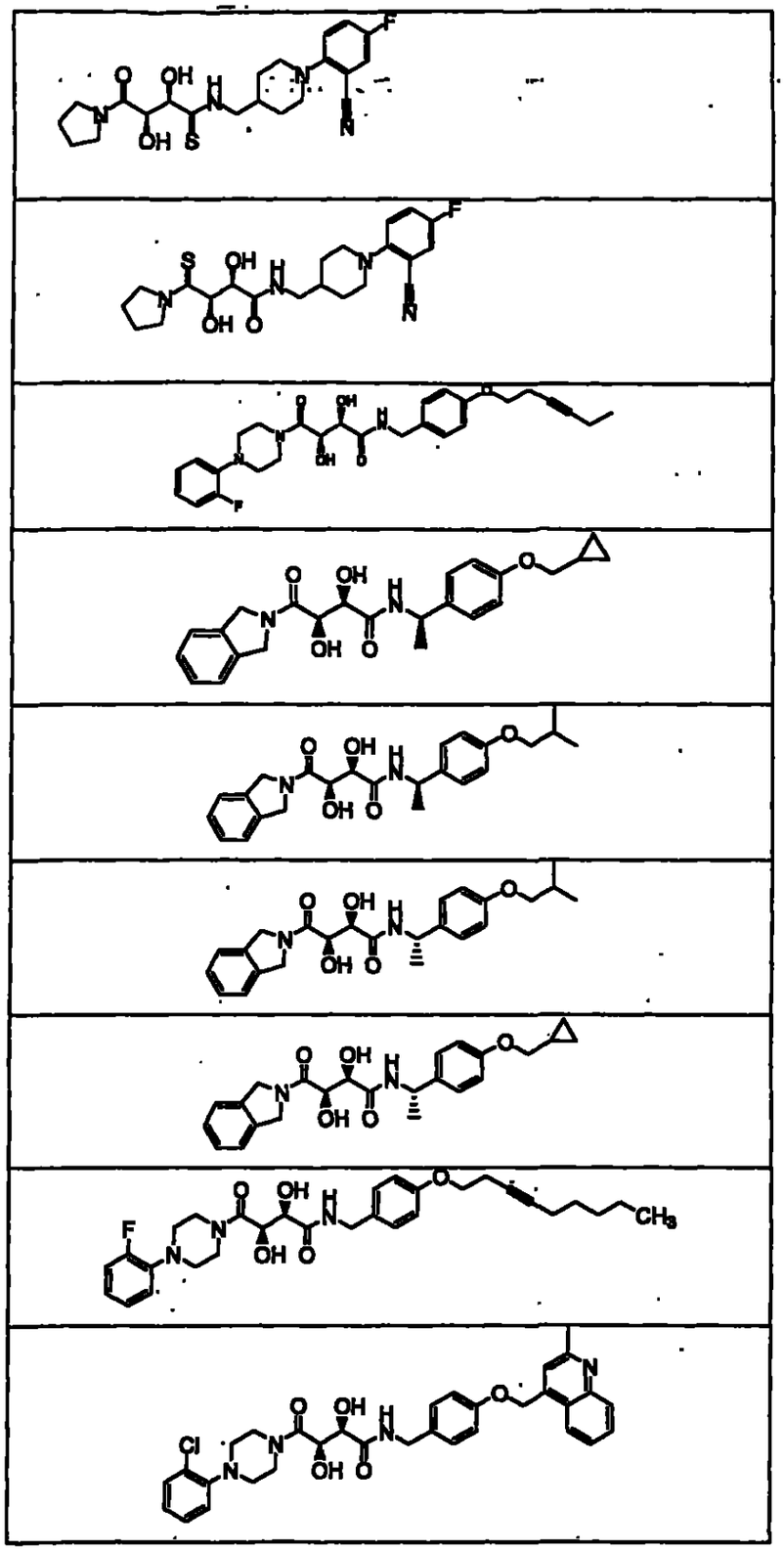


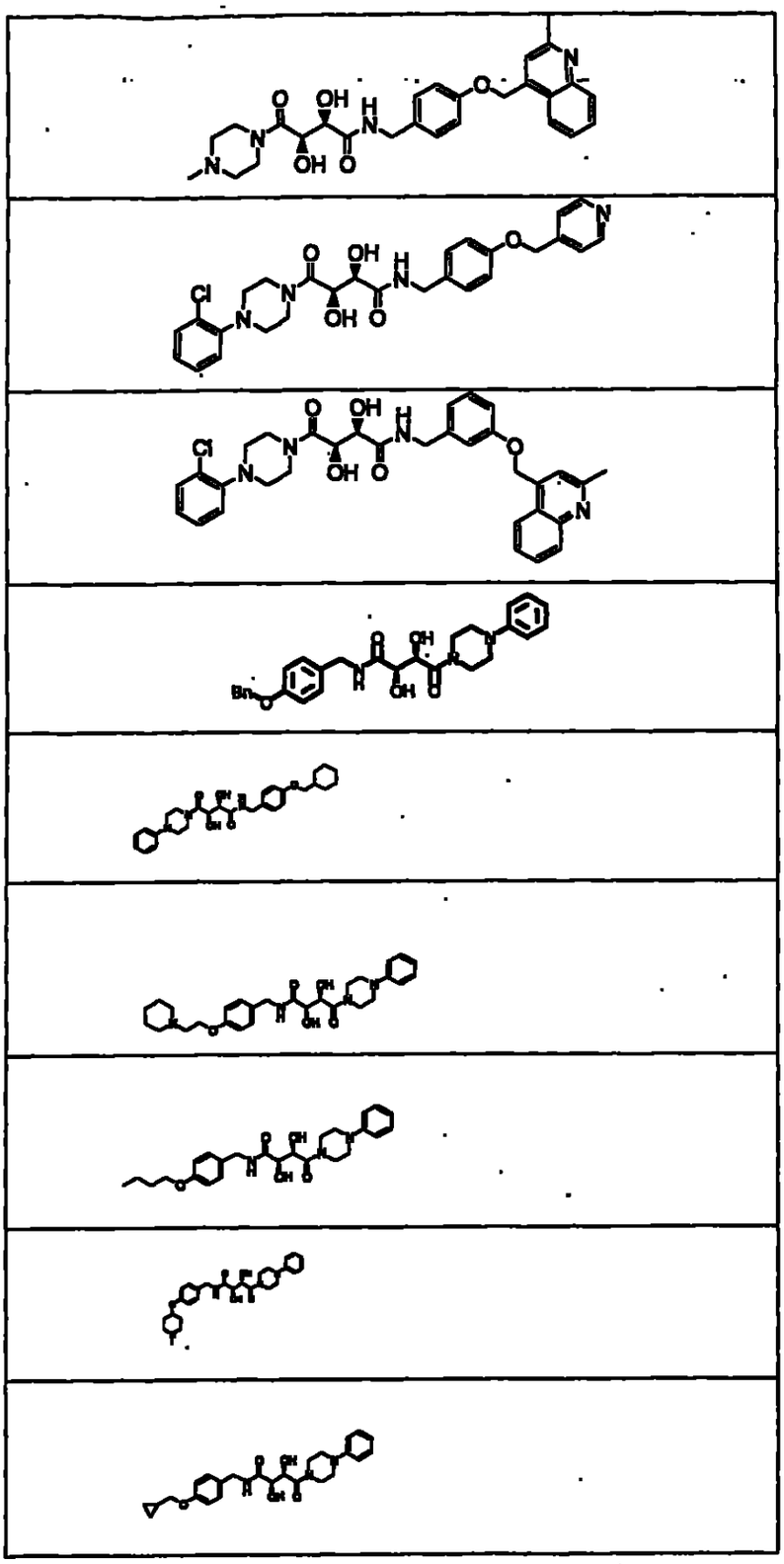


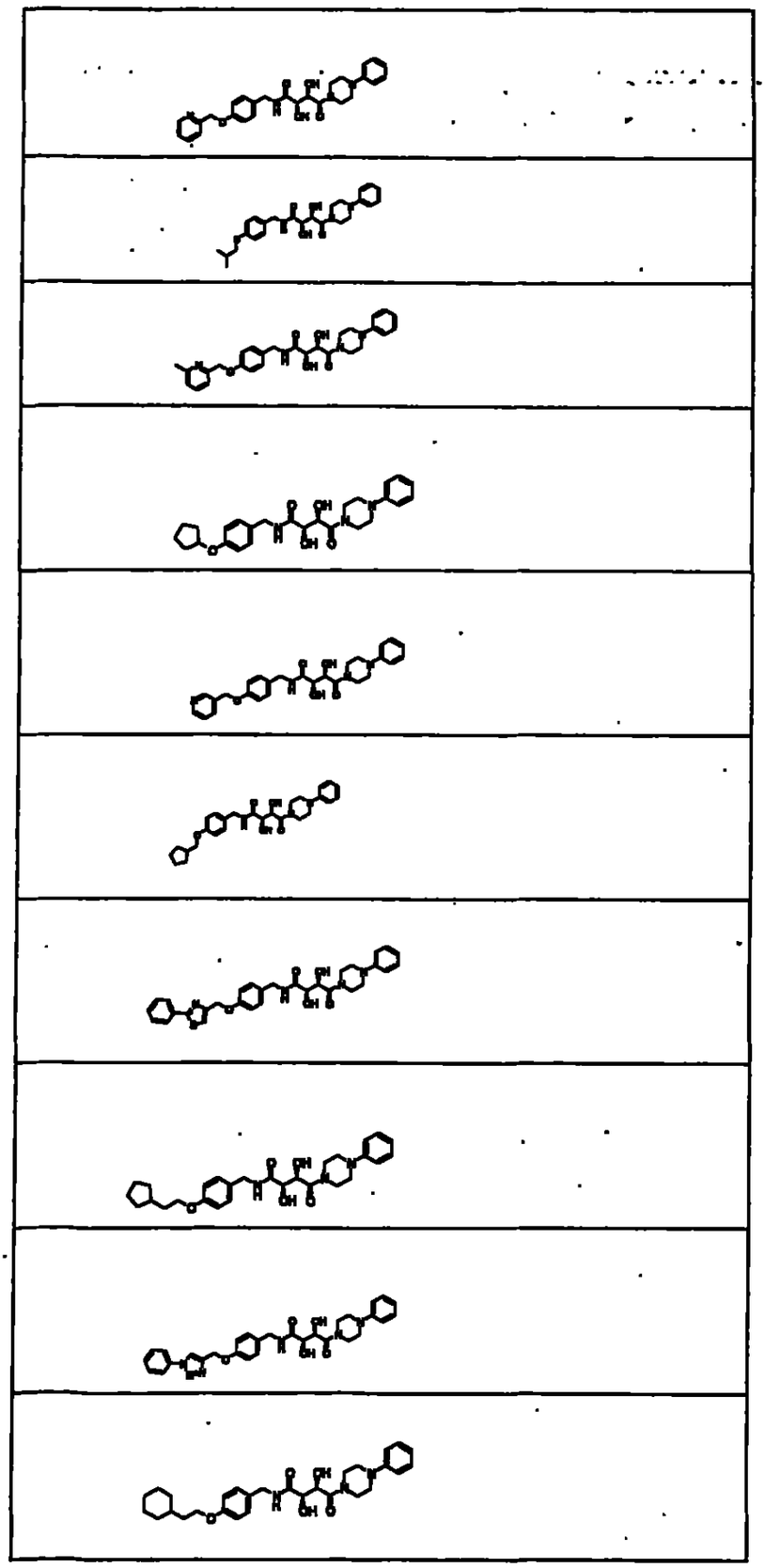


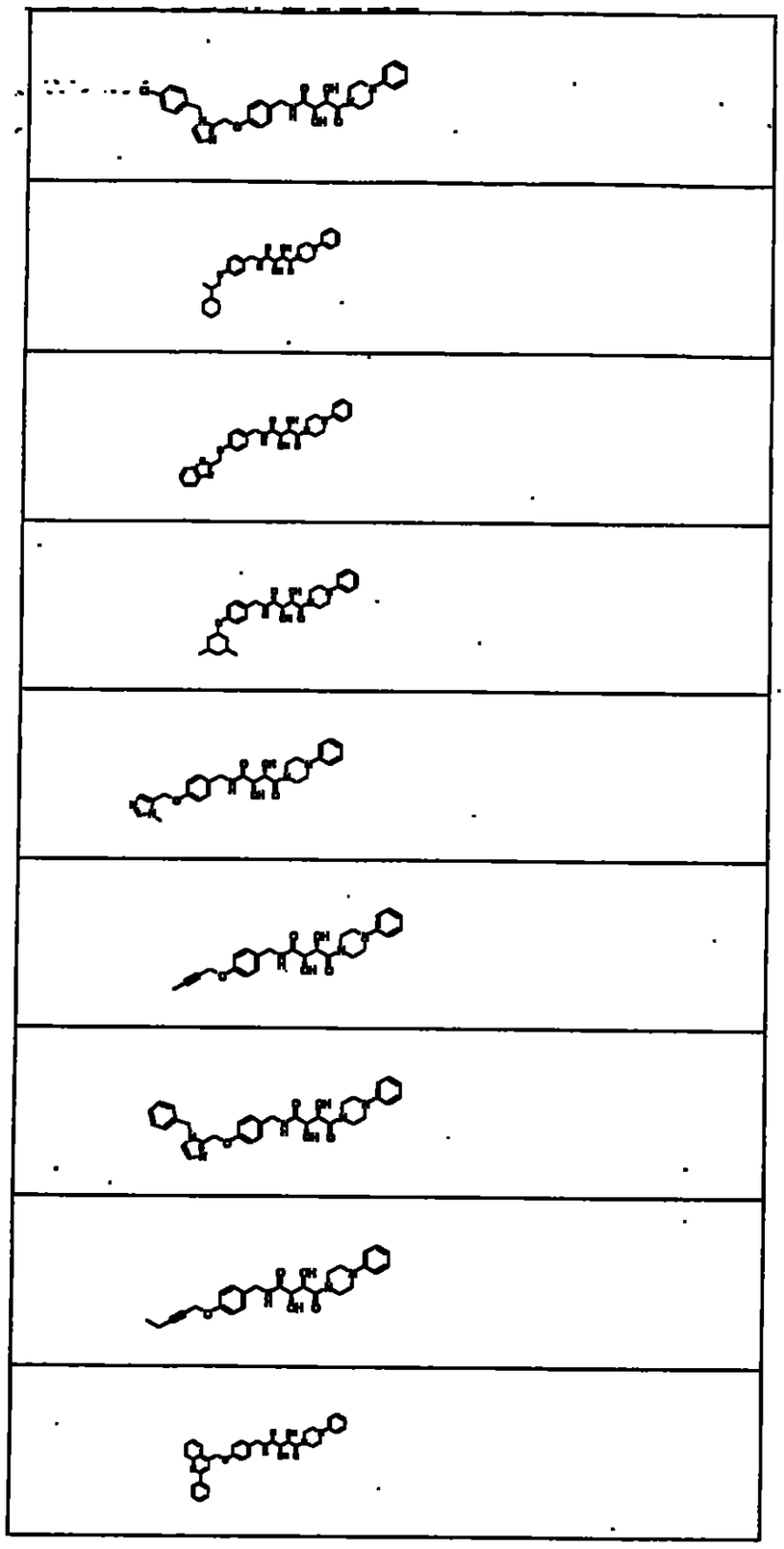


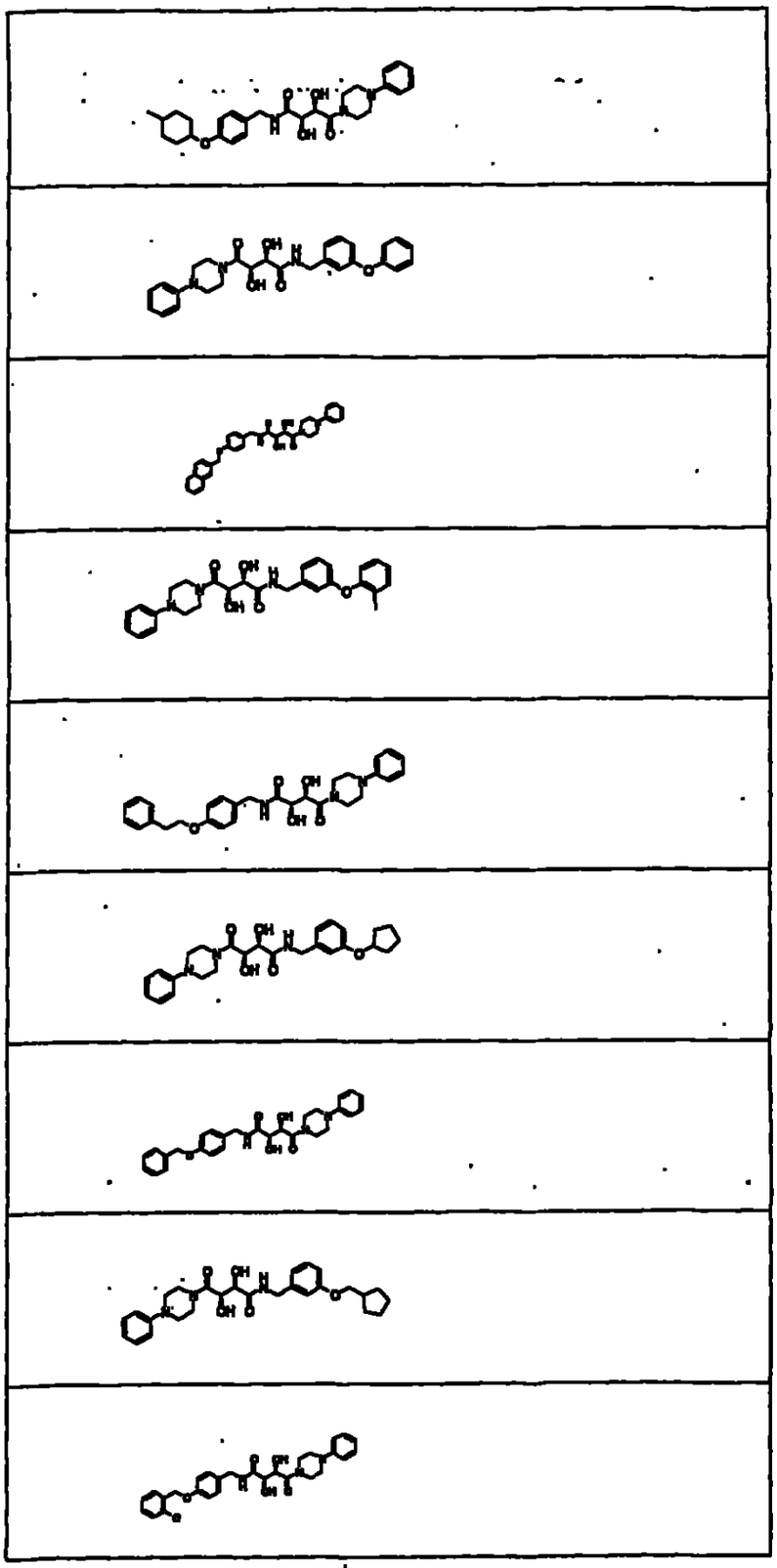


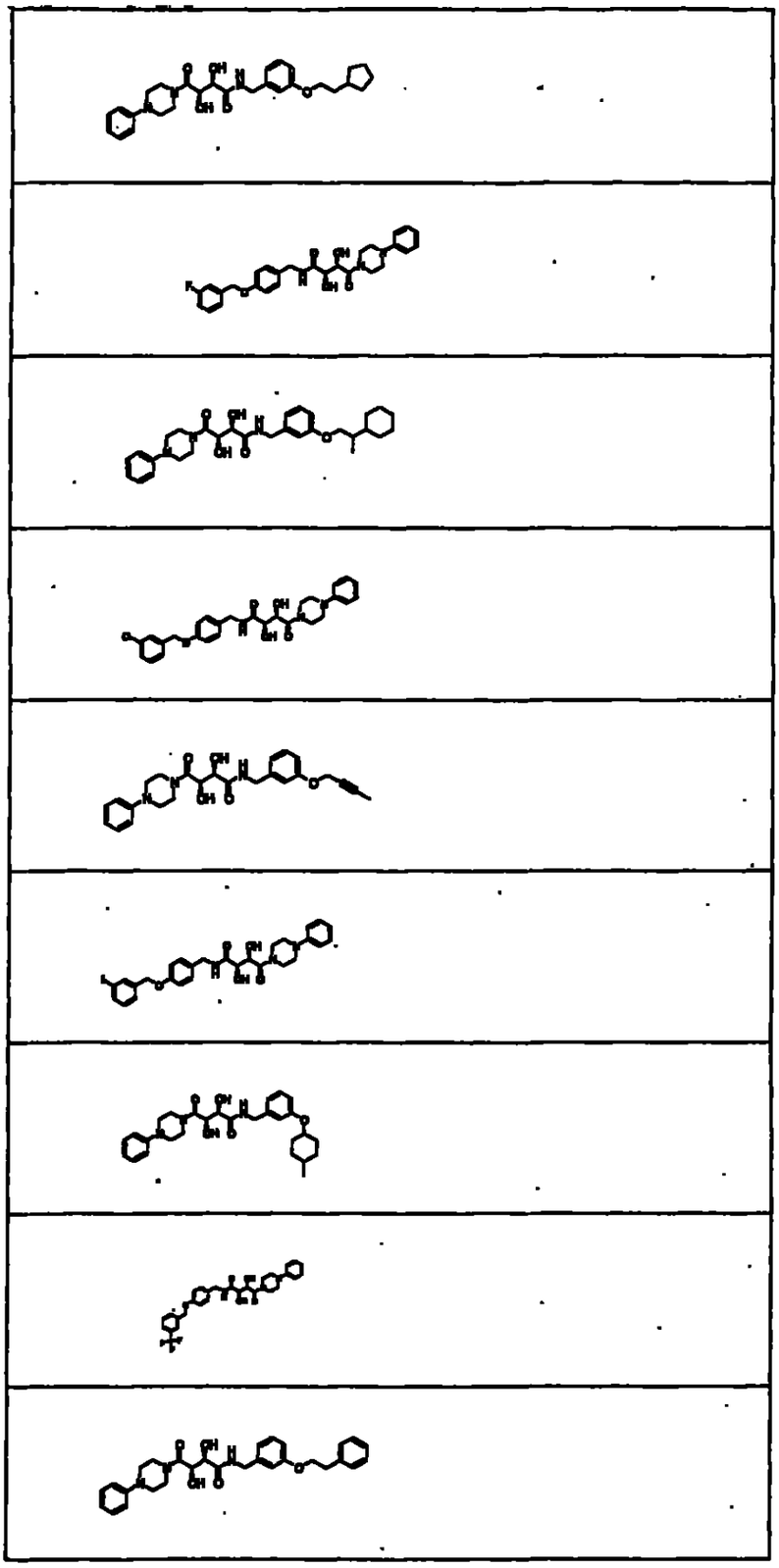


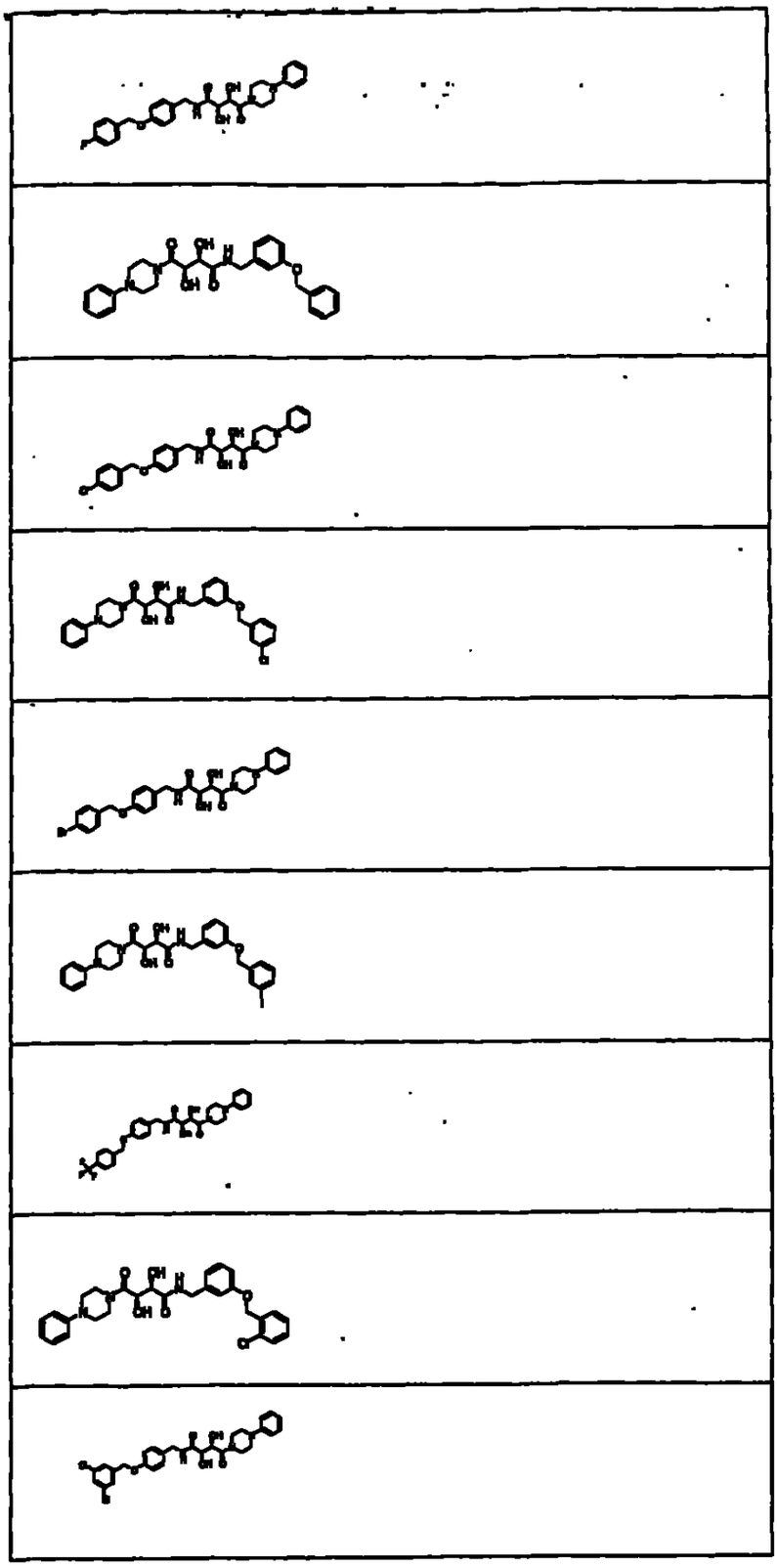


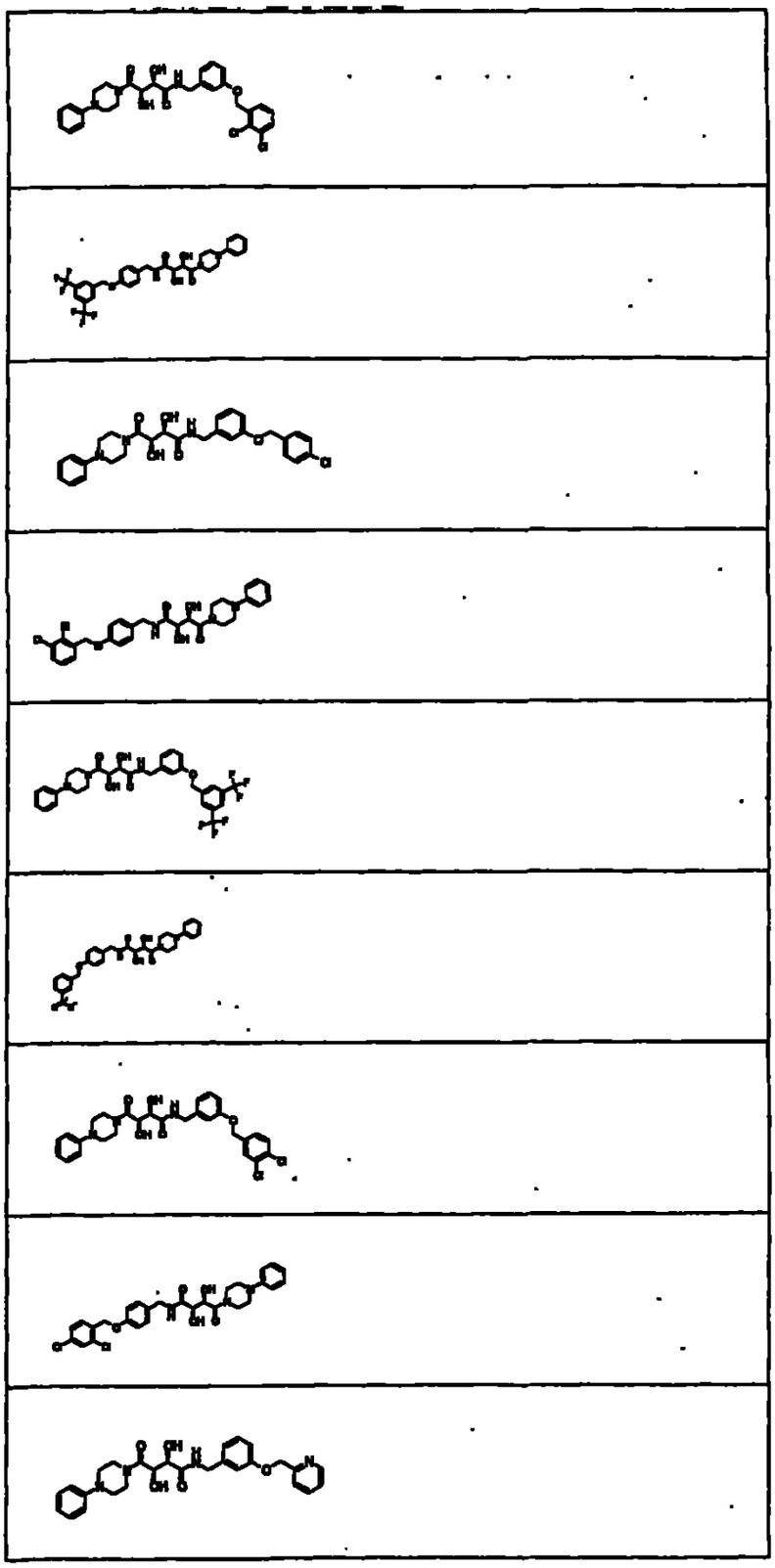


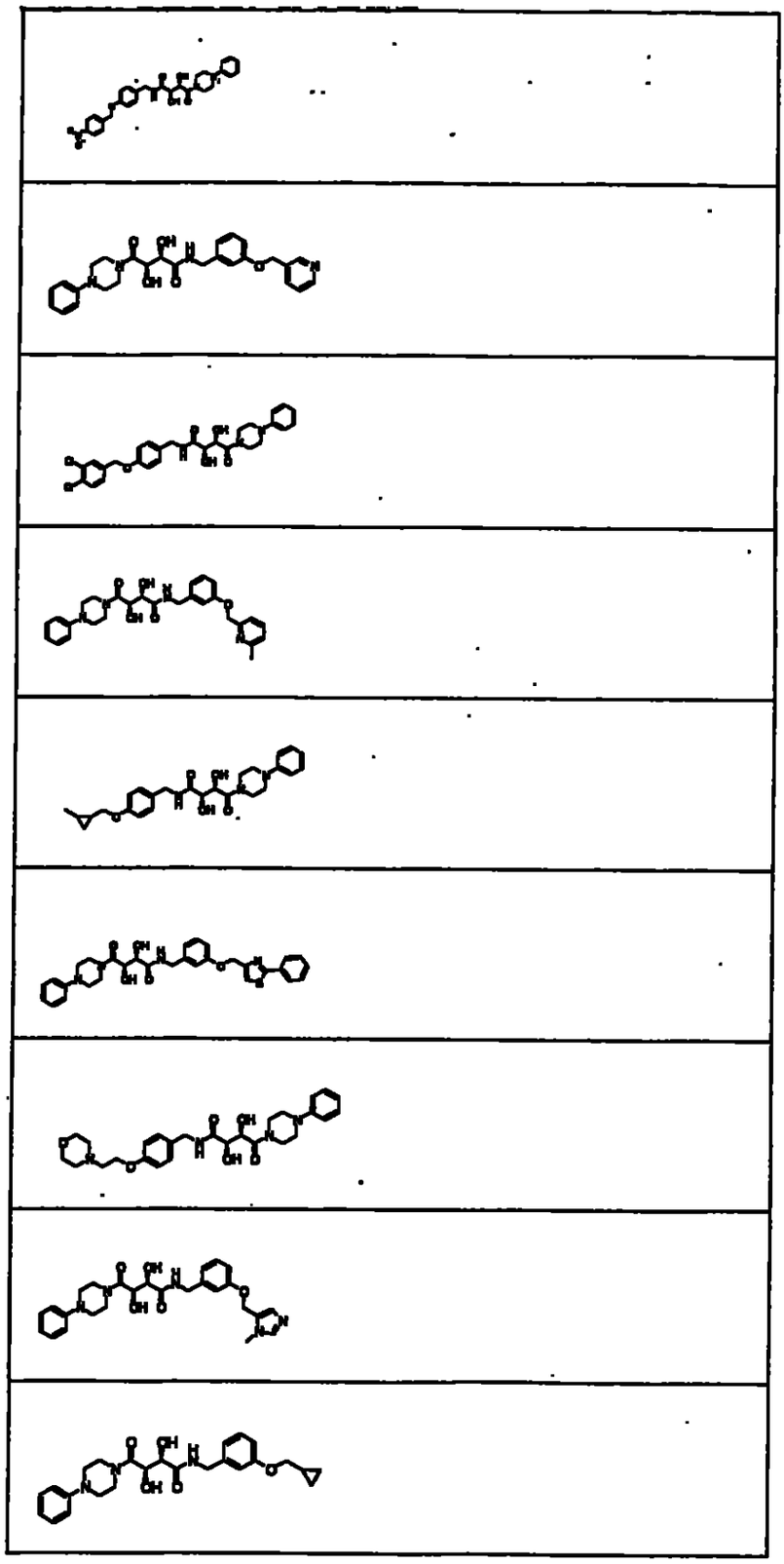


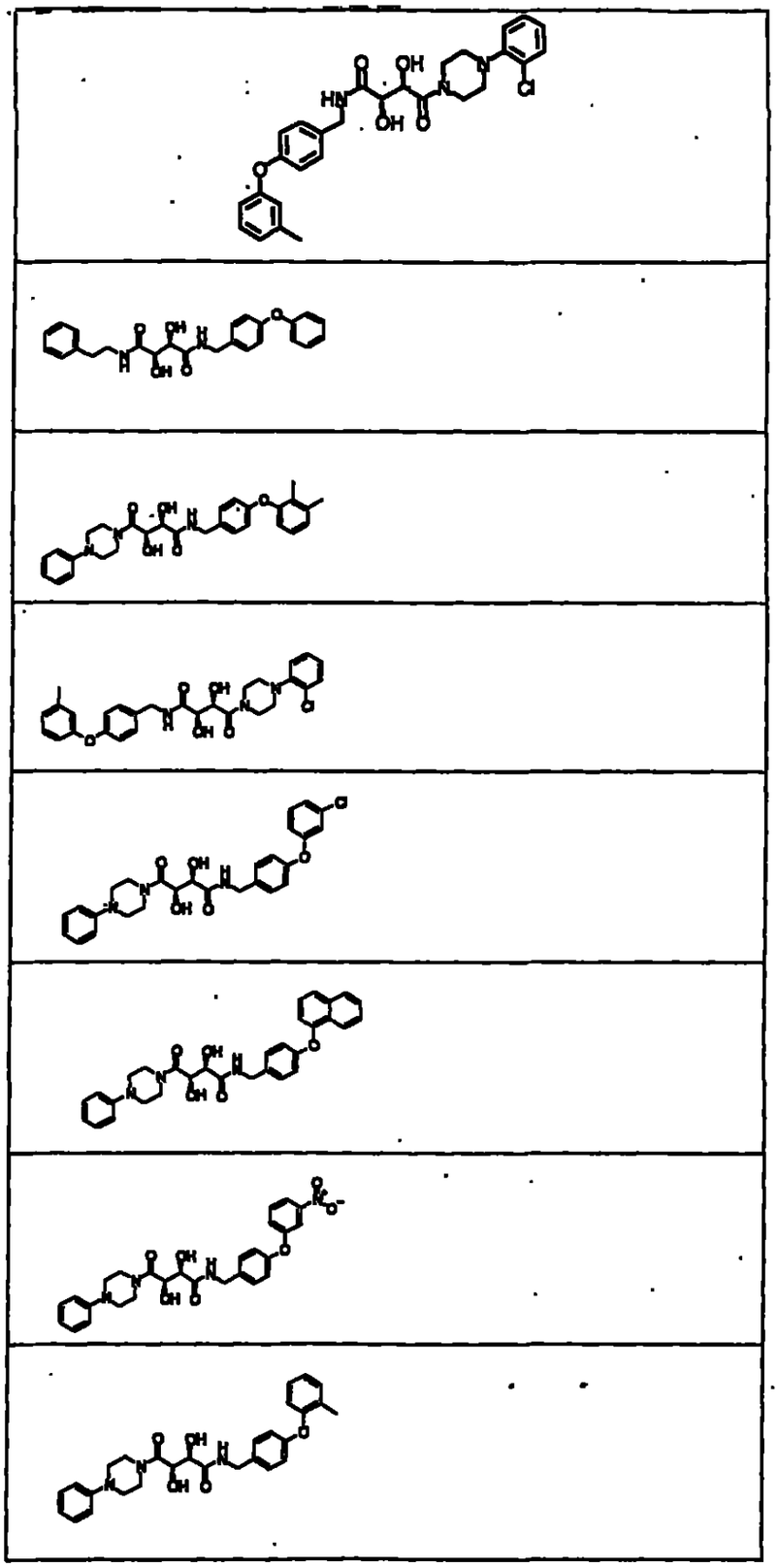


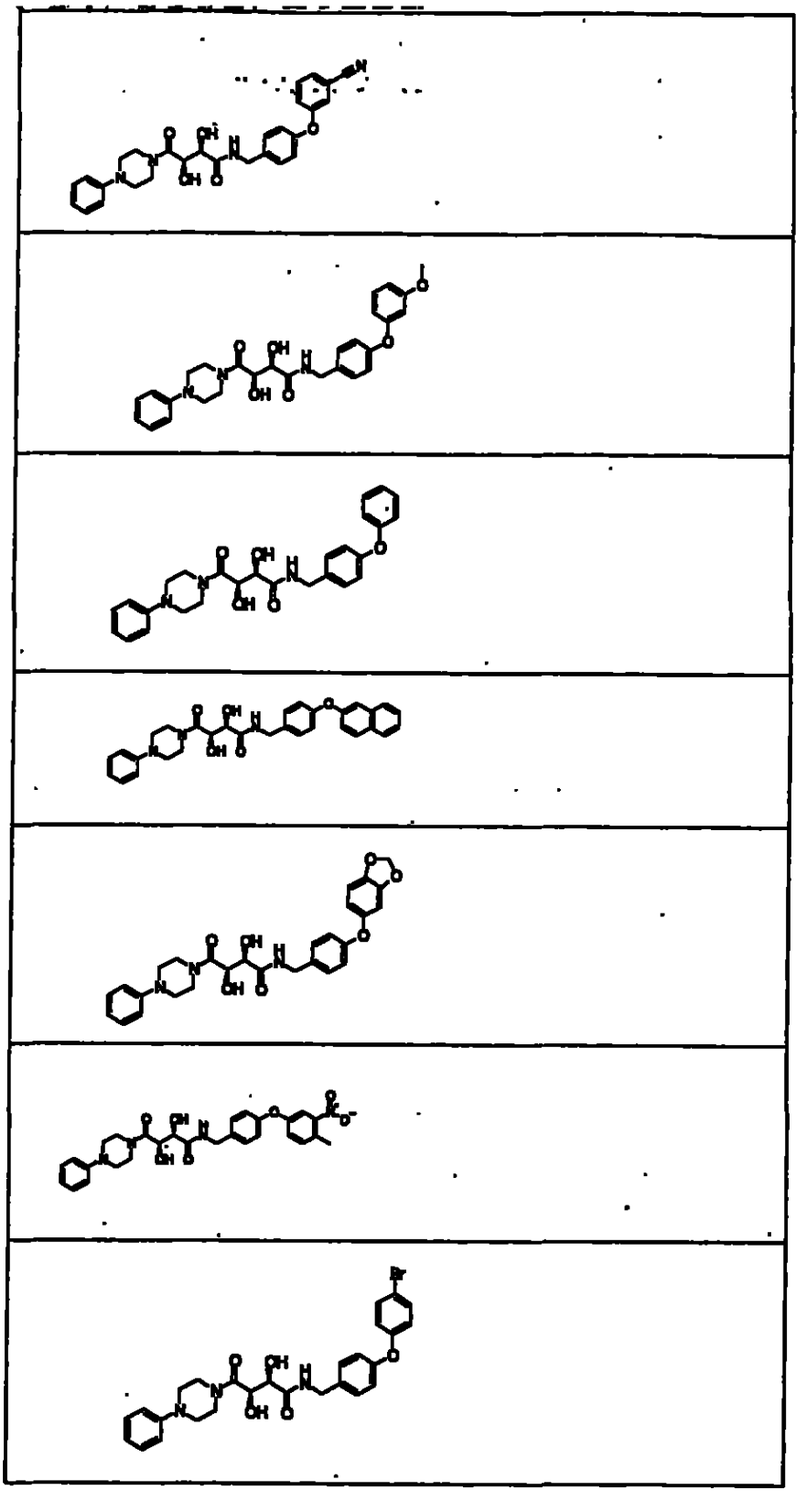


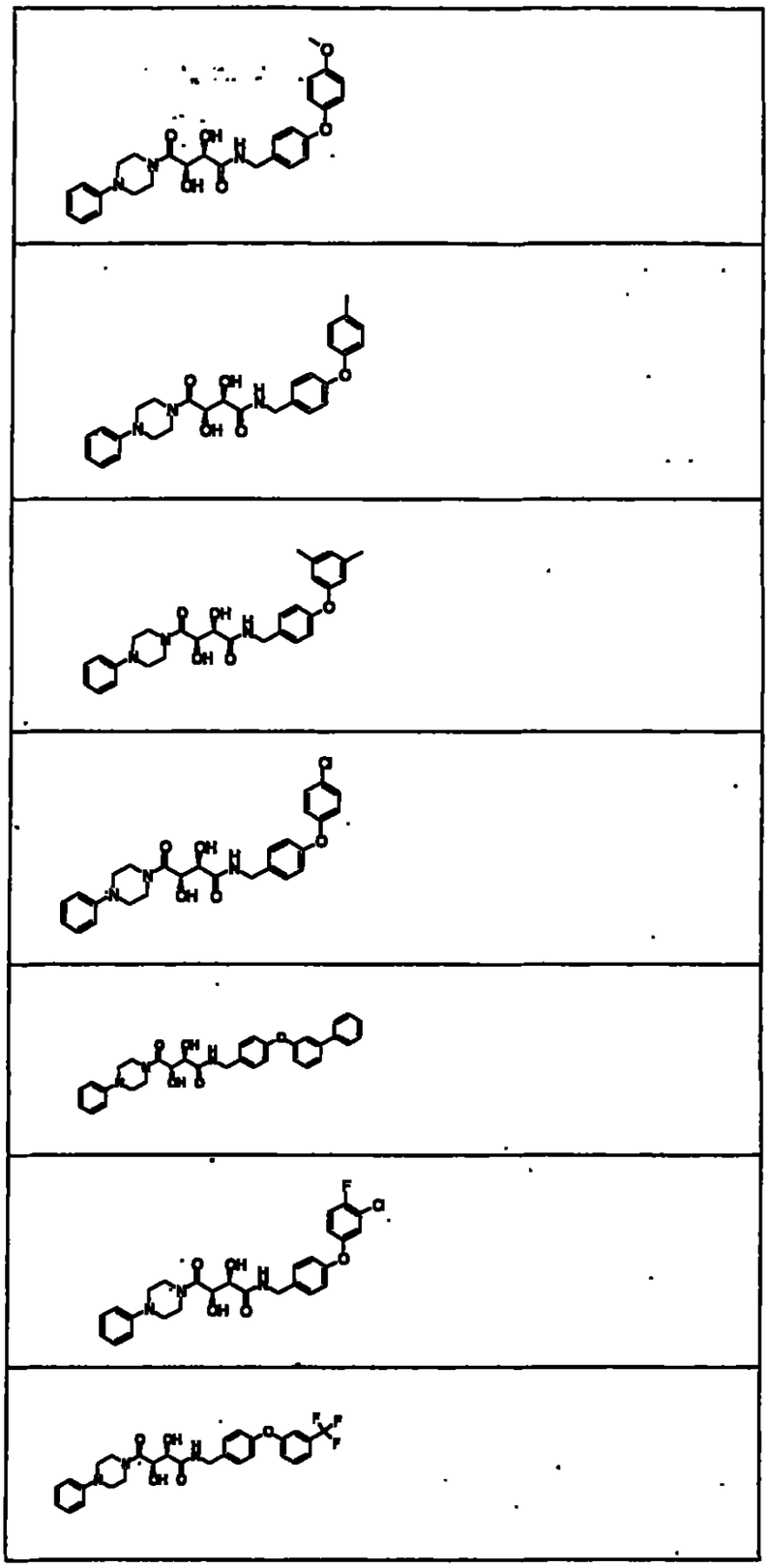


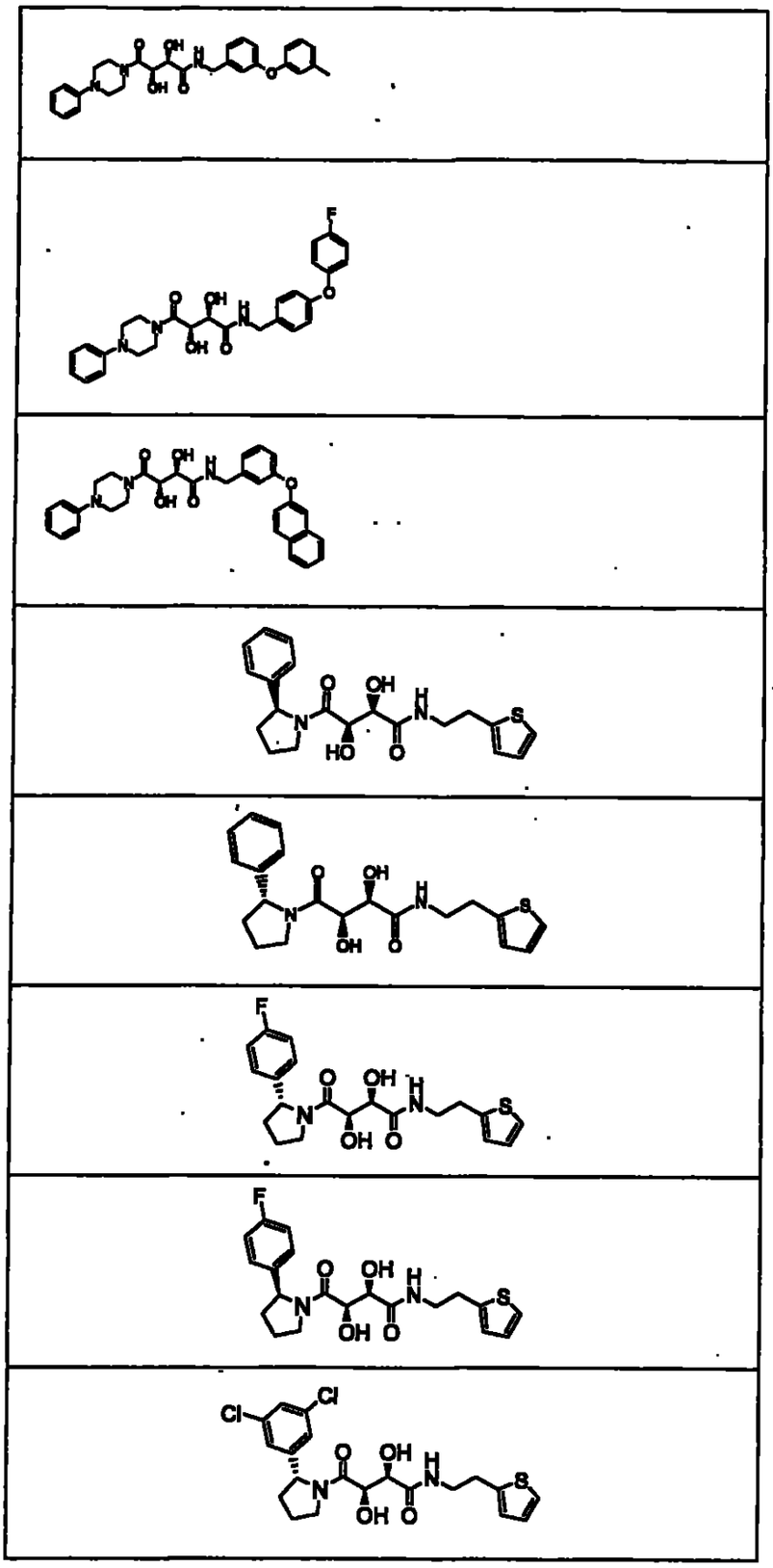


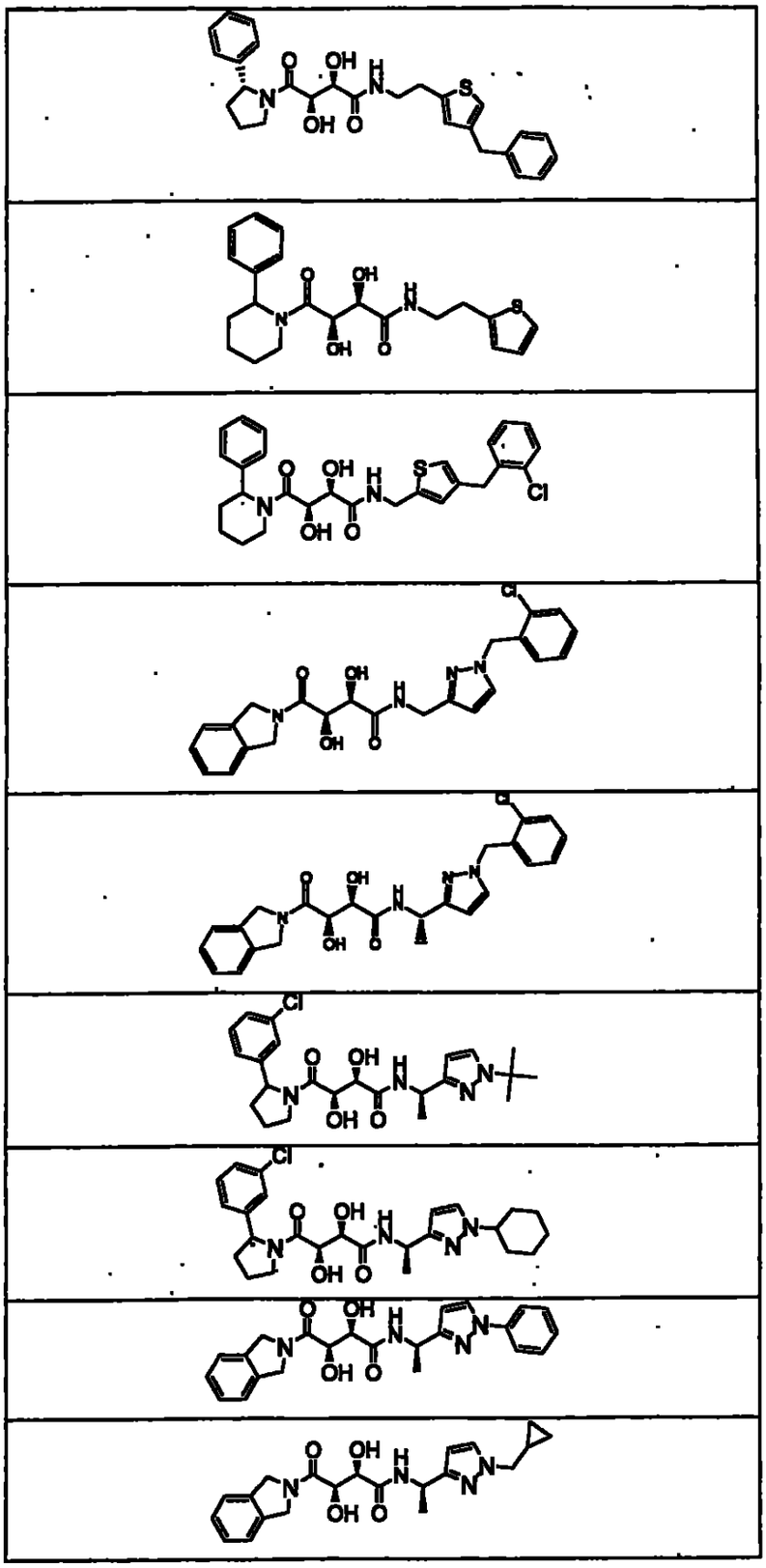


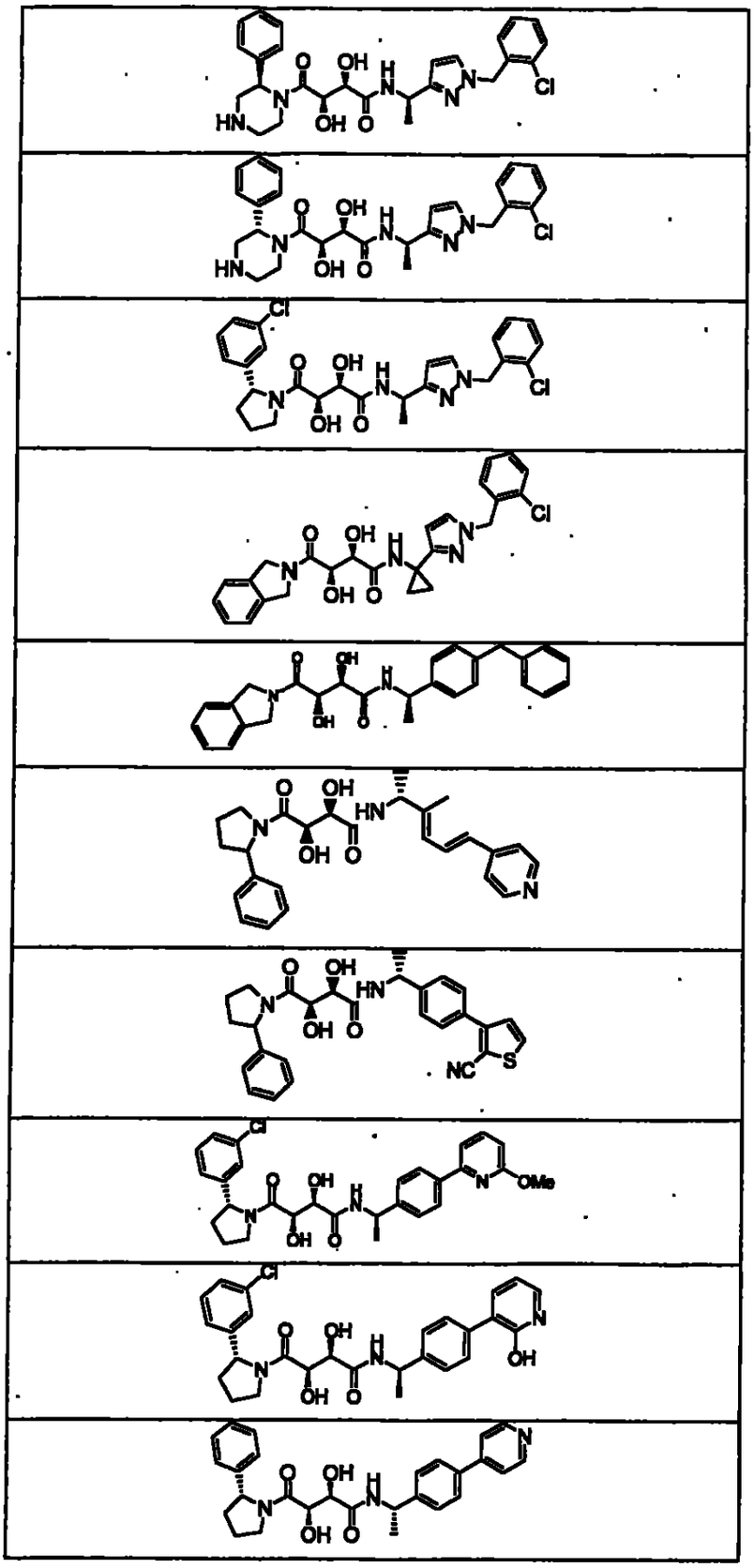


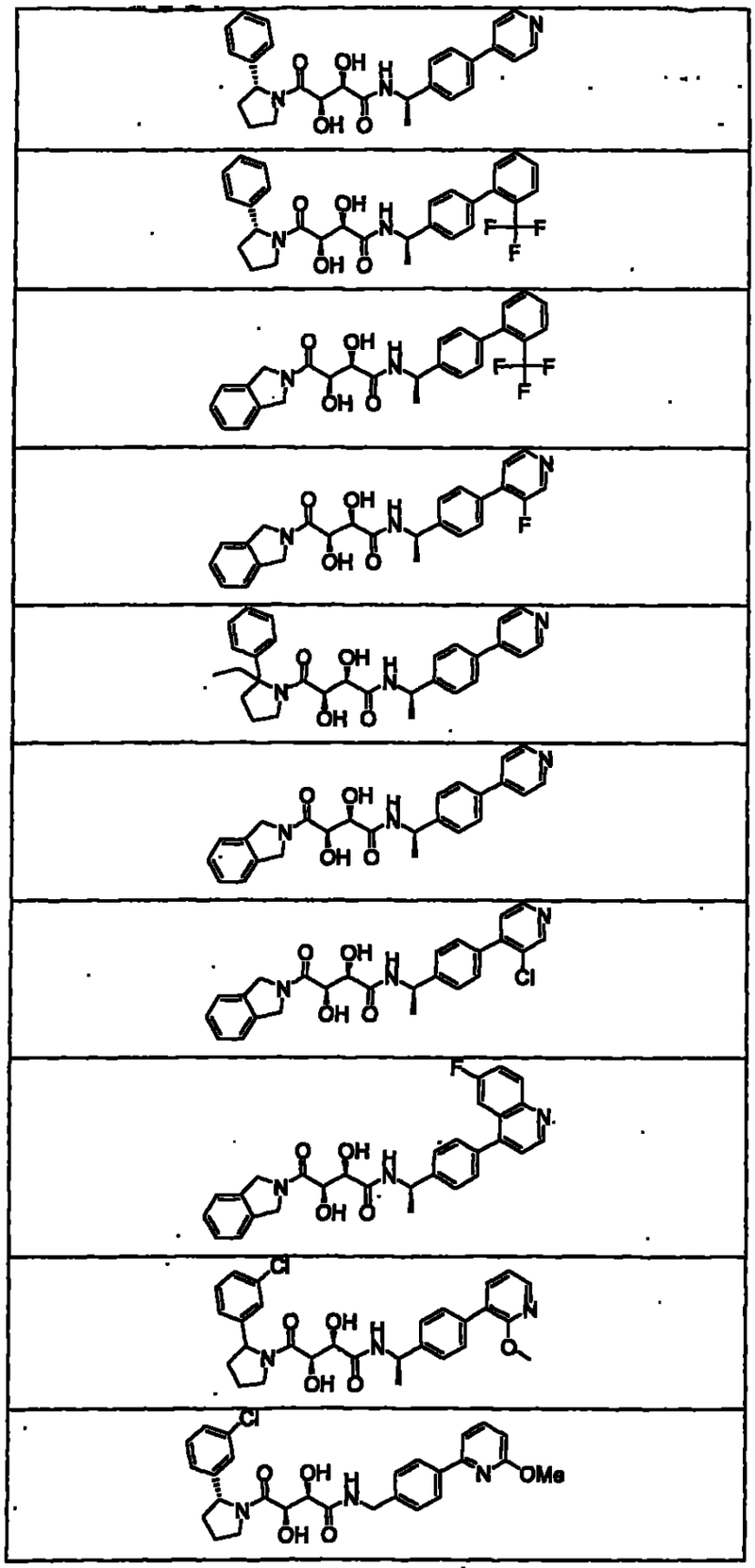


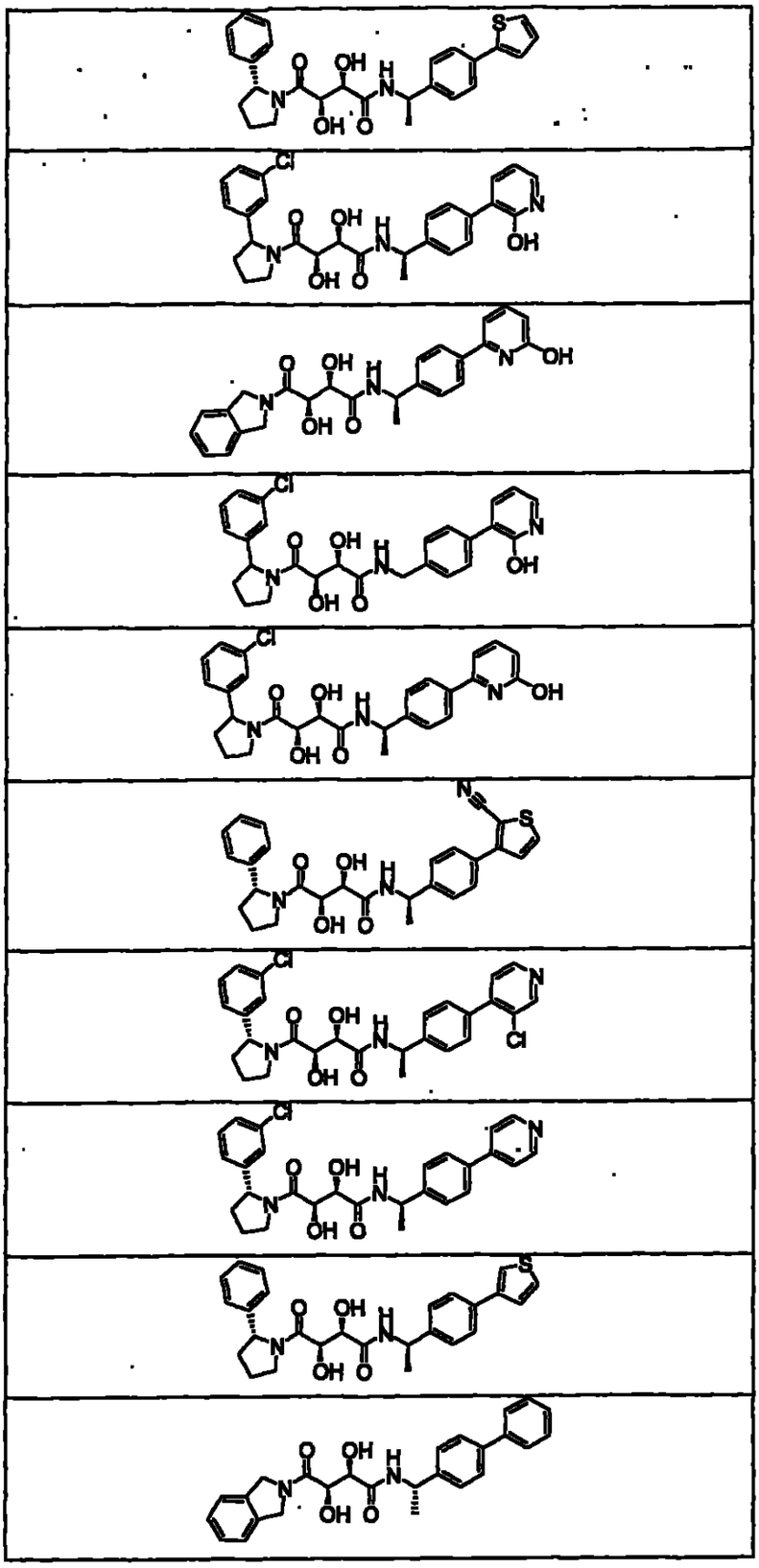


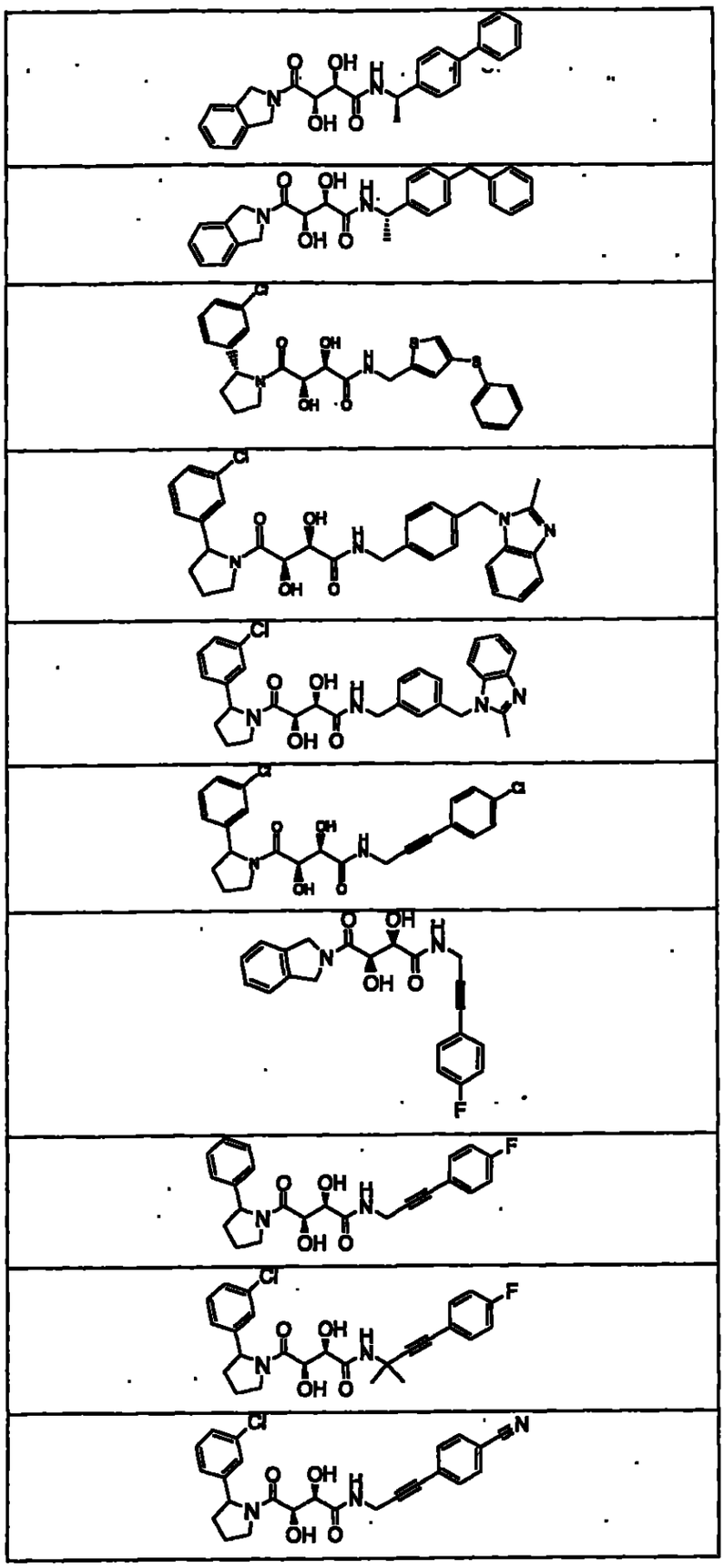


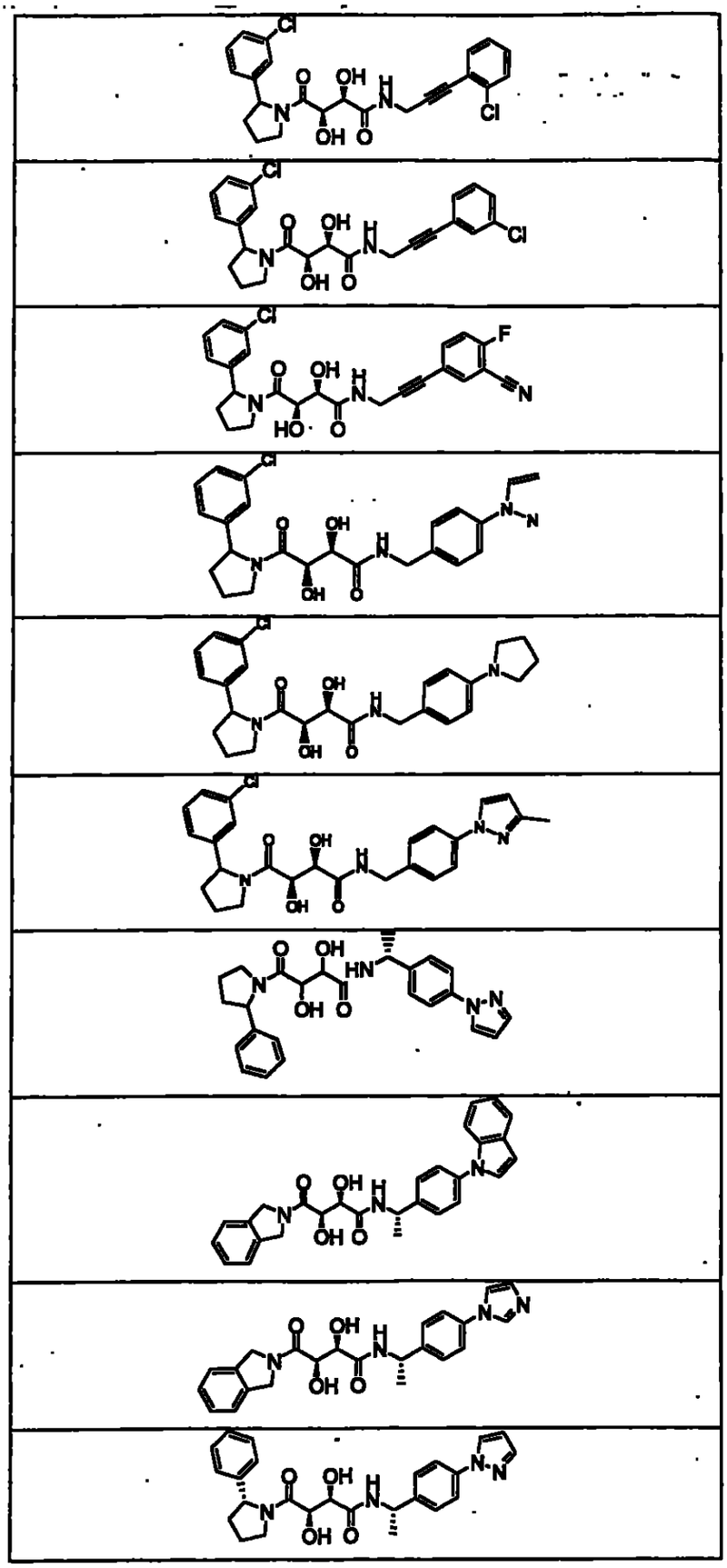


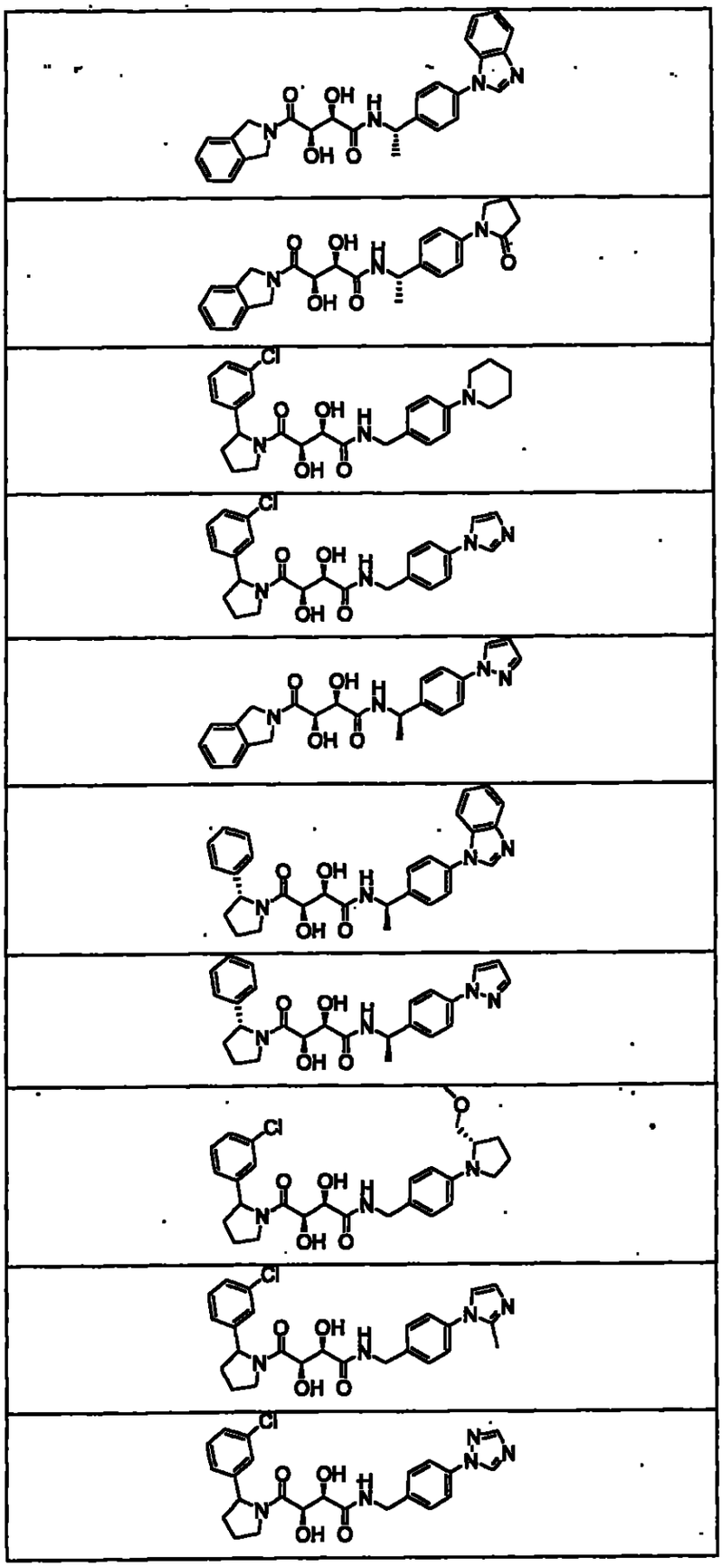




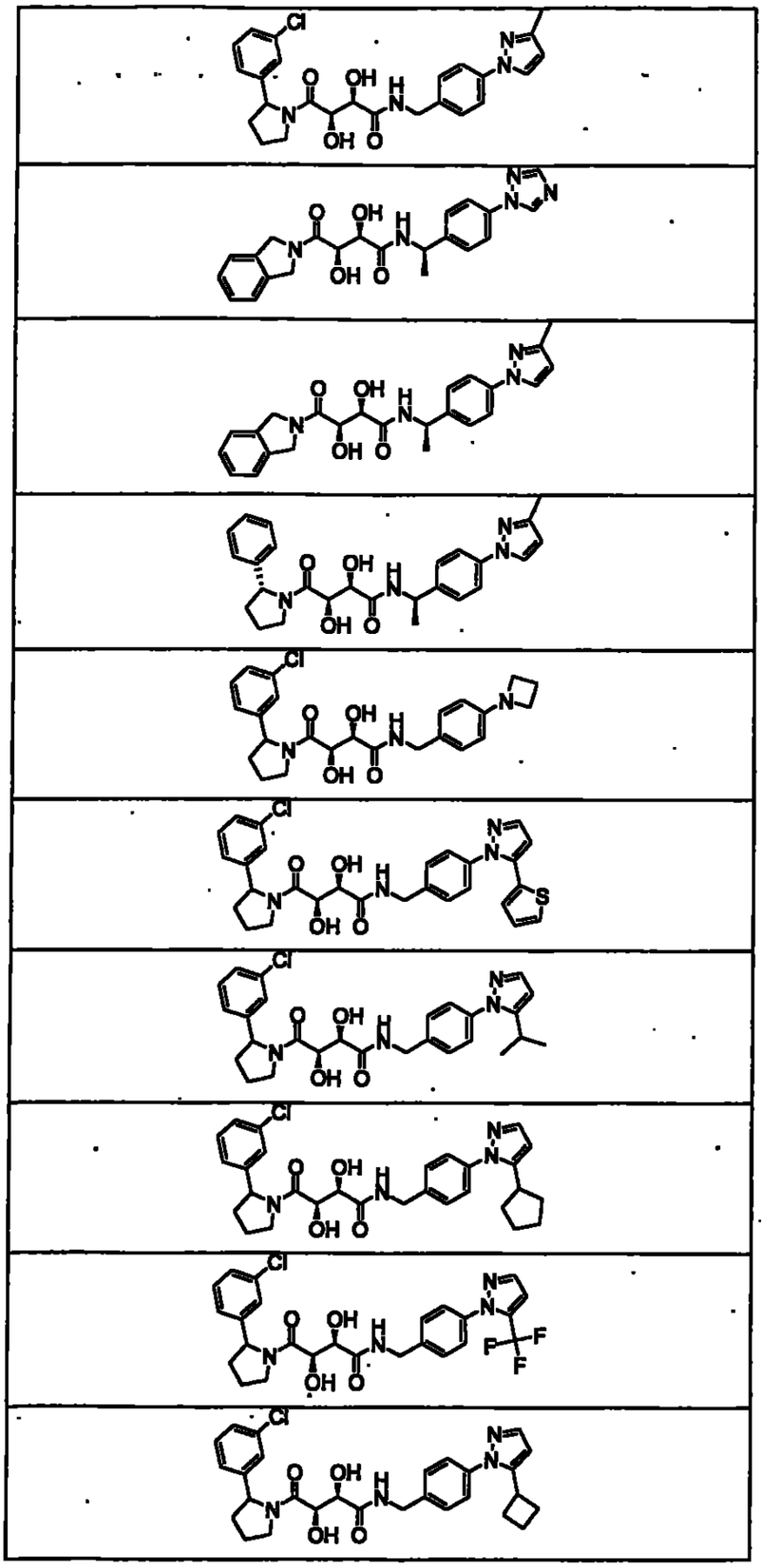


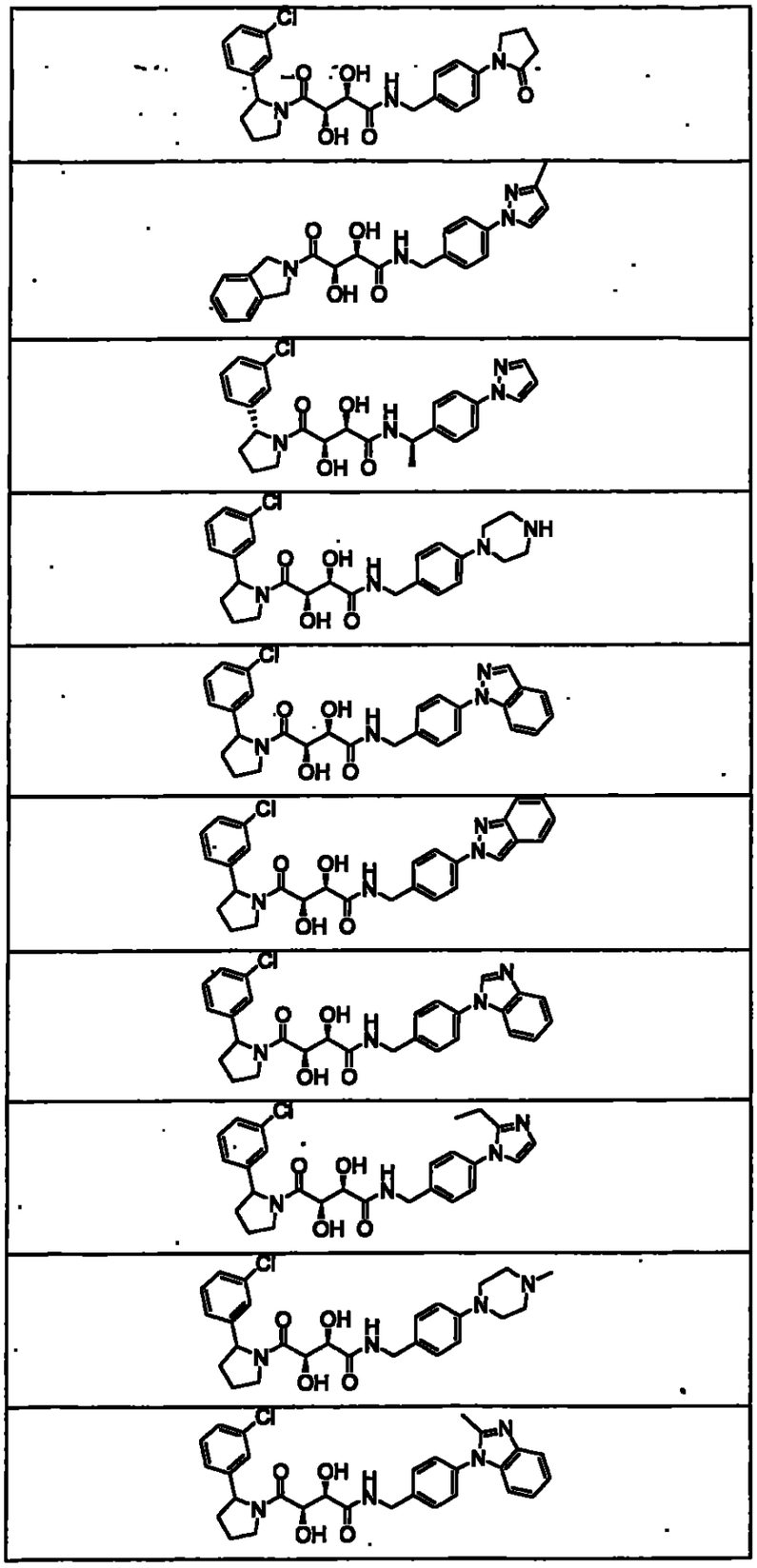


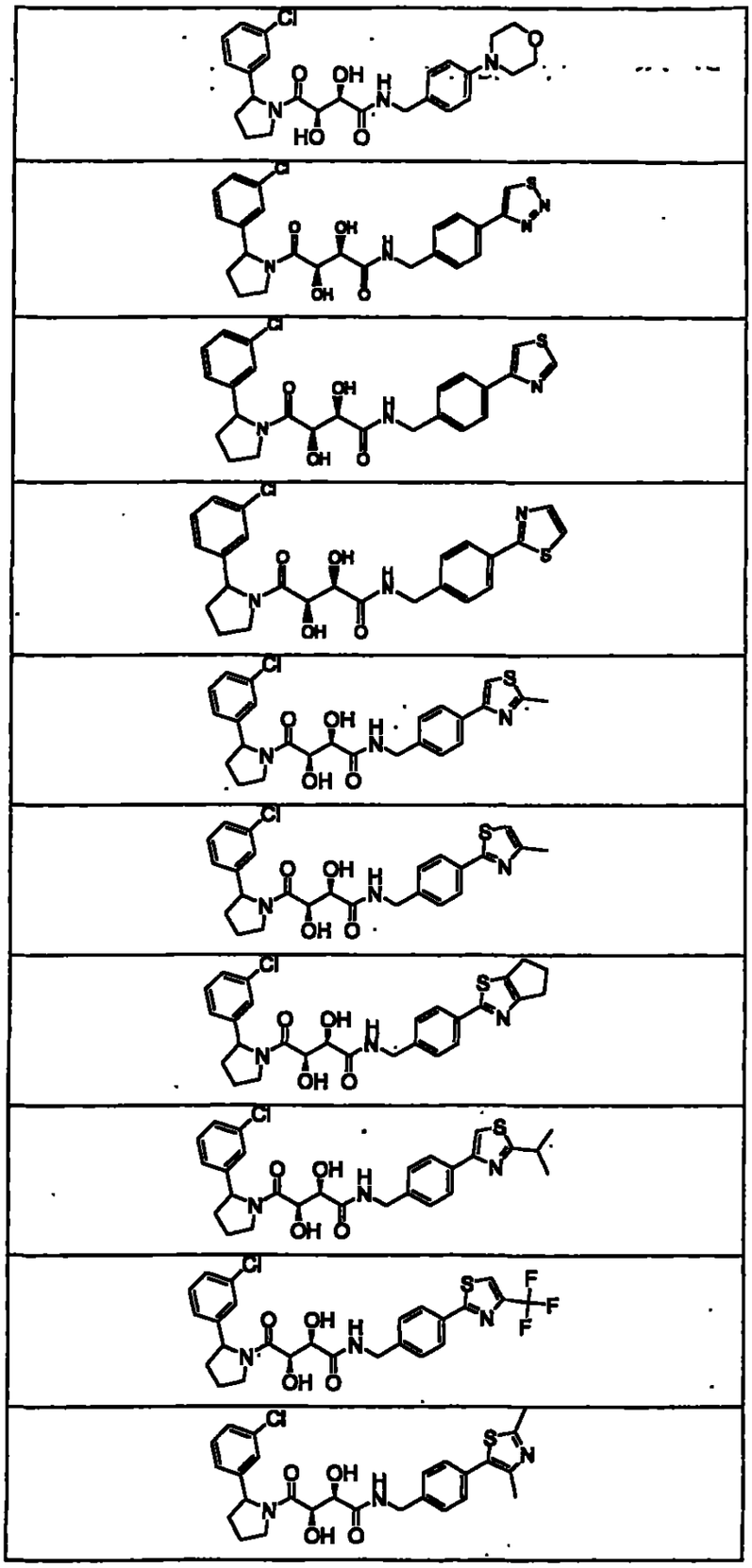


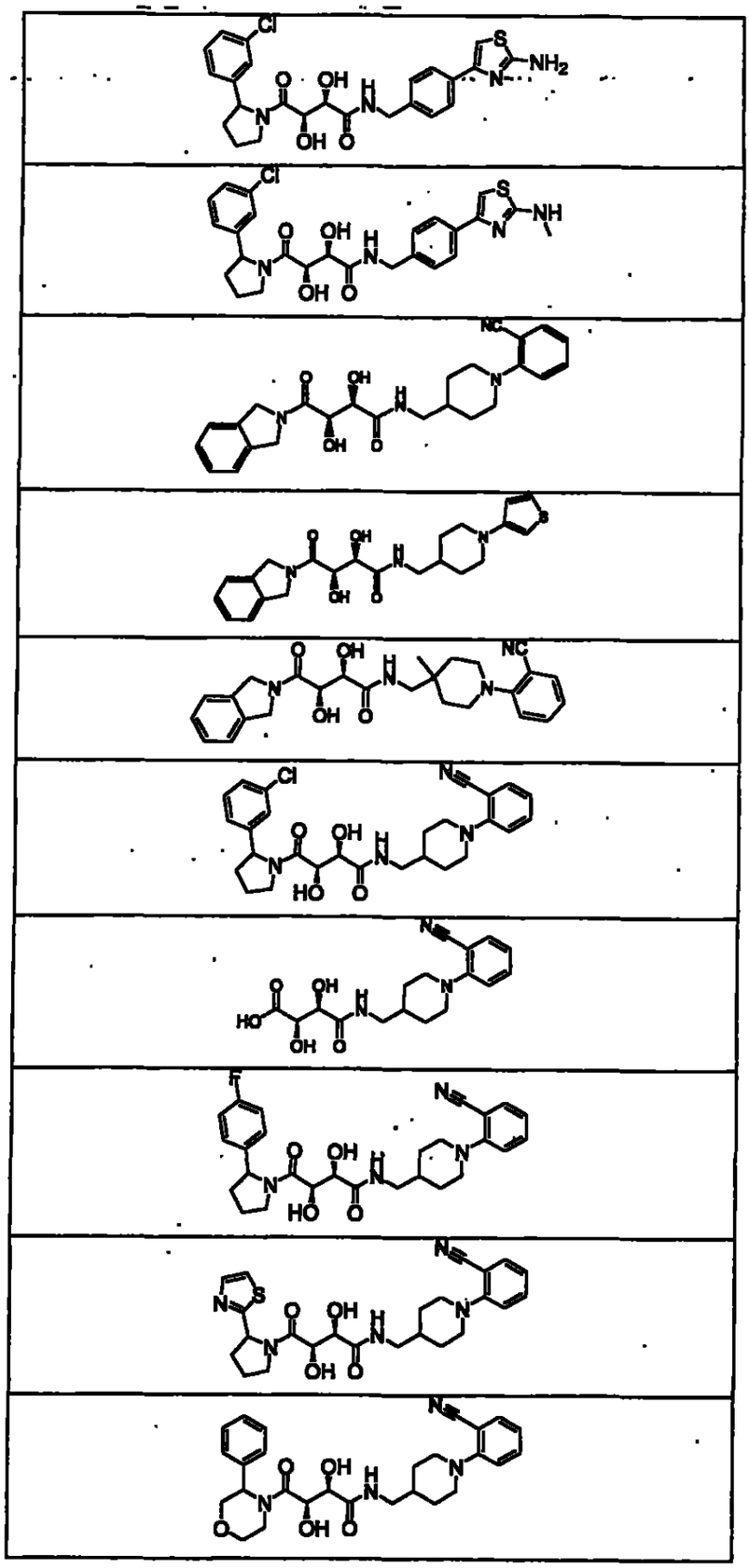


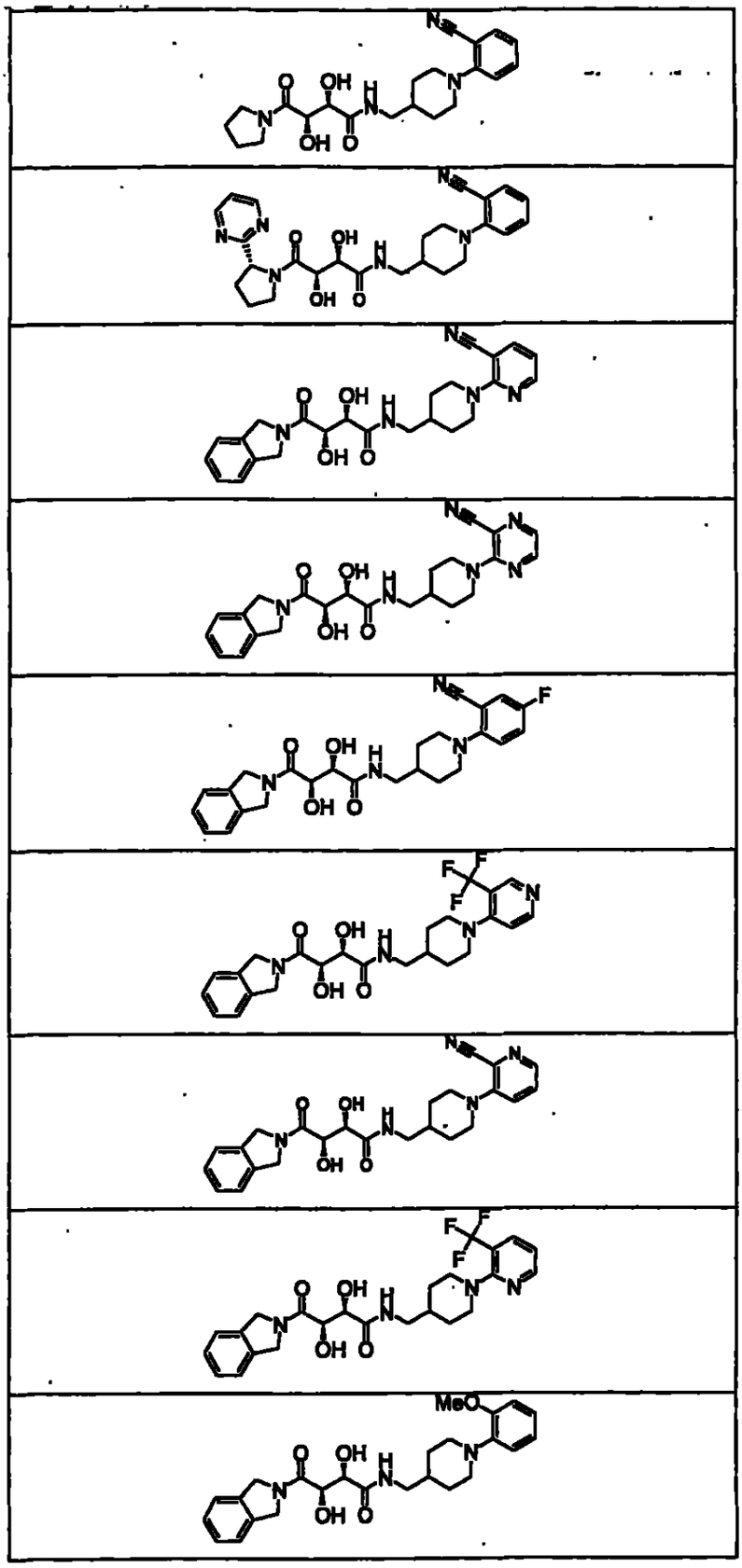
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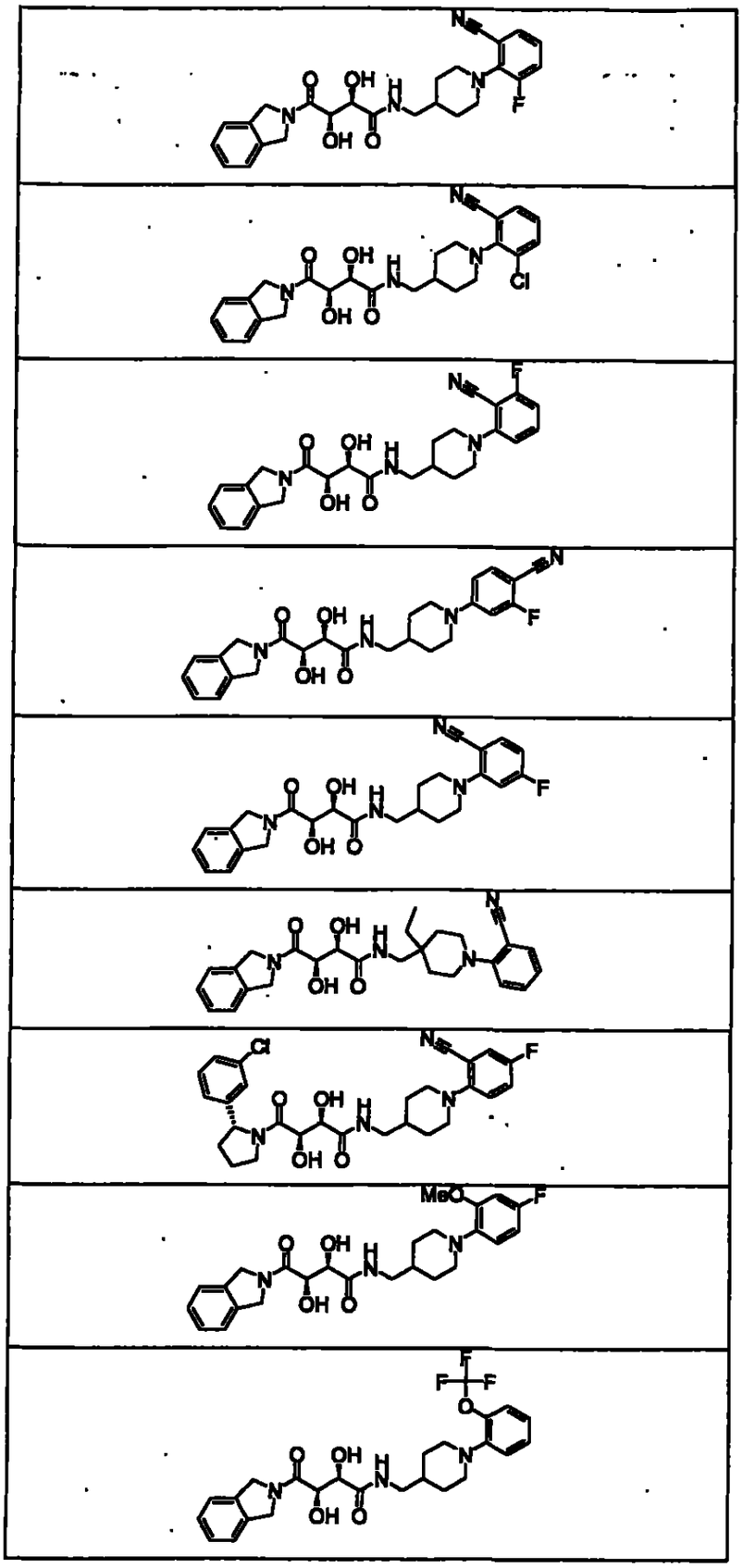


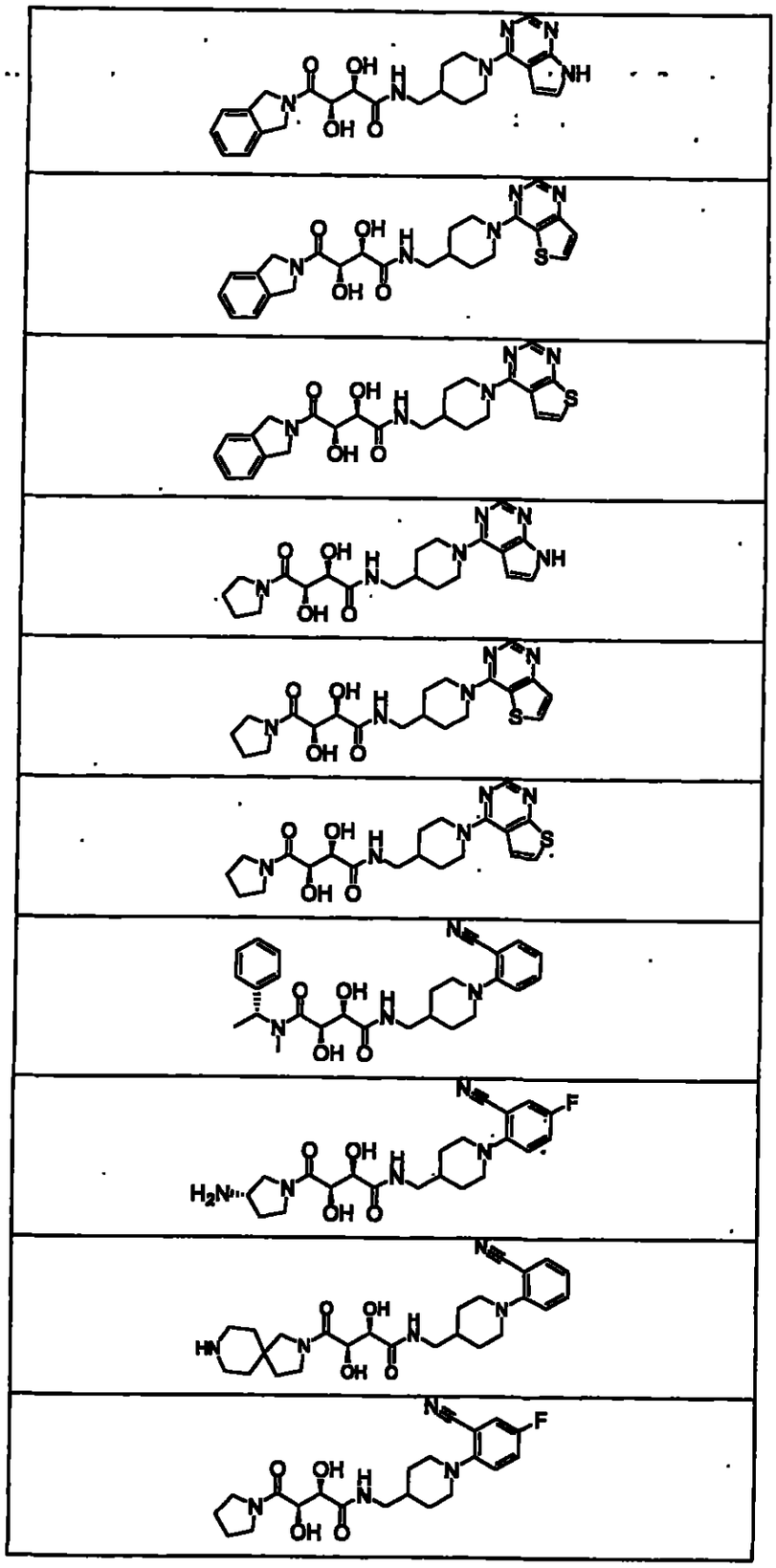


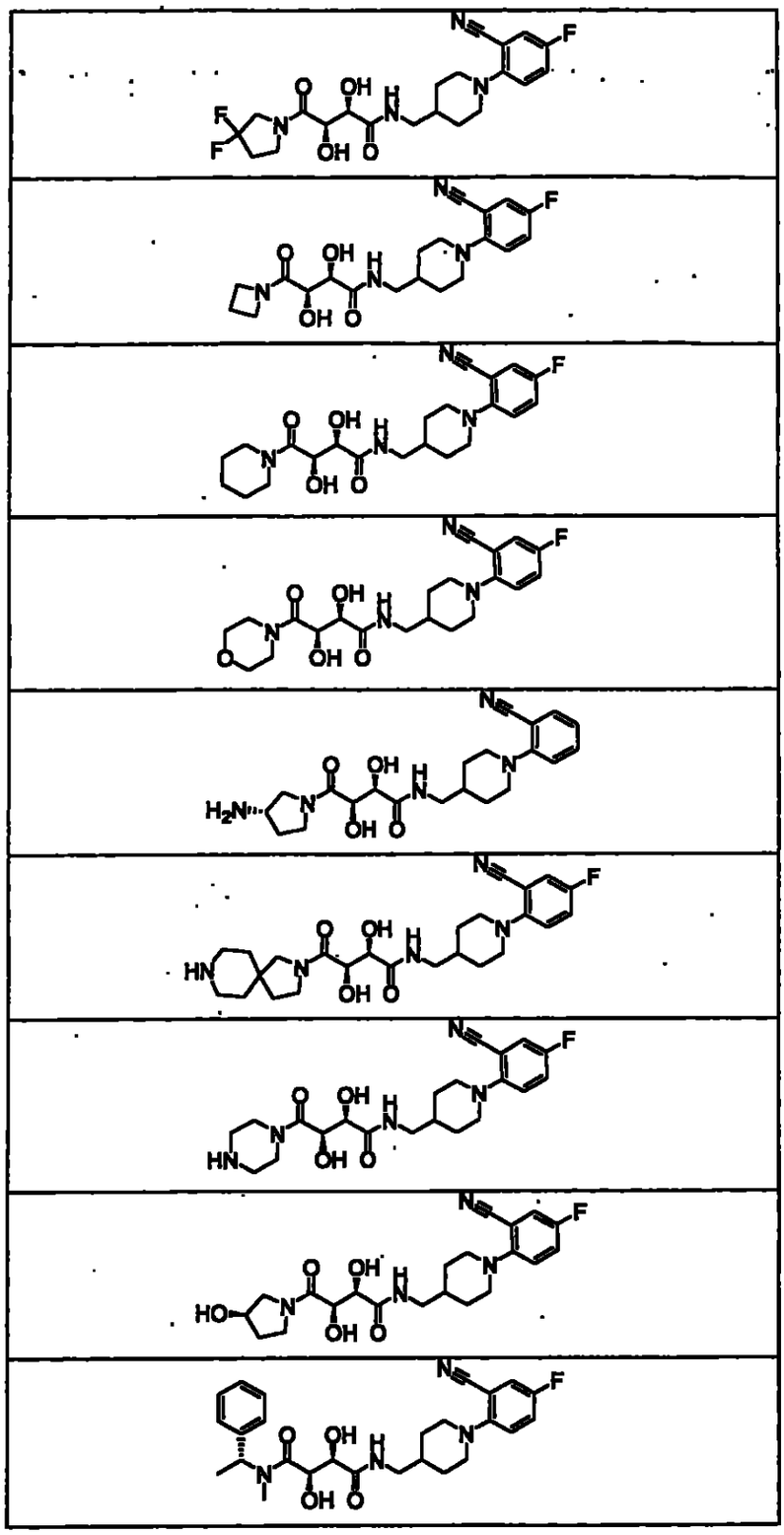


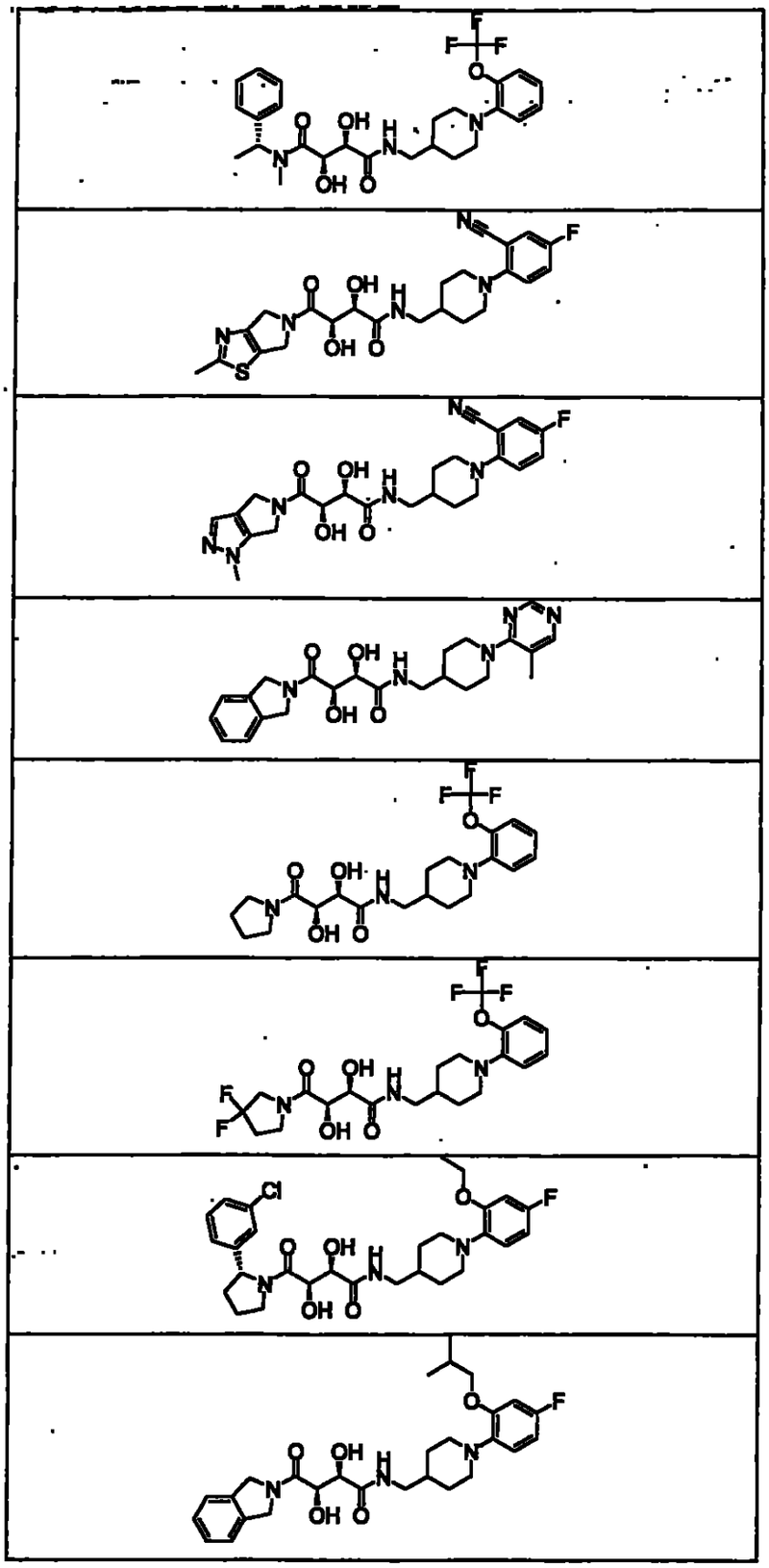


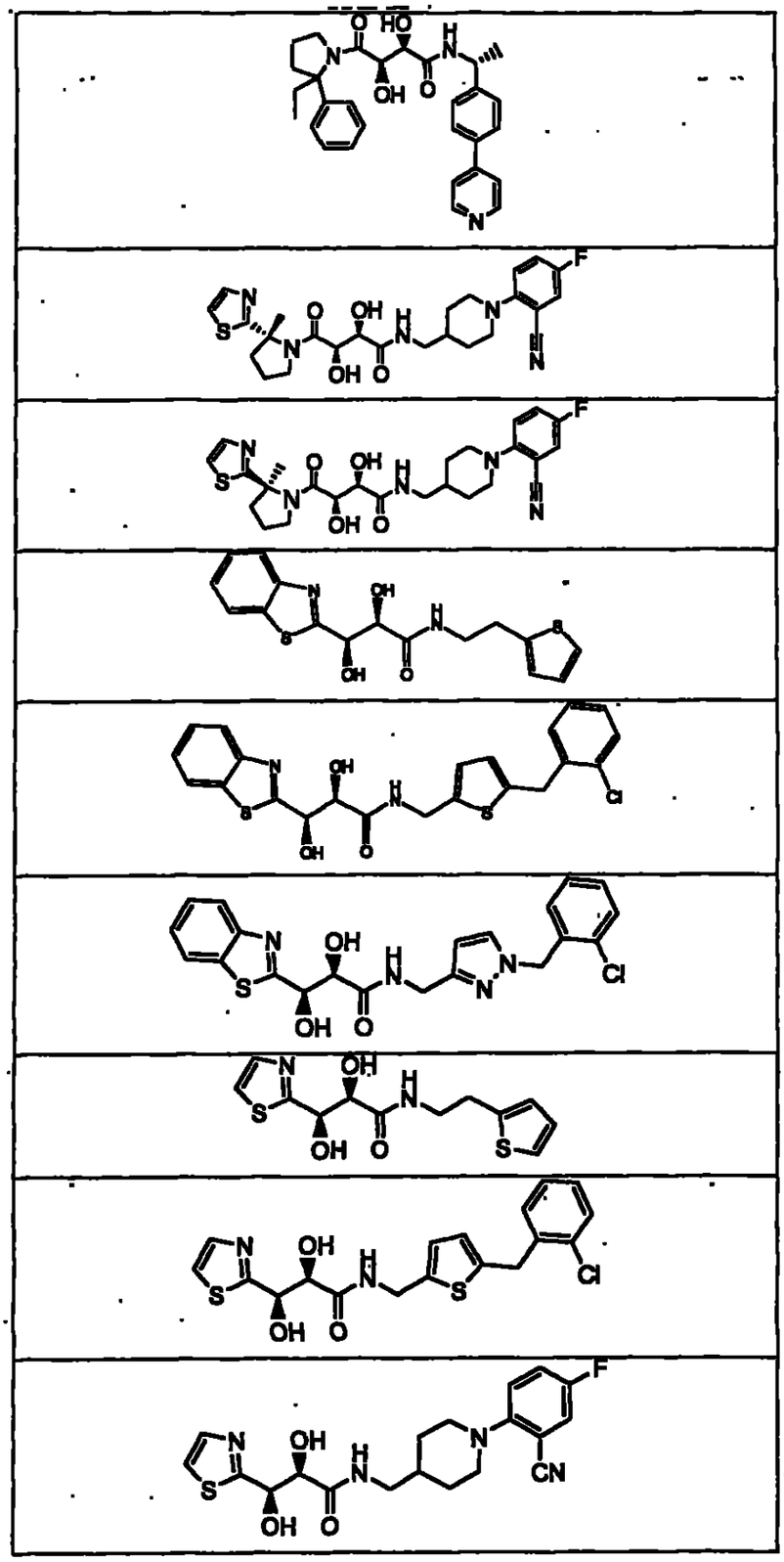


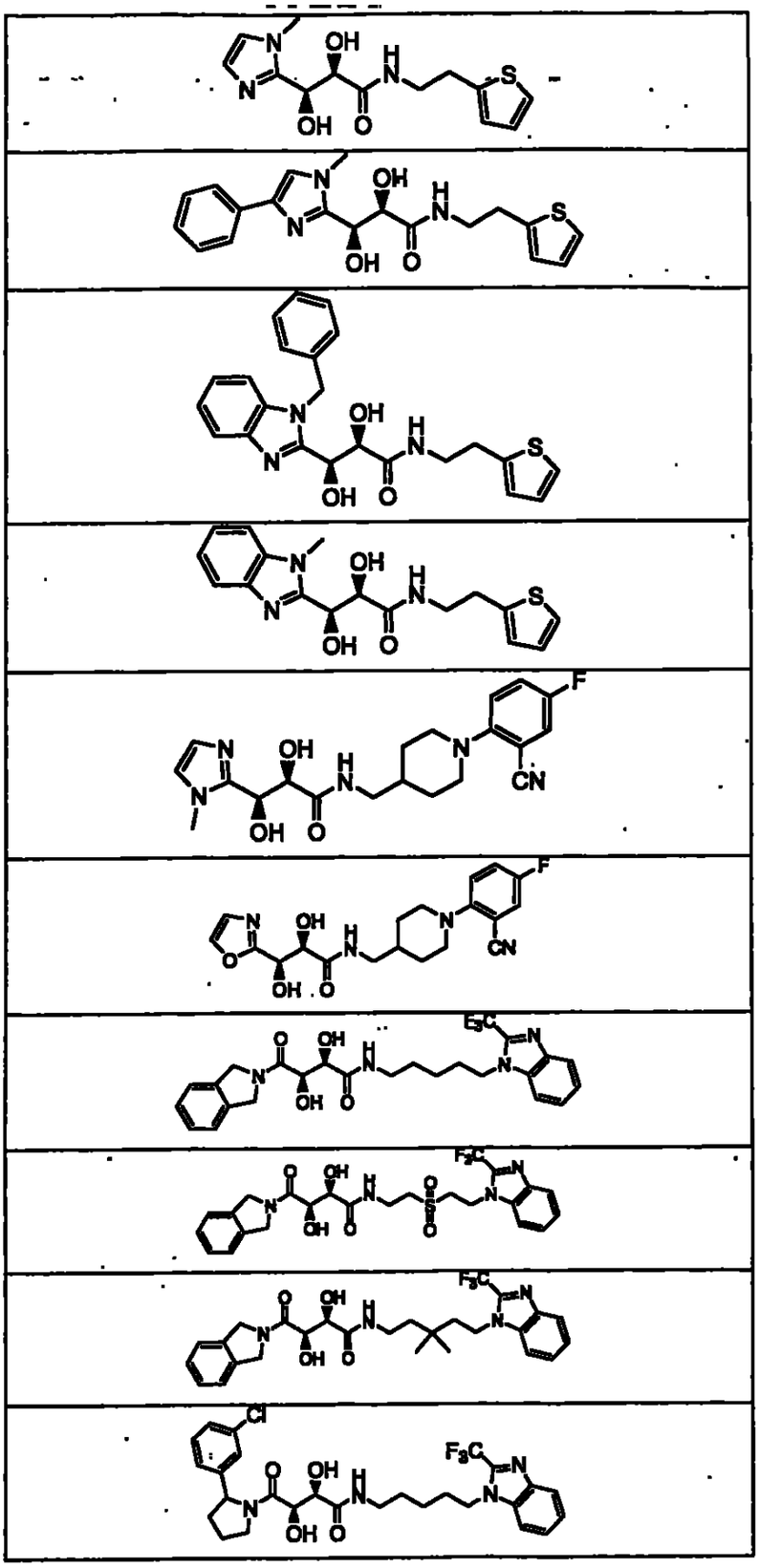


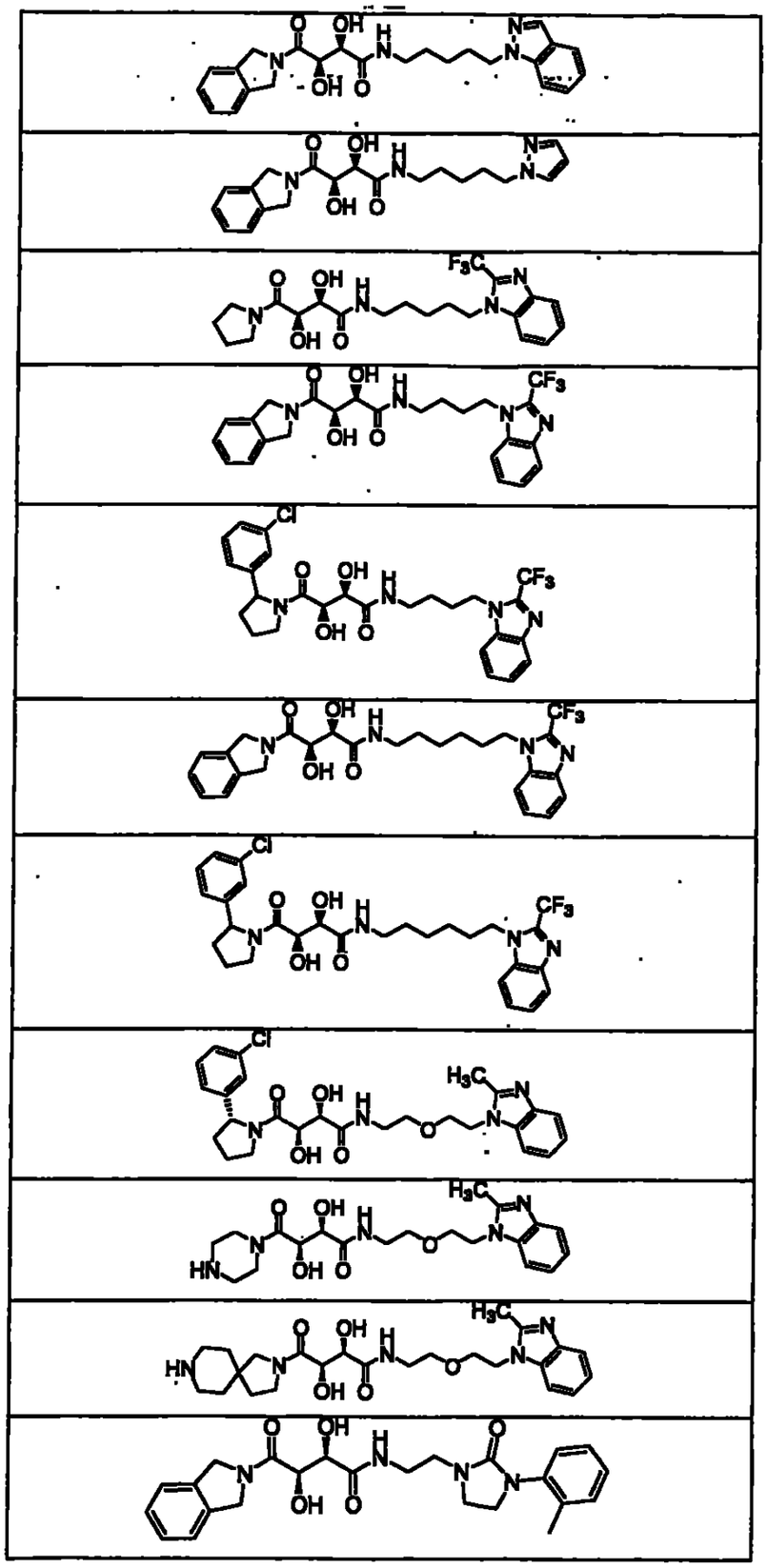


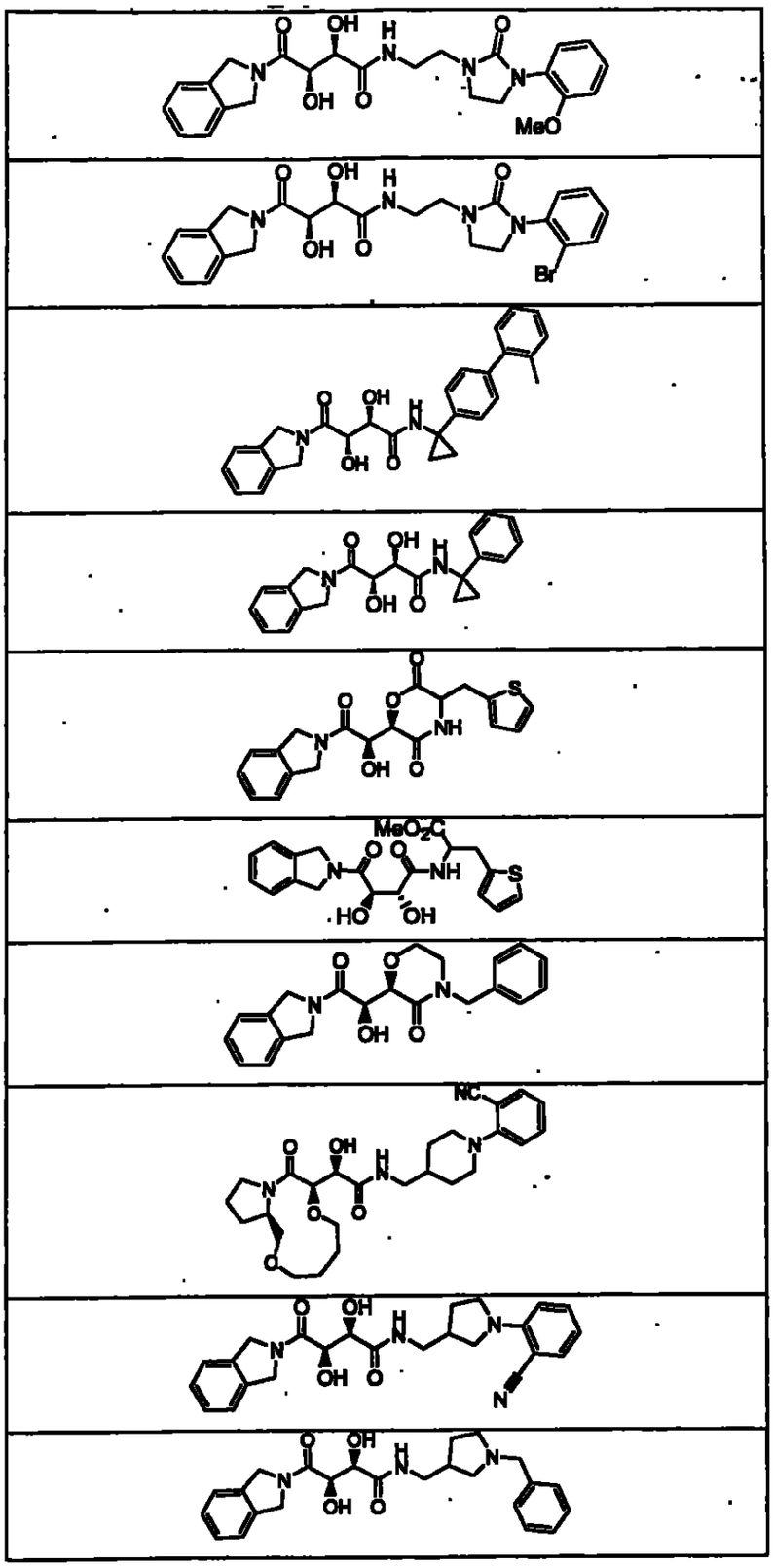


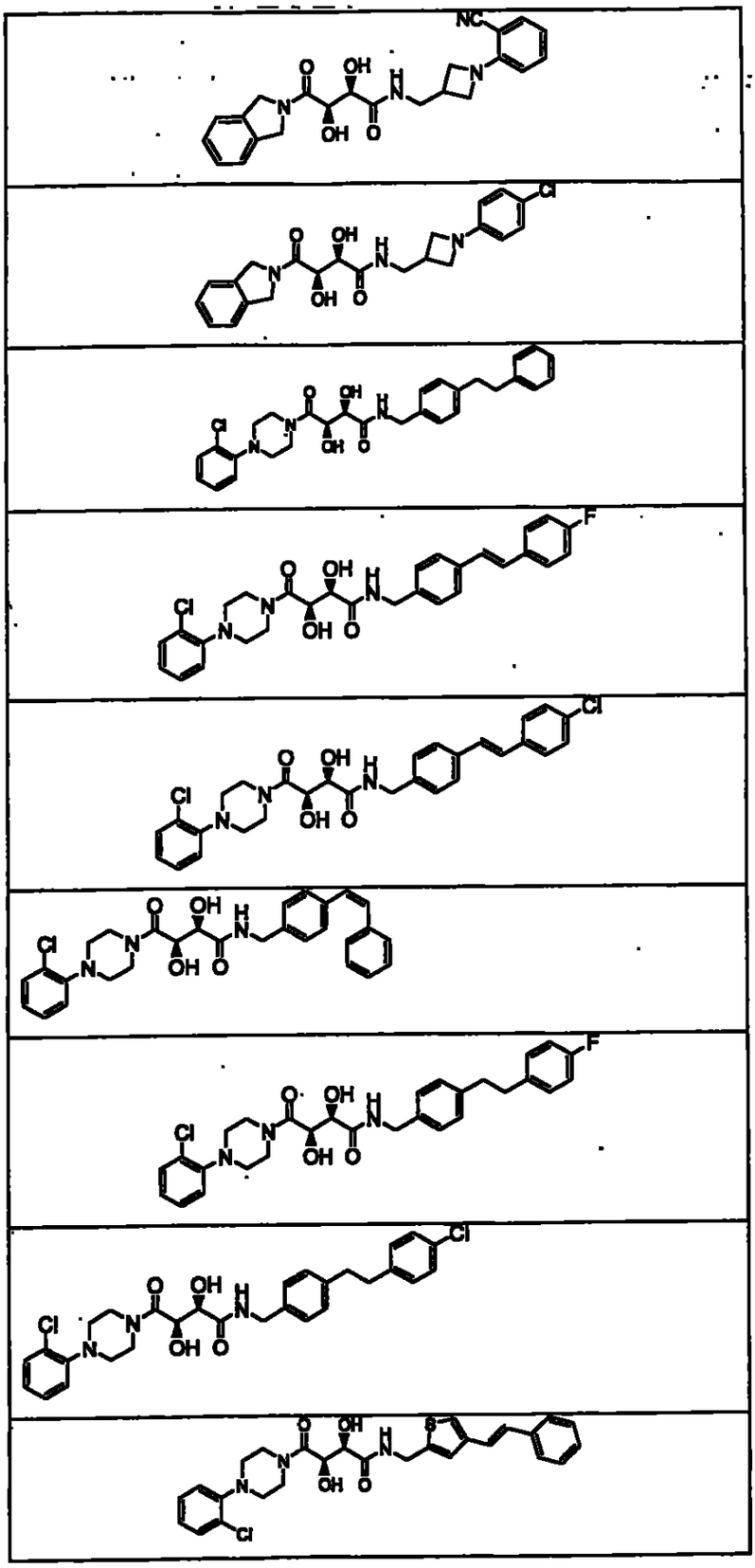


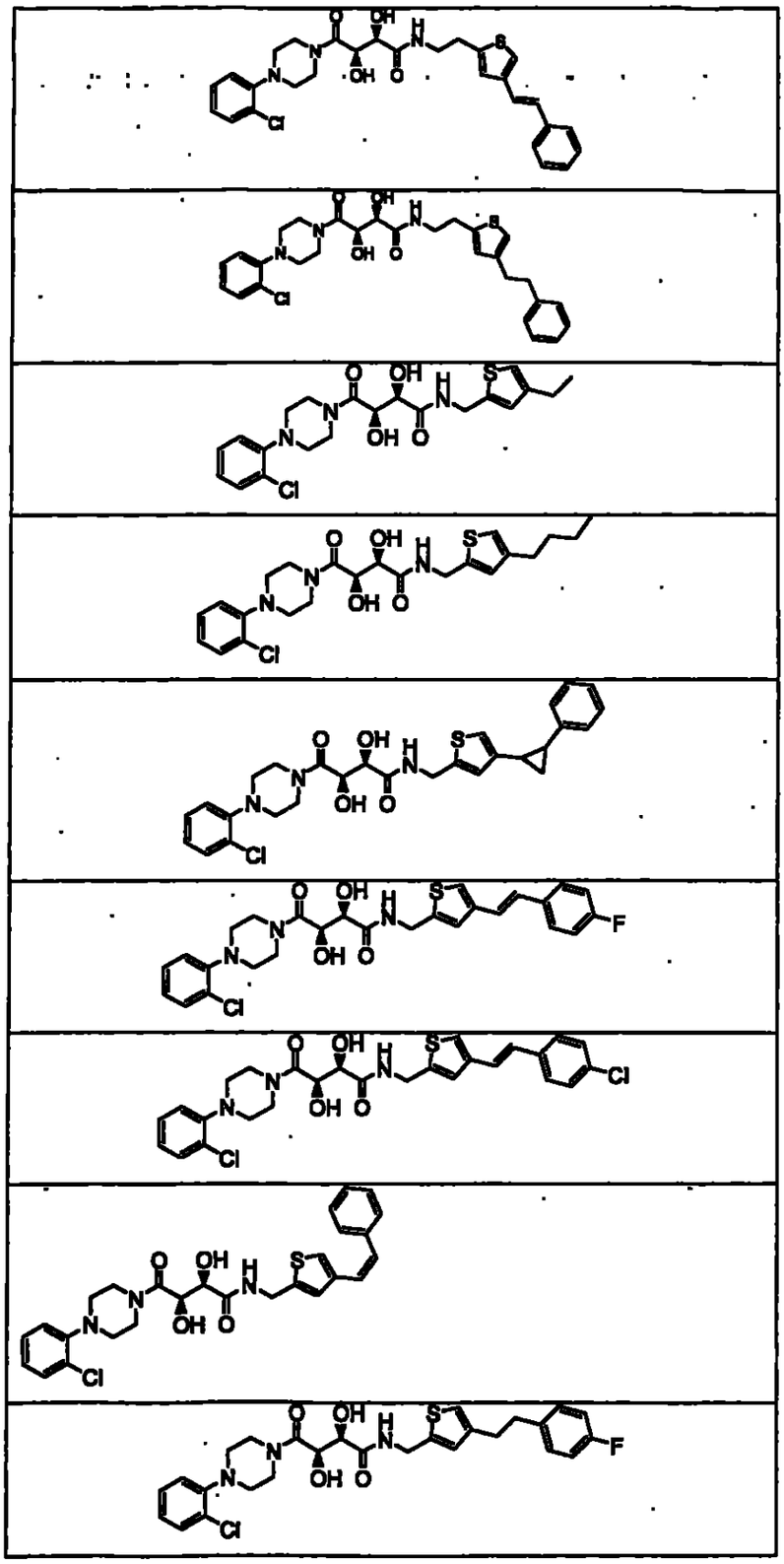


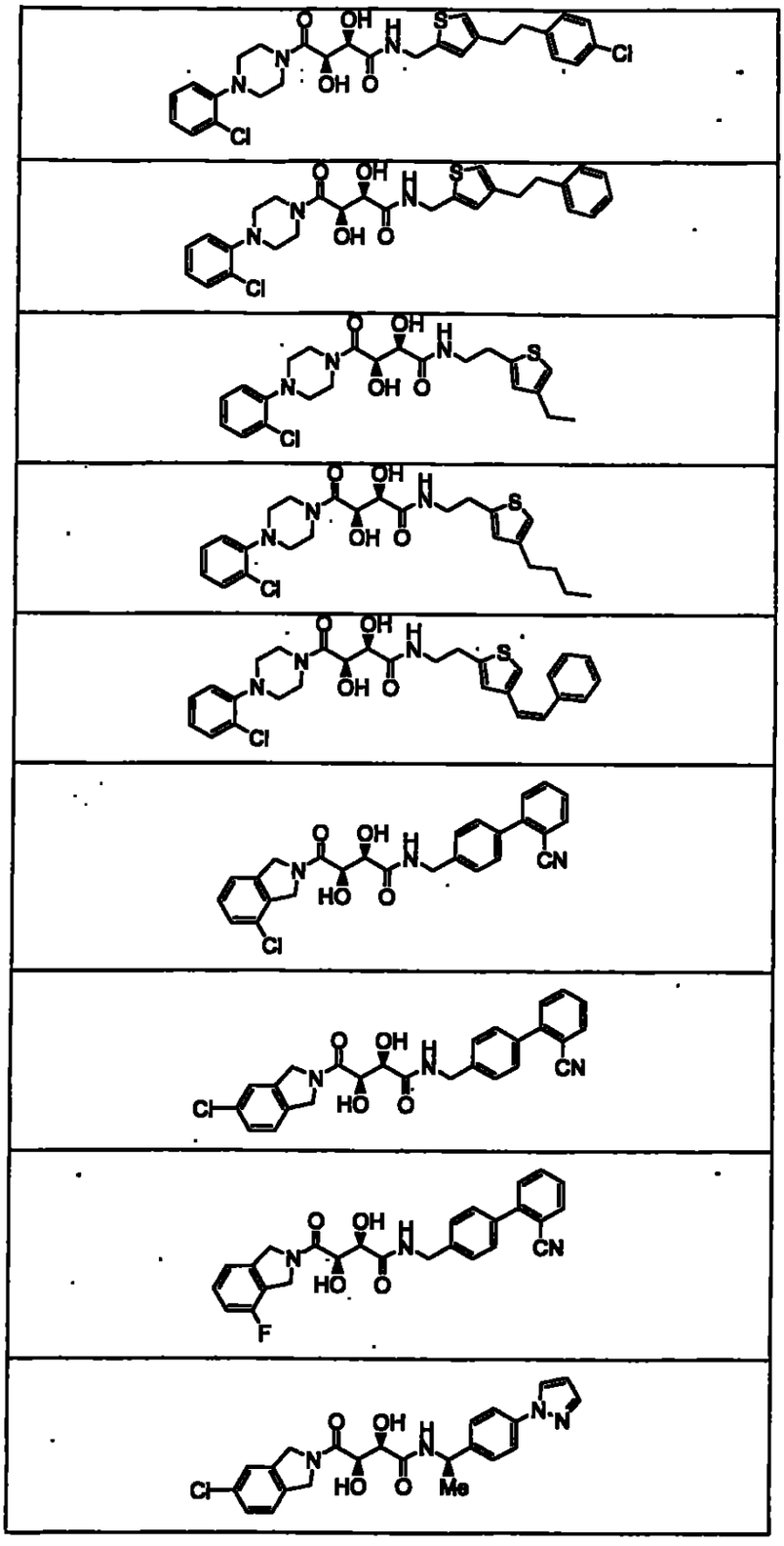


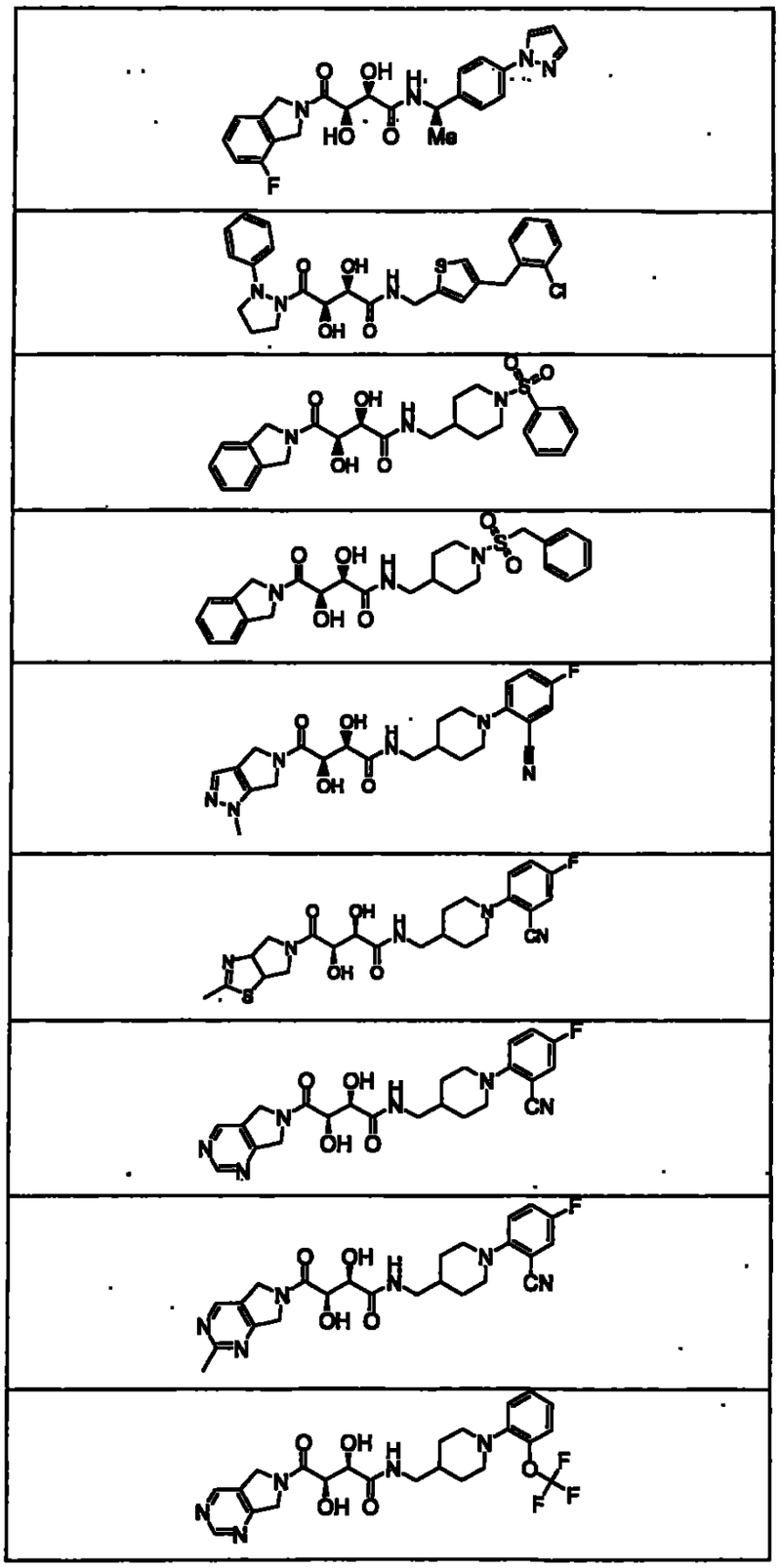


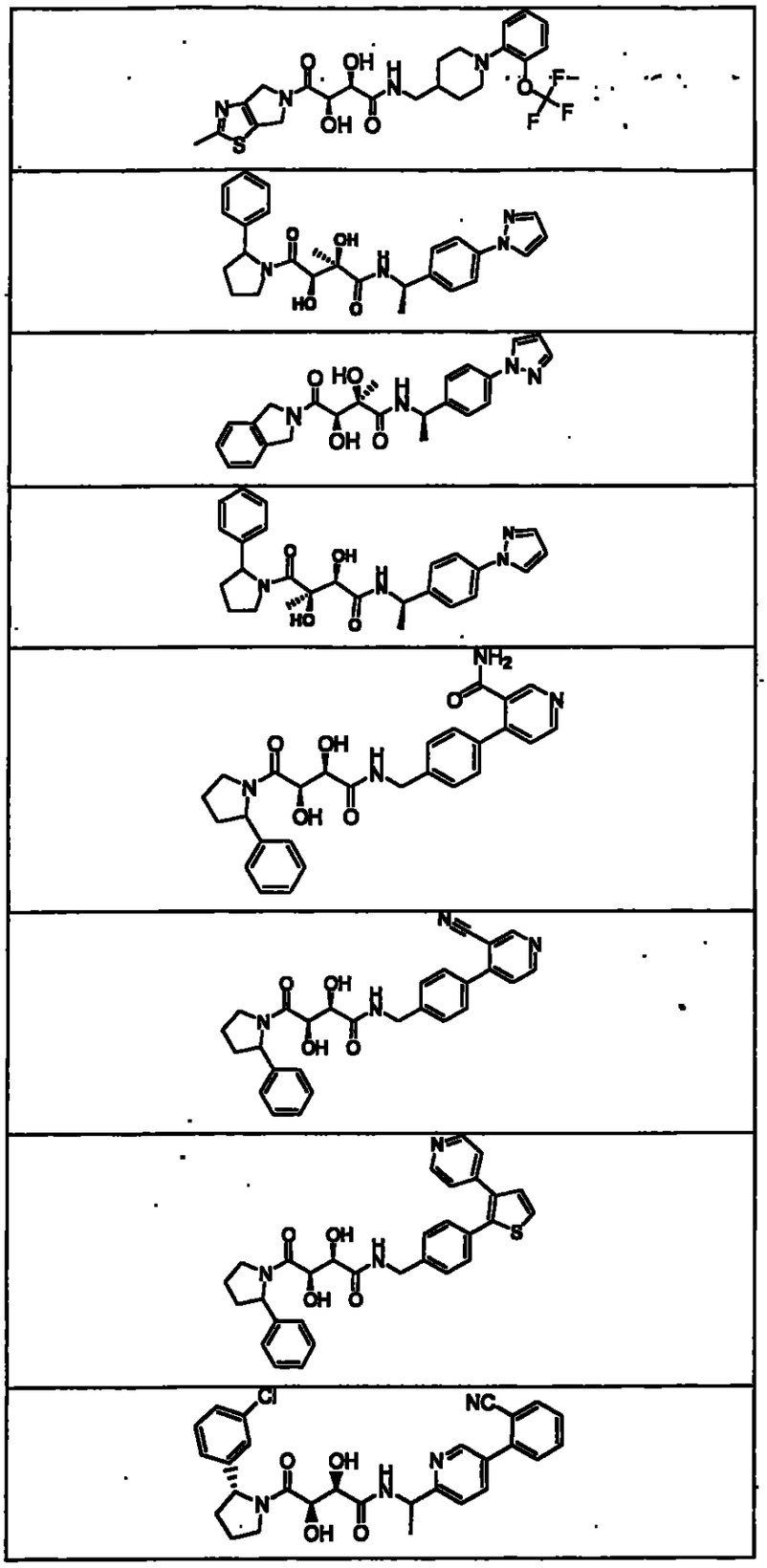

MeO
Br
MeO2C
HO
OH
NC
N

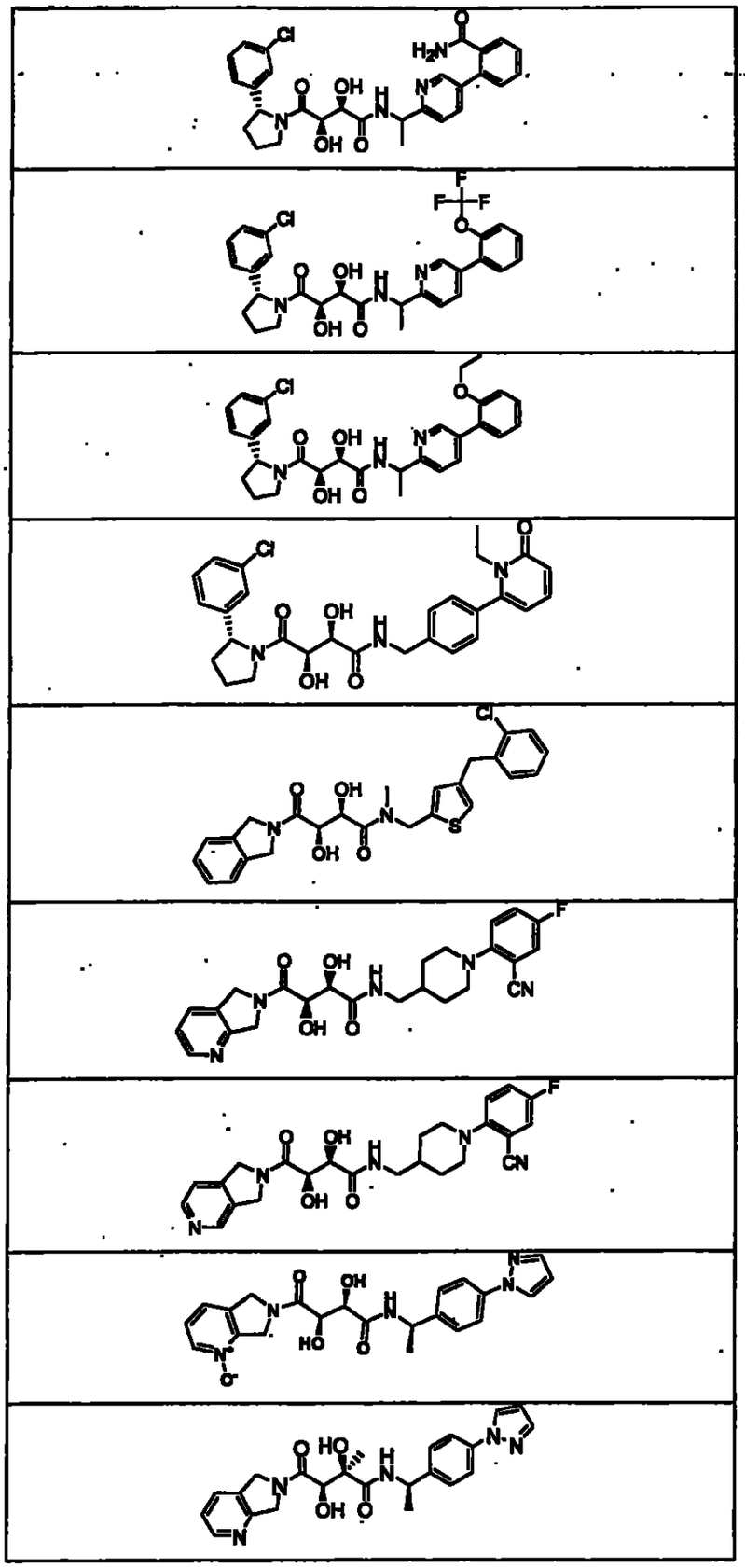


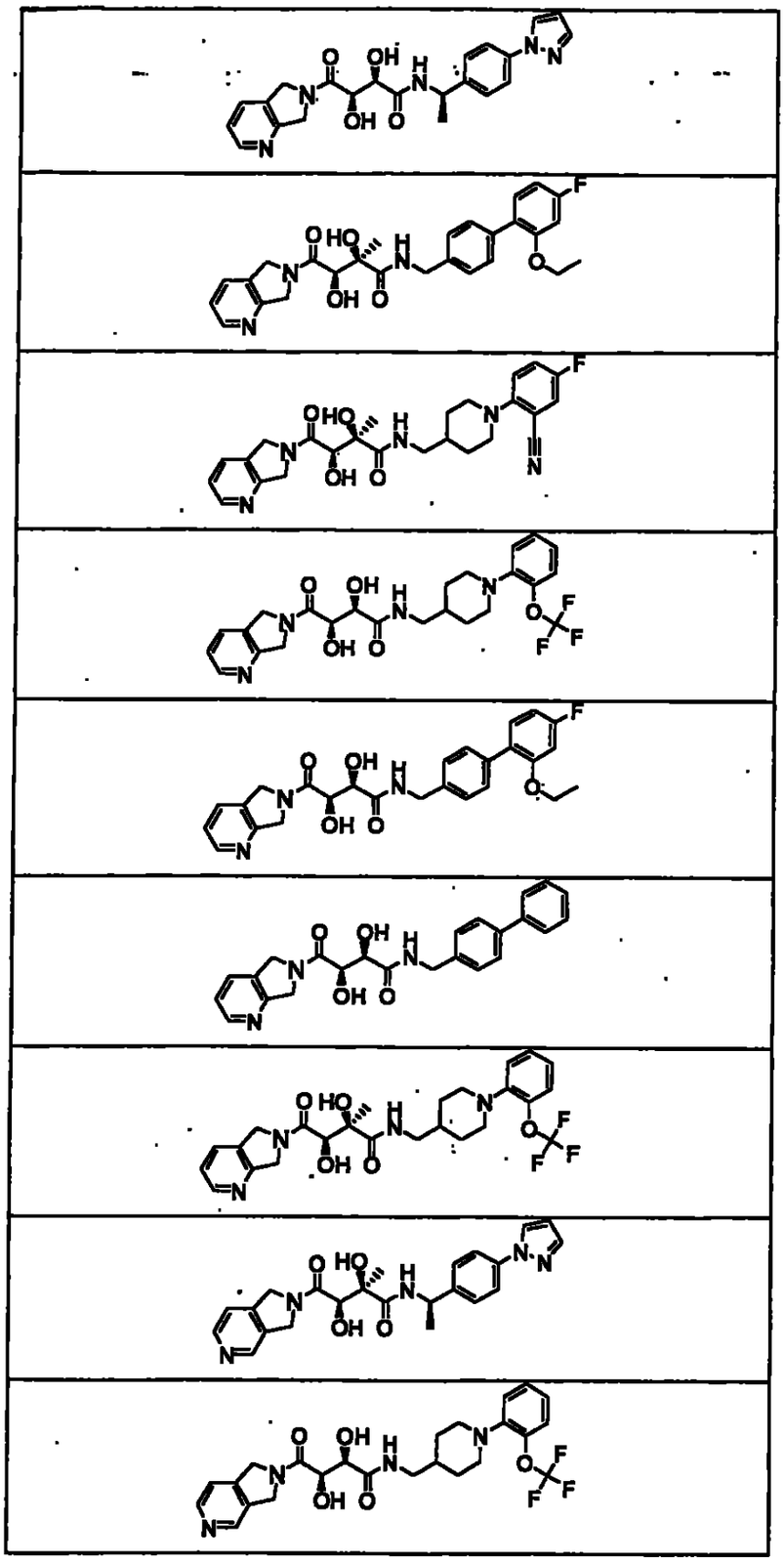




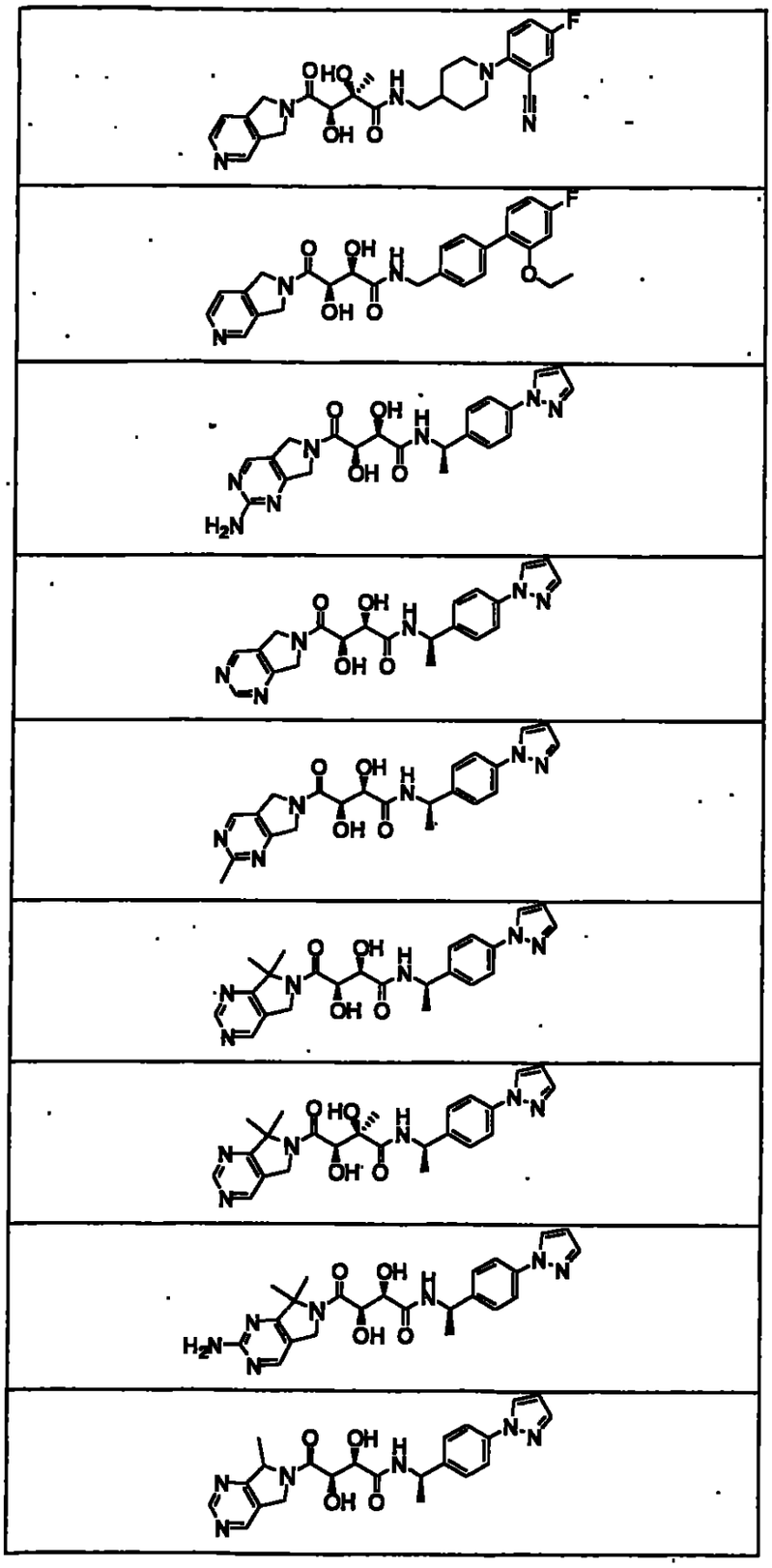


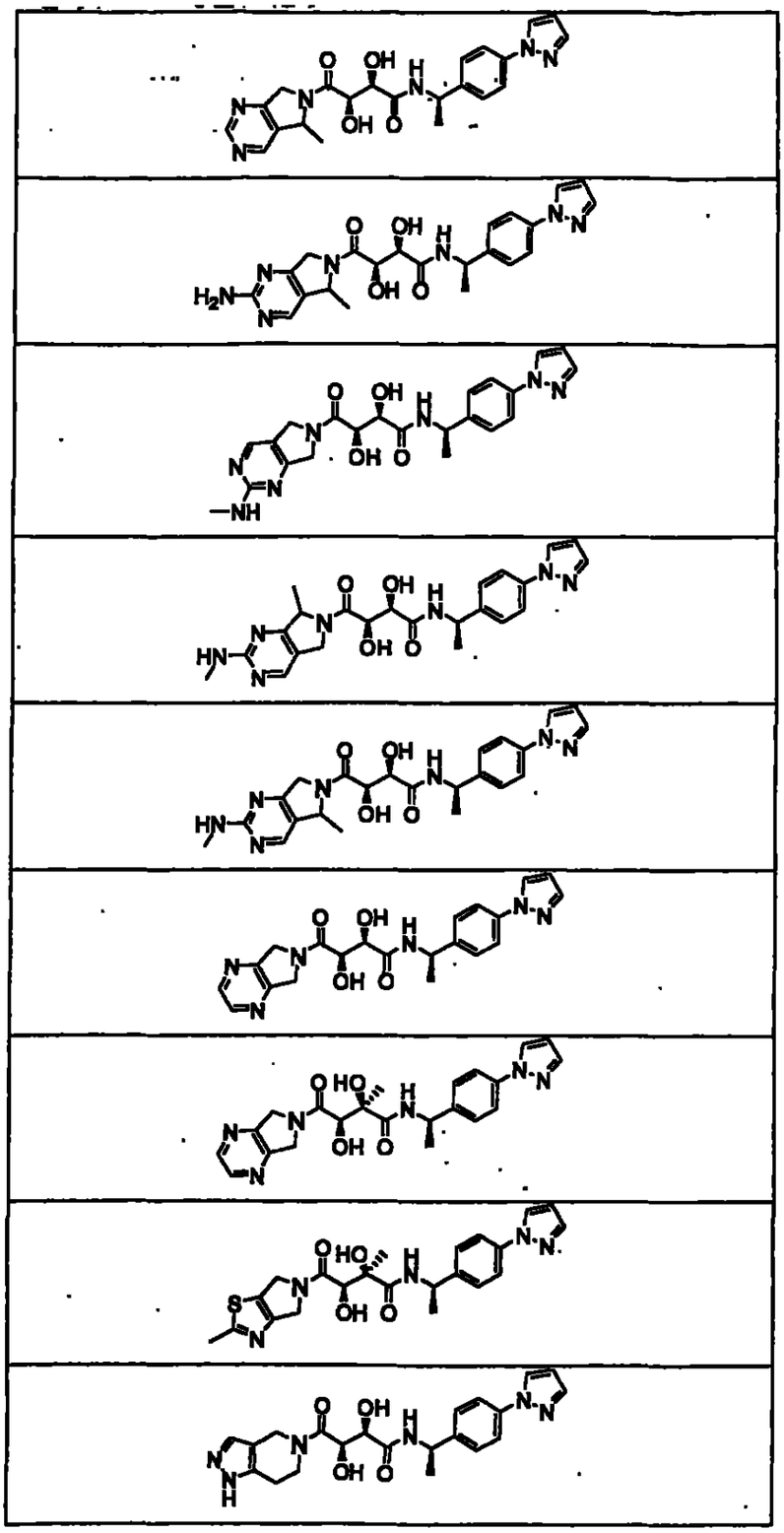


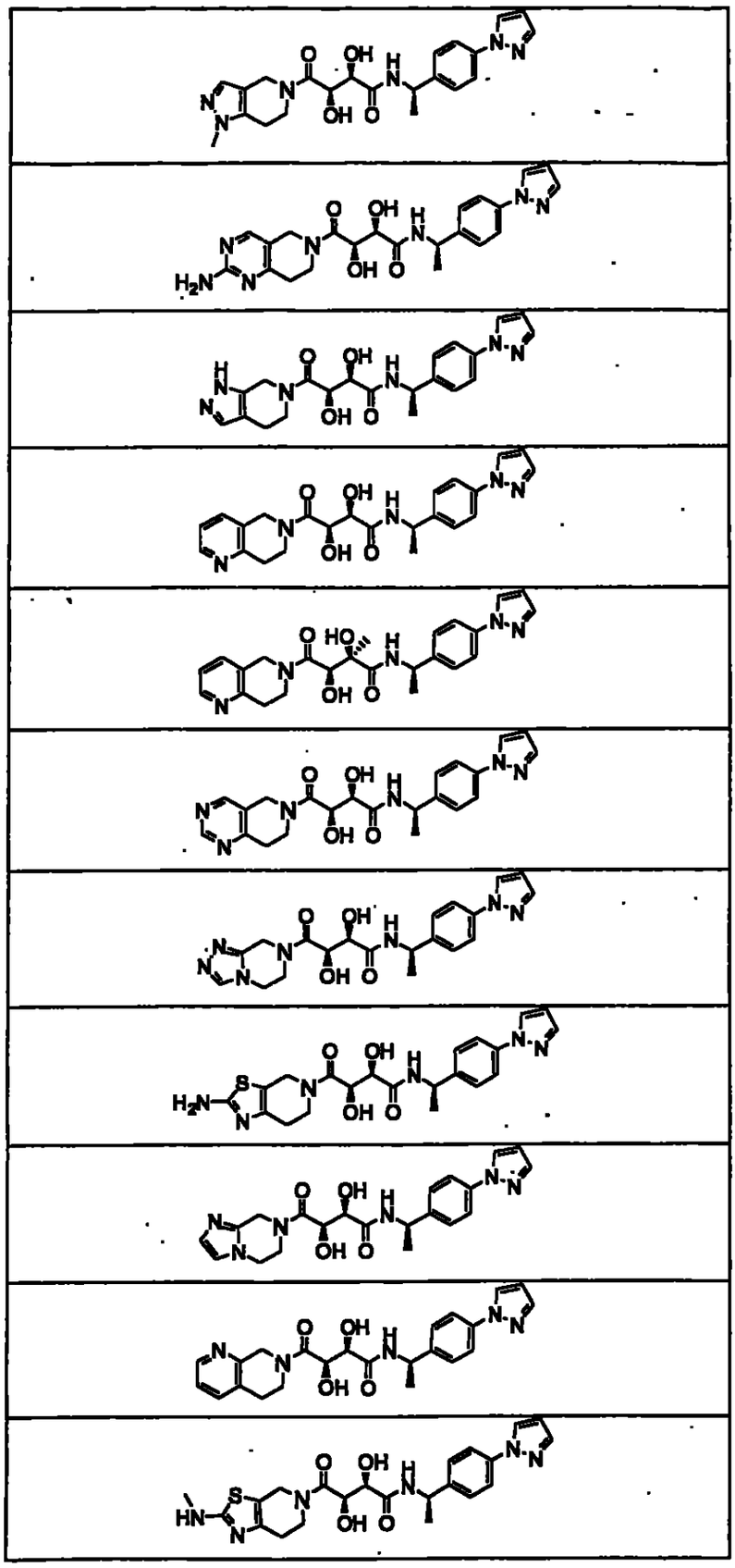


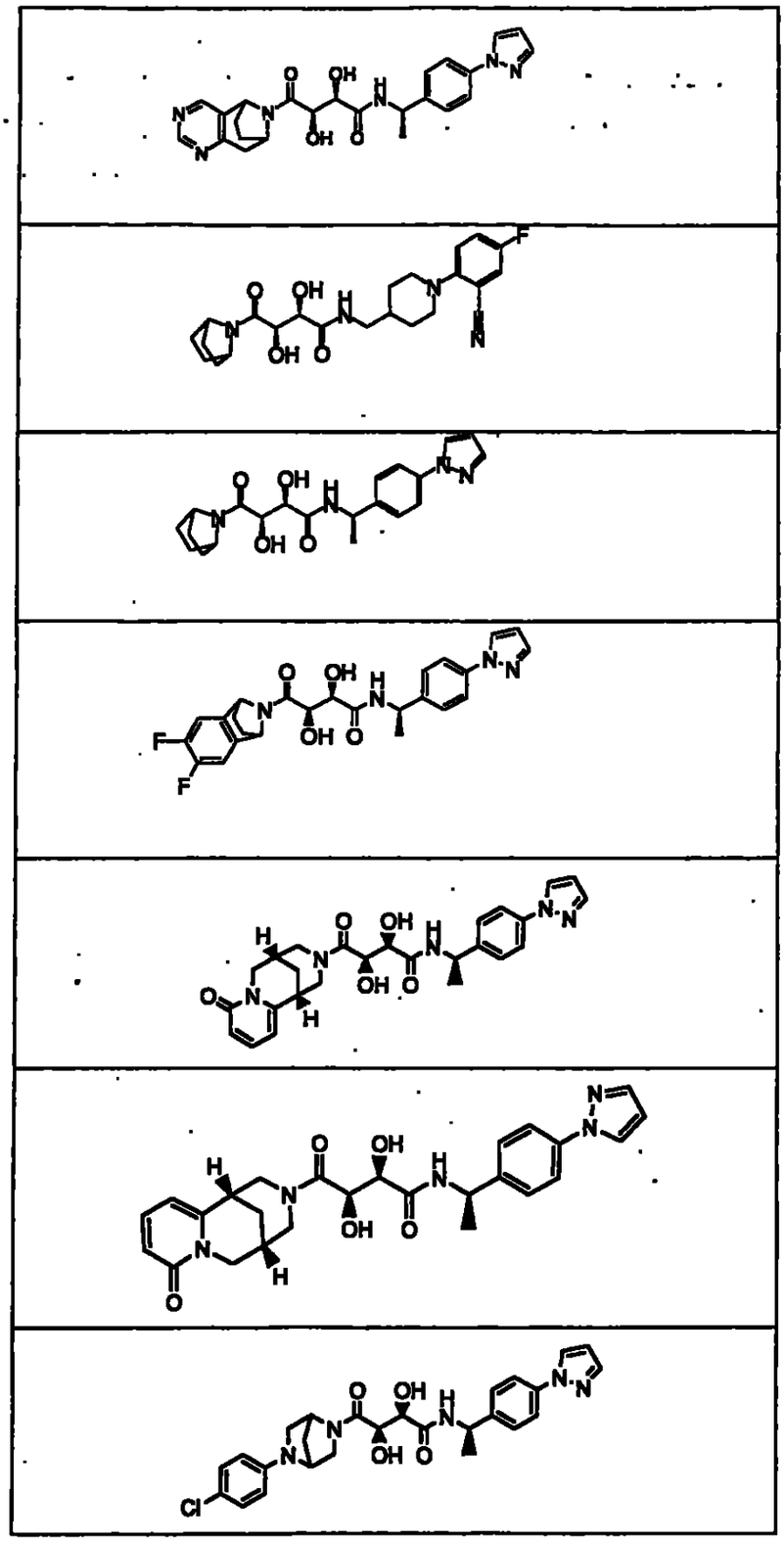


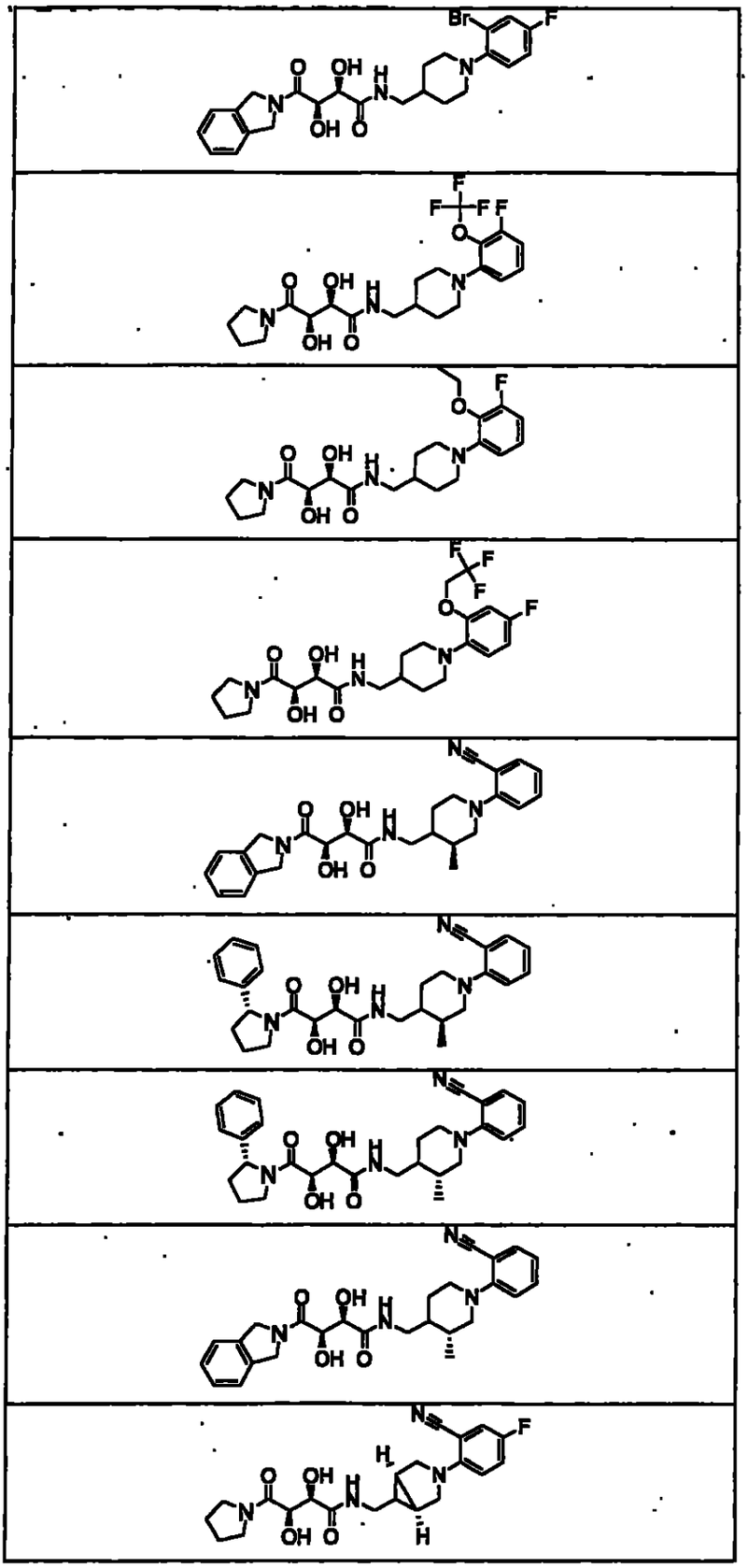
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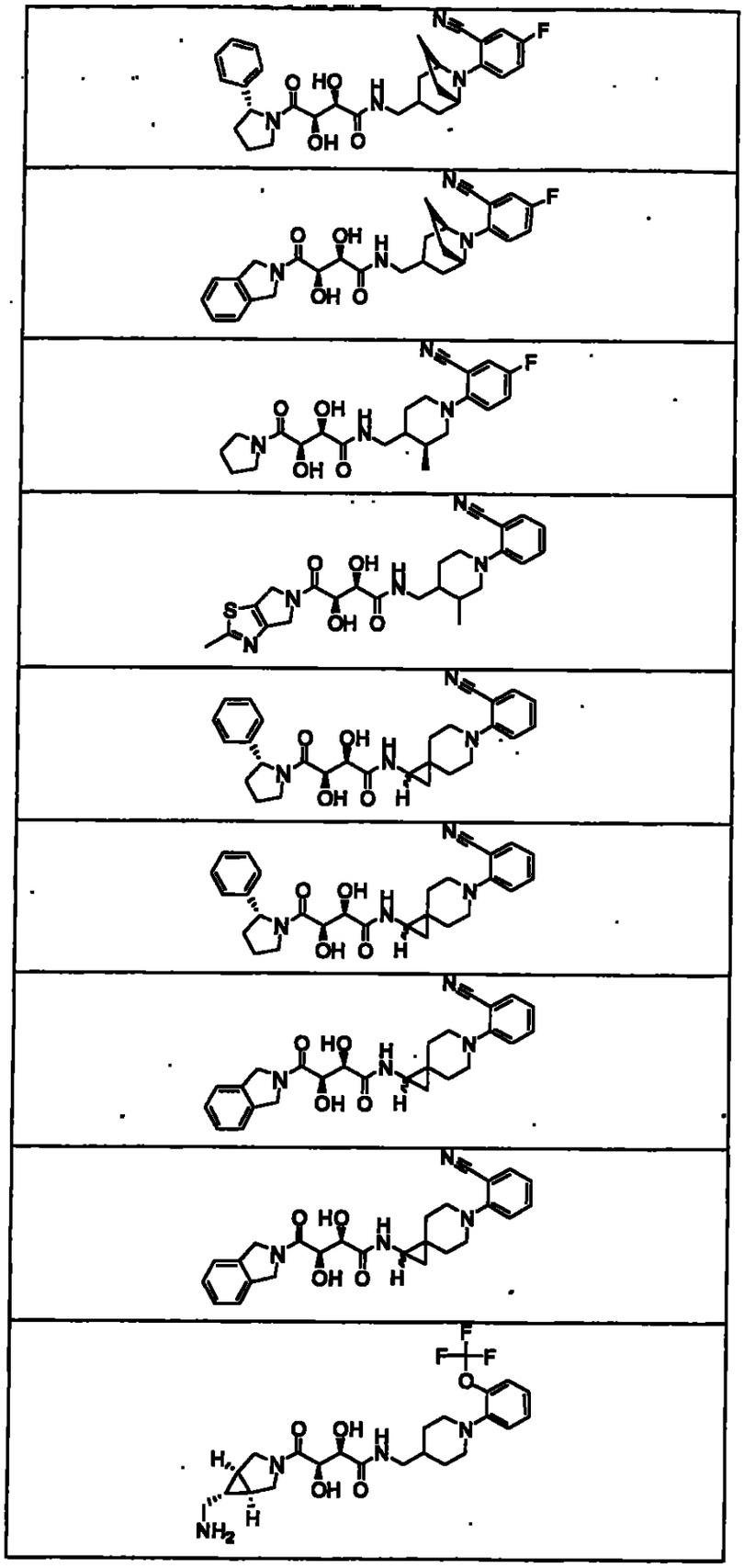


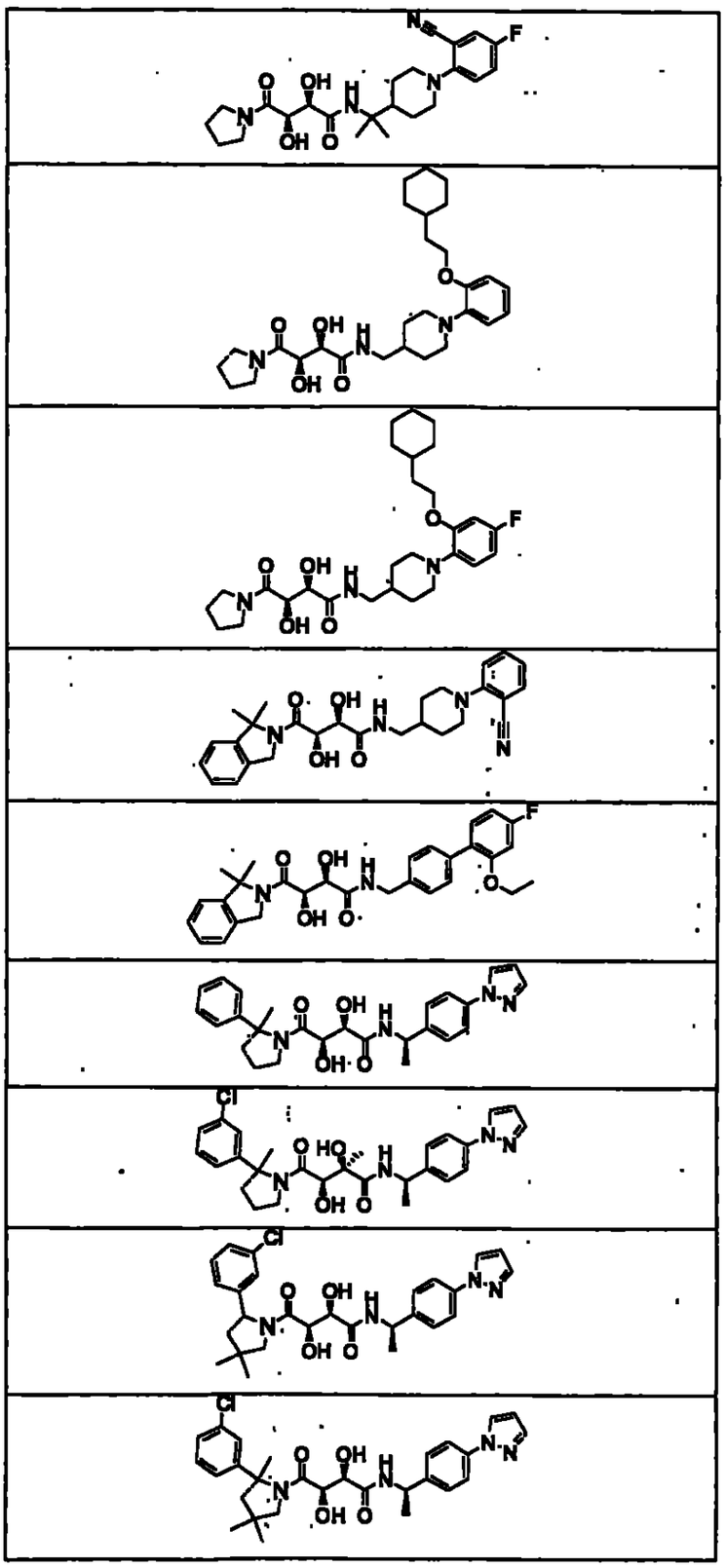


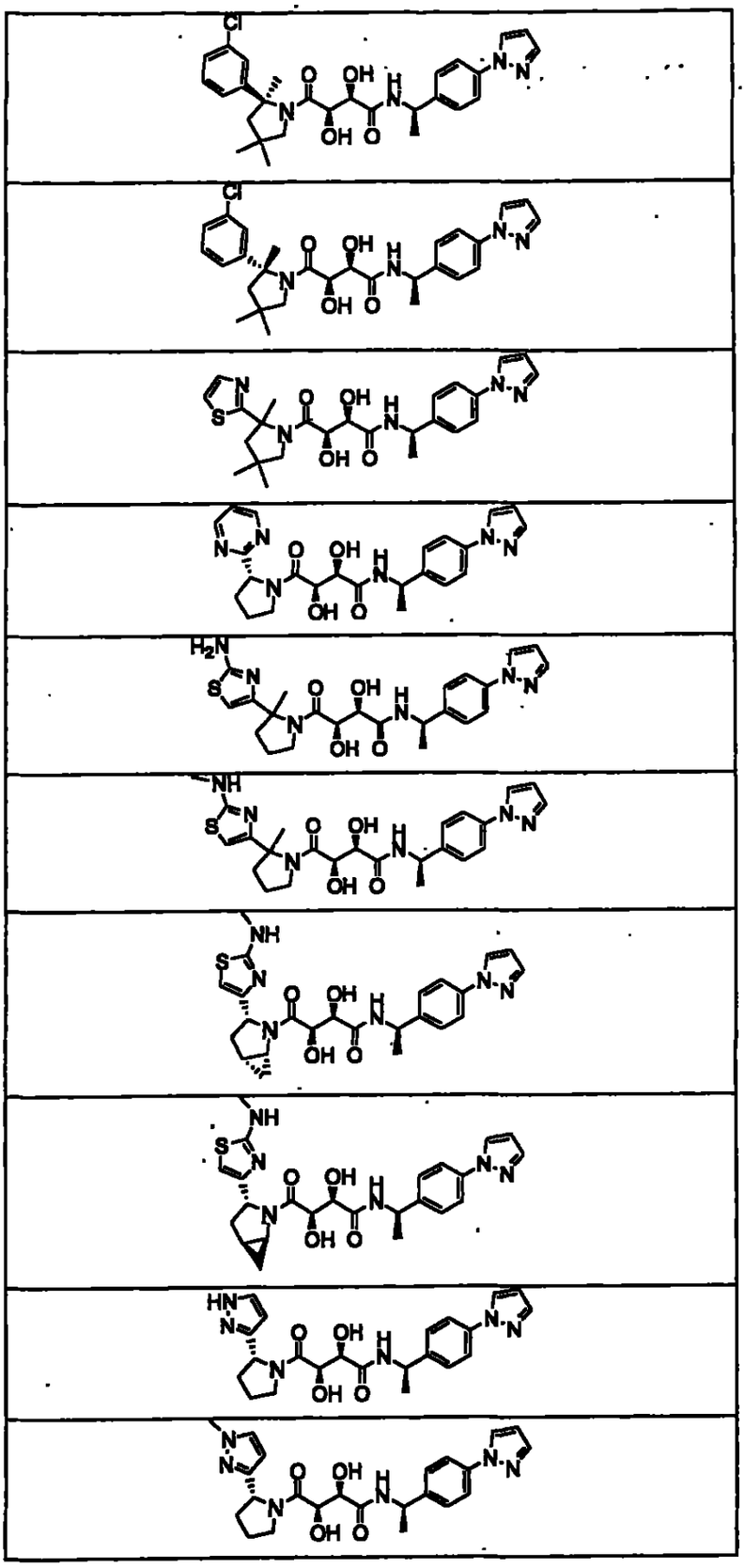


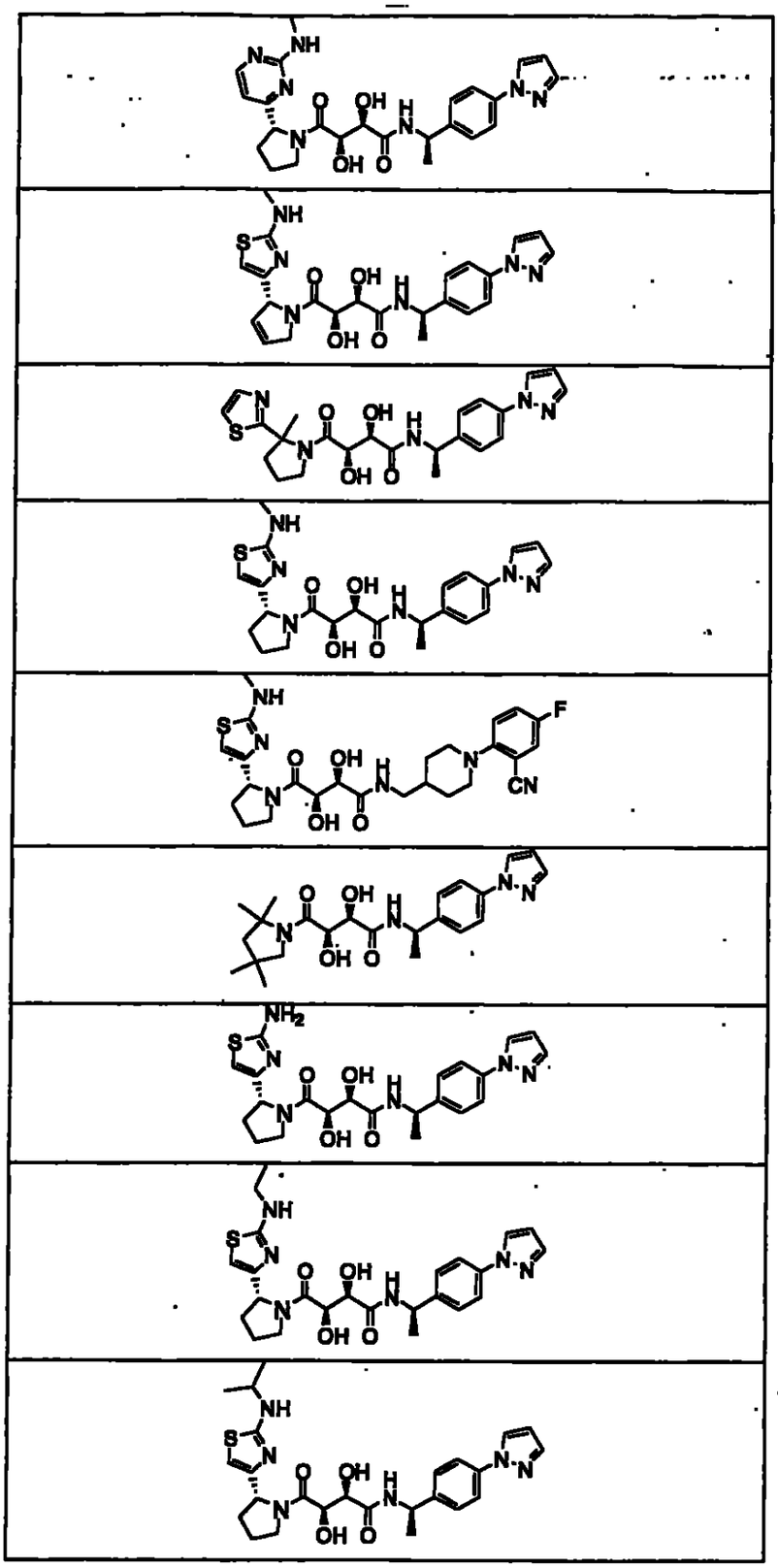


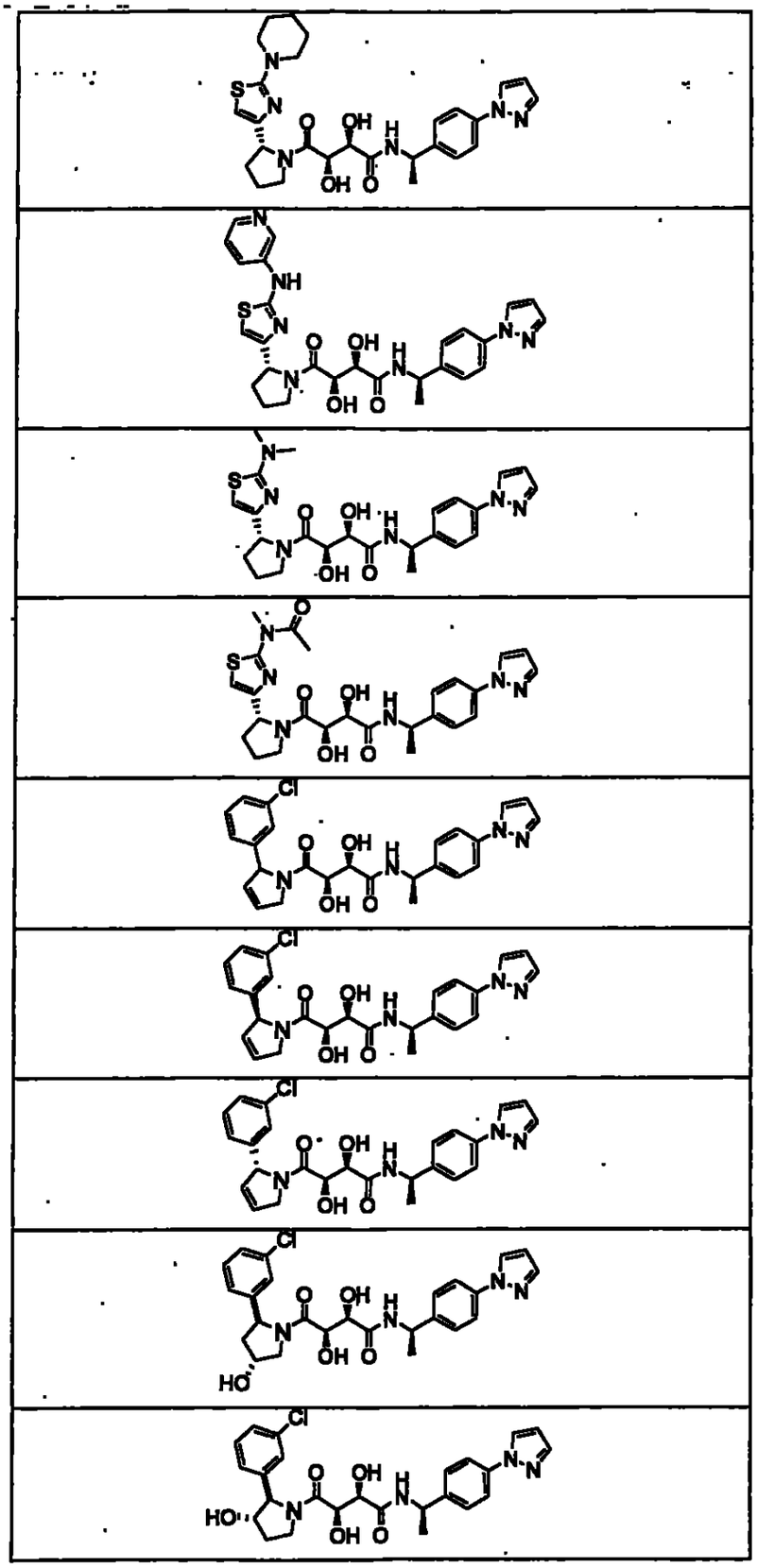


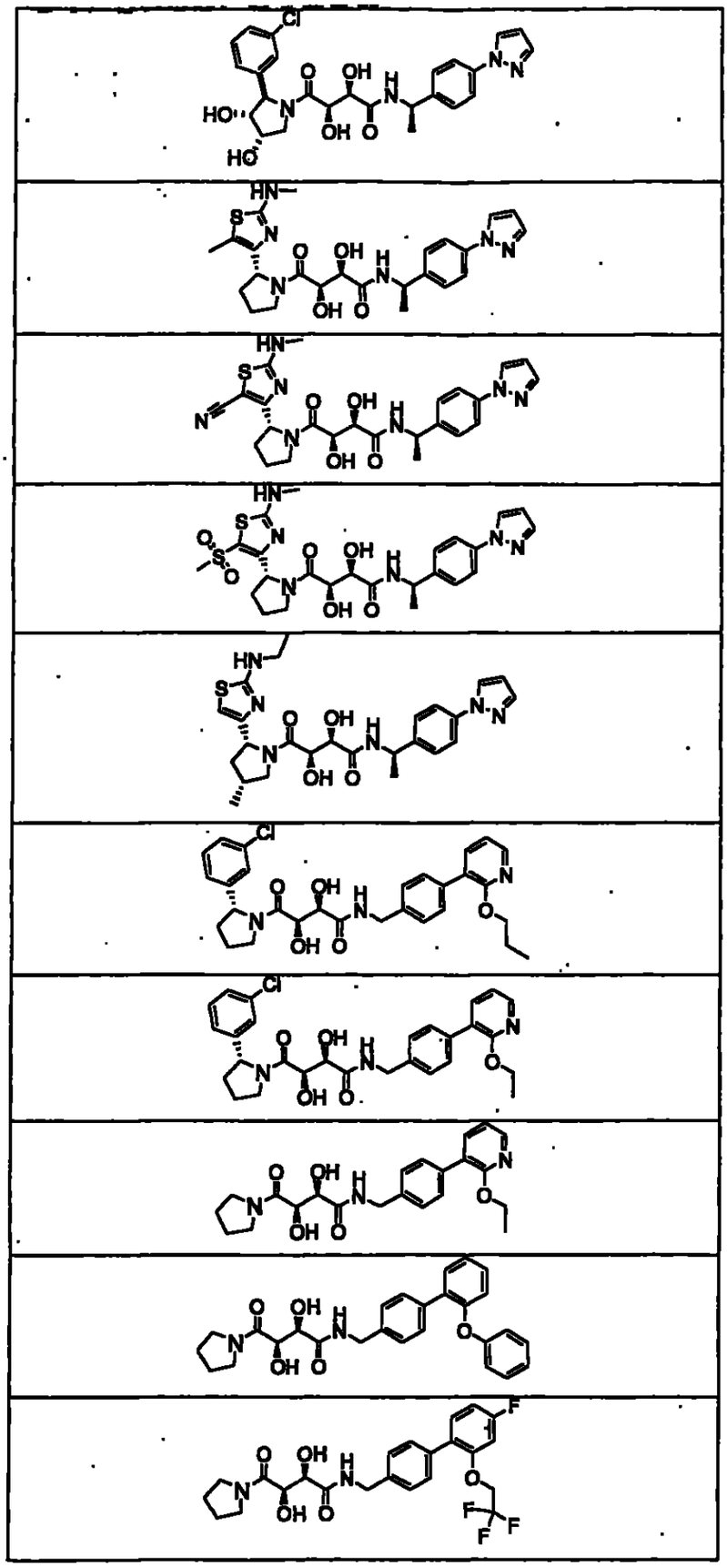


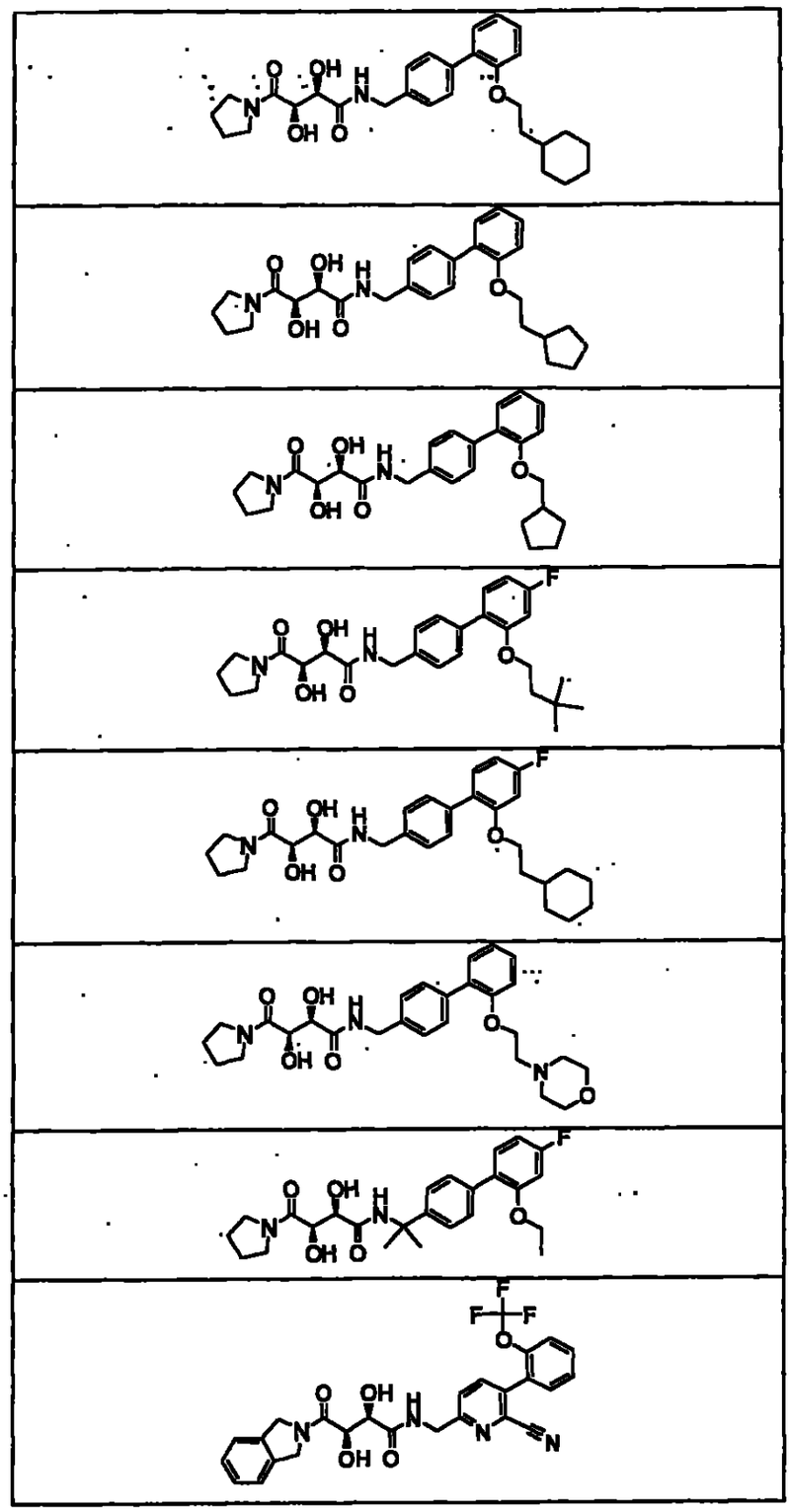


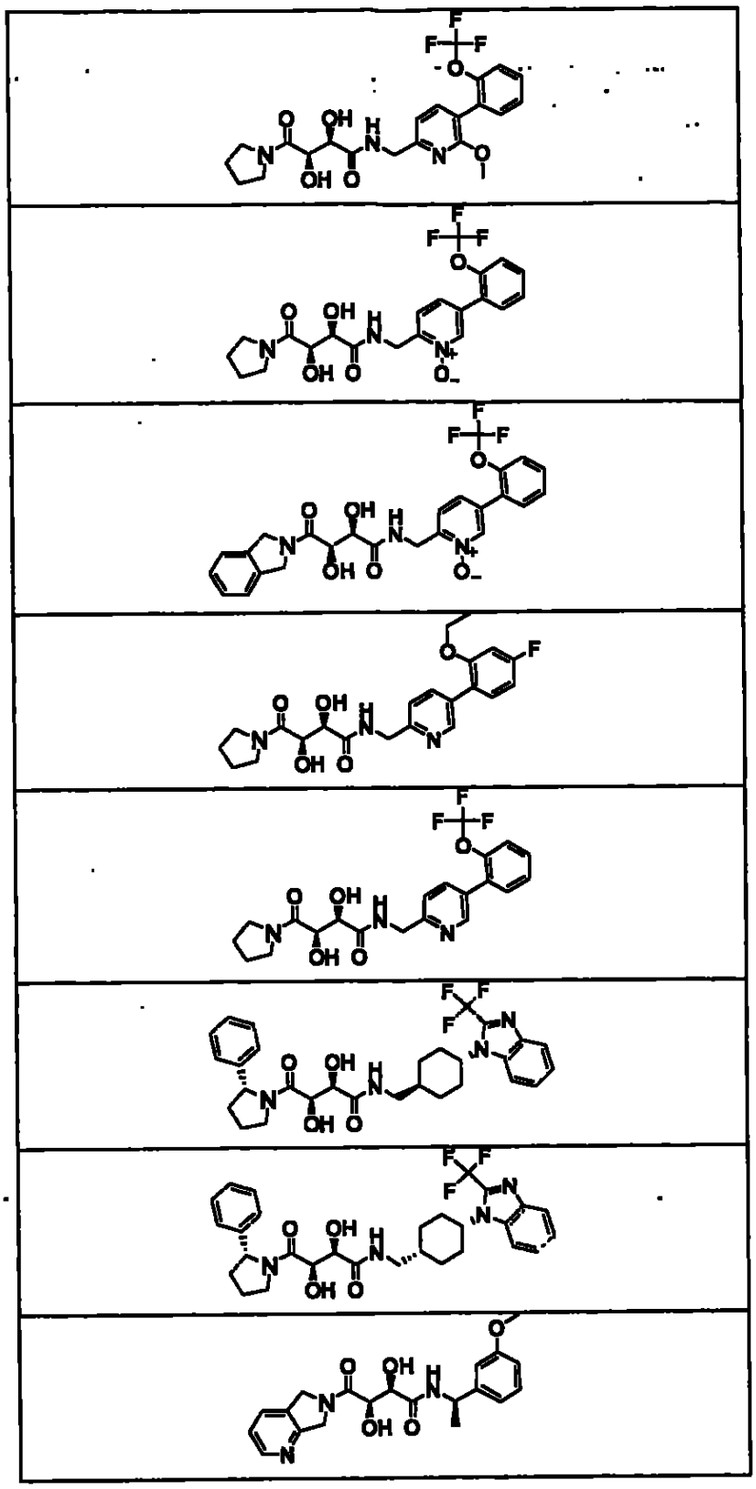


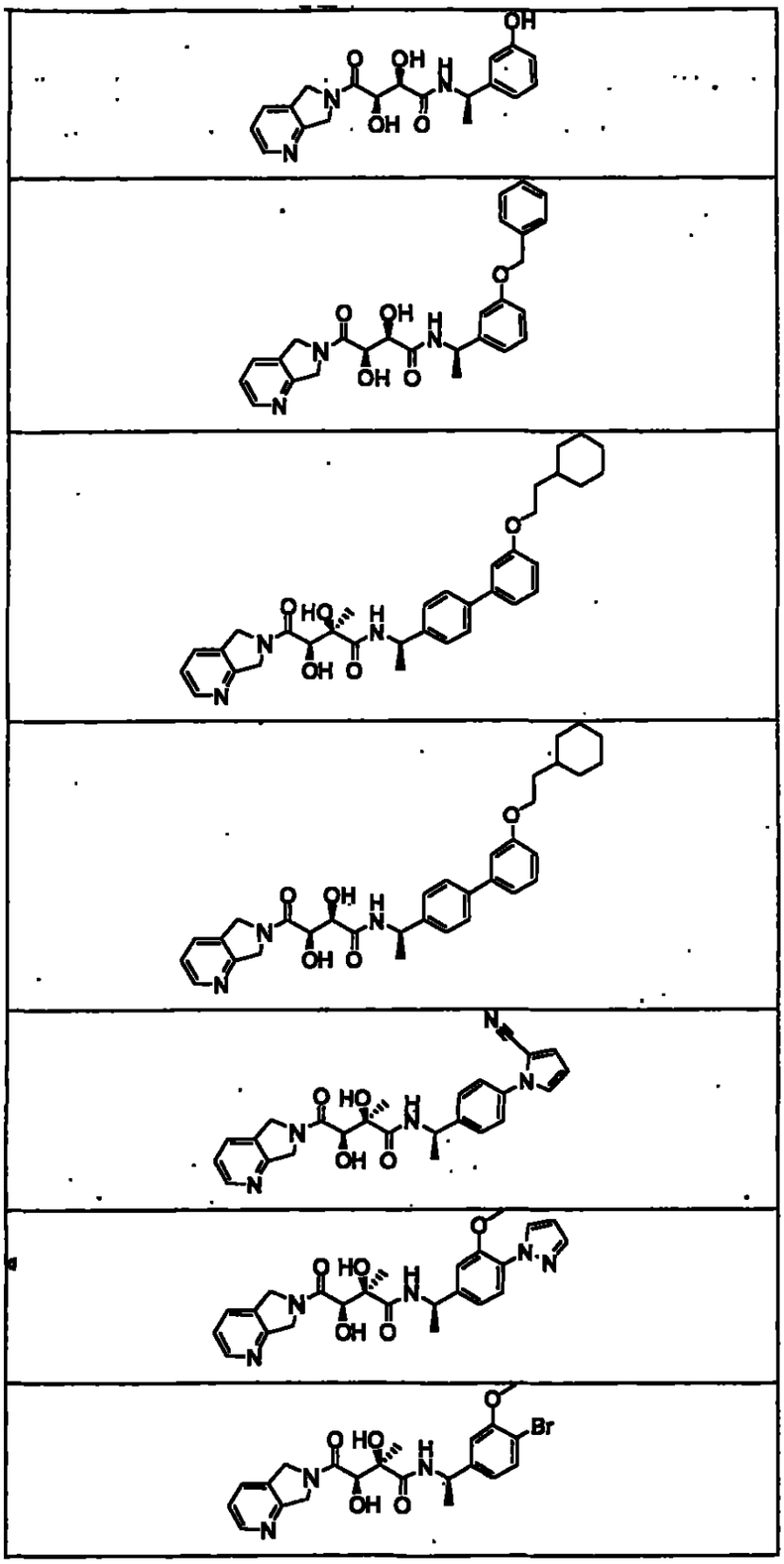


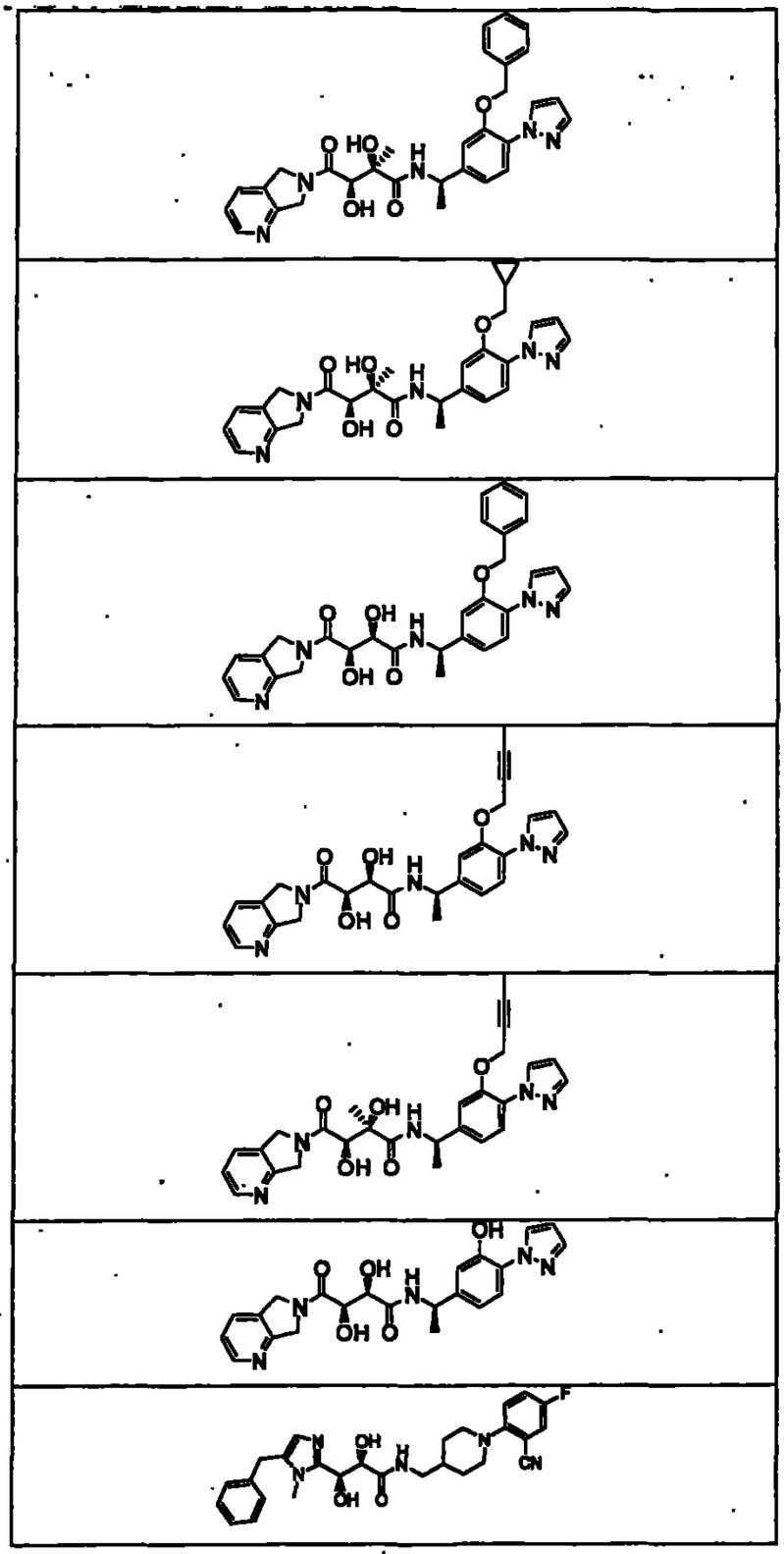


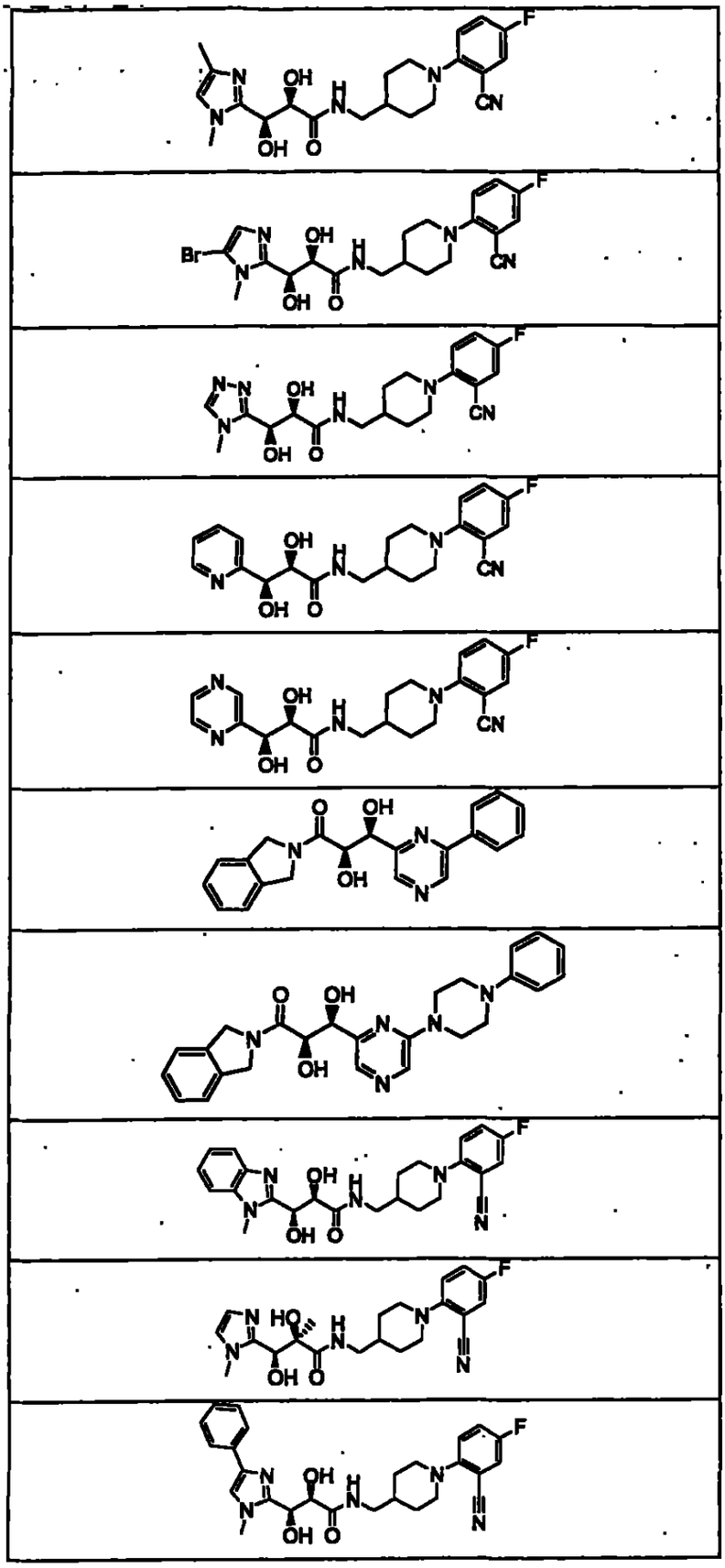


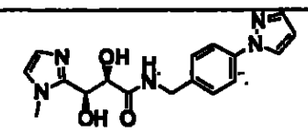
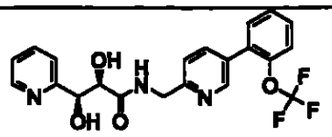
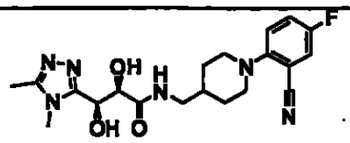
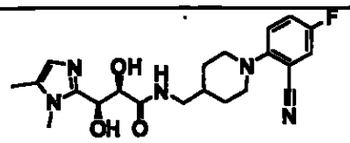
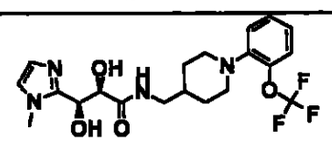
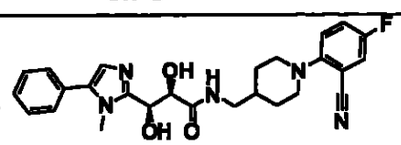
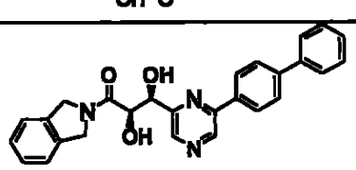
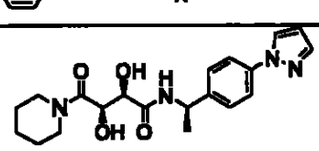
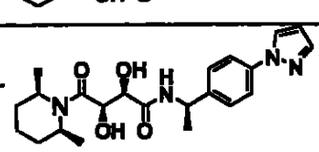
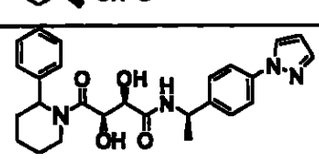
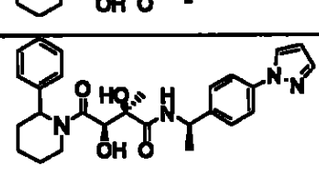


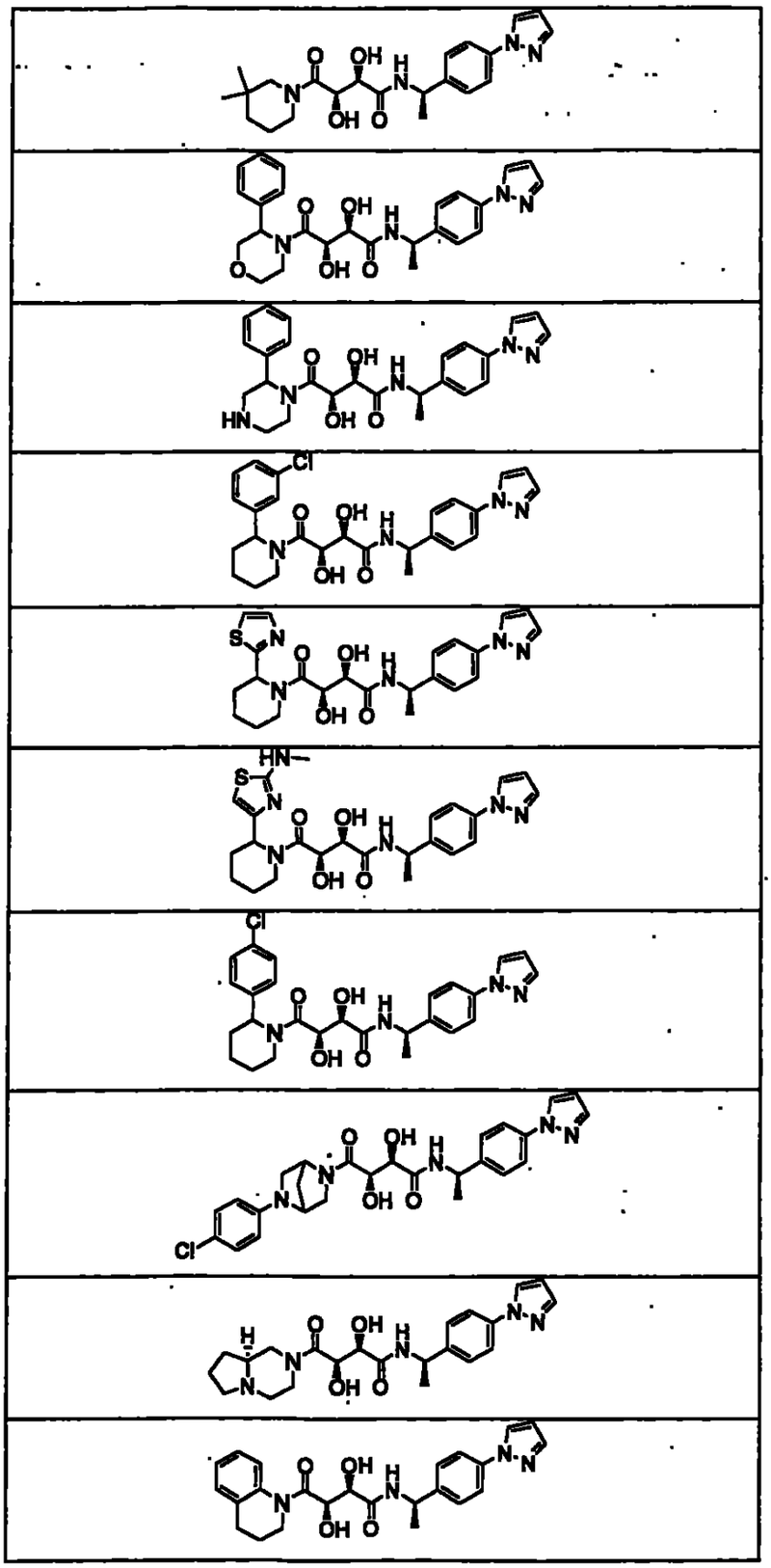


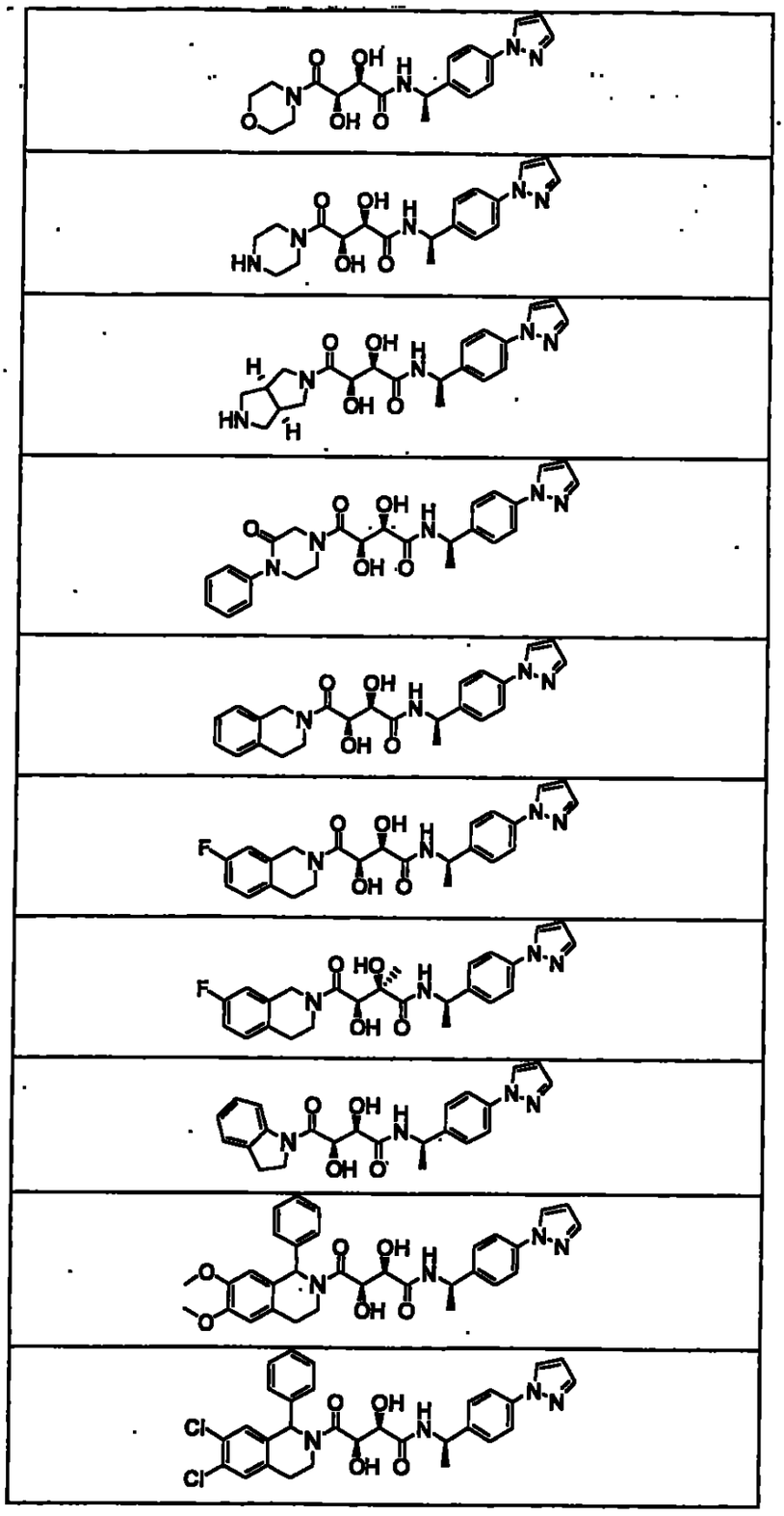


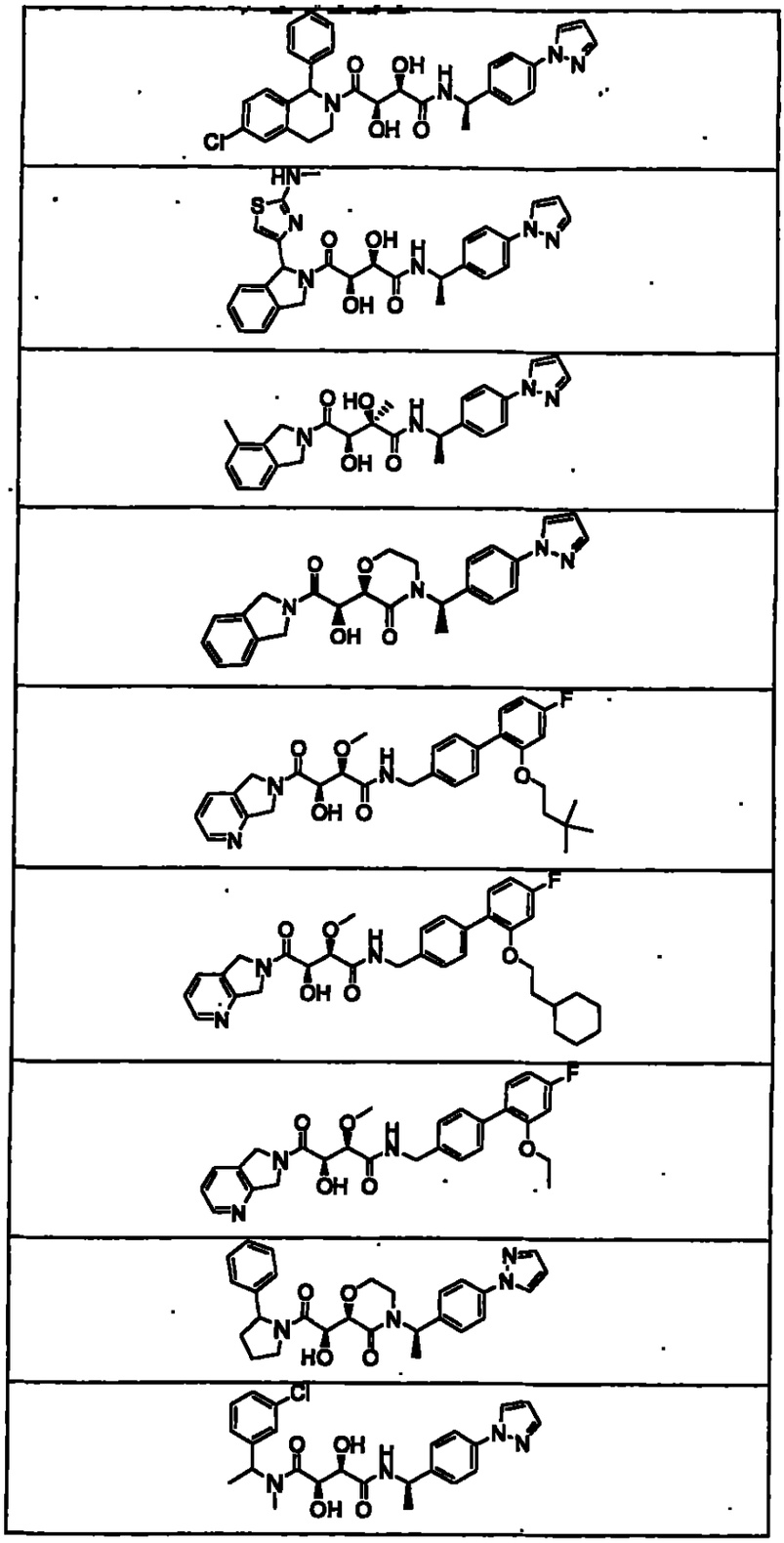


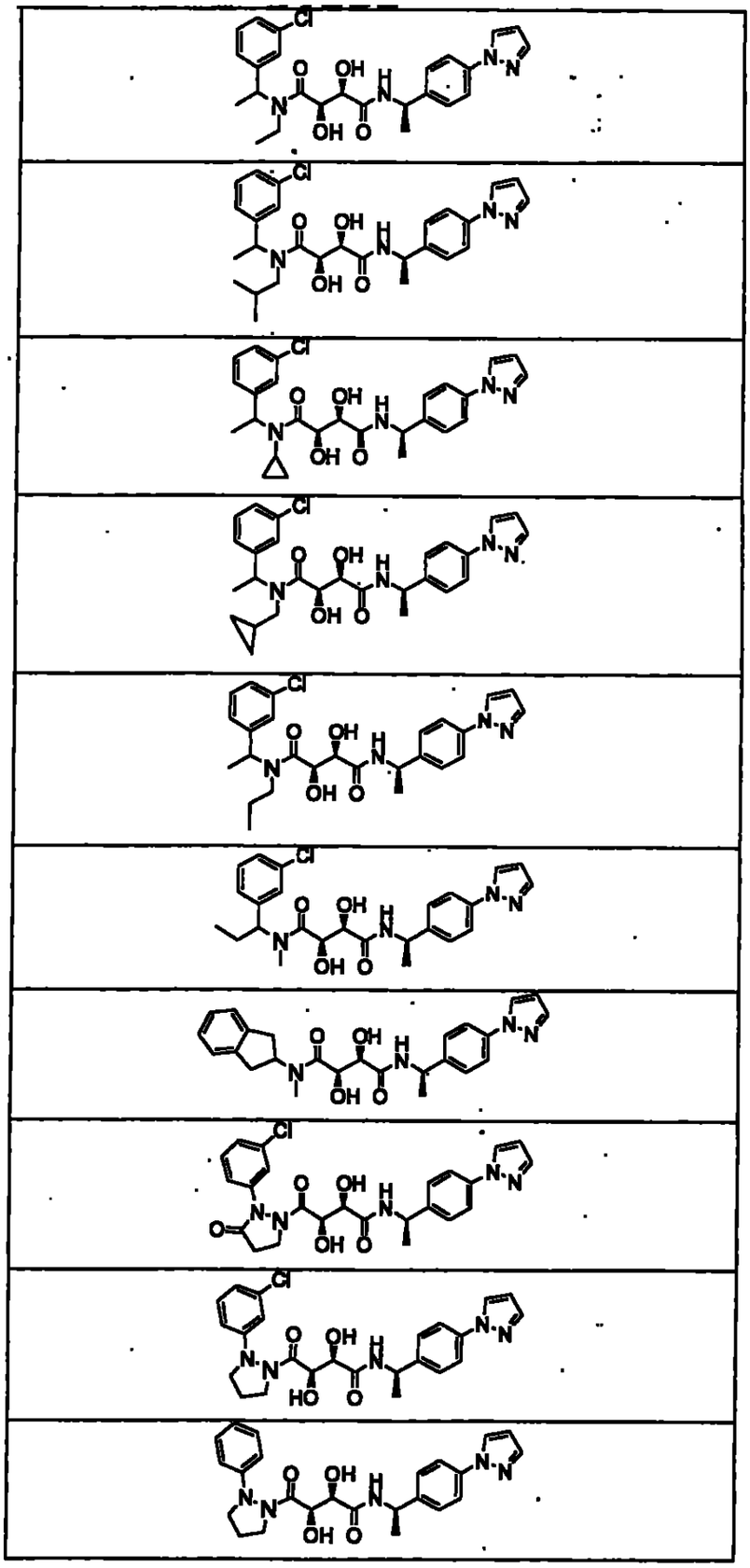


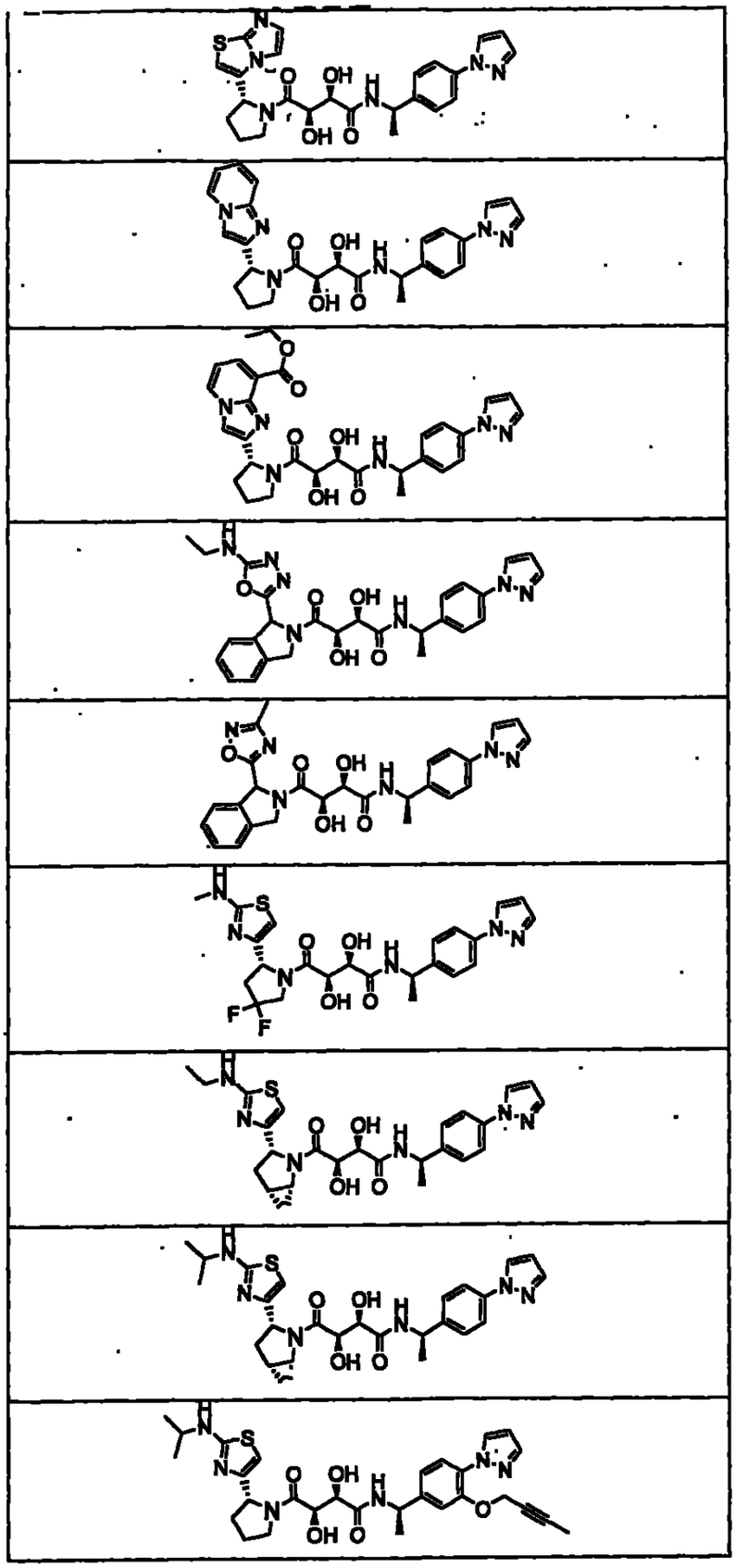












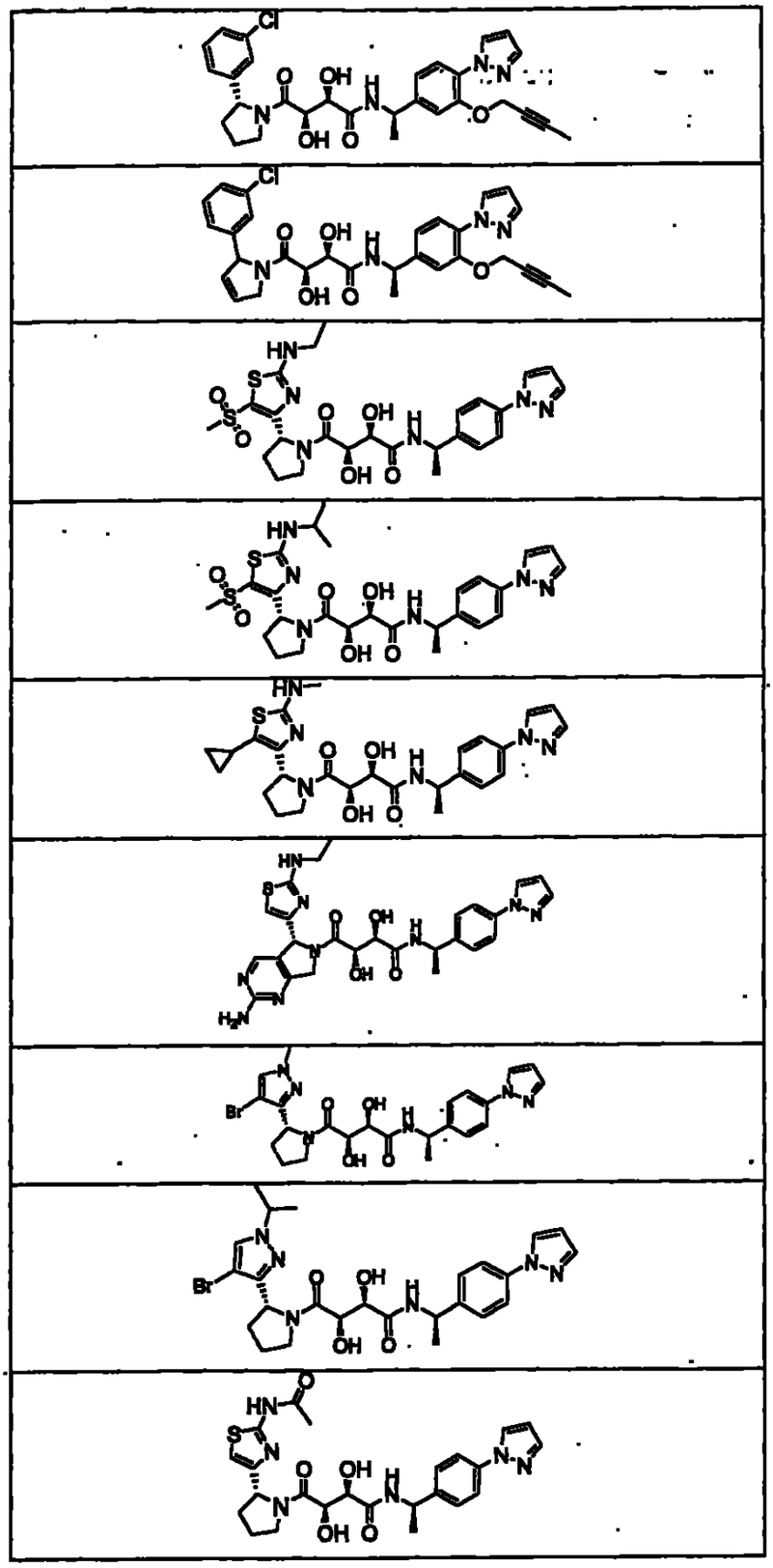


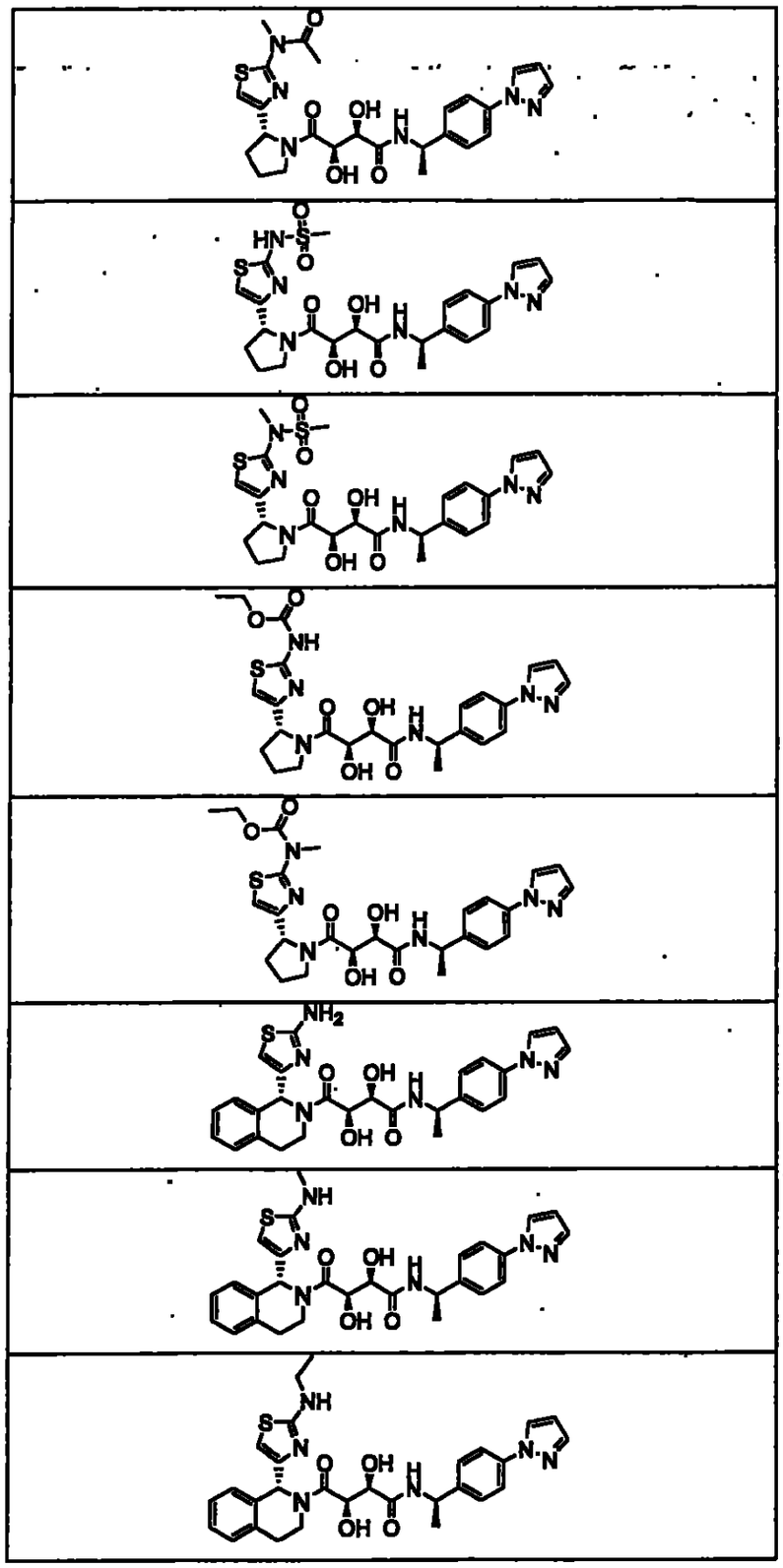


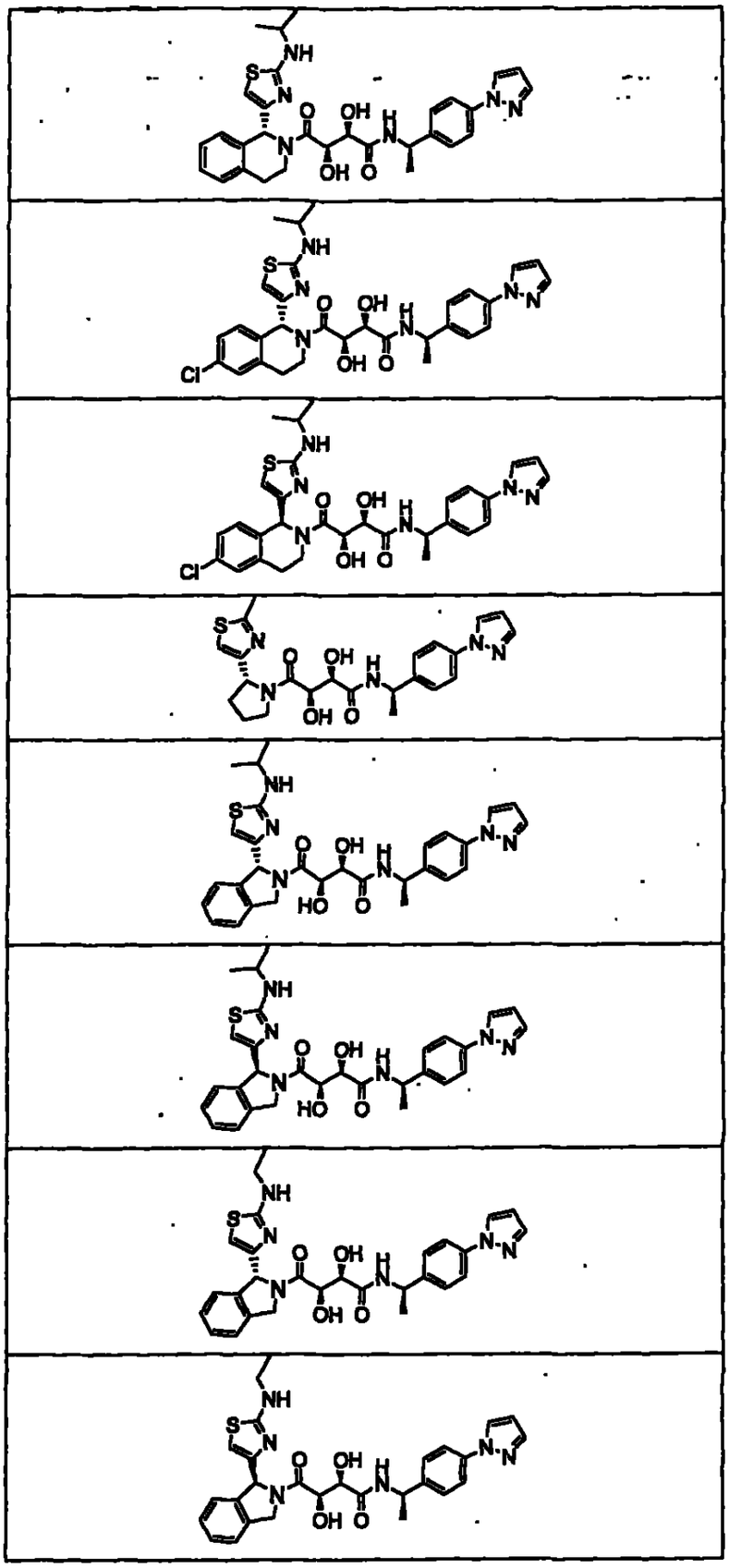


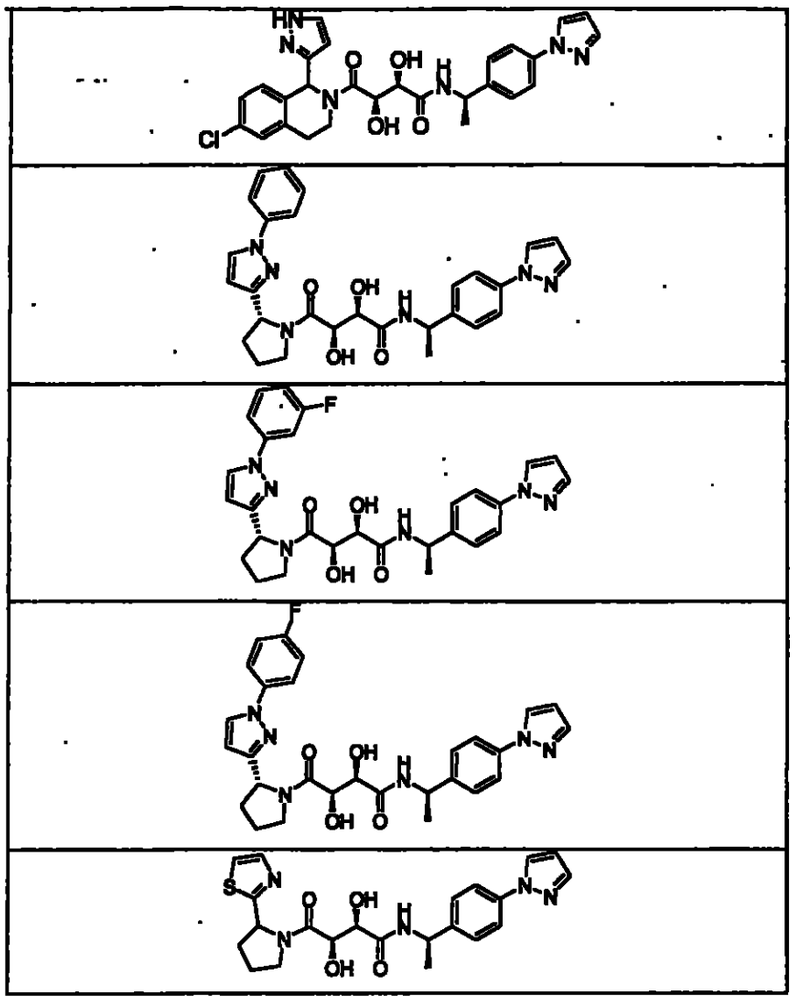




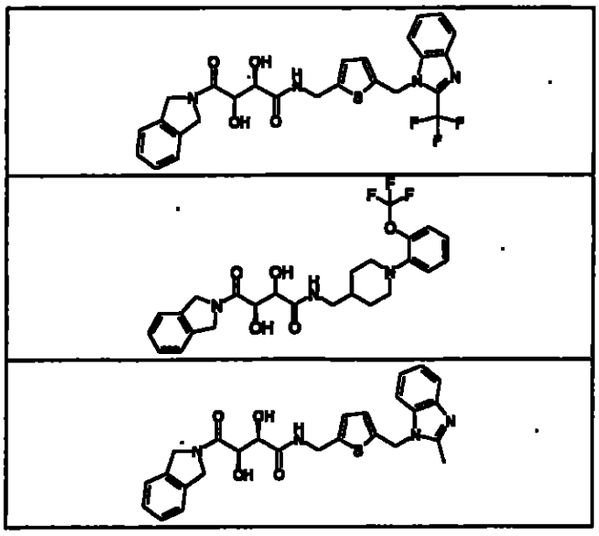


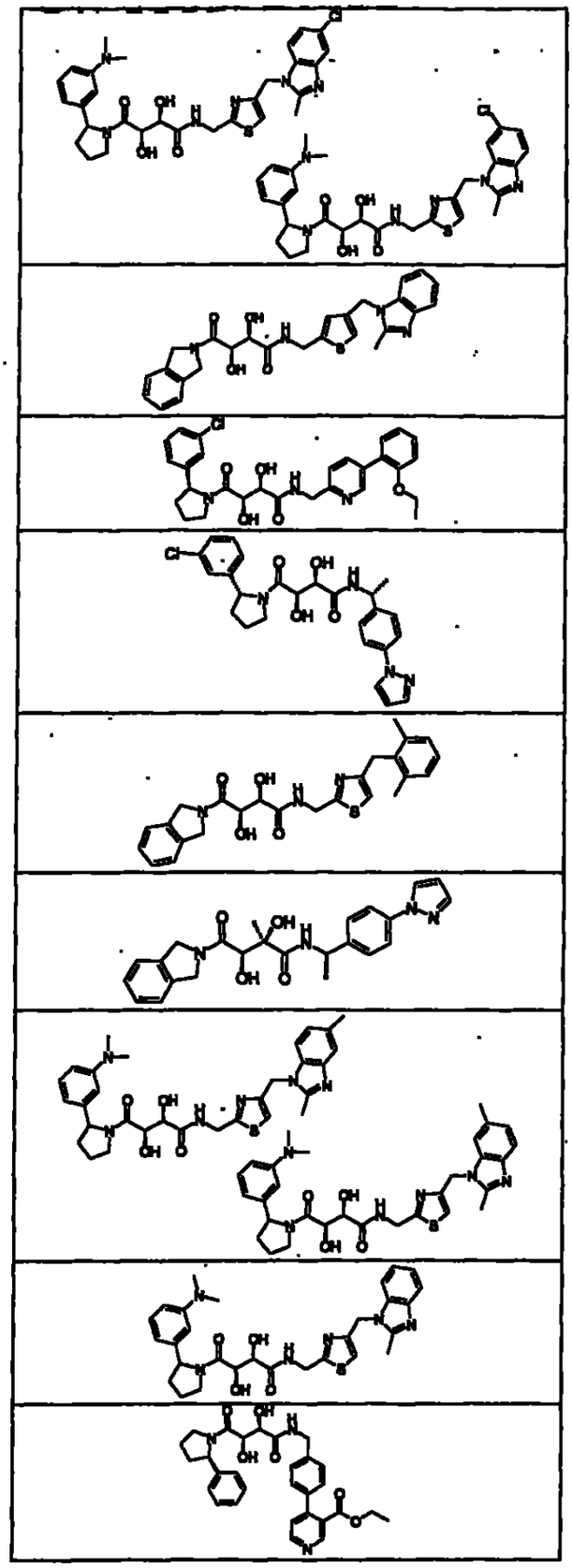


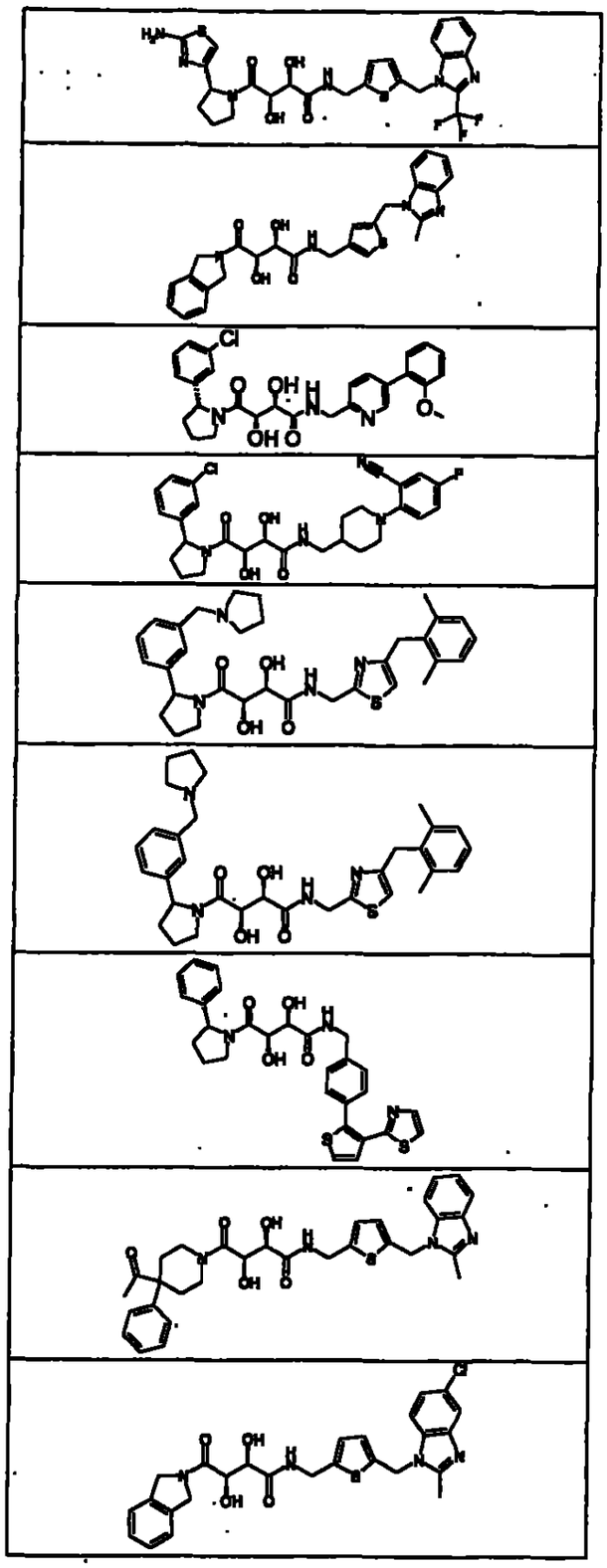


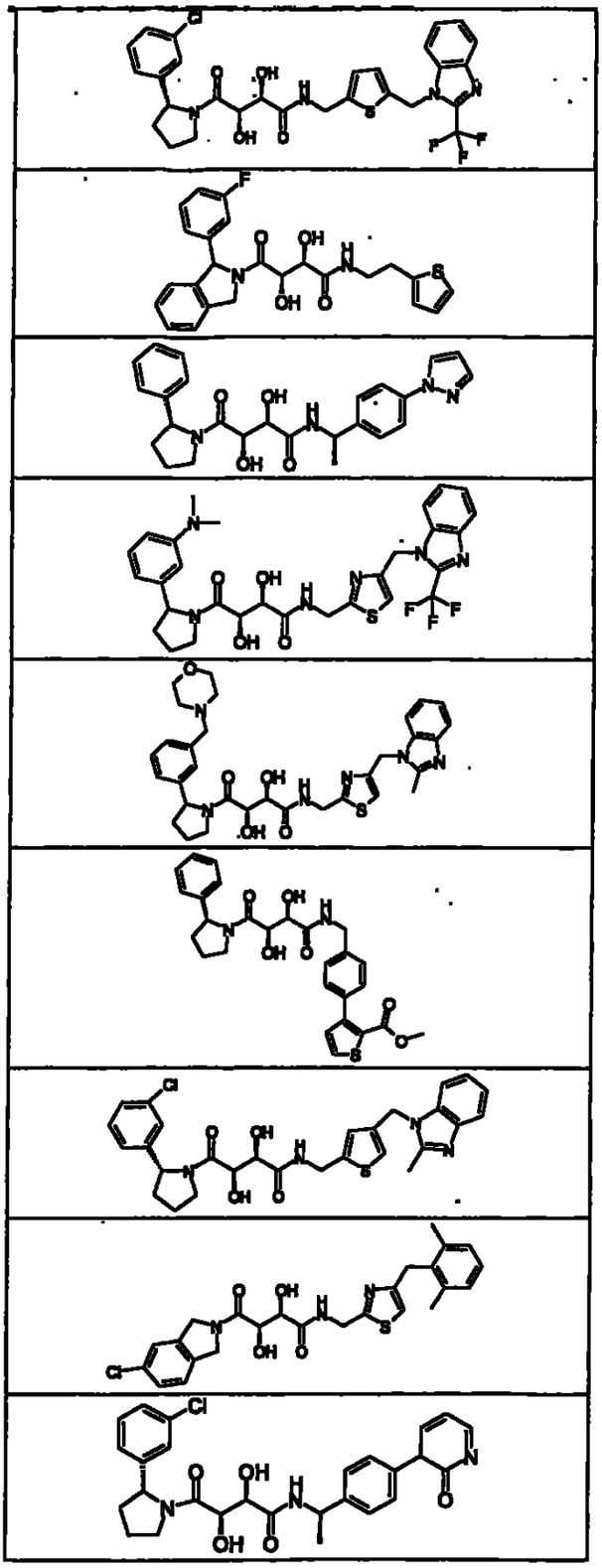


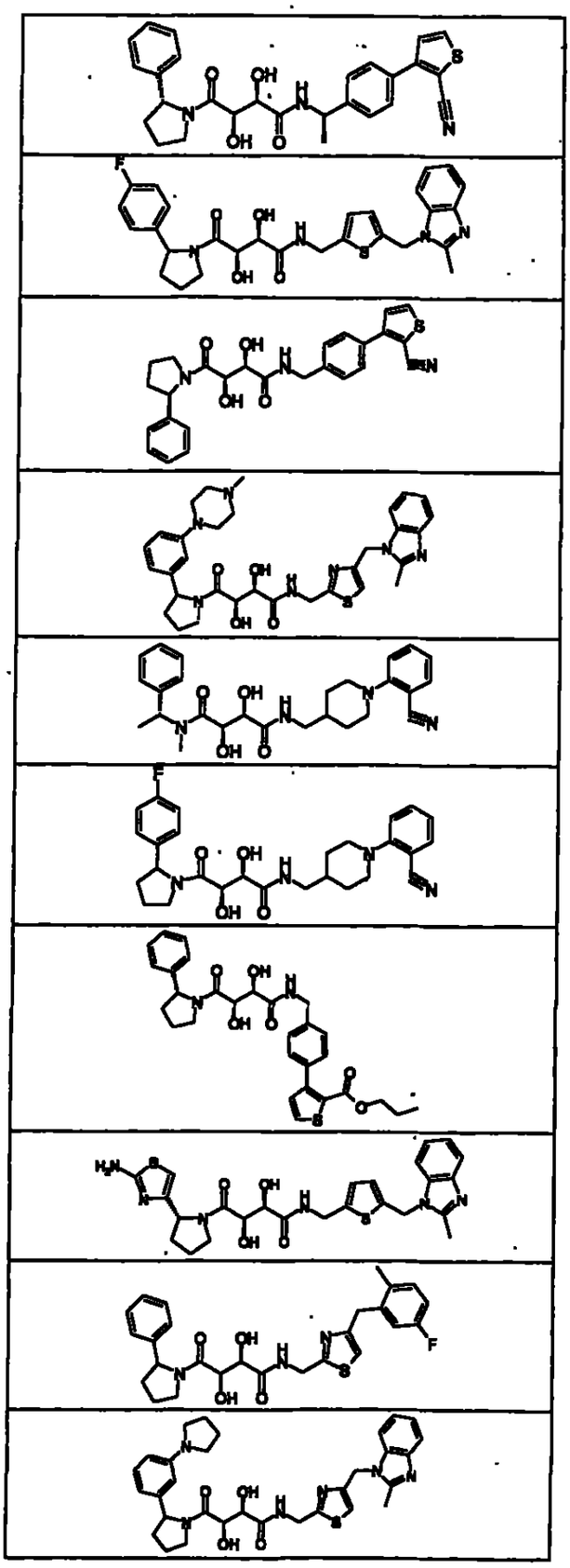
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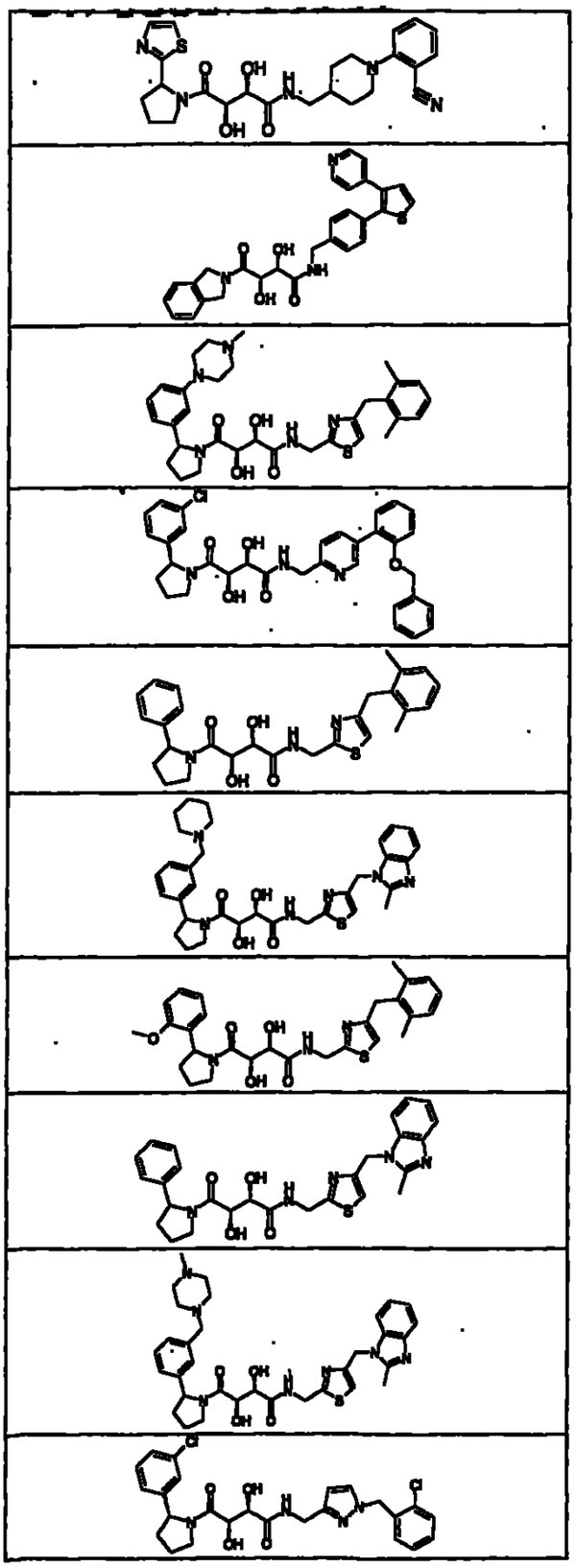


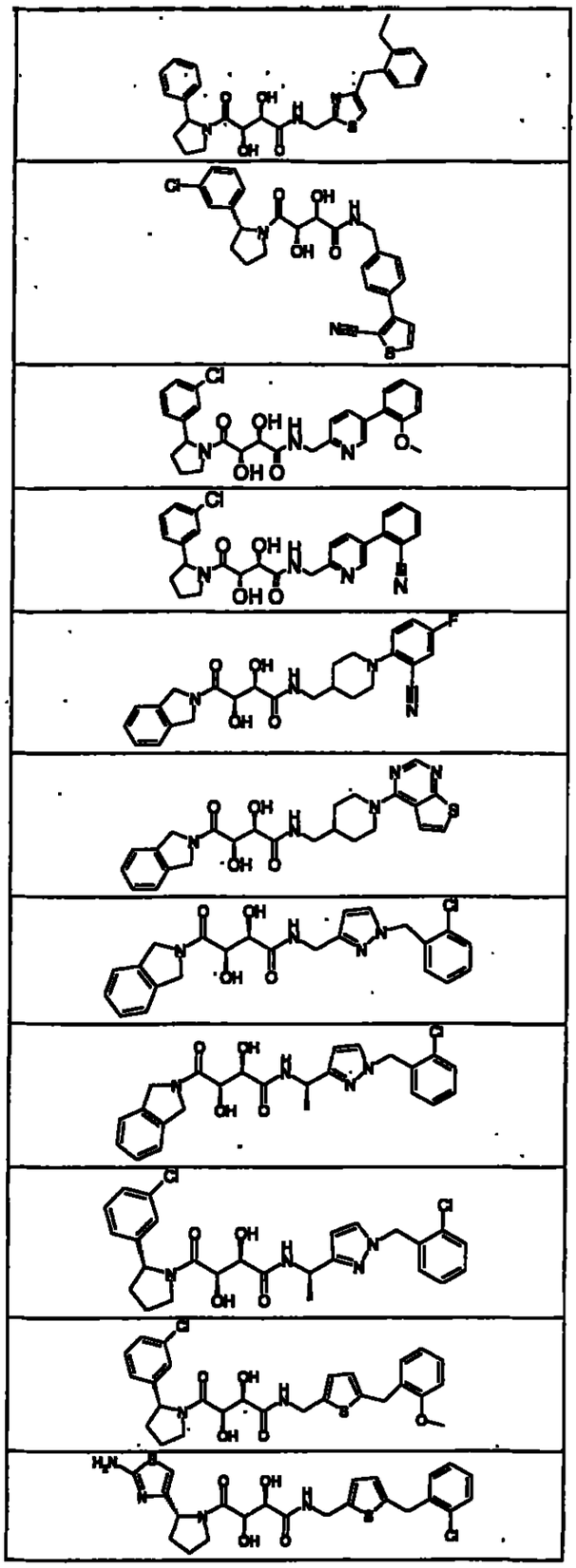


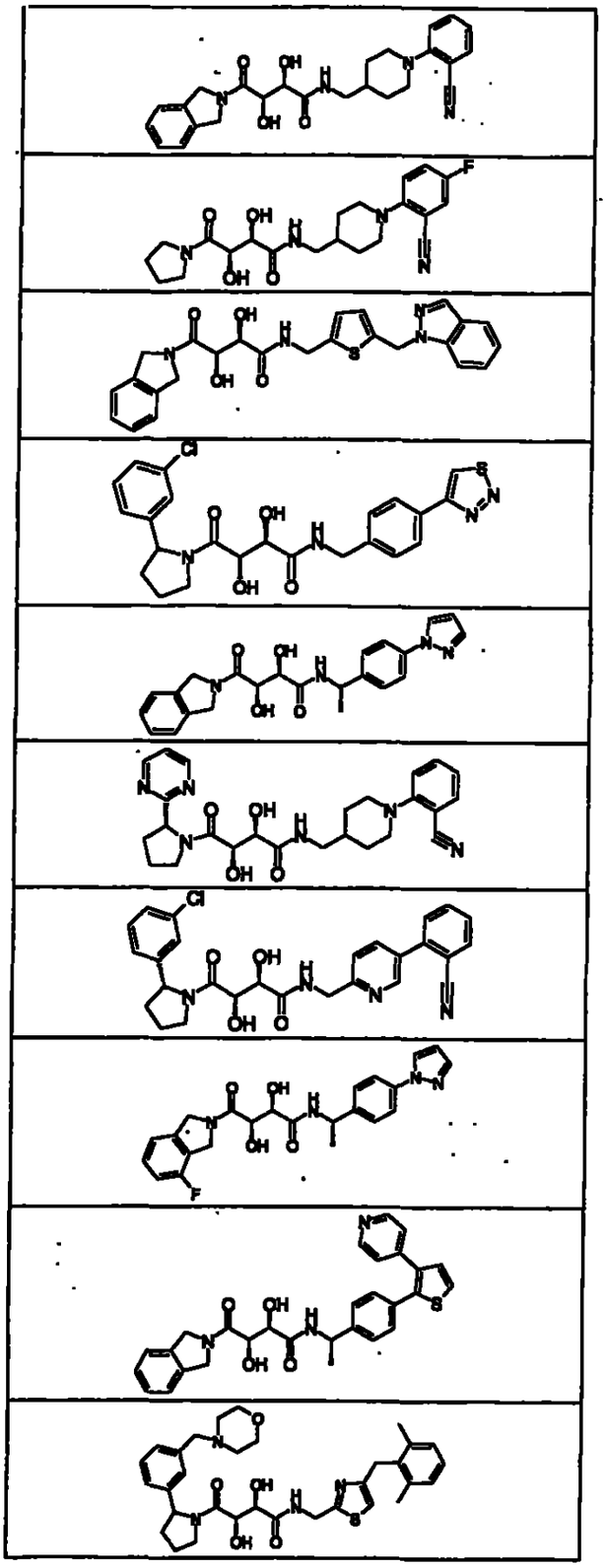


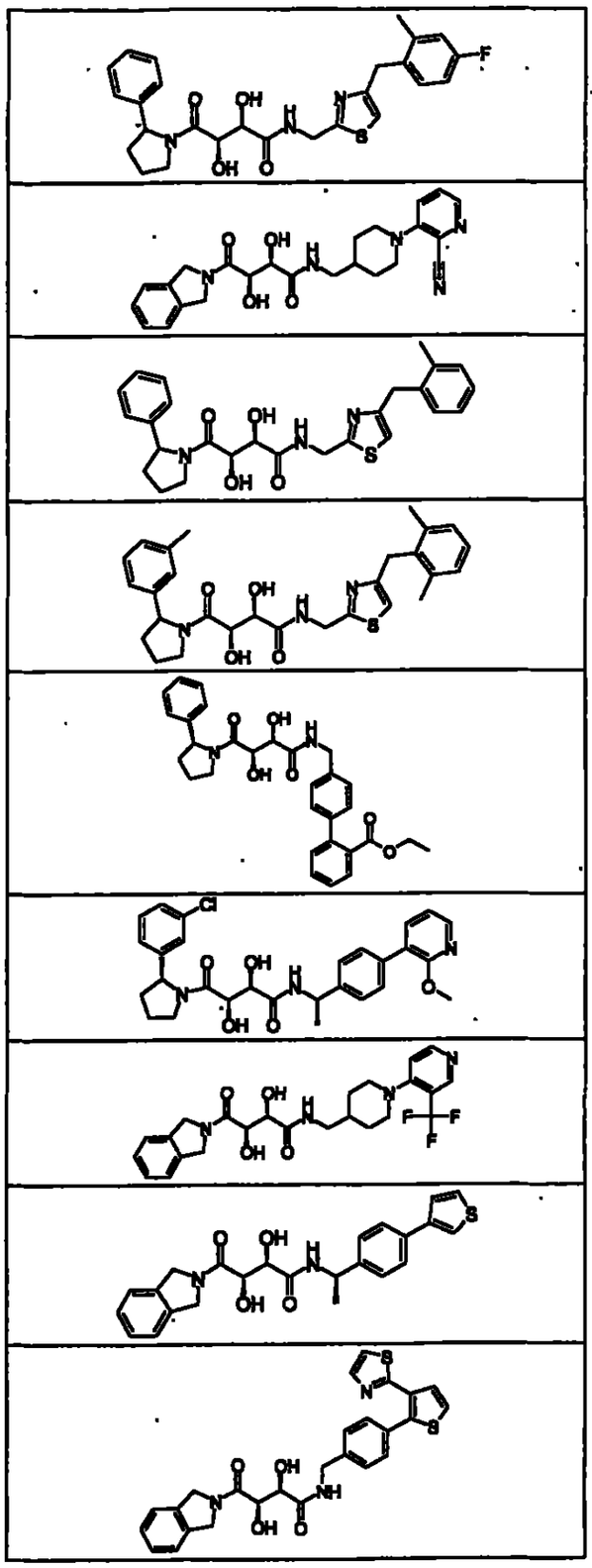


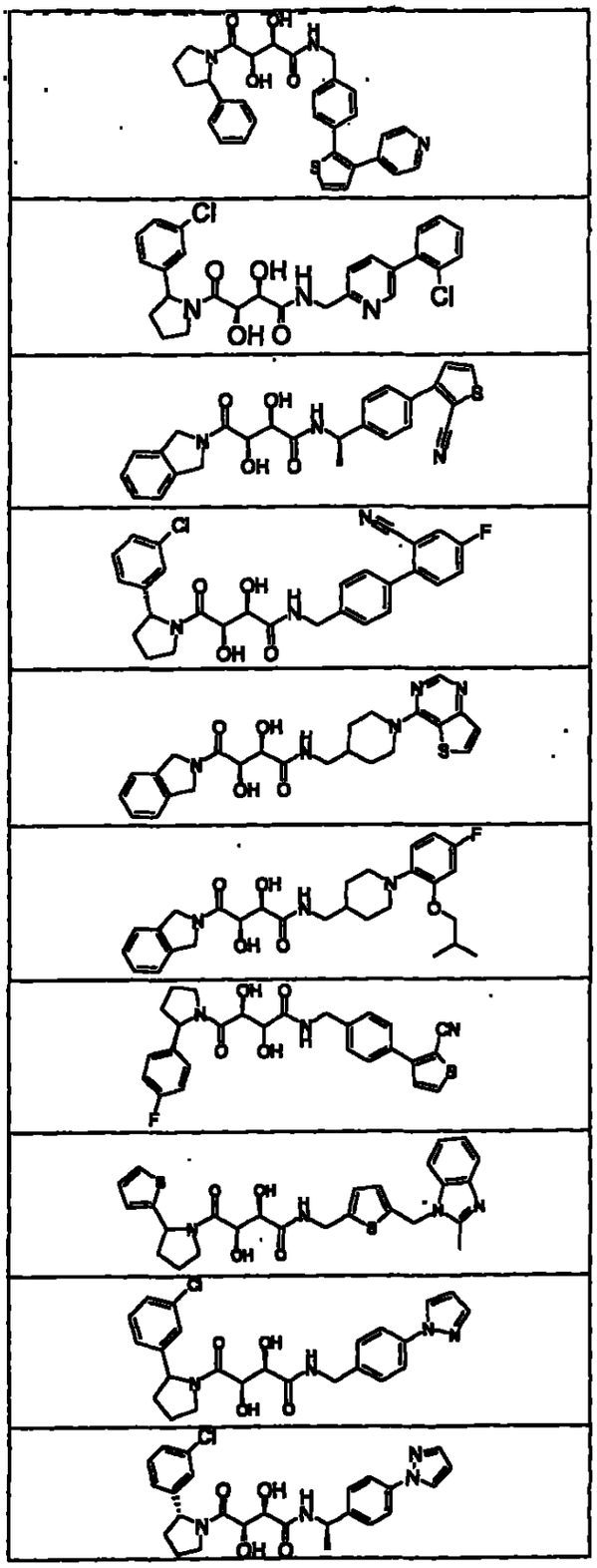


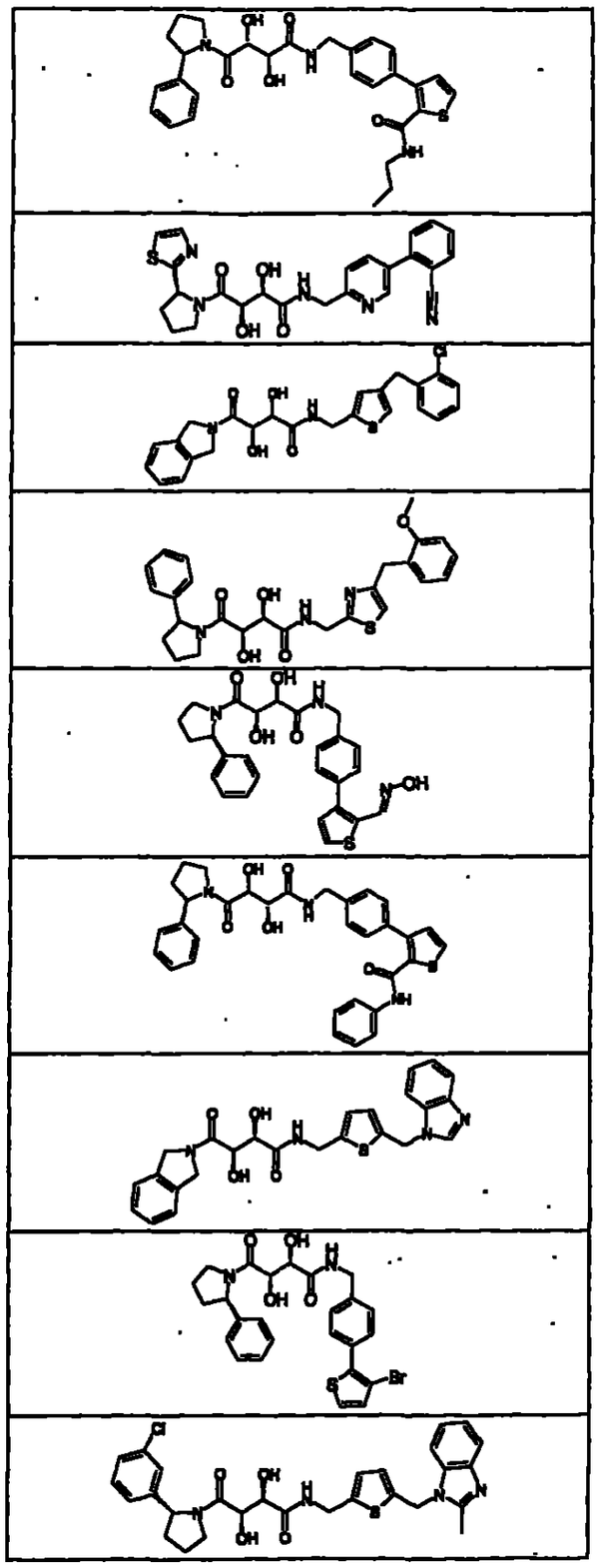


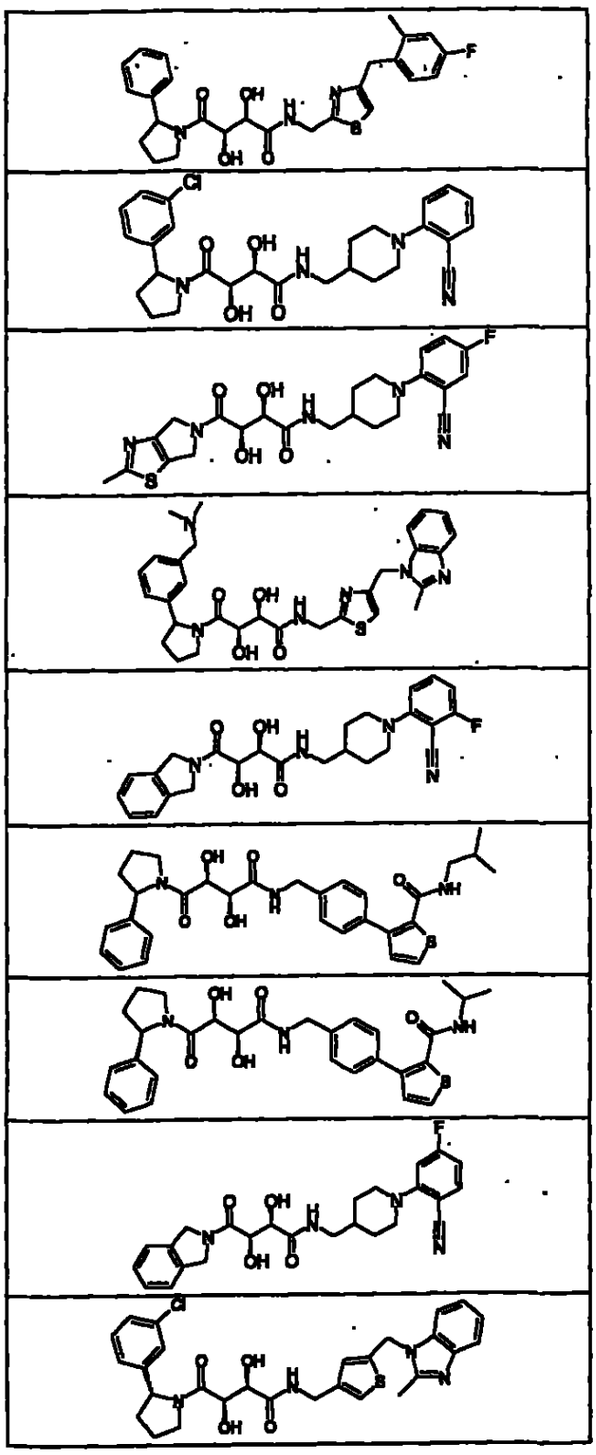


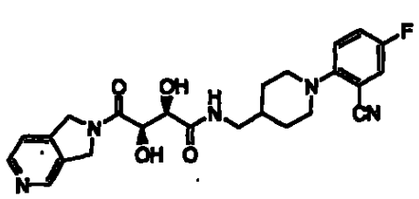


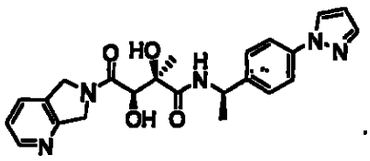


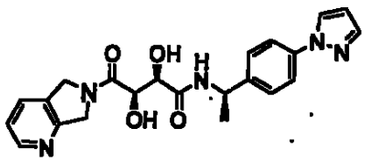


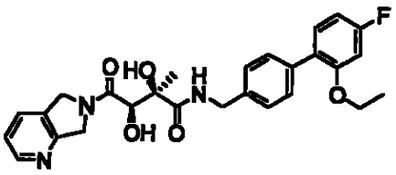


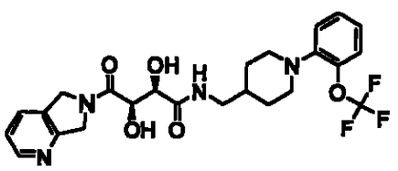


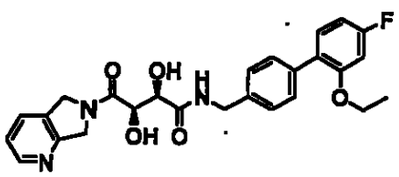


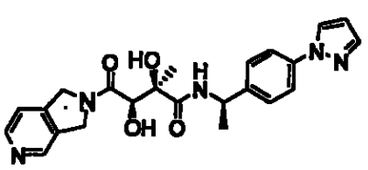


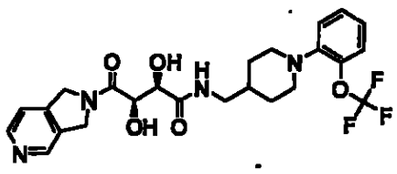


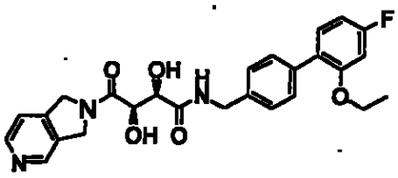


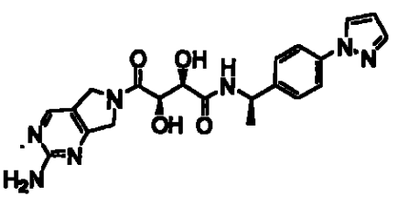




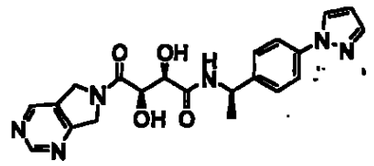


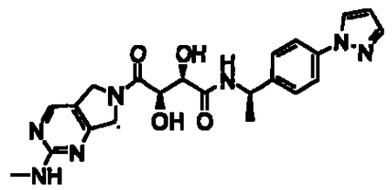


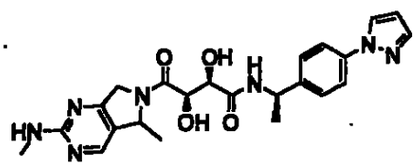


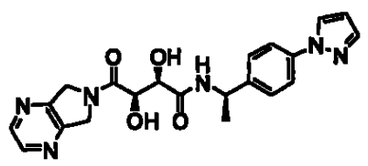


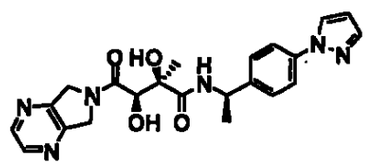


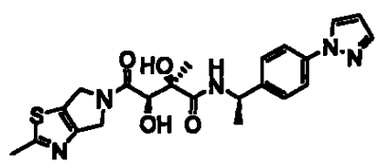


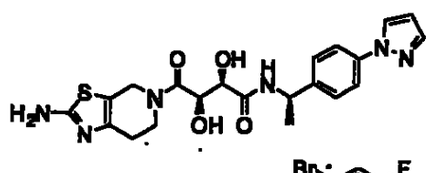


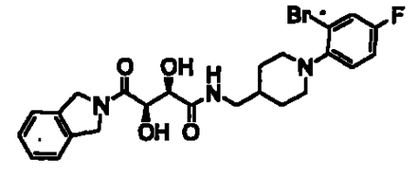


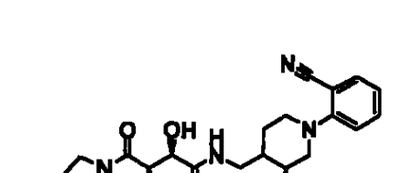


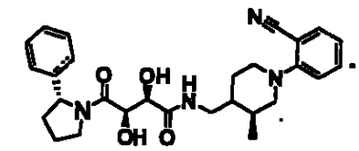


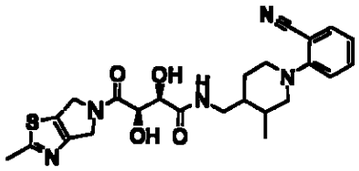


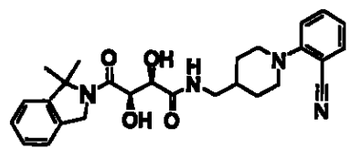


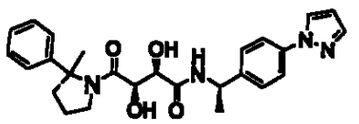


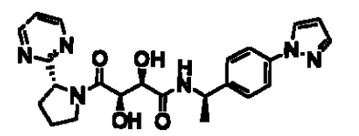


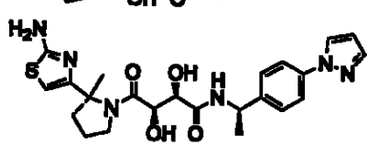


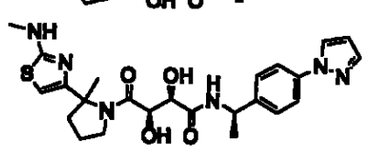


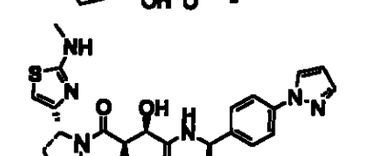


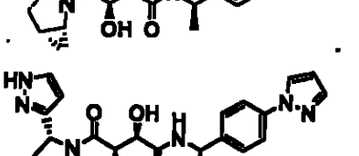


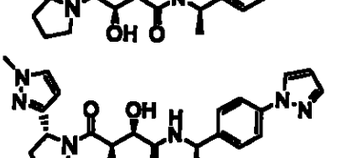


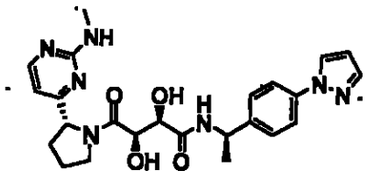


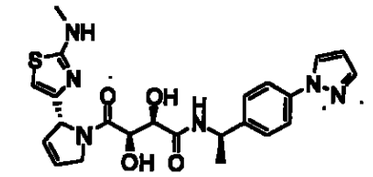


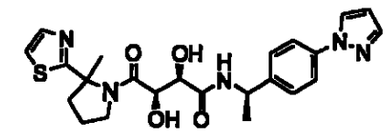


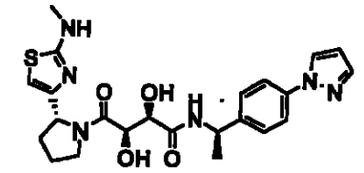


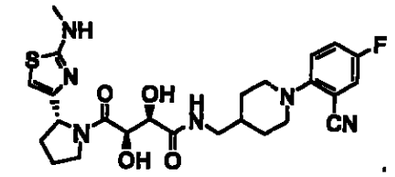


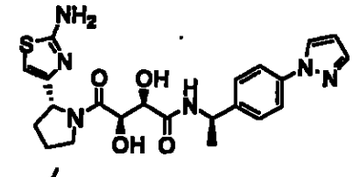


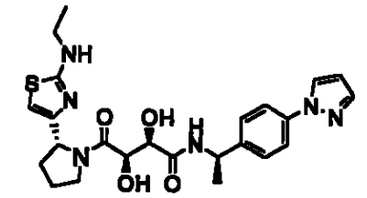


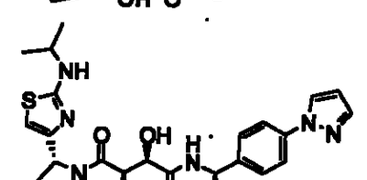


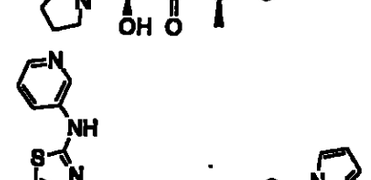


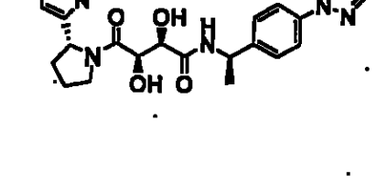


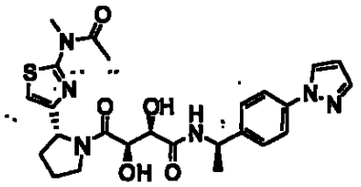


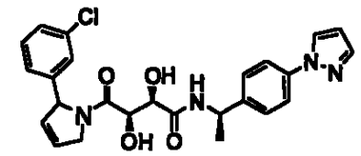


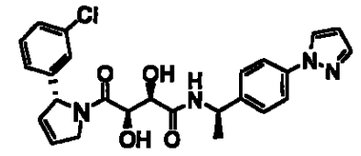


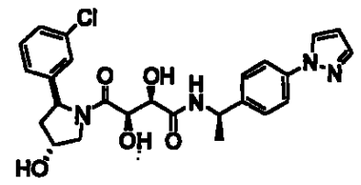


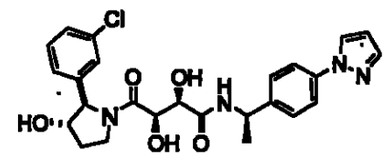


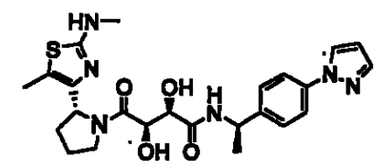


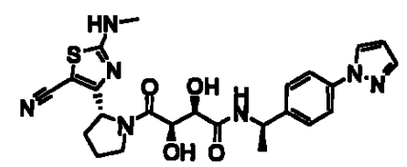


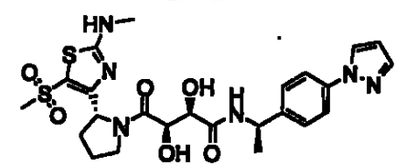


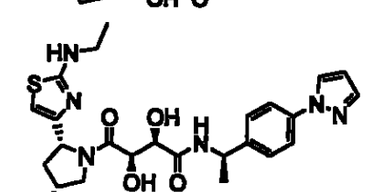


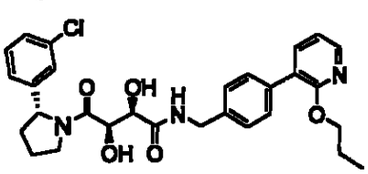


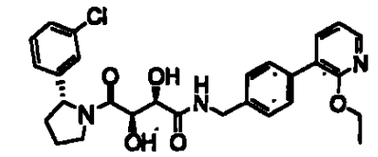


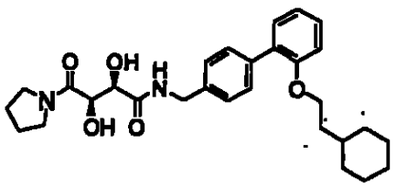


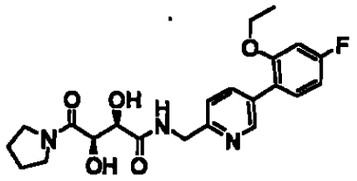


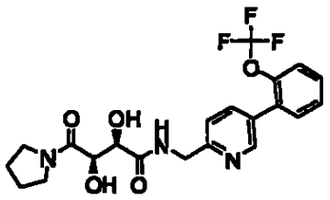


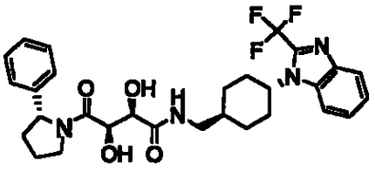


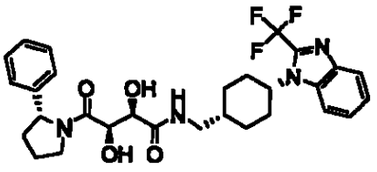


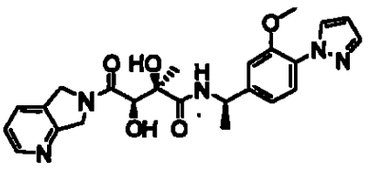


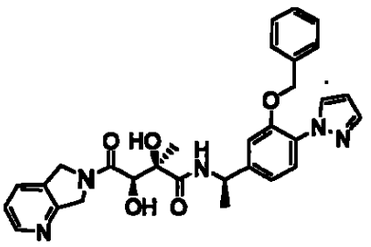


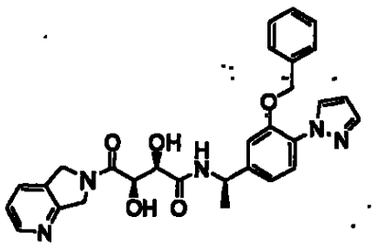


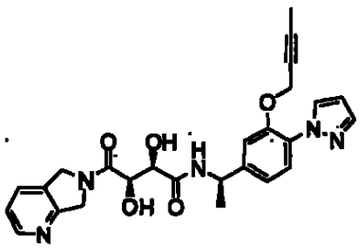


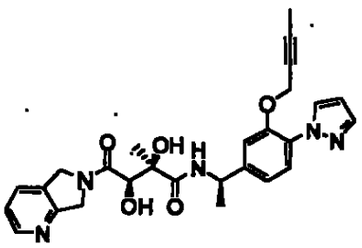


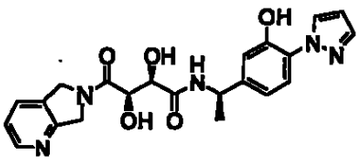


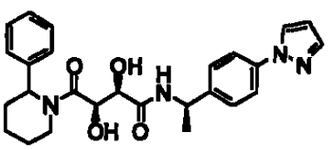


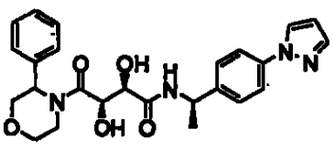


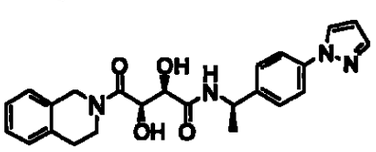


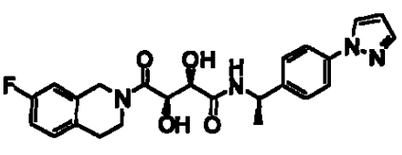


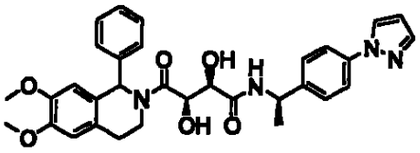


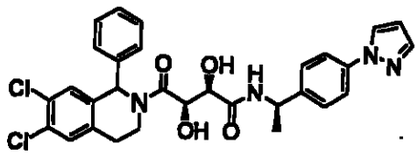


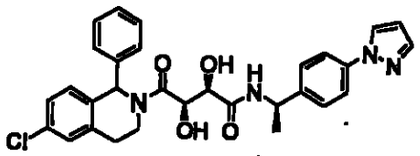


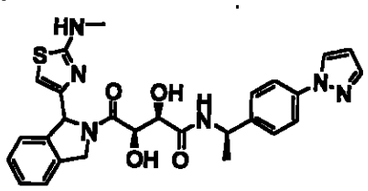


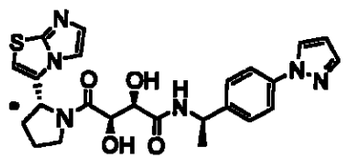


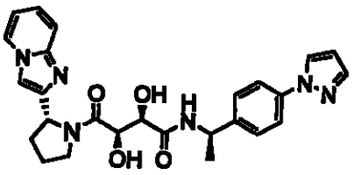


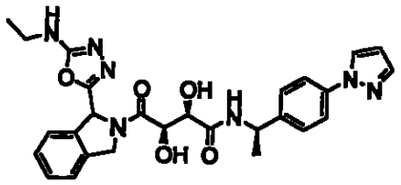


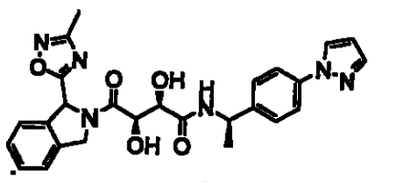


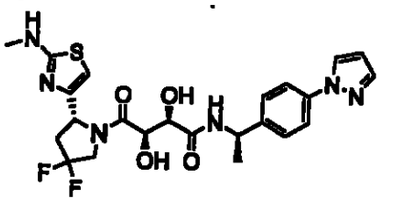


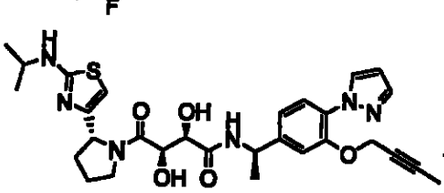


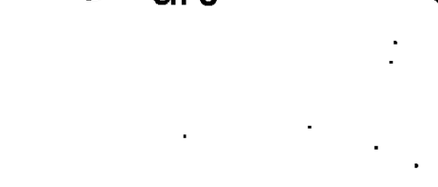


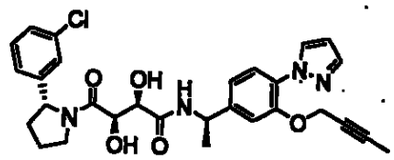


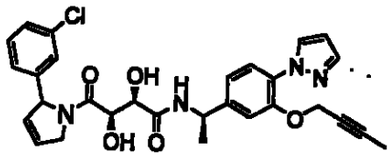


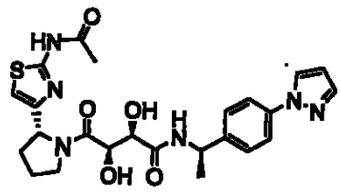


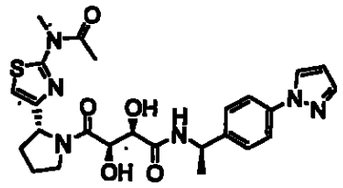


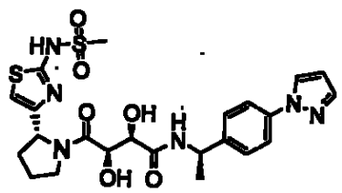


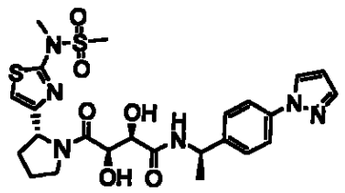


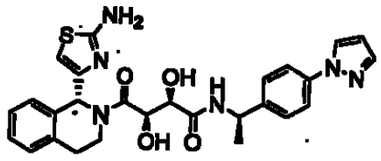


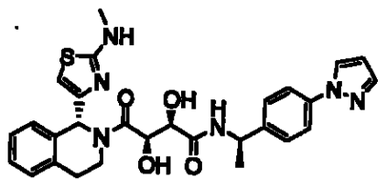


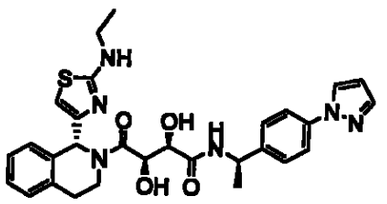


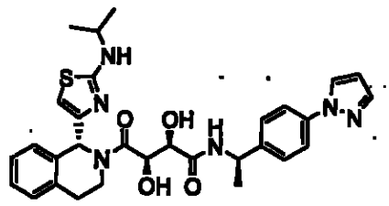


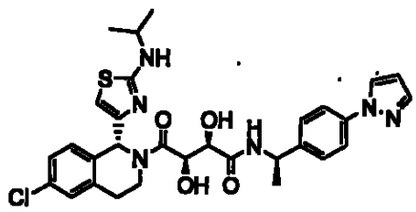


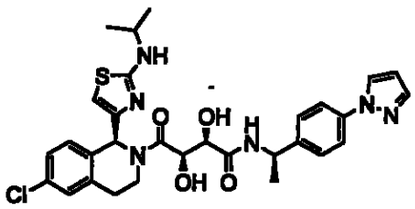


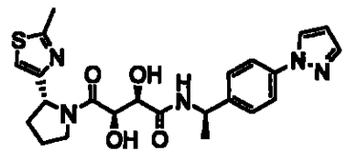


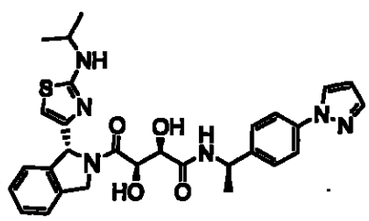


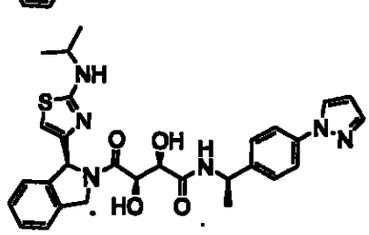


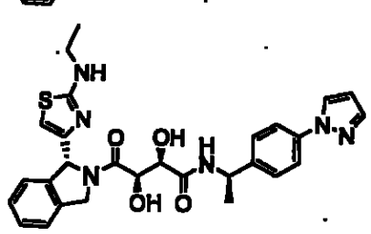


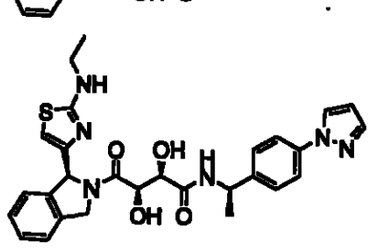


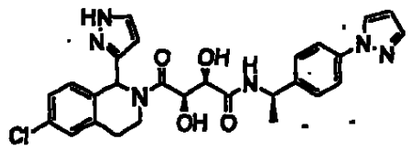


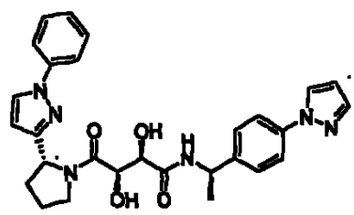


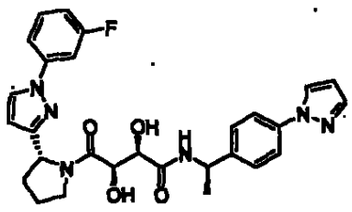




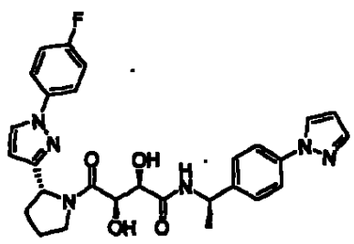






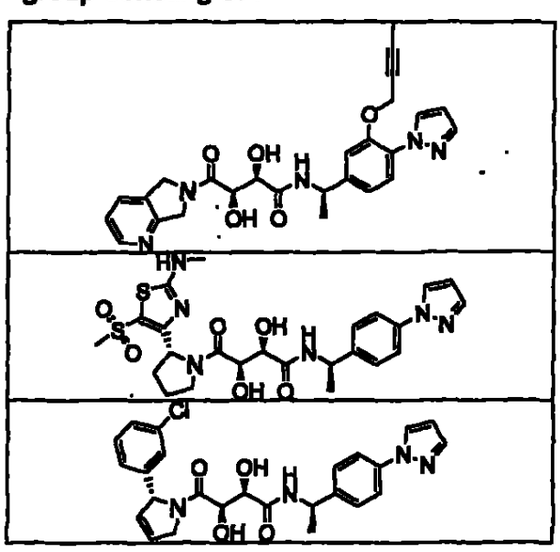


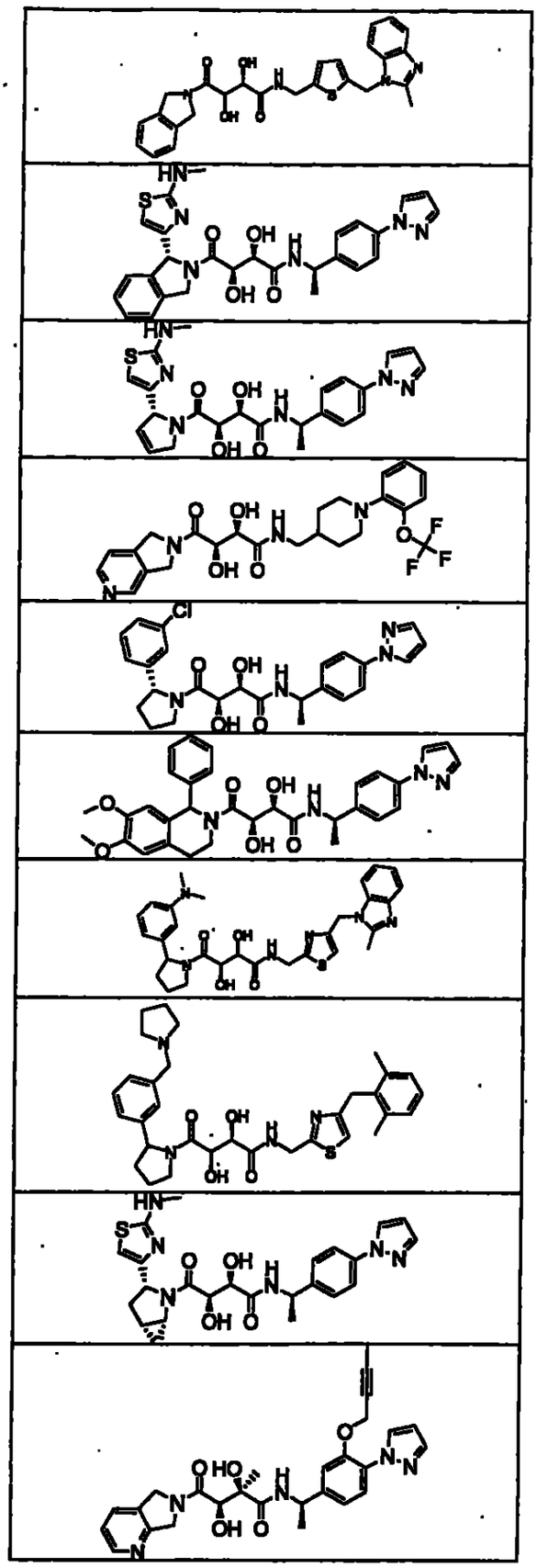
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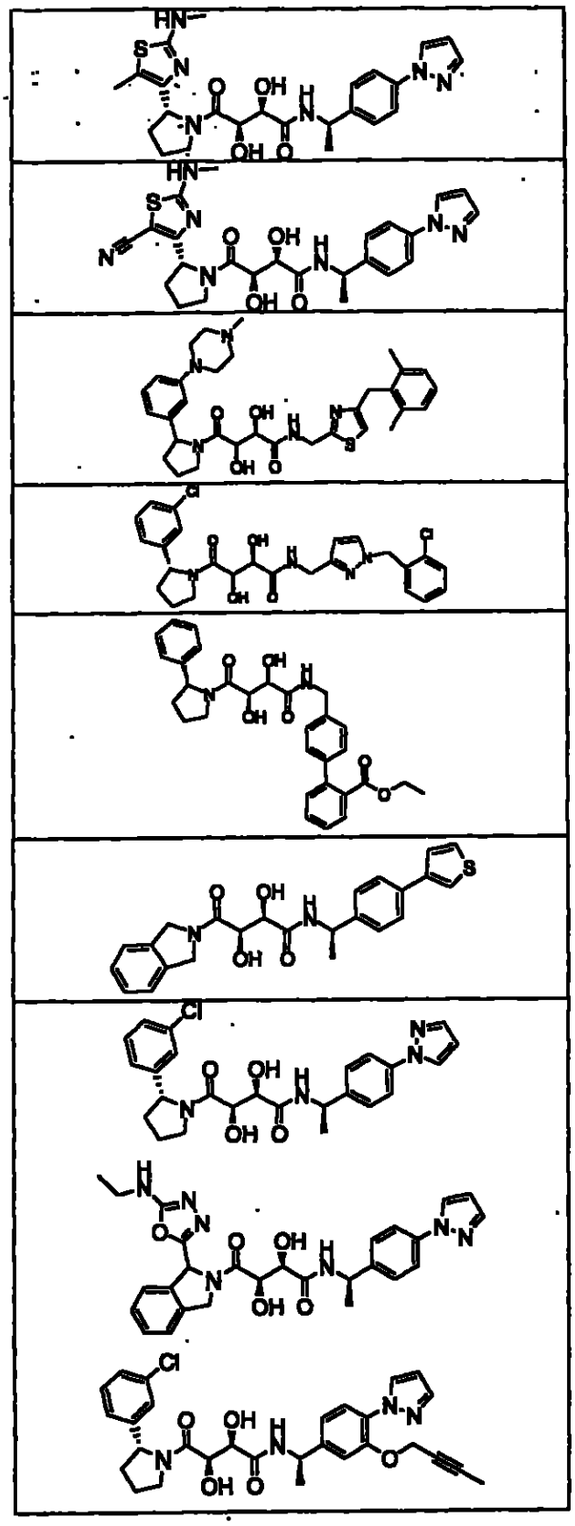


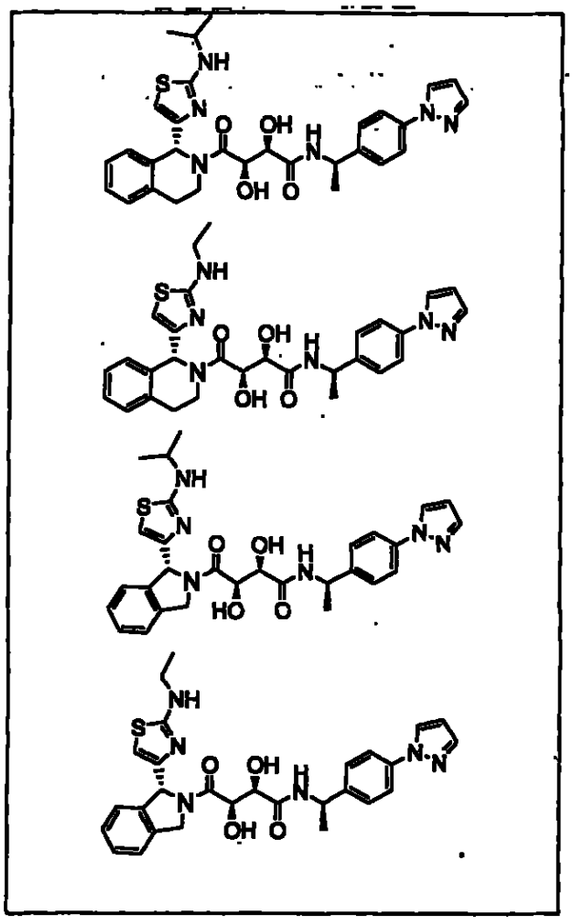
The above preferred compounds have TACE K_i values of less than 20nM.

In a more preferred embodiment, the compound is selected from the group consting of :









The above more preferred compounds have TACE K_i values of less than 5 nM.

In another aspect, the invention provides a pharmaceutical composition for treating disorders associated with TACE, TNF-α, MMP, ADAM or any combination thereof in a subject comprising, administering to the subject in need of such treatment a therapeutically effective amount of a compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a compound of formula 1 in purified form.

In another aspect, the invention provides a method of treating a condition or disease mediated by TACE, MMPs, TNF-α, aggrecanase (such as aggrecanase 1 or aggrecanase 2), or any combination thereof in a subject comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, inflammatory bowel disease, multiple sclerosis and psoriasis in a subject, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of fever, cardiovascular conditions, hemorrhage, coagulation, cachexia, anorexia, alcoholism, acute phase response, acute infection, shock, graft versus host reaction, autoimmune disease and HIV infection in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, osteo and rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, ureitis, Wegener's granulomatosis, Behcehe disease, Sjogren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, transplant rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis,

reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and bronchitis in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with COPD, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with rheumatoid arthritis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with Crohn's disease, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with psoriasis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with ankylosing spondylitis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with sciatica, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least

one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with complex regional pain syndrome, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with psoriatic arthritis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with multiple sclerosis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof, in combination with a compound selected from the group consisting of Avonex®, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis.

Additionally, a compound of the present invention may be co-administered or used in combination with disease-modifying antirheumatic drugs (DMARDS) such as methotrexate, azathioprine, leflunomide, pencillinamine, gold salts, mycophenolate mofetil, cyclophosphamide and other similar drugs. They may also be co-administered with or used in combination with NSAIDS such as piroxicam, naproxen, indomethacin, ibuprofen and the like; COX-2 selective inhibitors such as Vioxx® and Celebrex®; immunosuppressives such as steroids, cyclosporin, Tacrolimus, rapamycin and the like; biological response modifiers (BRMs) such as Enbrel®, Remicade®, IL-1 antagonists, anti-CD40, anti-CD28, IL-10, anti-adhesion molecules and the like; and other anti-inflammatory agents such as p38 kinase inhibitors, PDE4 inhibitors, other chemically different TACE inhibitors, chemokine receptor antagonists, Thalidomide and other small molecule inhibitors of pro-inflammatory cytokine production.

Also, a compound of the present invention may be co-administered or used in combination with an H1 antagonist for the treatment of seasonal allergic rhinitis and/or asthma. Suitable H1 antagonists may be, for example, Claritin®, Clarinex®, Allegra®, or Zyrtec®.

In another aspect, the invention provides a method of treating a condition or disease mediated by TACE, MMPs, TNF-α, aggrecanase, or any combination thereof in a subject comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof in combination with a therapeutically effective amount of at least one medicament selected from the group consisting of disease modifying anti-rheumatic drugs (DMARDS), NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, biological response modifiers (BRMs), anti-inflammatory agents and H1 antagonists.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, inflammatory bowel disease, multiple sclerosis and psoriasis in a subject, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof in combination with a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDS, NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, BRMs, anti-inflammatory agents and H1 antagonists.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's

disease and colitis, osteo and rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, adult-Still's disease, uveitis, Wegener's granulomatosis, Behcehe disease, Sjogren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, transplant rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and bronchitis in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof in combination with a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDS, NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, BRMs, anti-inflammatory agents and H1 antagonists.

In another aspect, the invention provides a method for treating RA comprising administering a compound of the formula I in combination with compound selected from the class consisting of a COX-2 inhibitor e.g. Celebrex® or Vioxx®; a COX-1 inhibitor e.g. Feldene®; an immunosuppressive e.g. methotrexate or cyclosporin; a sterold e.g. β-methasone; and anti-TNF-α compound, e.g. Enbrel® or Remicade®; a PDE IV inhibitor, or other classes of compounds indicated for the treatment of RA.

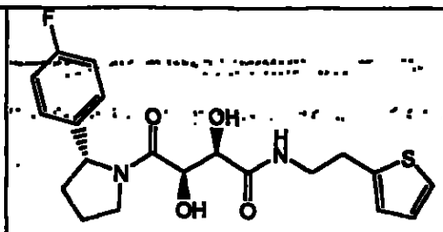
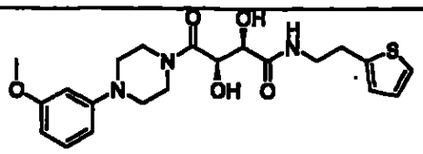
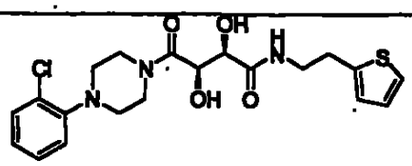
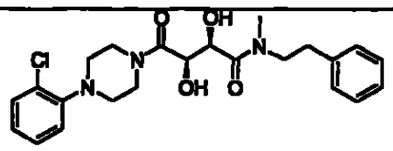
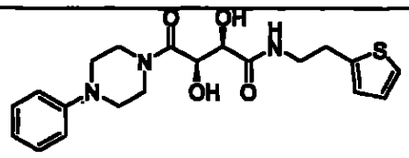
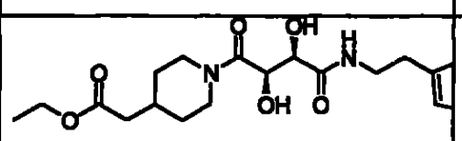
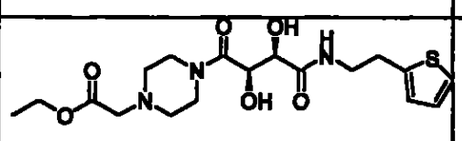
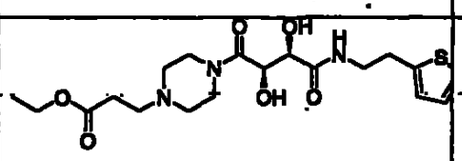
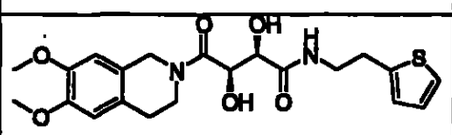
In another aspect, the invention provides a method for treating multiple sclerosis comprising administering a compound of the formula I in combination with a compound selected from the group consisting of Avonex®, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis.

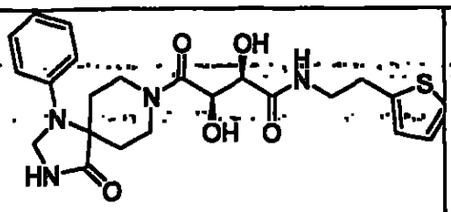
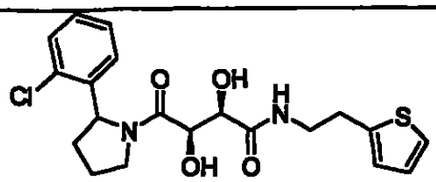
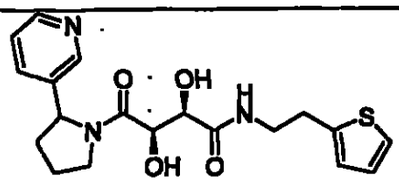
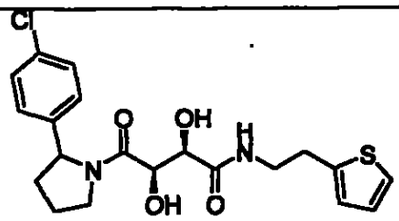
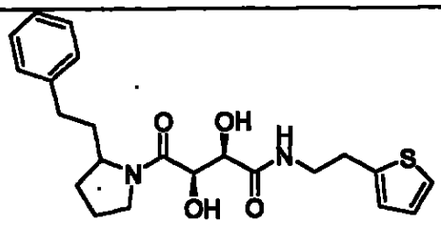
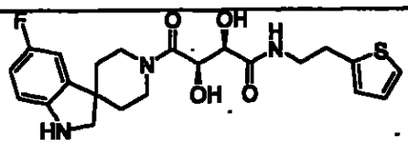
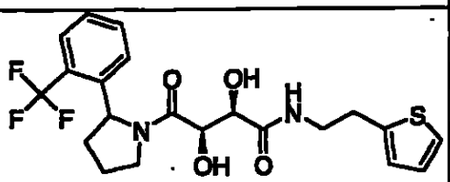
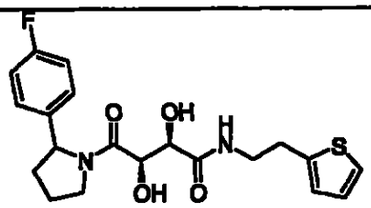
TACE activity is determined by a kinetic assay measuring the rate of increase in fluorescent intensity generated by TACE catalyzed cleavage of an internally quenched peptide substrate (SPDL-3). The purified catalytic domain of recombinant human TACE (rhTACEc, Residue 215 to 477 with two *mutation (S266A and N452Q) and a 6xHis tail) is used in the assay.* It is purified from the baculovirus/HI5 cells expression system using affinity chromatography. The substrate SPDL-3 is an internally quenched peptide (MCA-Pro-Leu-Ala-Gln-Ala-Val-Arg-Ser-Ser-Ser-Dpa-Arg-NH2), with its sequence derived from the pro-TNFα cleavage site. MCA is (7-Methoxycoumarin-4-yl)acetyl. Dpa is N-3-(2,4-Dinitrophenyl)-L-2,3-diaminopropionyl.

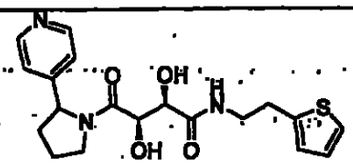
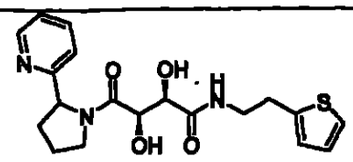
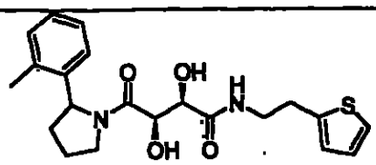
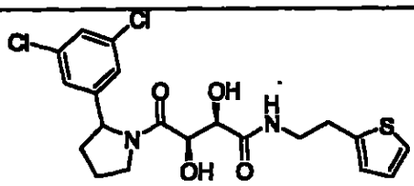
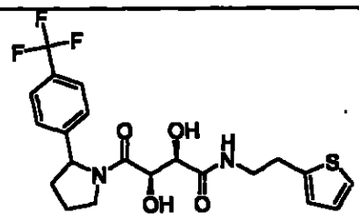
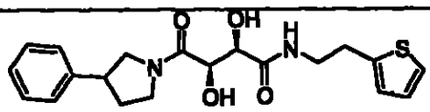
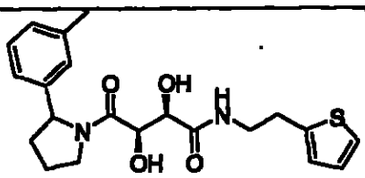
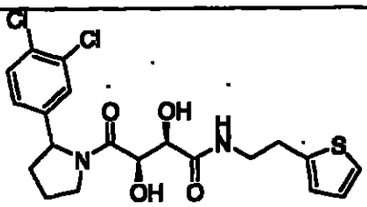
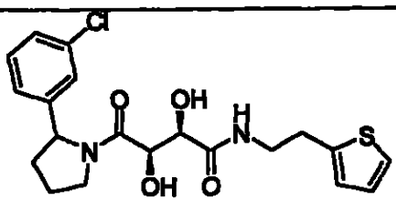
A 50 µl assay mixture contains 20 mM HEPES, pH 7.3, 5 mM $CaCl_2$, 100 µM $ZnCl_2$, 2 % DMSO, 0.04% Methylcellulose, 30 µM SPDL-3, 70 pM rhTACEc and a test compound. RhTACEc is pre-incubated with the testing compound for 90 min. at 25 °C. Reaction is started by addition of the substrate. The fluorescent intensity (excitation at 320 nm, emission at 405 nm) was measured every 45 seconds for 30 min. using a fluorospectrometer (GEMINI XS, Molecular Devices). Rate of enzymatic reaction is shown as Units per second. Effect of a test compound is shown as % of TACE activity in the absence of the compound.

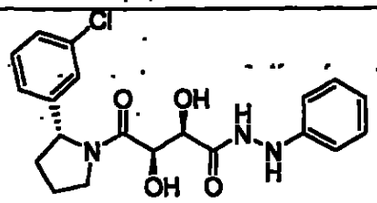
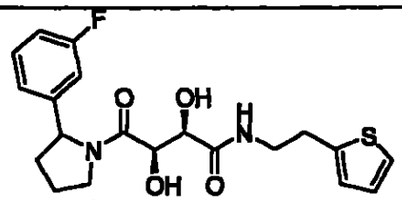
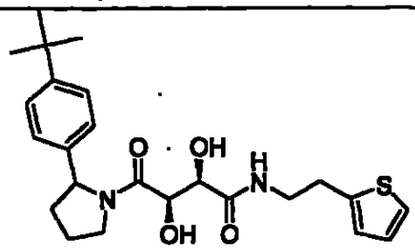
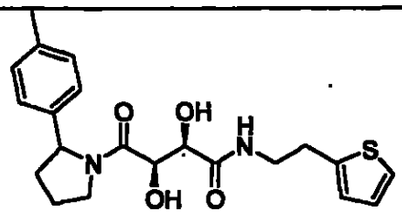
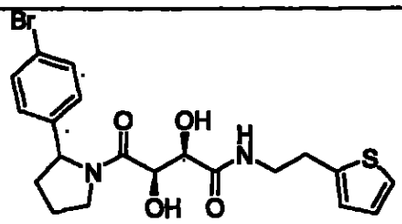
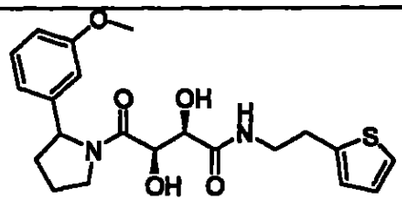
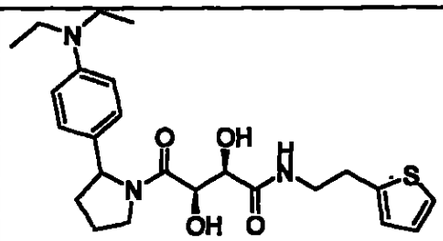
TACE inhibitory activities for representative compounds are shown in the table below. K_i values greater than 1000 nM (1 µM) are designated as D class. K_i values between 100 nM (0.1 µM) and 1000 nM (1 µM)are designated as C class. K_i values between 20 nM (0.02 µM) and 100 nM (0.1 µM) are designated as B class. K_i values less than 20 nM (0.02 µM) are designated as A class.

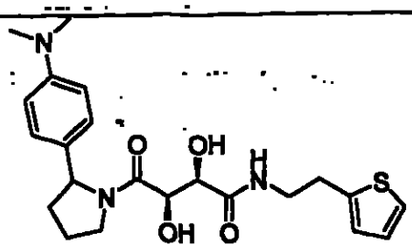
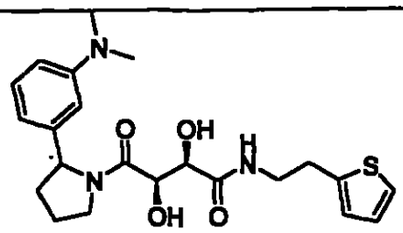
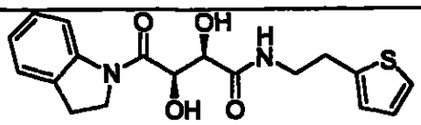
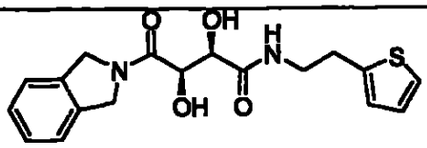
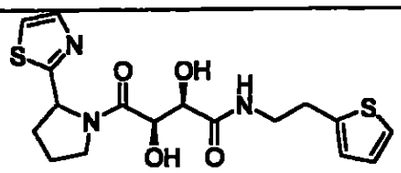
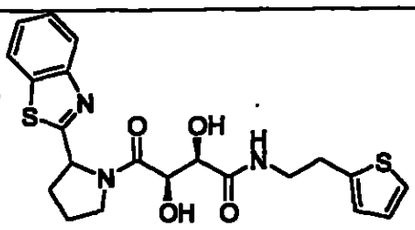
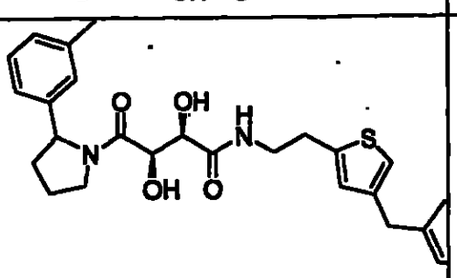
Compound #	Structure	K_i (nM)

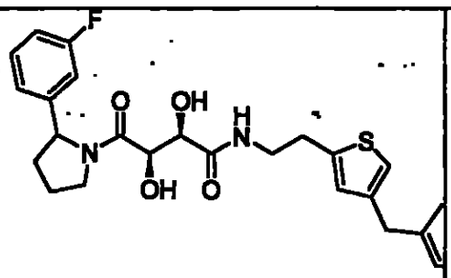
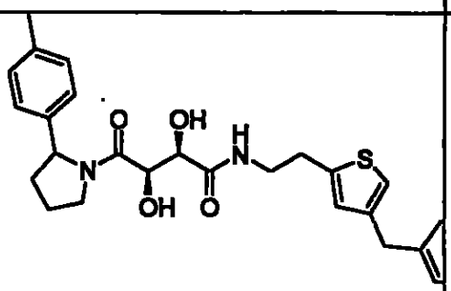
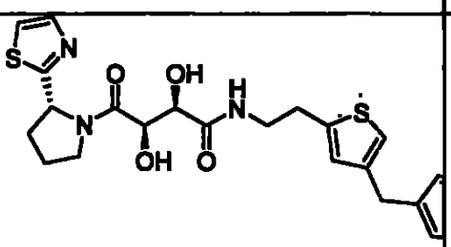
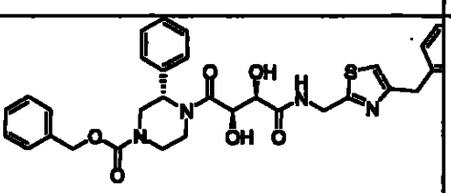
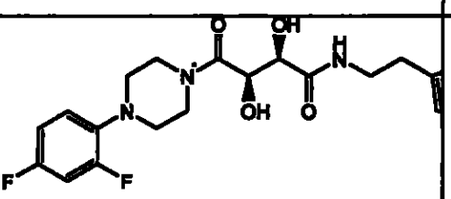
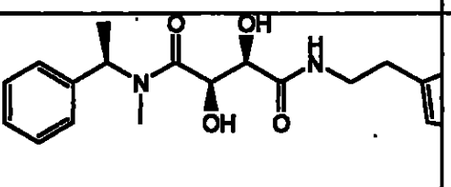
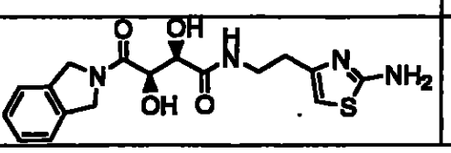
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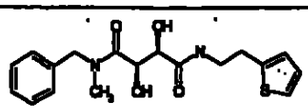
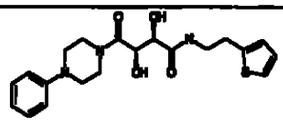
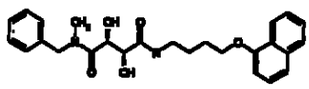
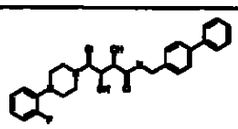
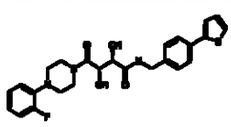
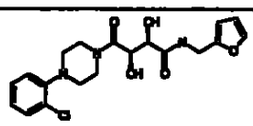
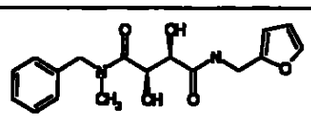
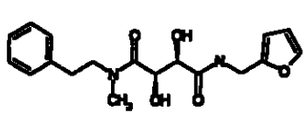
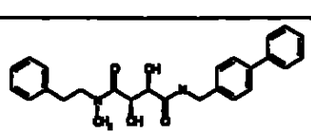
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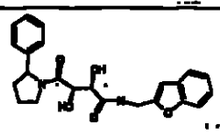
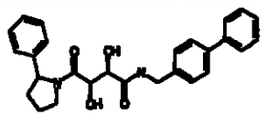
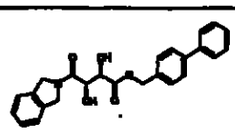
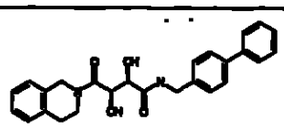
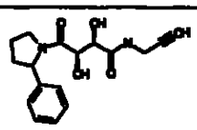
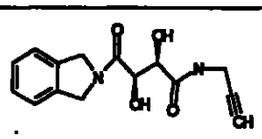
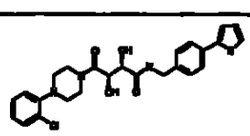
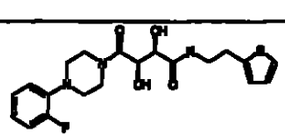
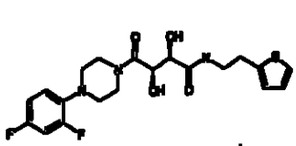
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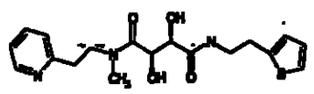
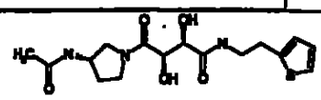
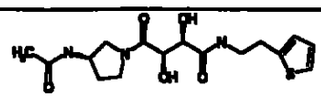
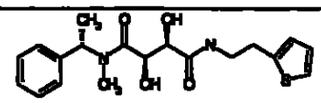
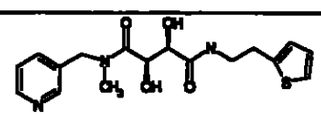
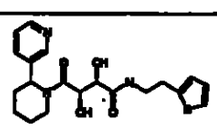
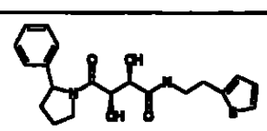
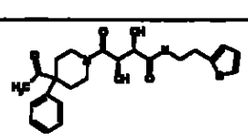
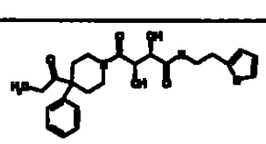
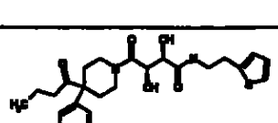
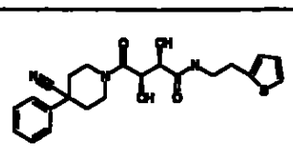
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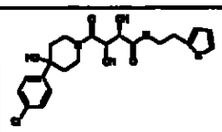
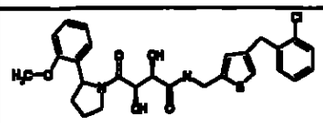
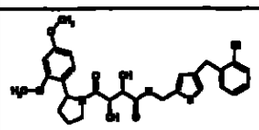
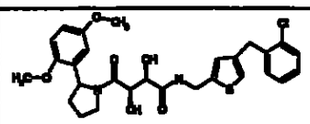
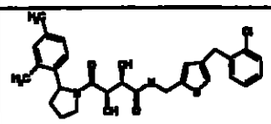
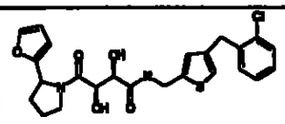
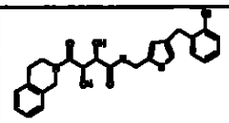
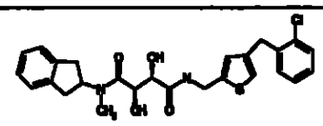
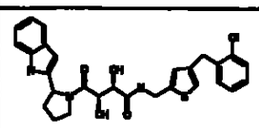
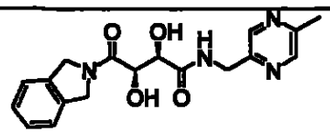
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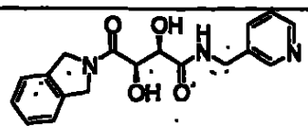
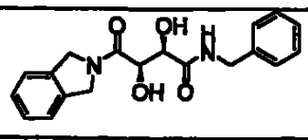
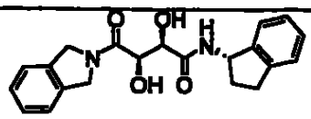
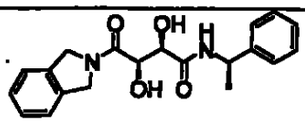
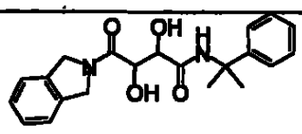
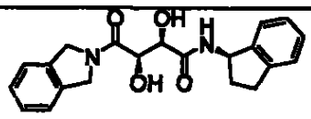
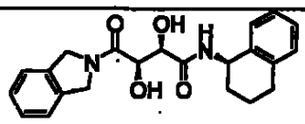
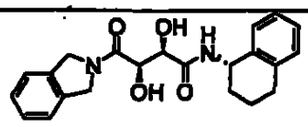
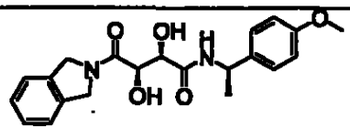
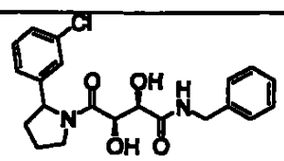
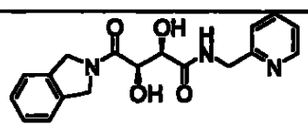
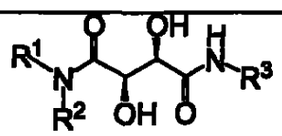
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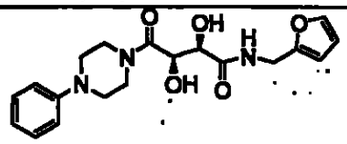
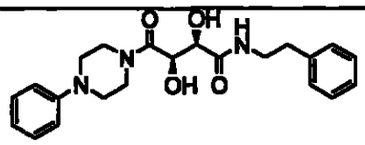
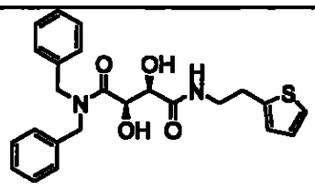
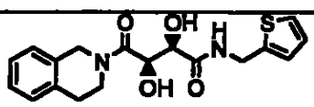
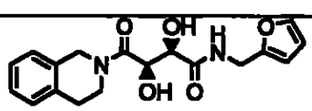
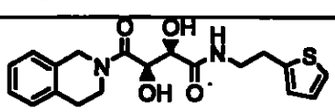
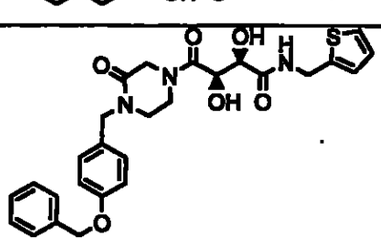
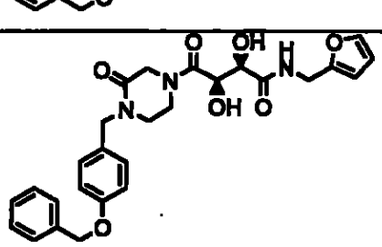
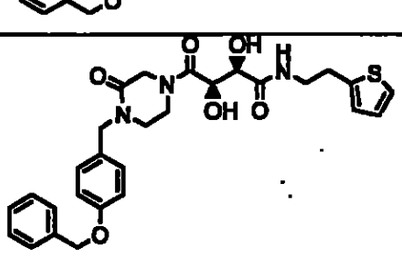
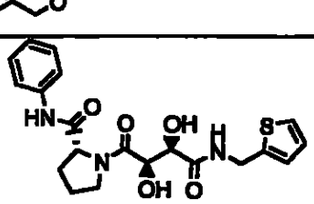
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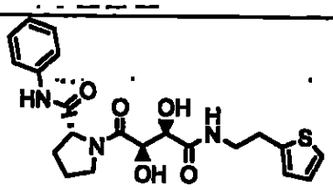
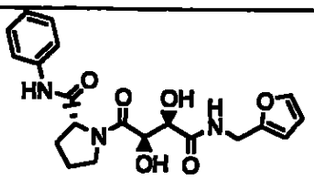
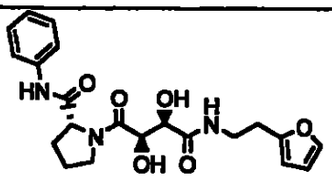
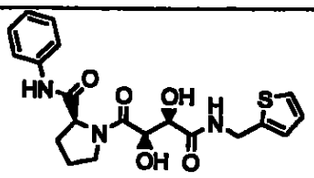
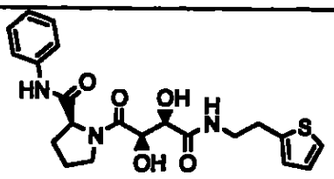
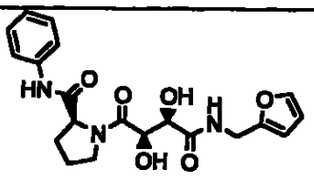
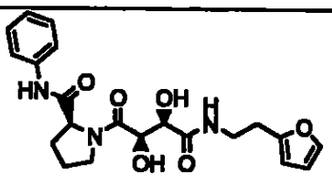
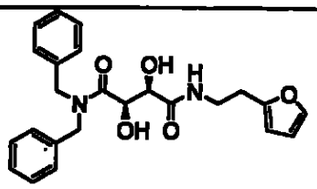
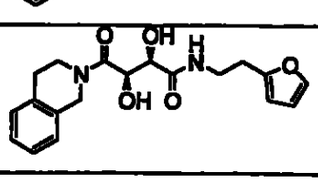
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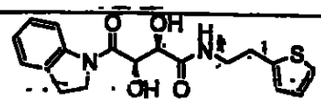
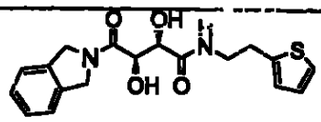
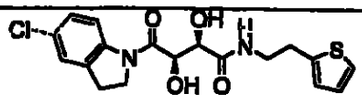
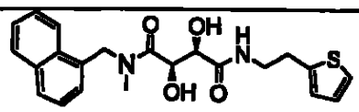
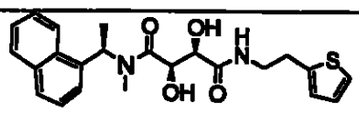
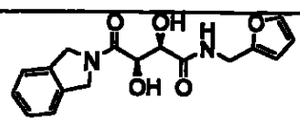
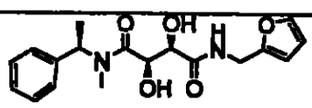
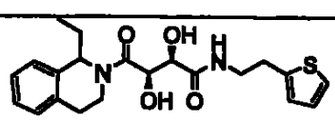
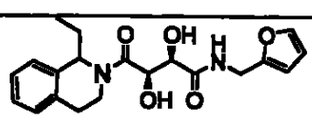
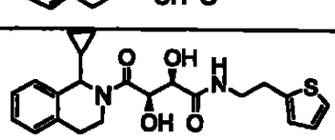
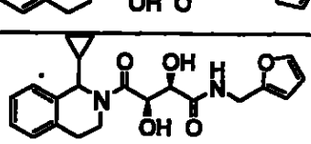
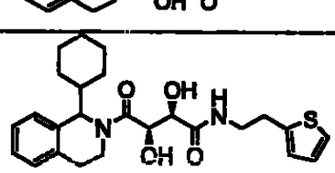
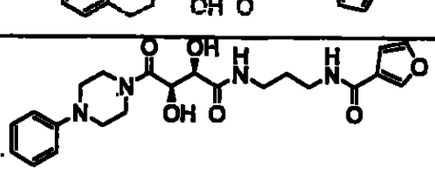
		
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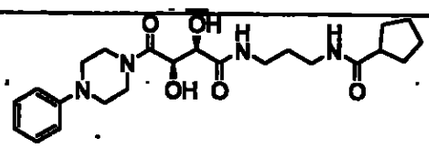
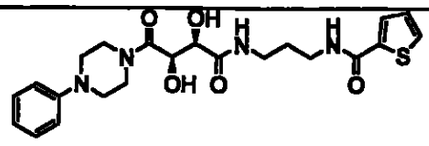
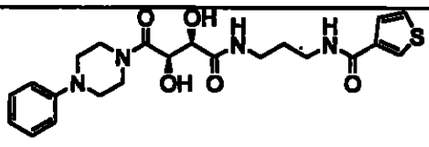
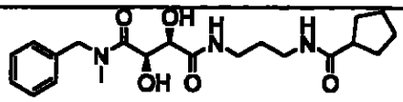
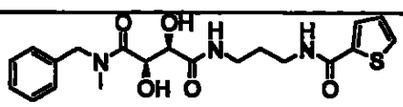
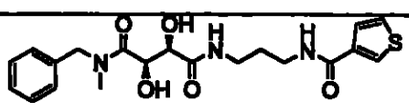
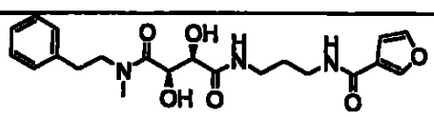
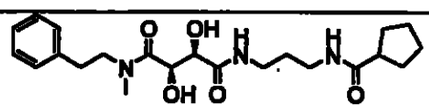
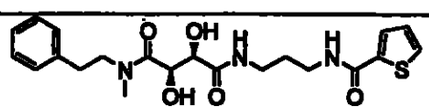
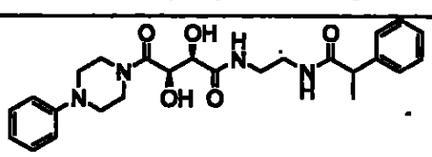
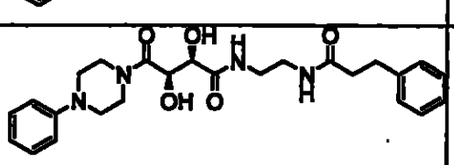
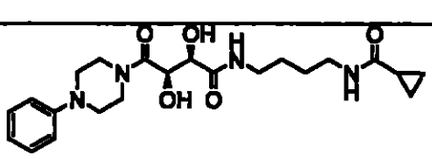
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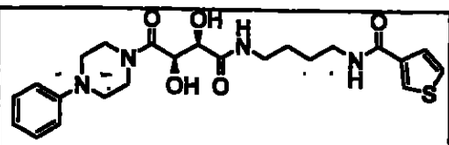
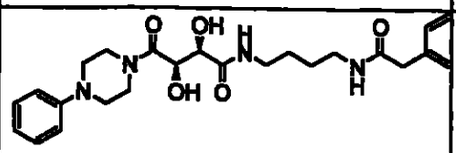
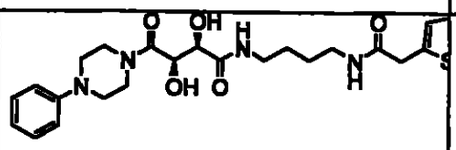
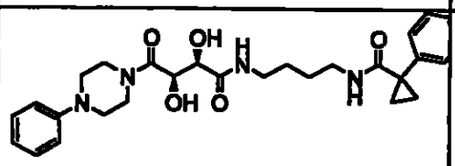
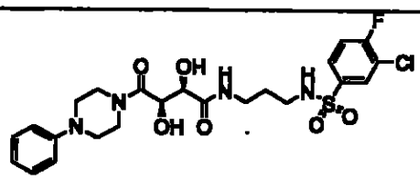
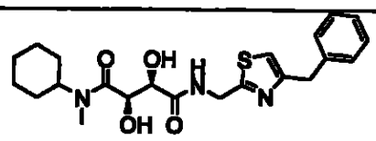
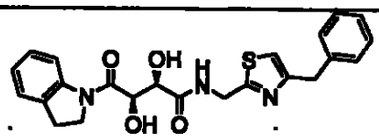
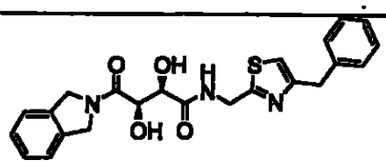
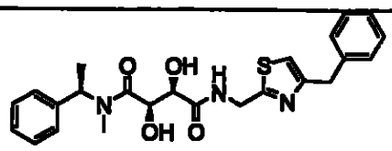
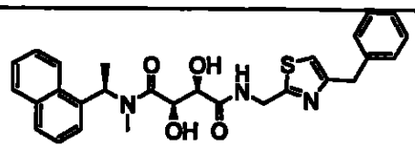
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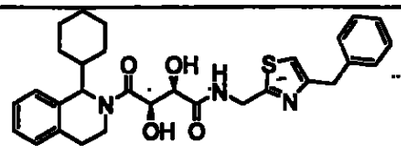
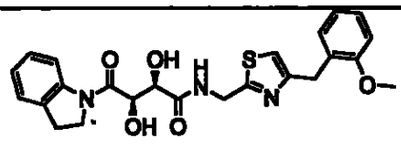
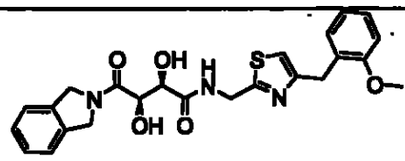
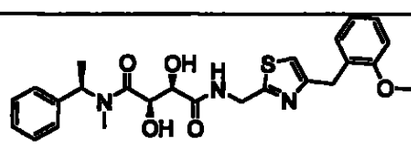
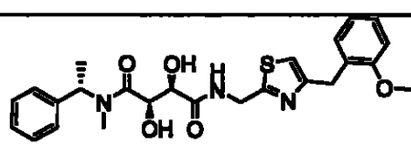
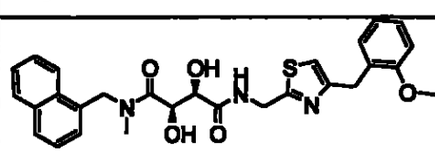
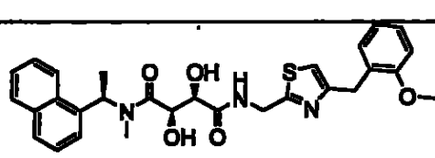
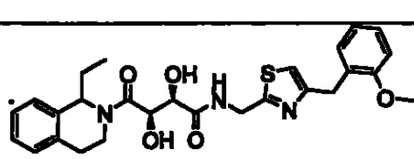
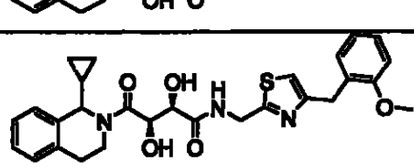
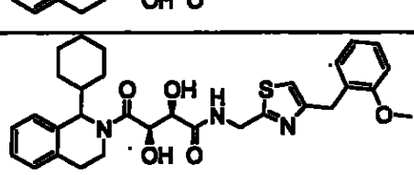
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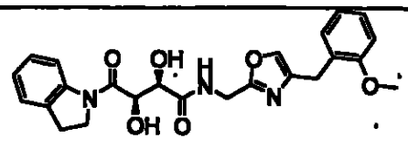
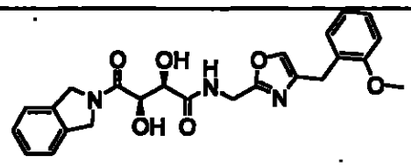
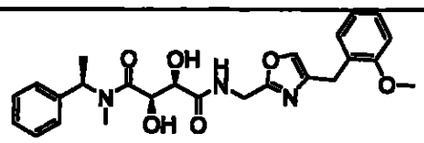
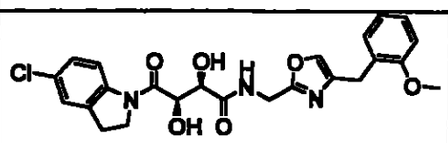
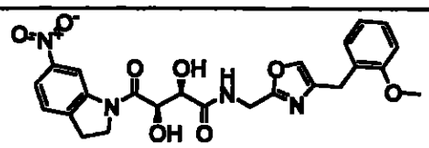
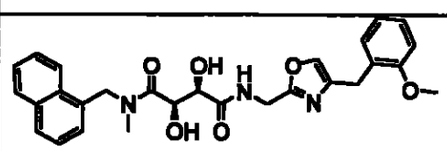
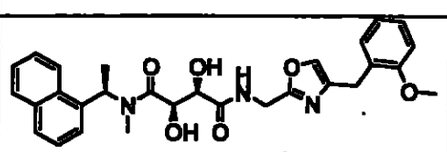
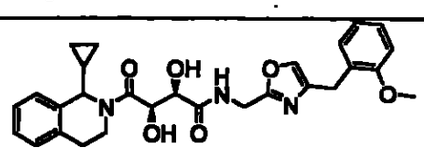
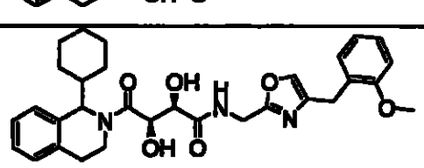
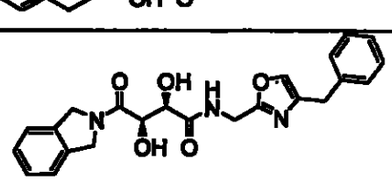
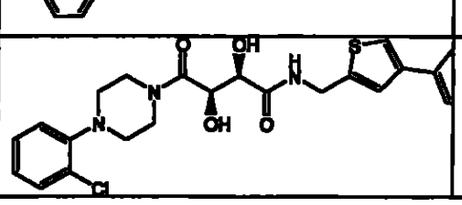
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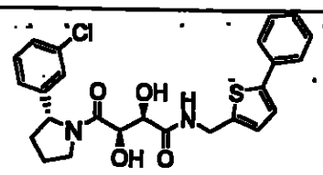
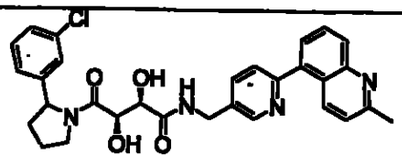
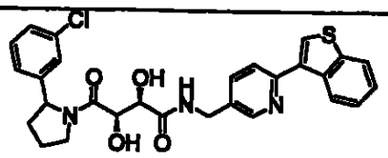
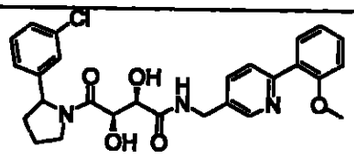
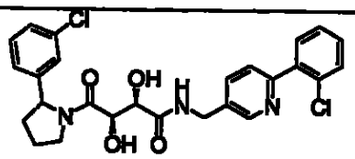
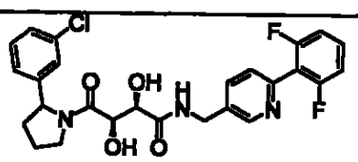
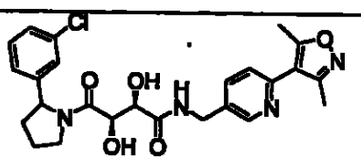
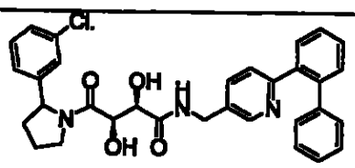
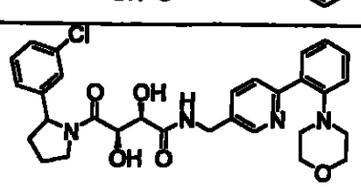
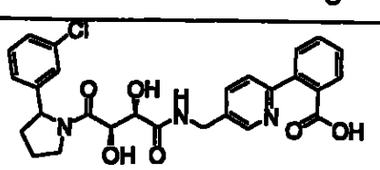
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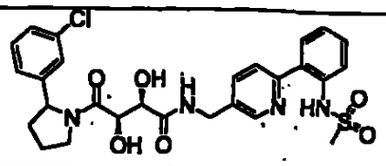
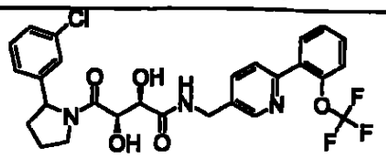
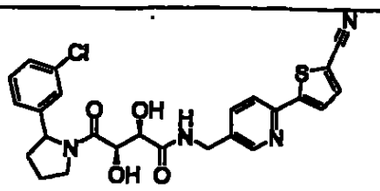
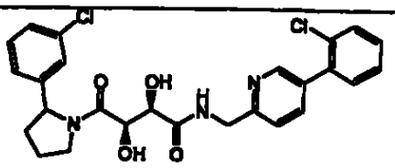
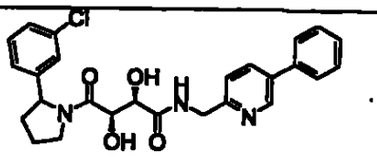
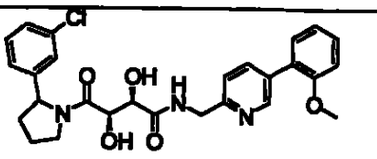
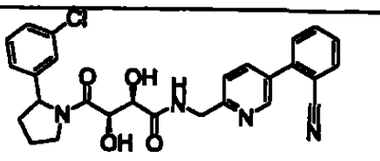
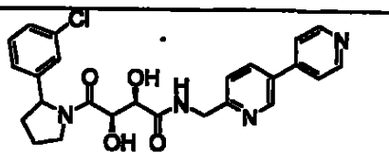
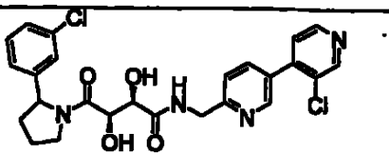
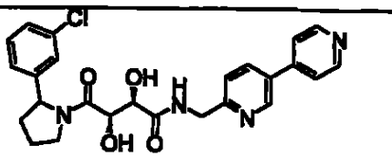
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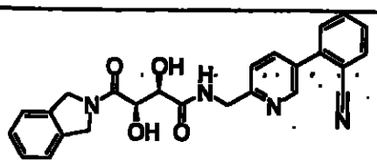
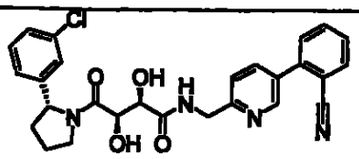
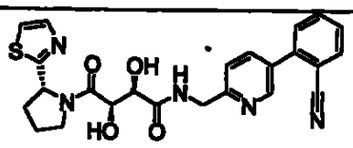
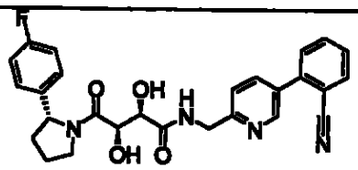
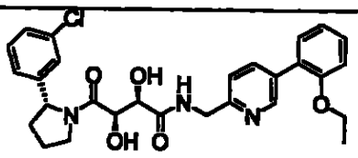
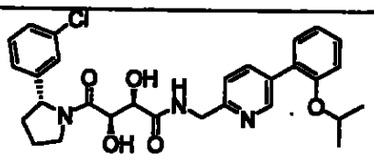
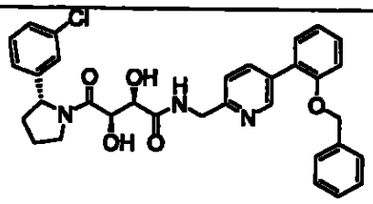
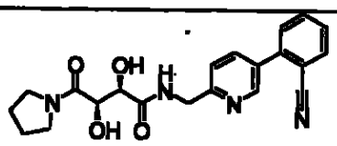
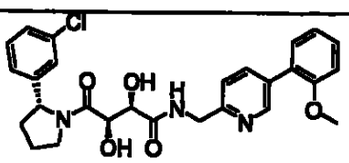
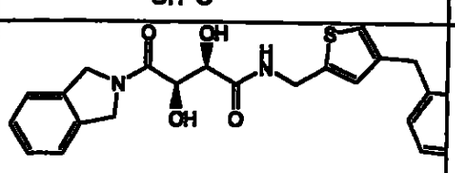
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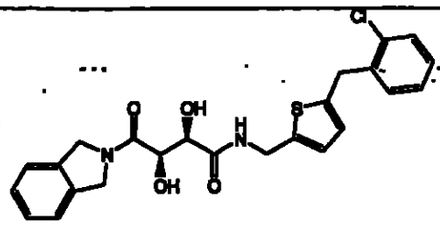
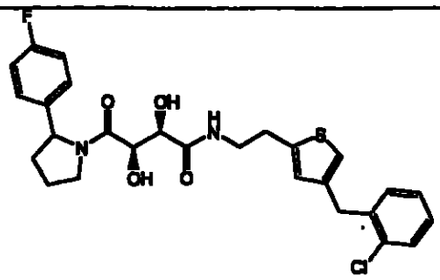
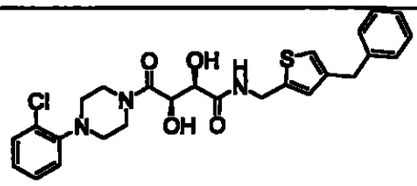
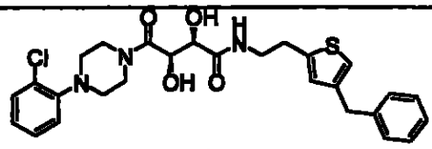
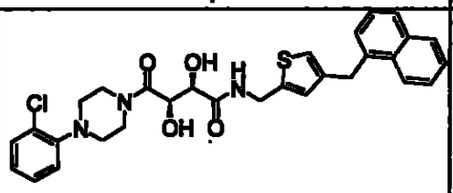
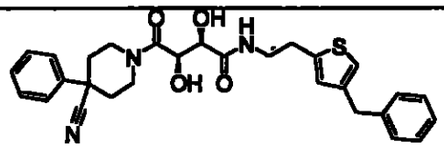
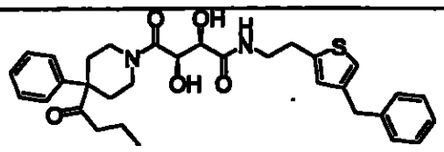
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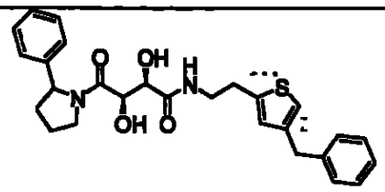
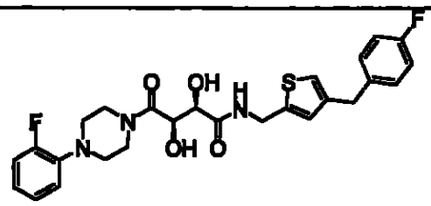
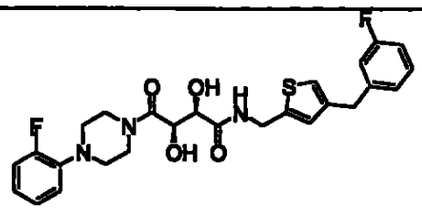
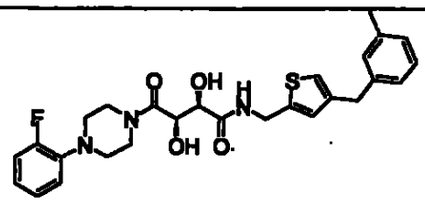
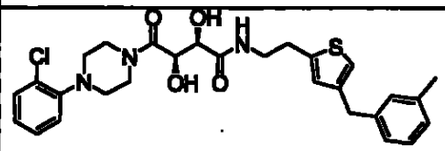
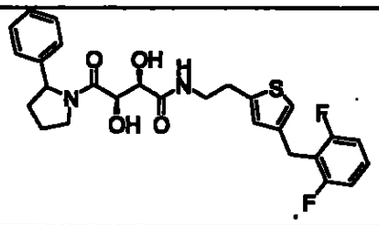
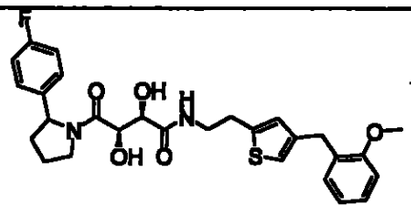
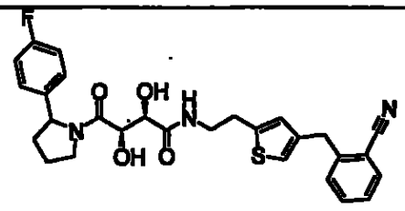
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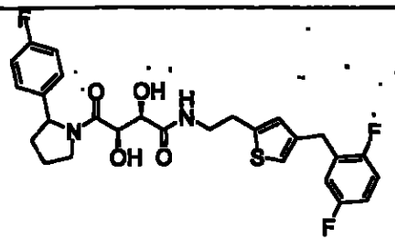
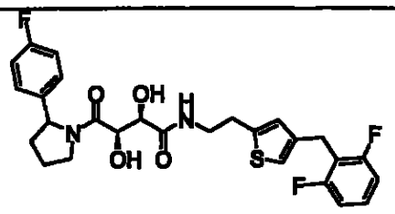
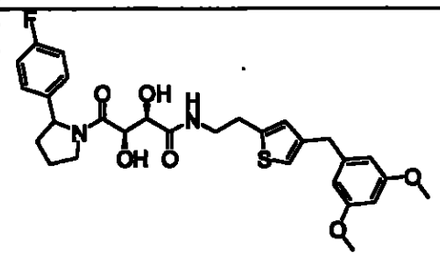
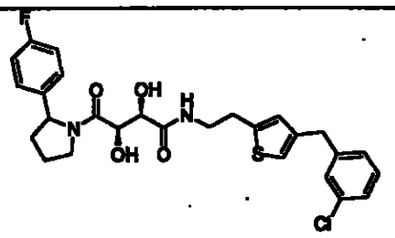
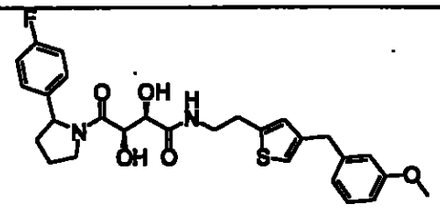
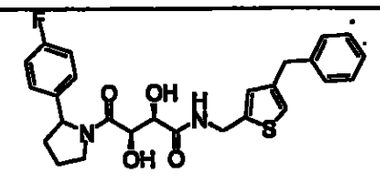
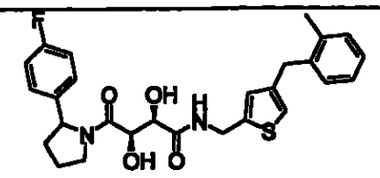
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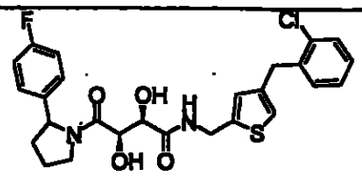
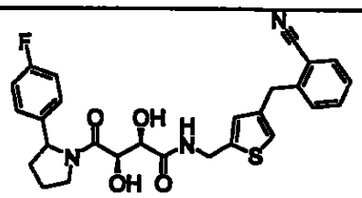
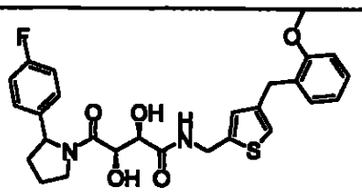
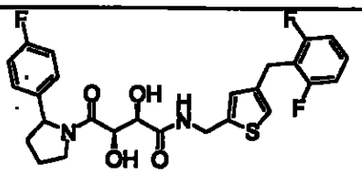
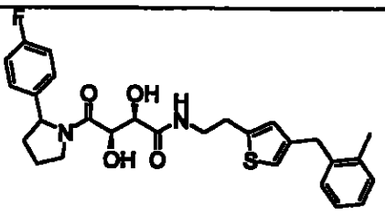
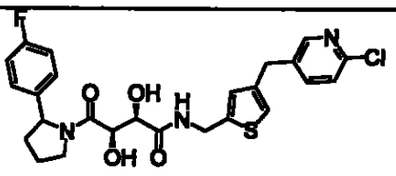
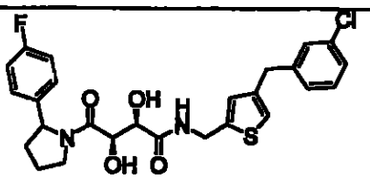
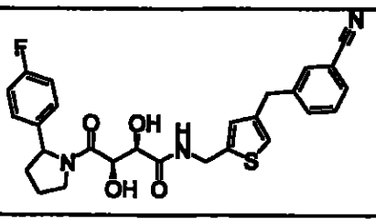
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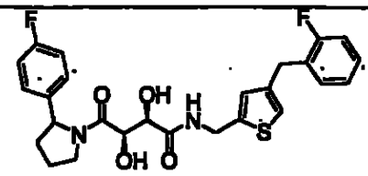
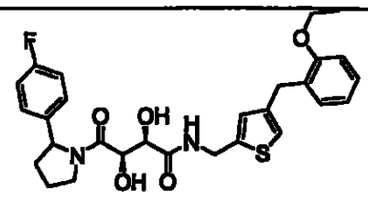
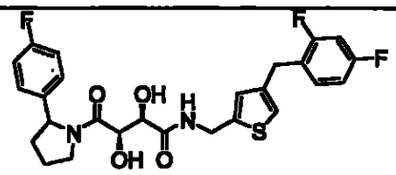
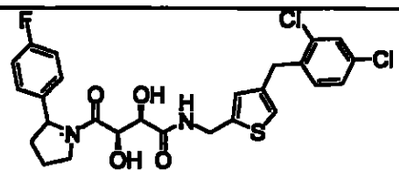
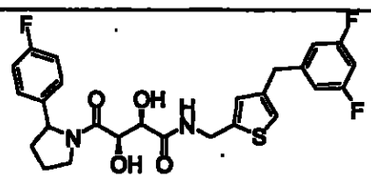
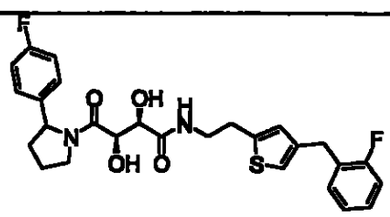
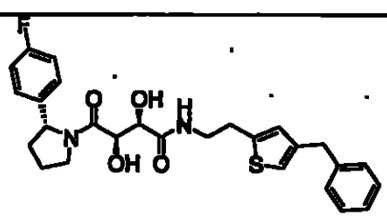
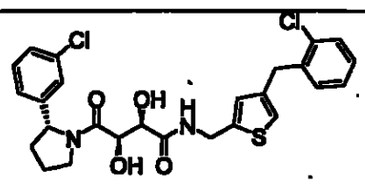
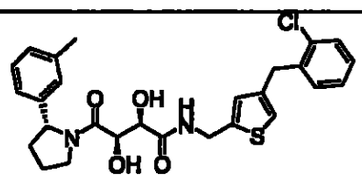
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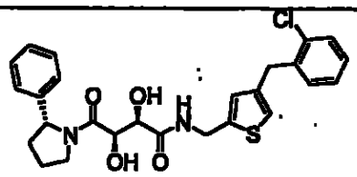
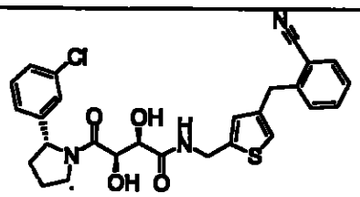
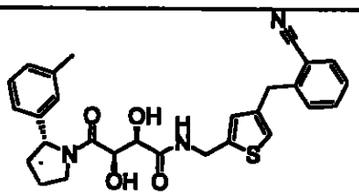
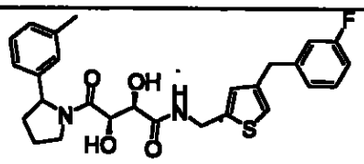
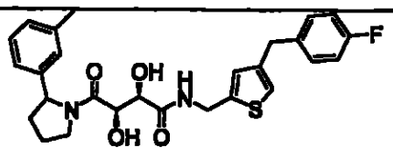
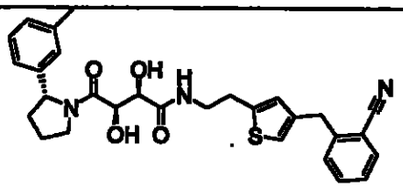
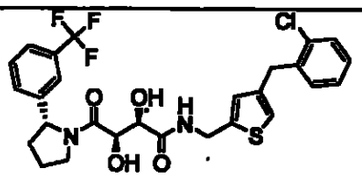
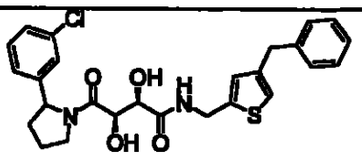
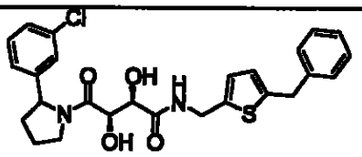
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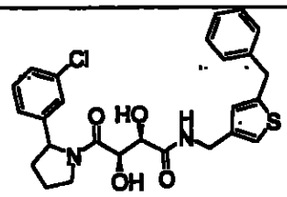
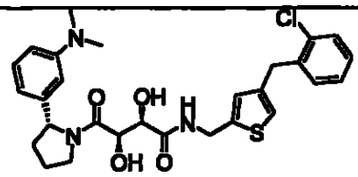
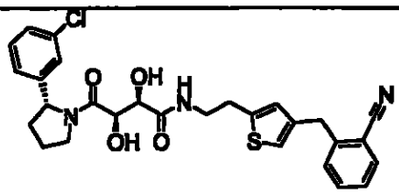
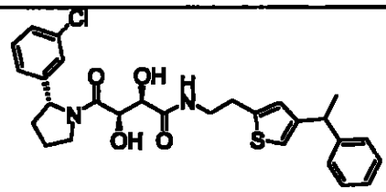
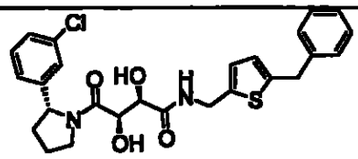
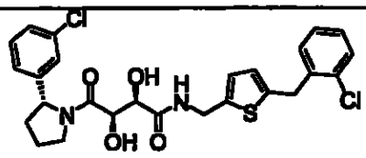
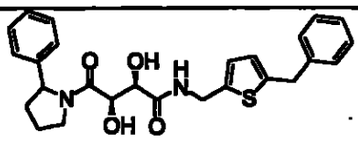
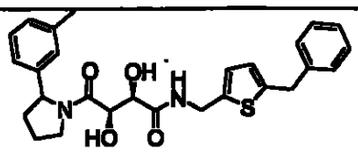
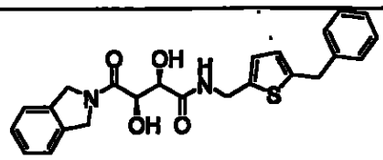
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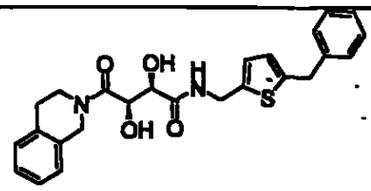
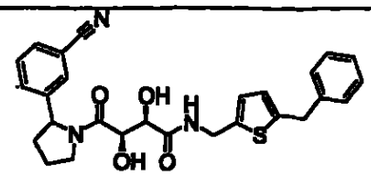
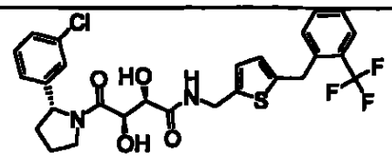
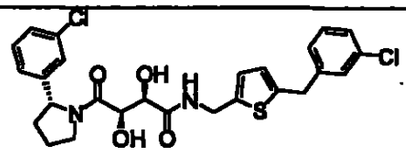
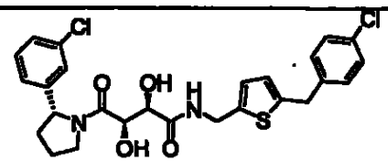
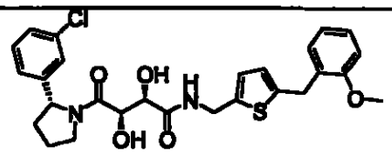
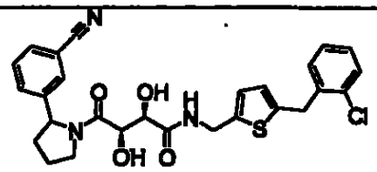
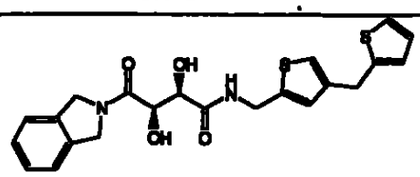
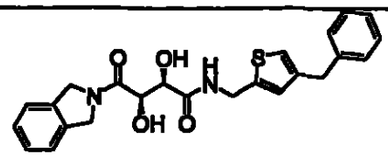
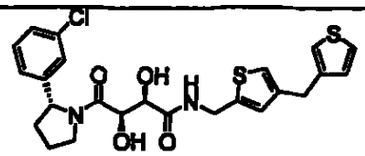
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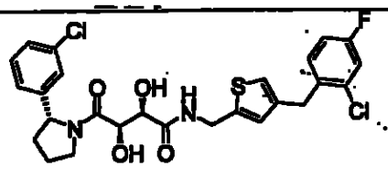
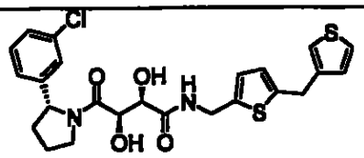
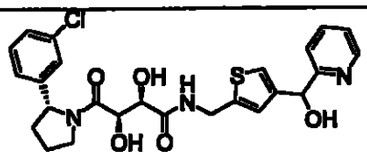
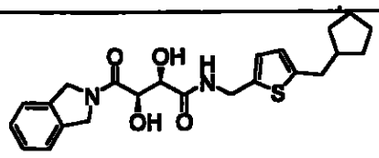
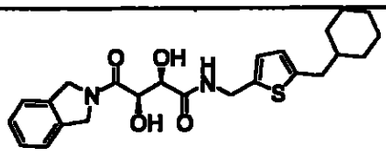
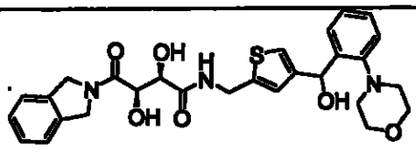
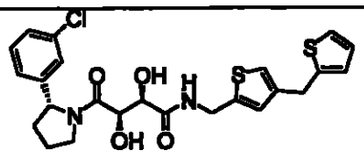
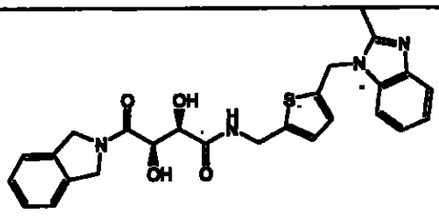
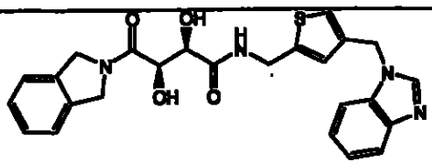
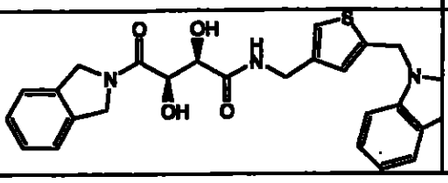
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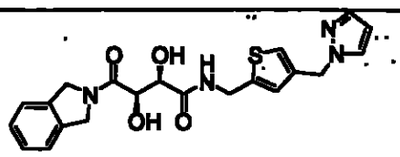
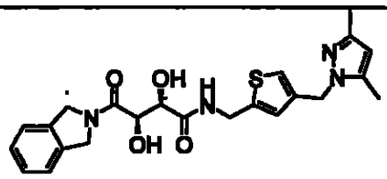
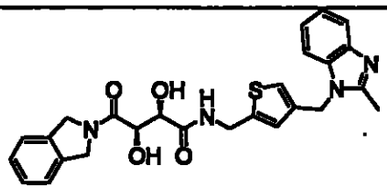
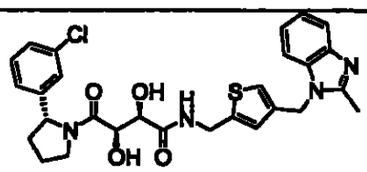
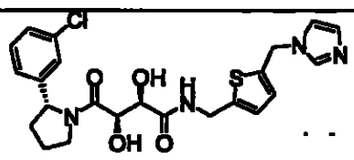
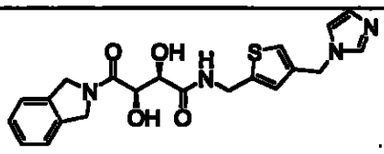
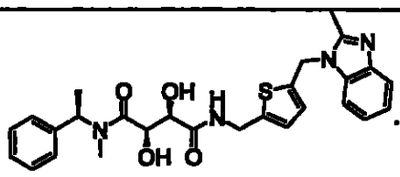
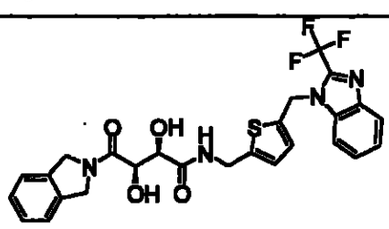
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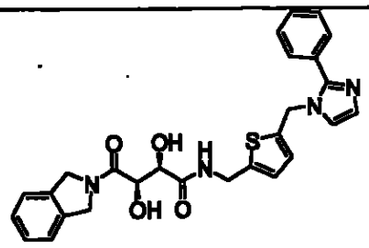
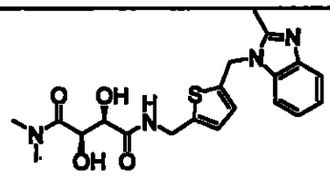
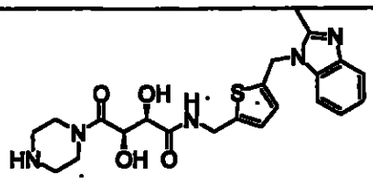
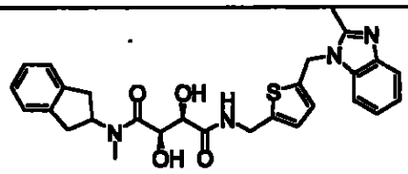
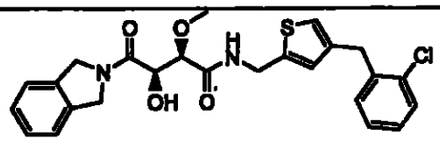
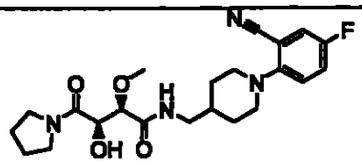
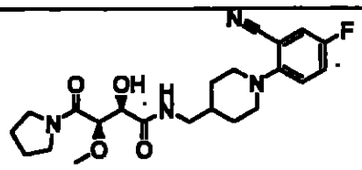
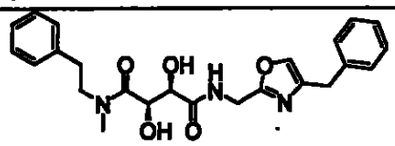
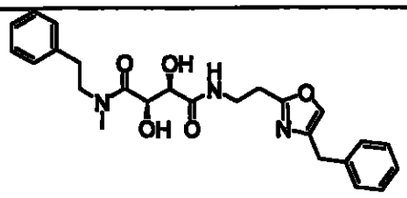
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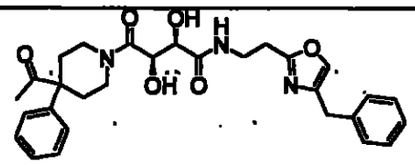
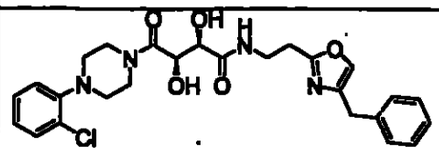
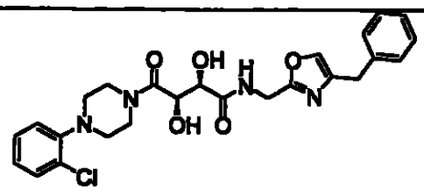
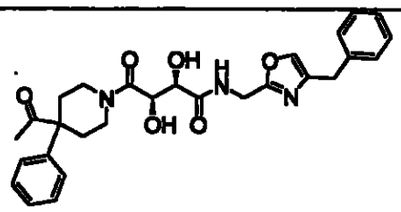
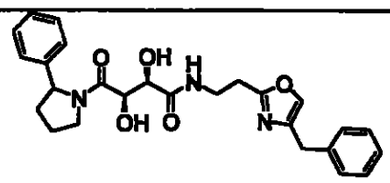
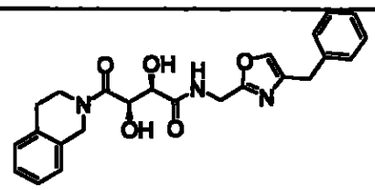
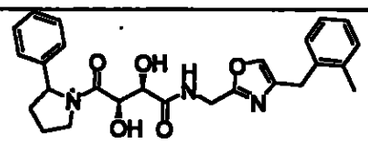
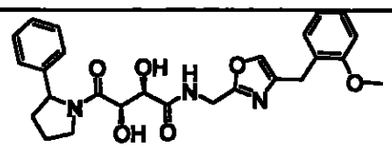
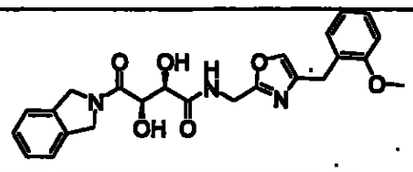
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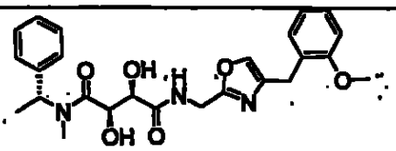
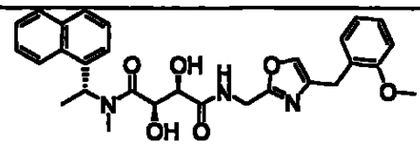
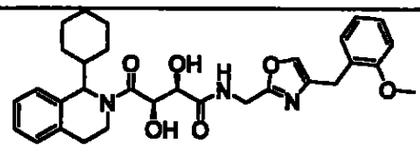
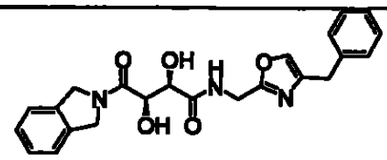
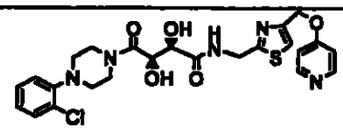
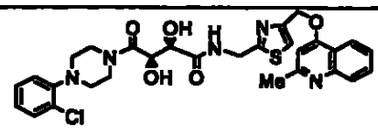
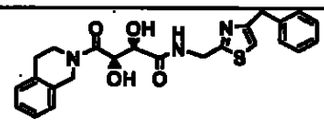
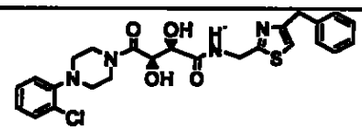
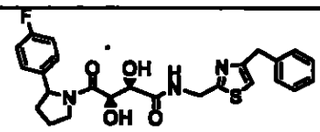
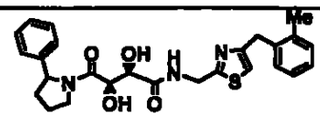
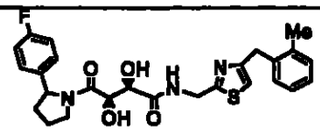
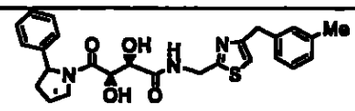
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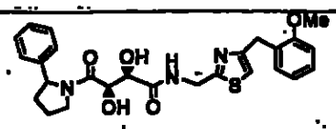
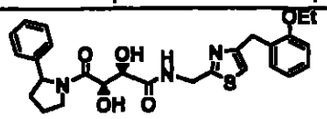
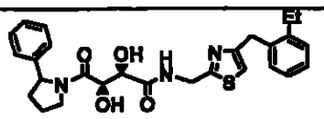
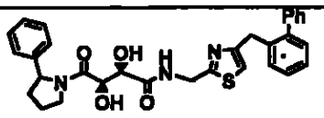
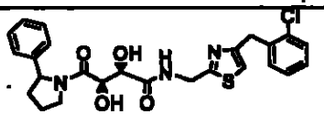
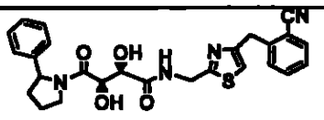
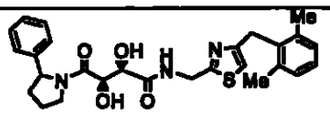
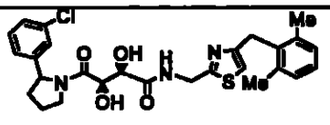
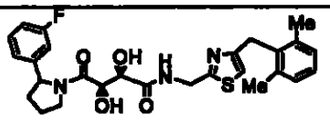
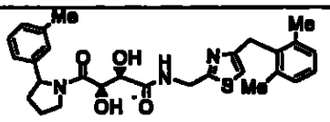
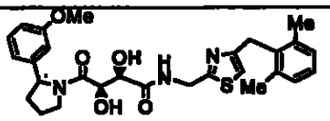
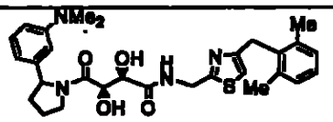
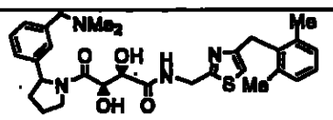
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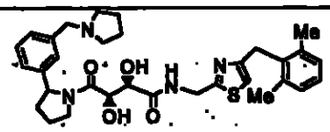
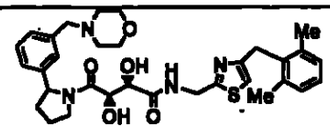
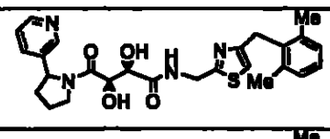
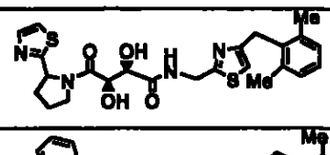
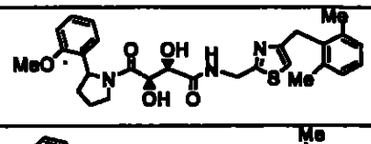
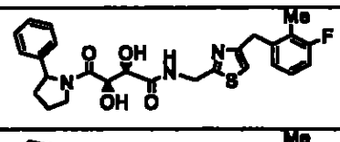
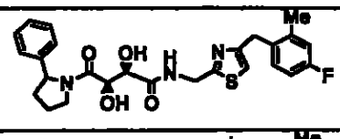
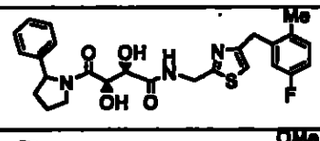
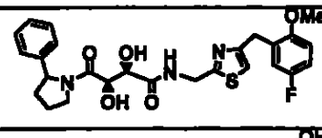
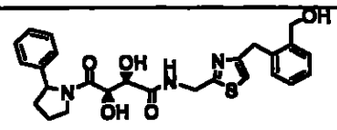
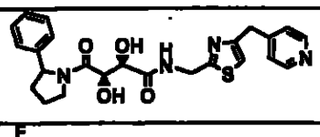
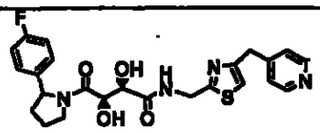
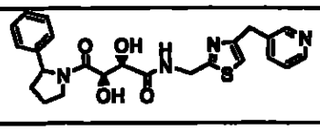
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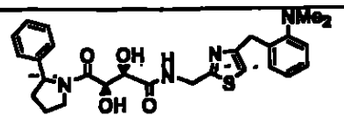
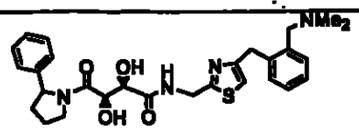
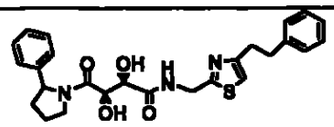
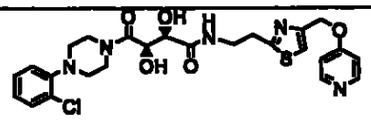
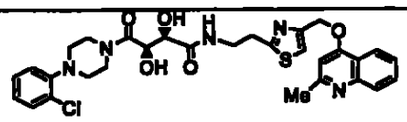
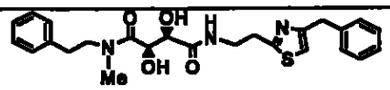
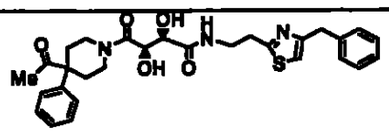
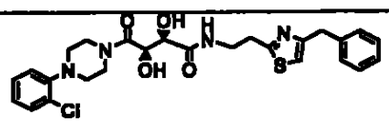
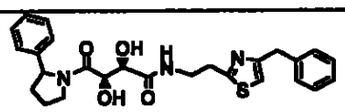
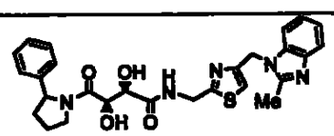
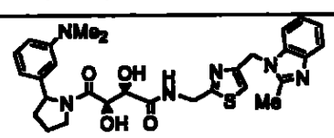
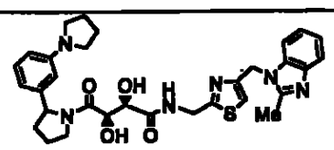
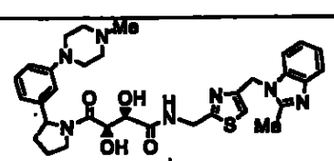
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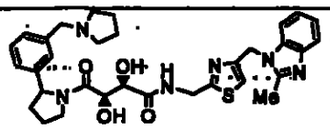
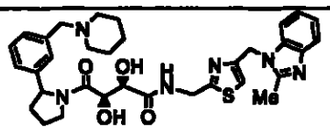
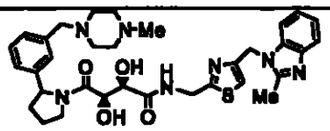
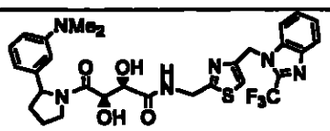
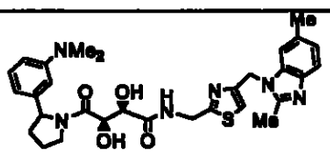
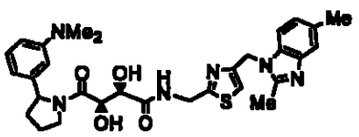
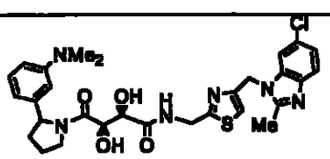
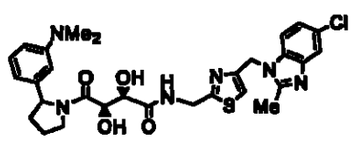
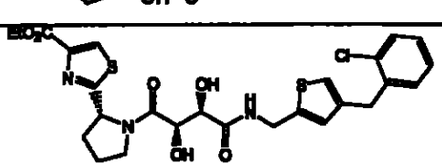
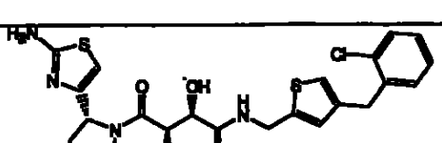
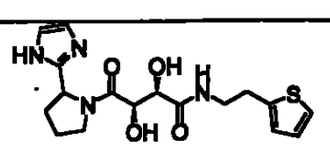
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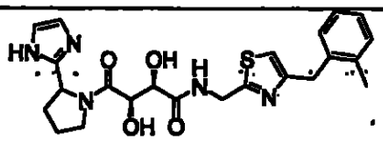
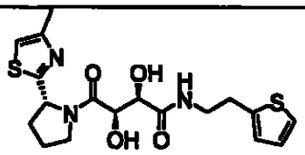
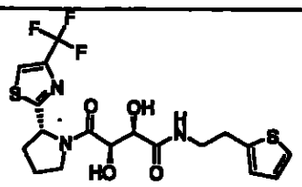
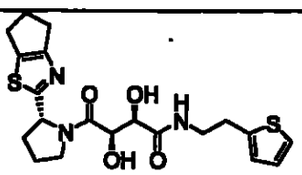
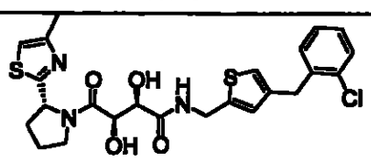
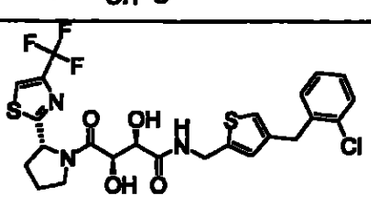
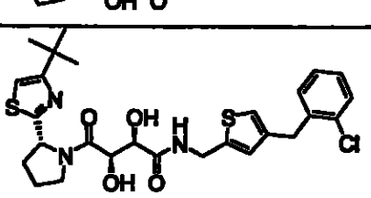
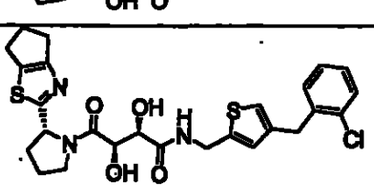
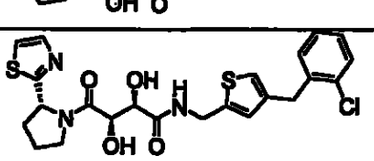
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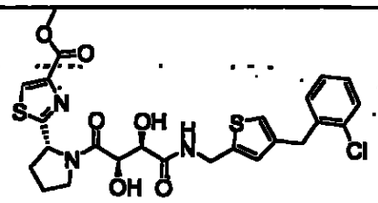
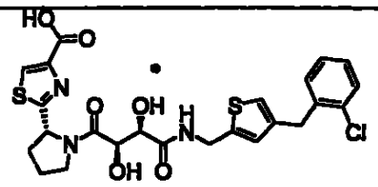
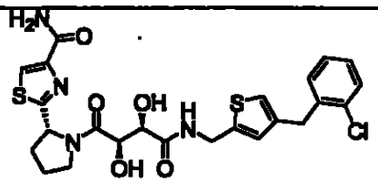
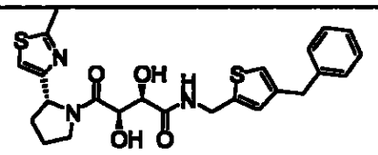
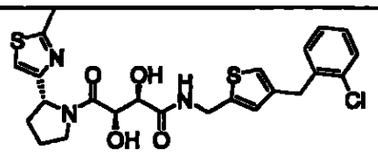
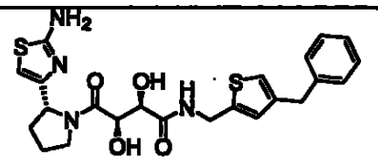
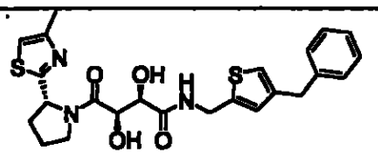
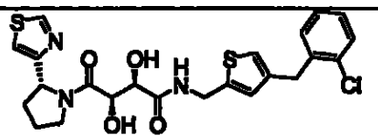
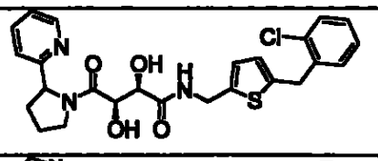
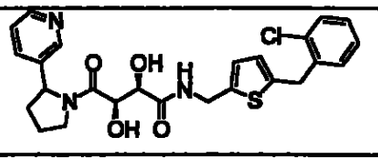
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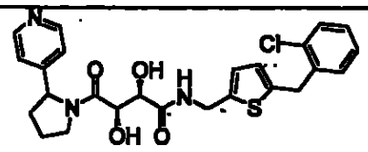
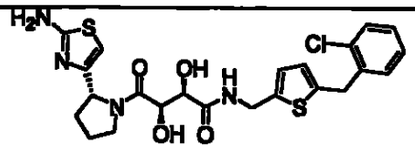
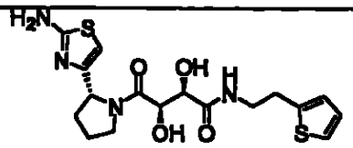
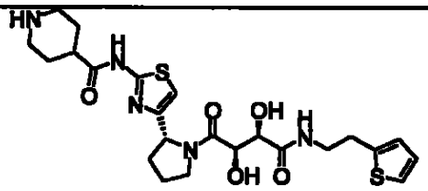
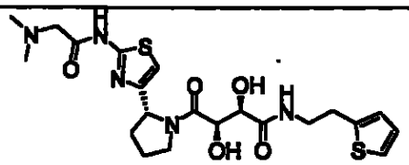
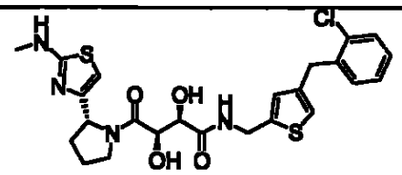
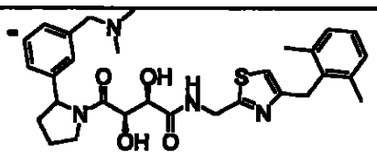
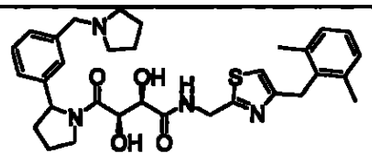
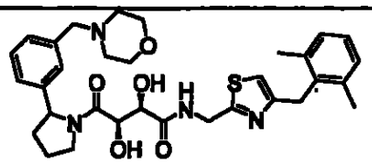
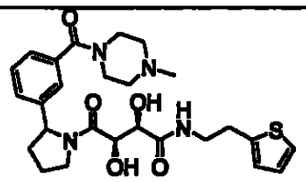
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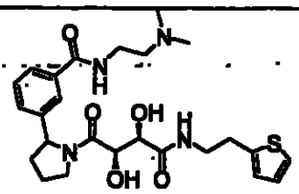
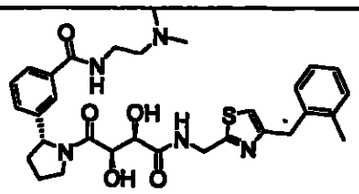
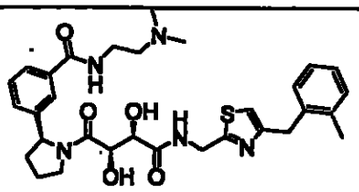
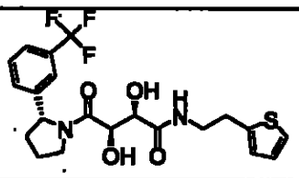
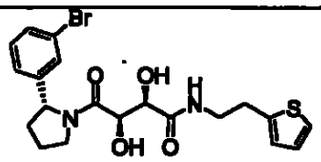
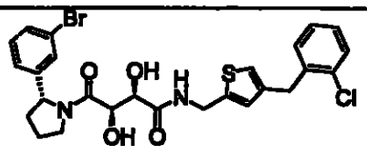
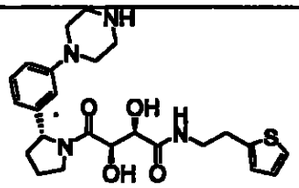
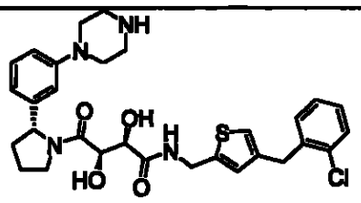
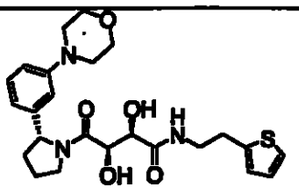
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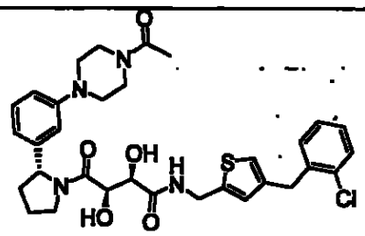
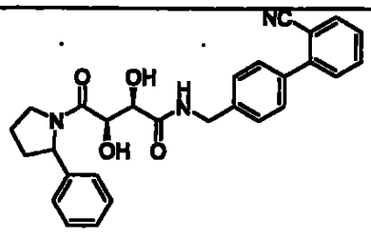
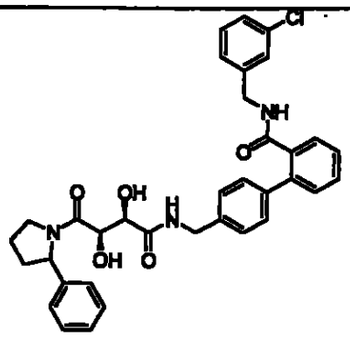
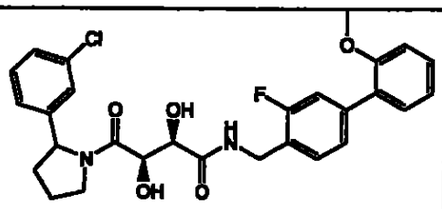
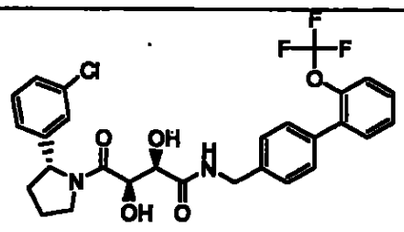
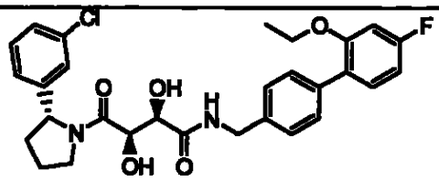
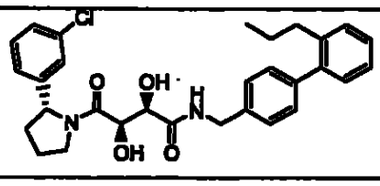
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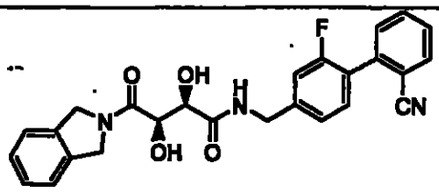
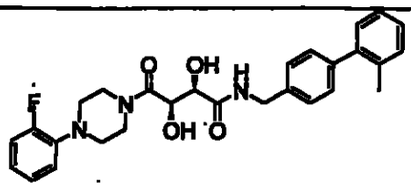
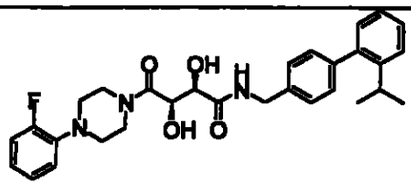
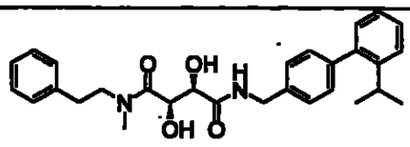
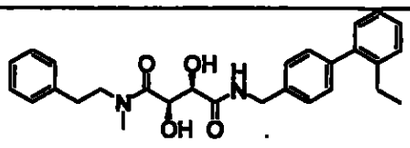
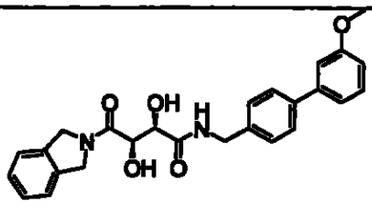
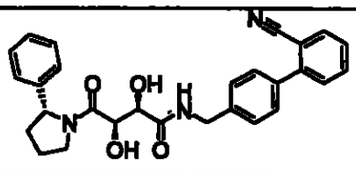
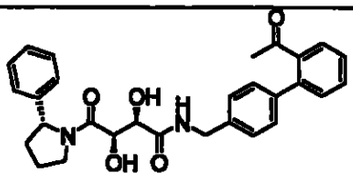
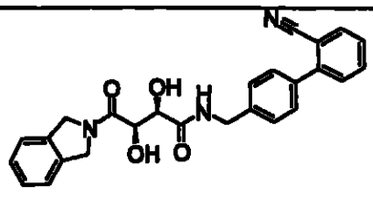
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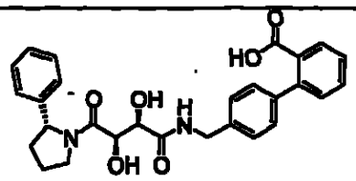
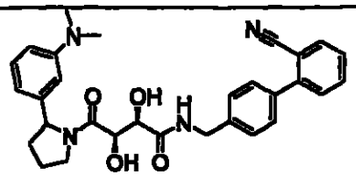
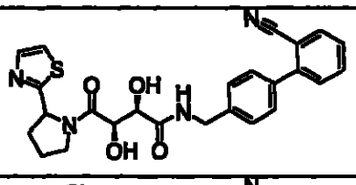
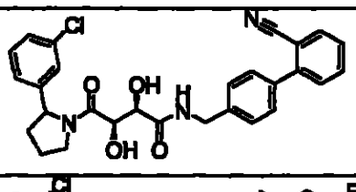
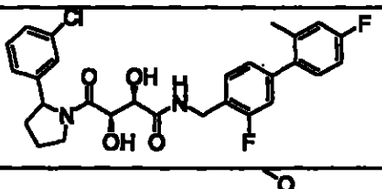
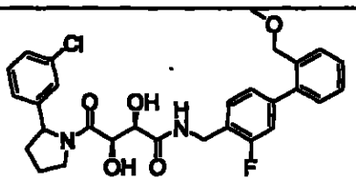
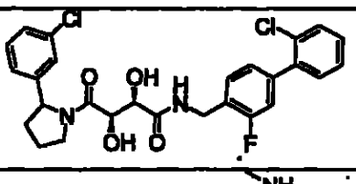
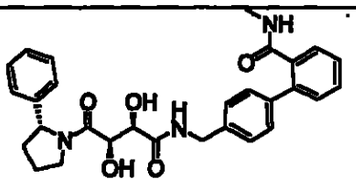
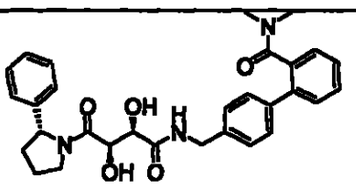
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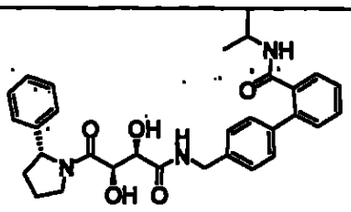
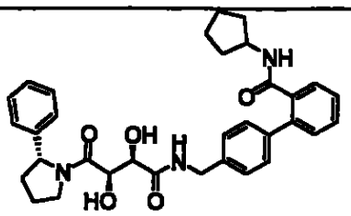
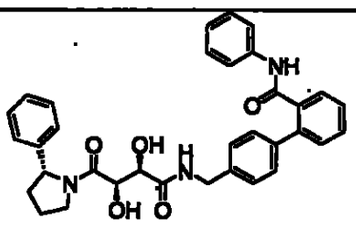
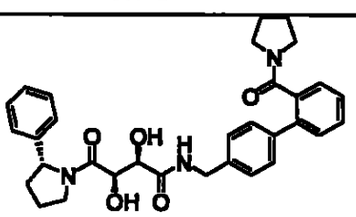
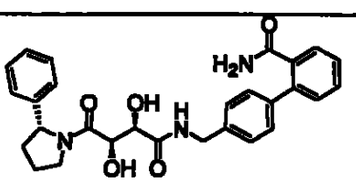
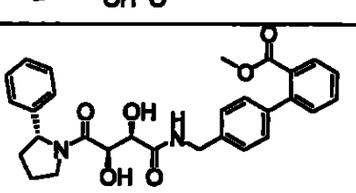
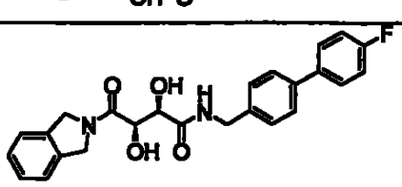
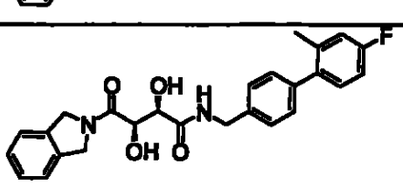
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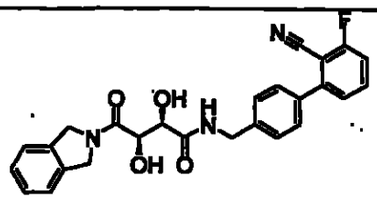
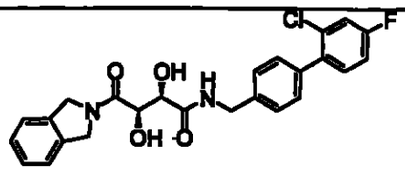
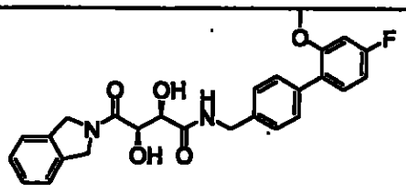
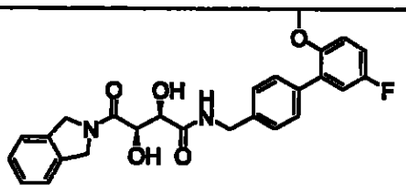
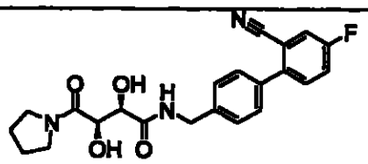
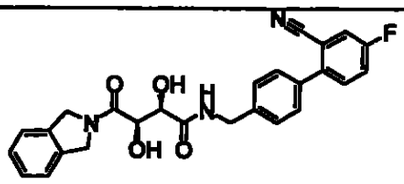
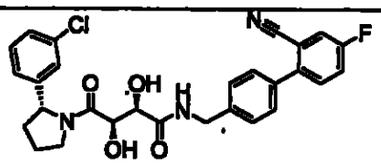
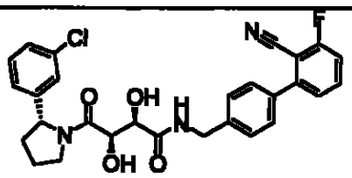
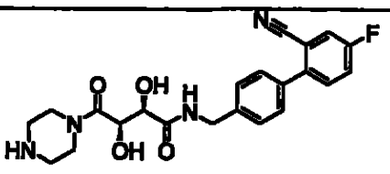
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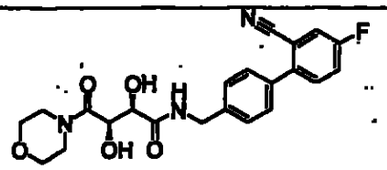
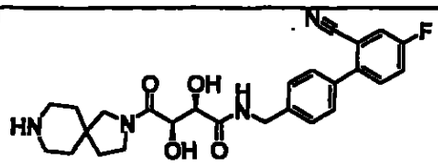
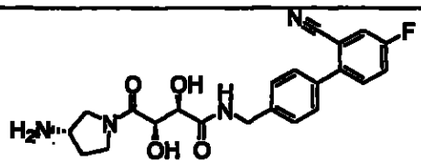
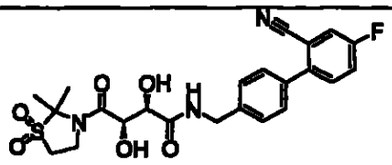
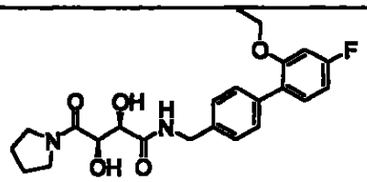
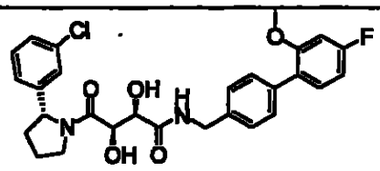
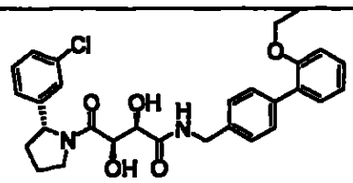
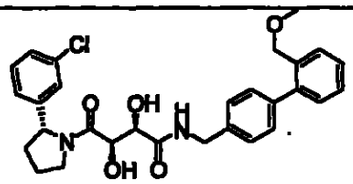
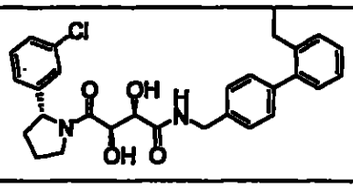
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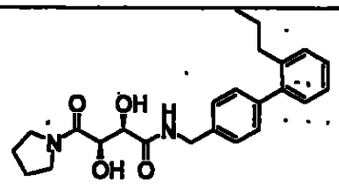
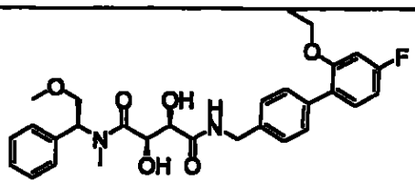
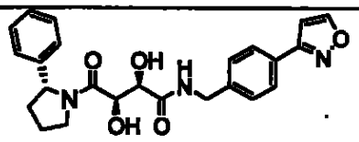
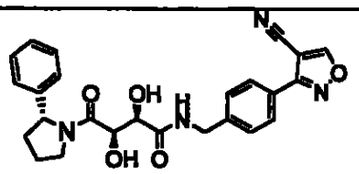
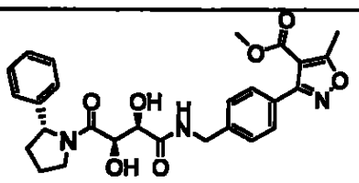
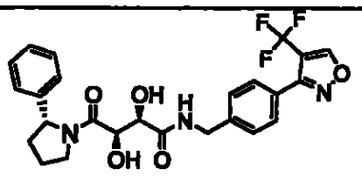
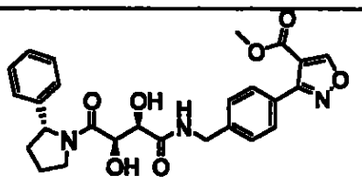
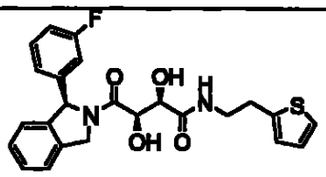
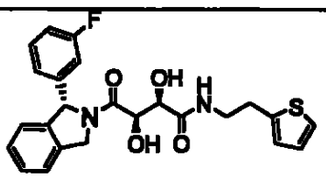
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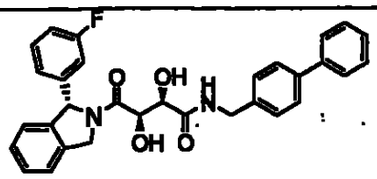
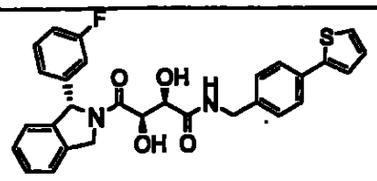
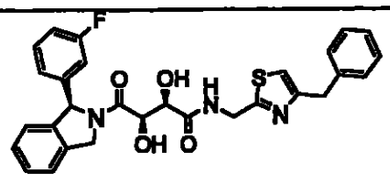
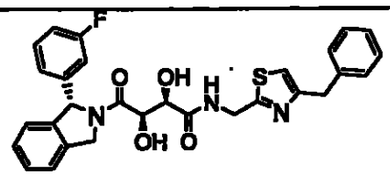
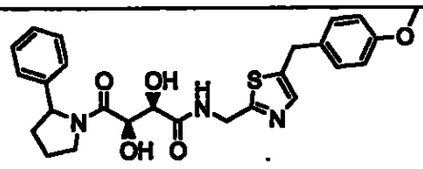
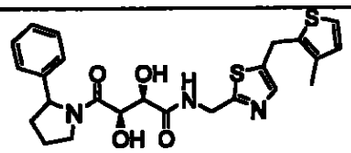
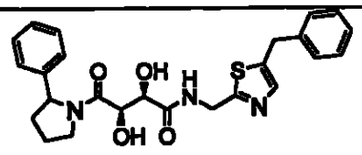
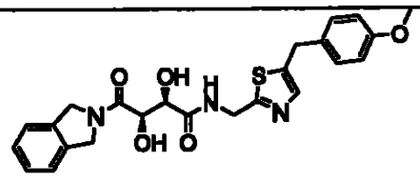
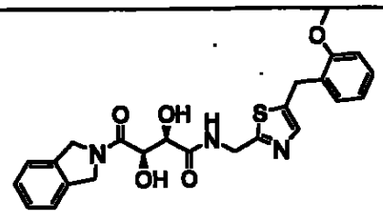
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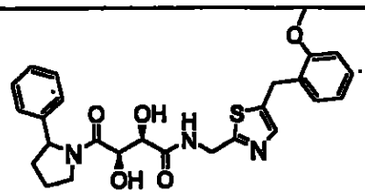
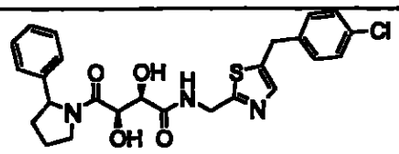
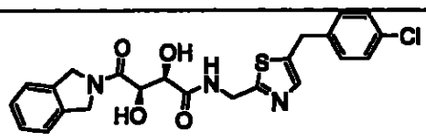
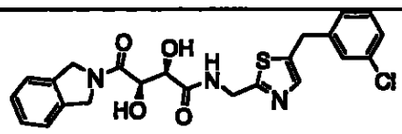
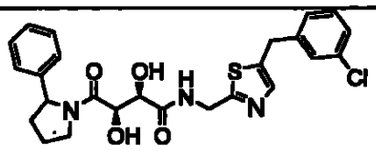
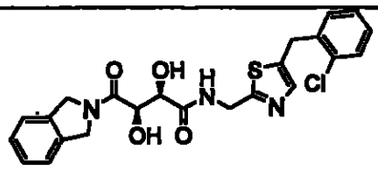
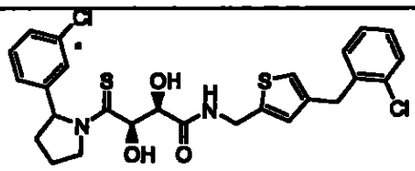
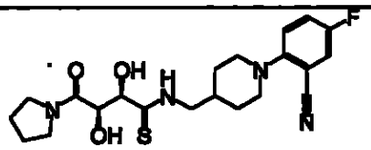
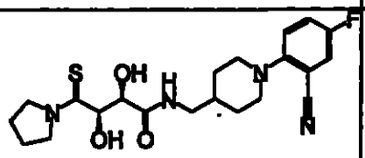
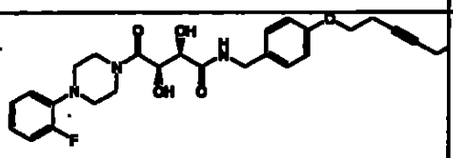
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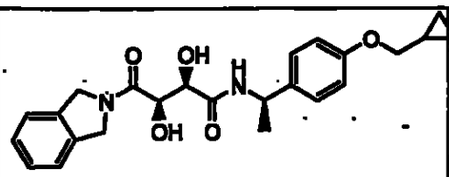
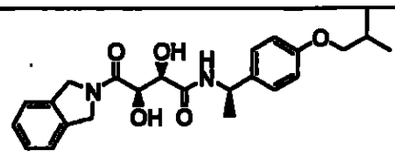
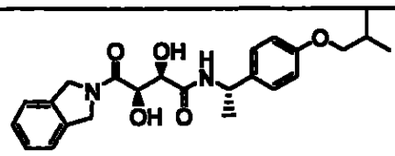
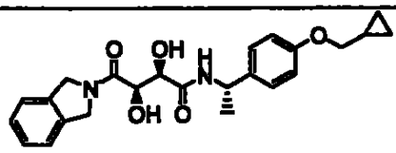
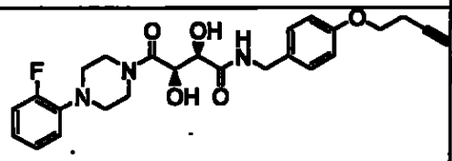
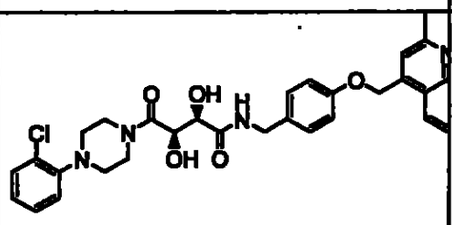
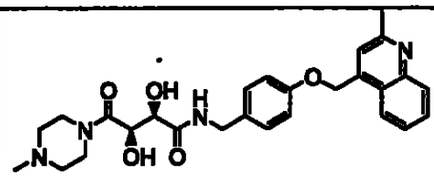
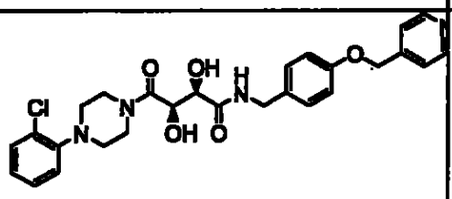
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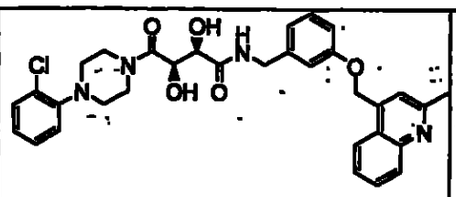
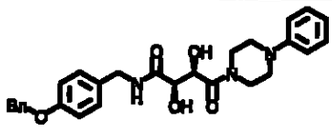
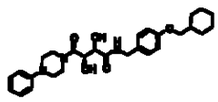
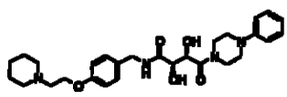
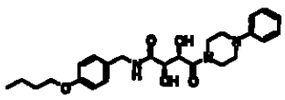
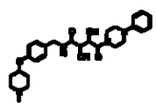
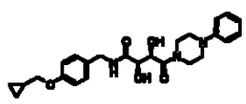
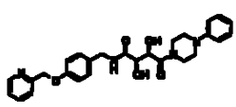
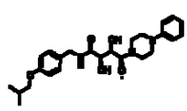
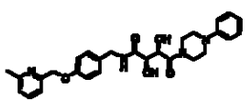
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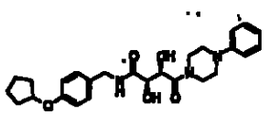
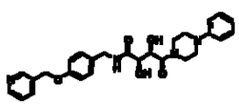
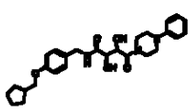
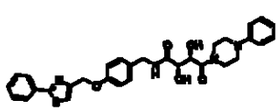
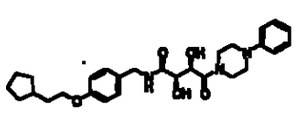
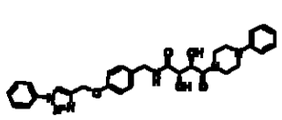
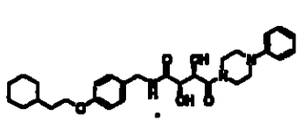
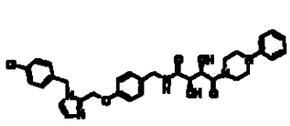
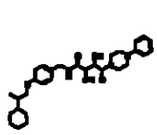
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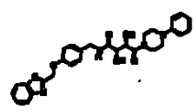
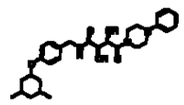
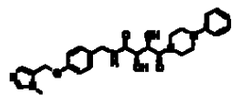
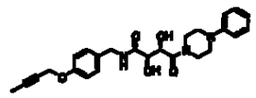
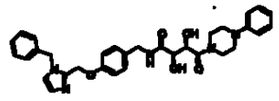
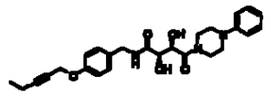
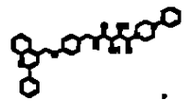
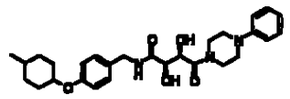
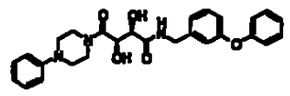
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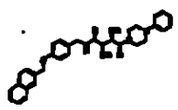
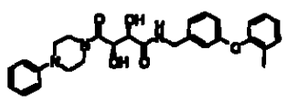
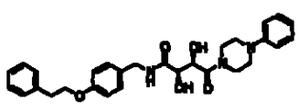
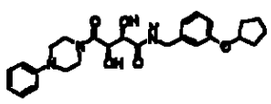
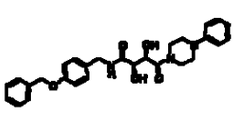
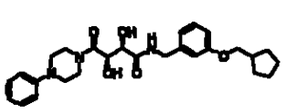
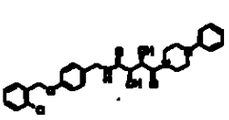
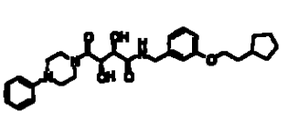
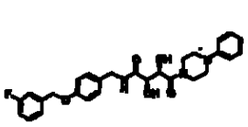
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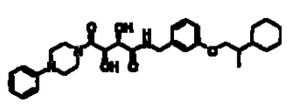
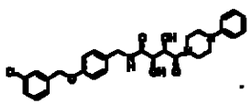
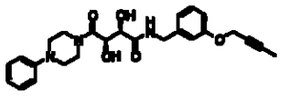
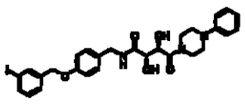
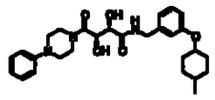
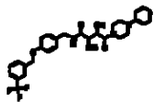
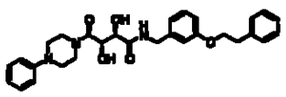
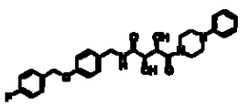
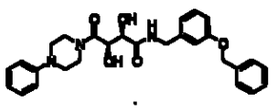
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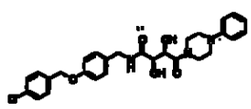
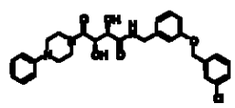
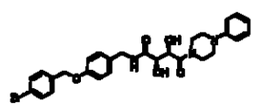
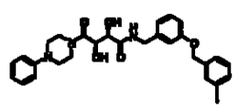
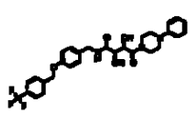
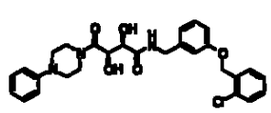
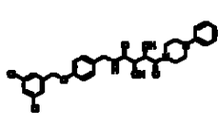
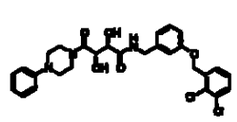
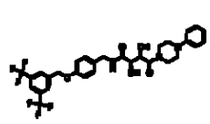
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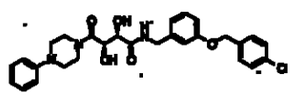
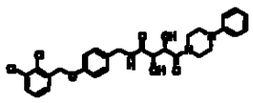
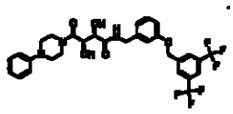
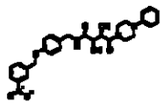
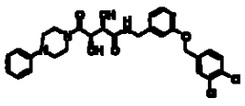
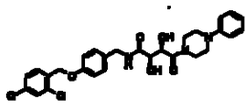
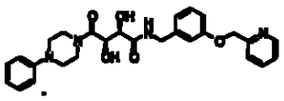
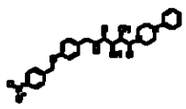
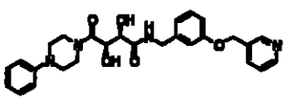
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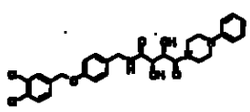
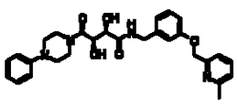
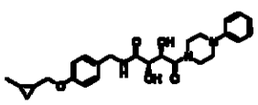
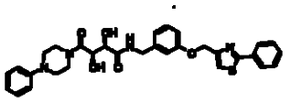
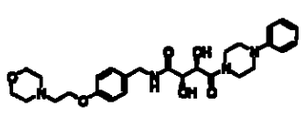
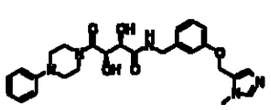
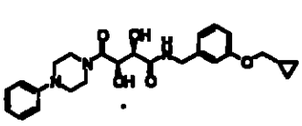
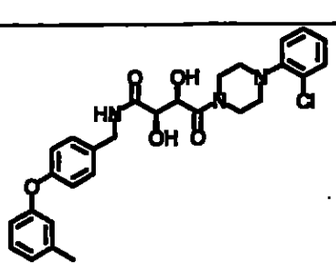
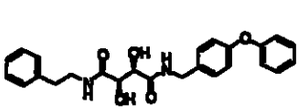
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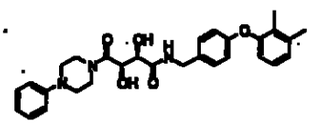
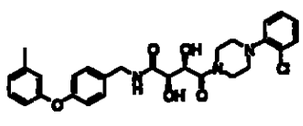
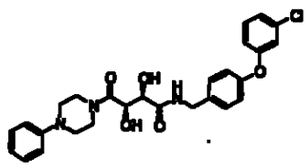
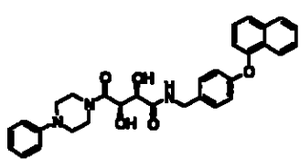
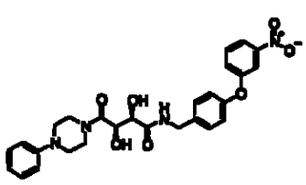
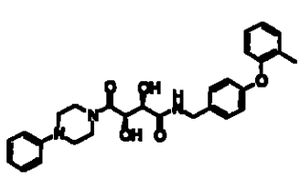
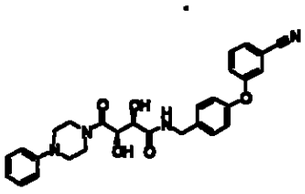
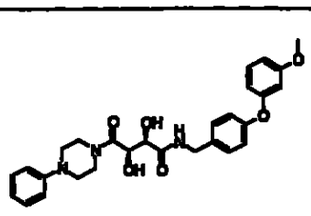
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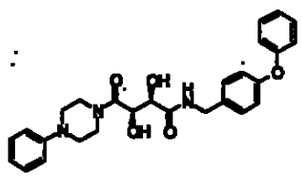
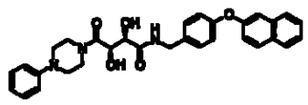
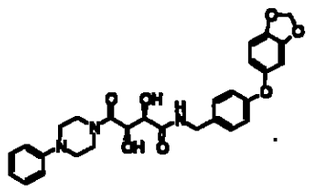
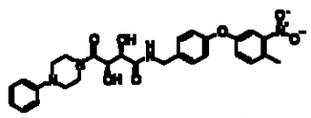
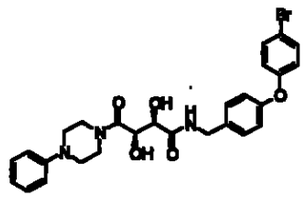
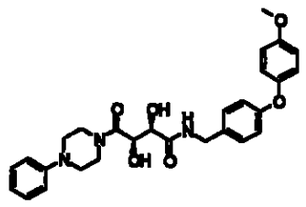
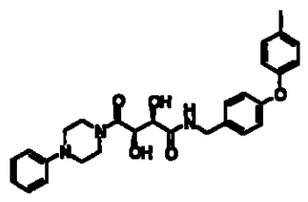
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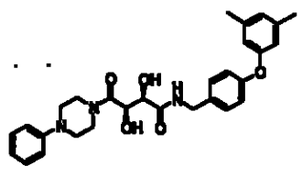
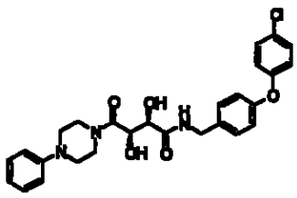
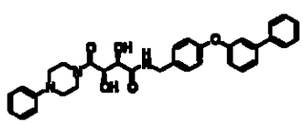
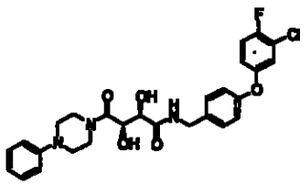
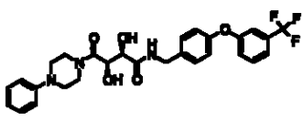
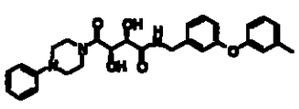
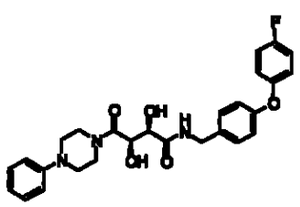
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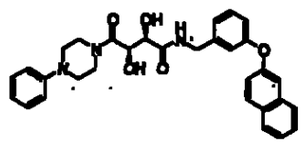
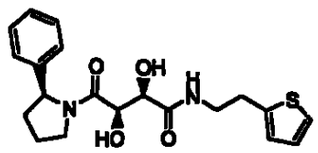
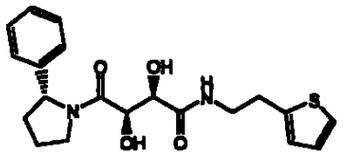
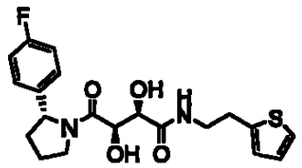
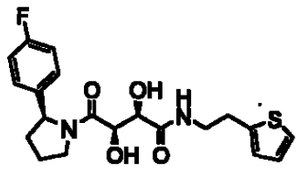
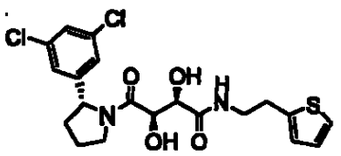
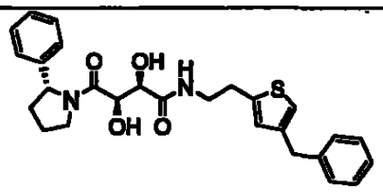
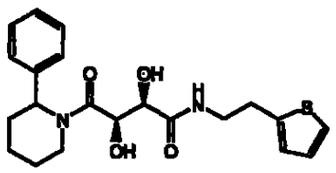
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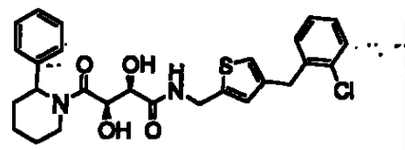
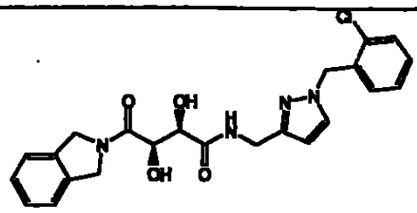
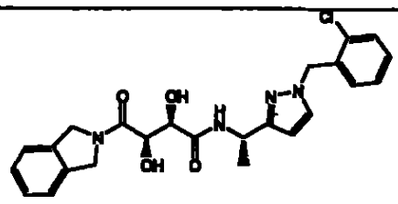
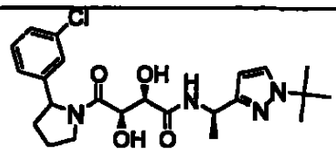
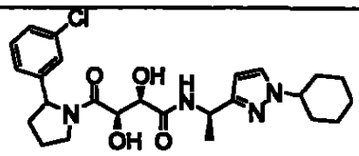
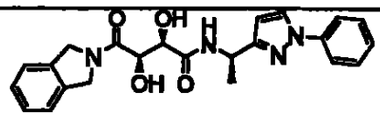
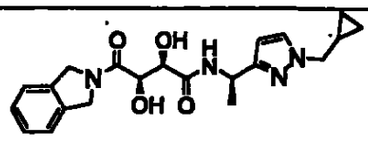
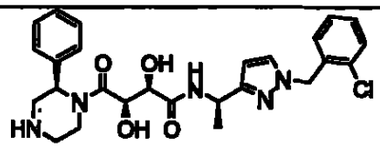
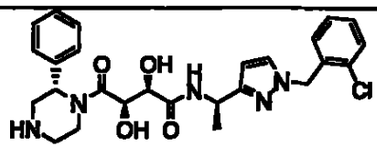
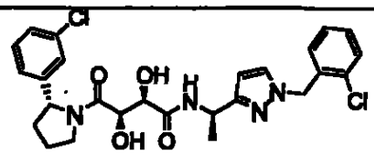
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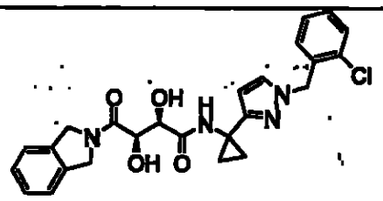
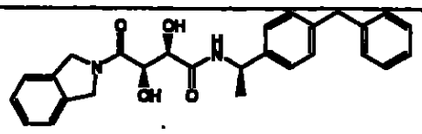
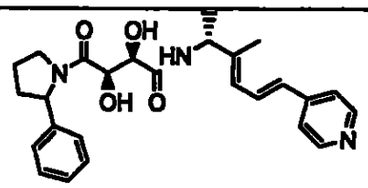
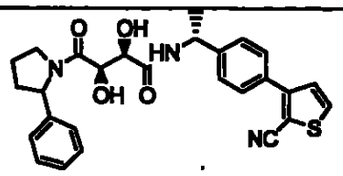
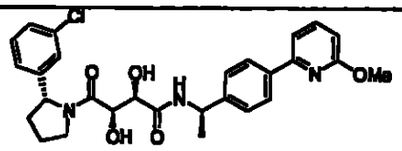
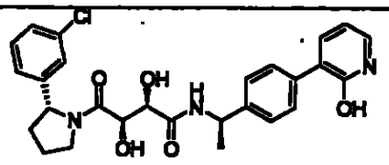
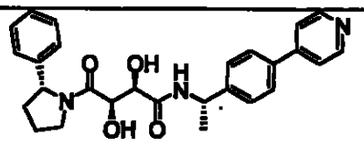
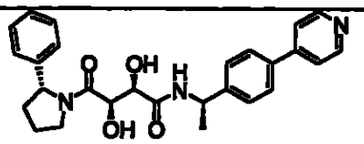
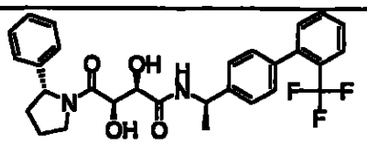
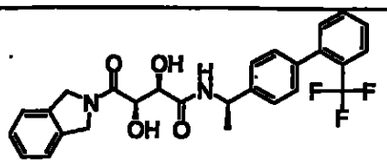
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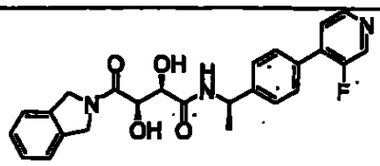
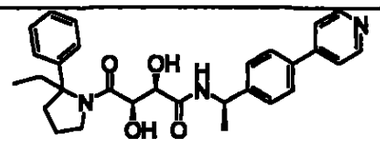
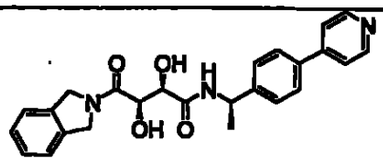
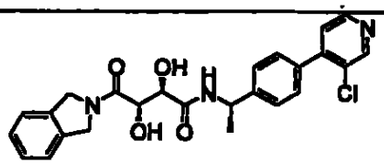
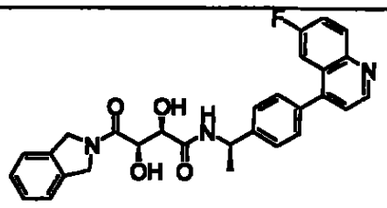
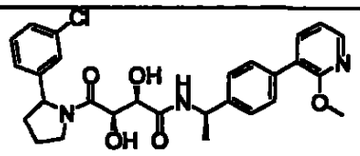
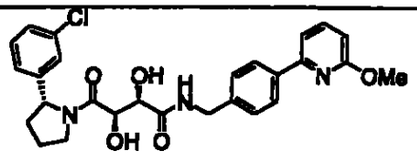
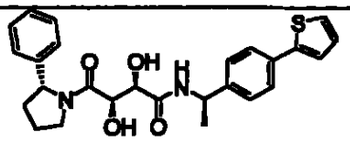
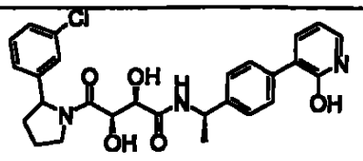
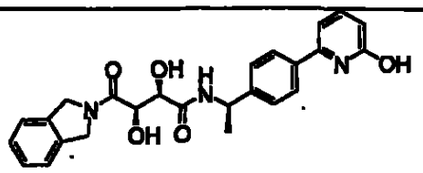
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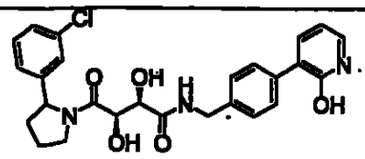
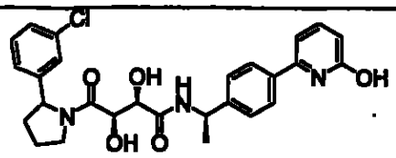
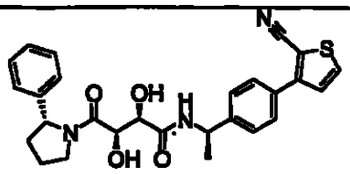
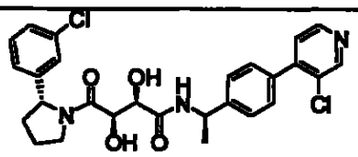
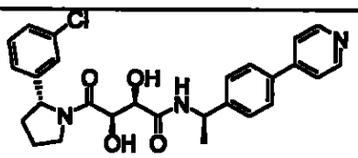
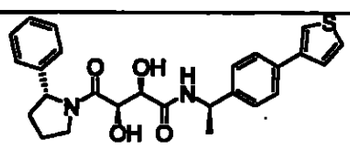
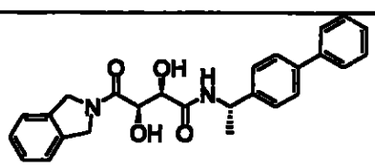
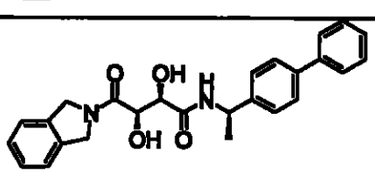
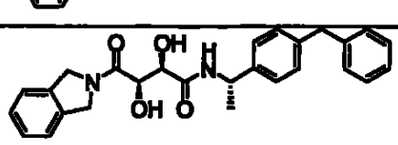
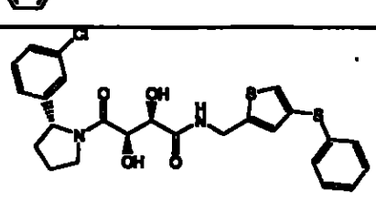
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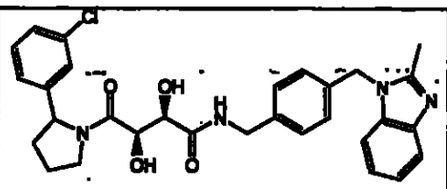
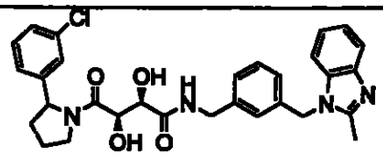
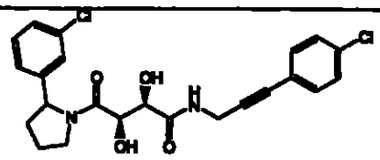
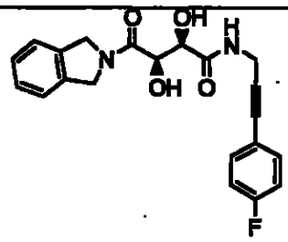
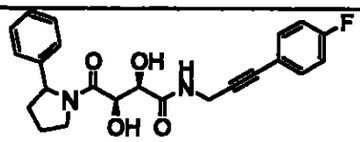
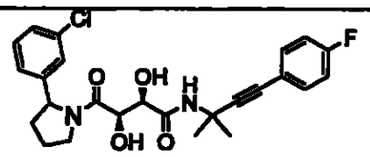
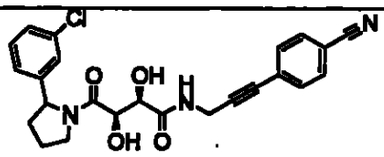
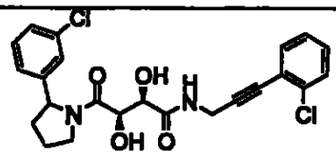
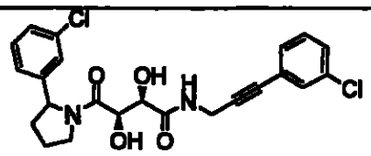
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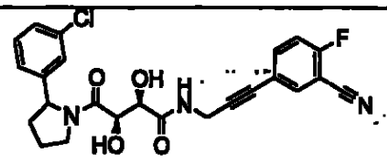
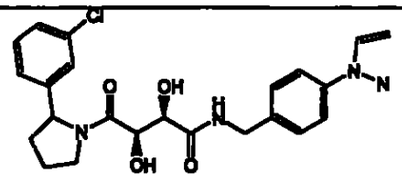
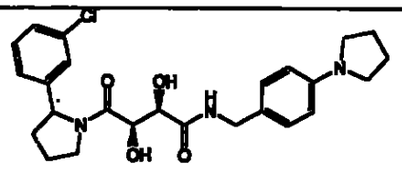
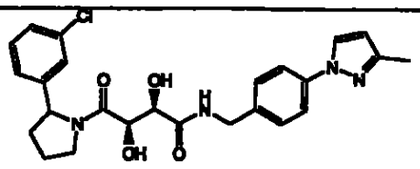
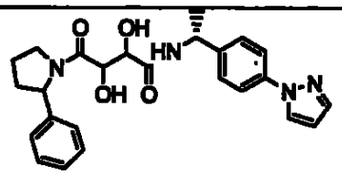
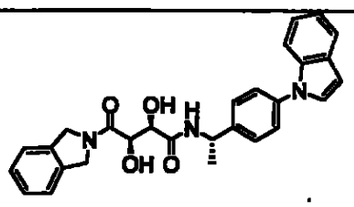
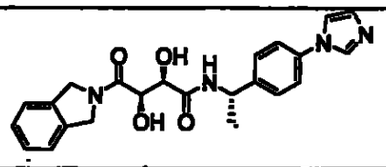
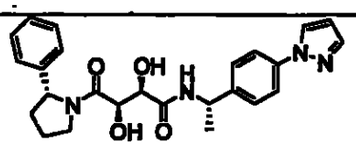
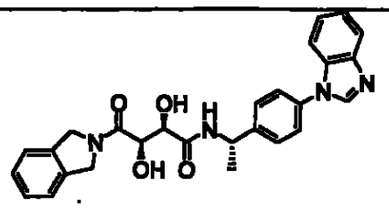
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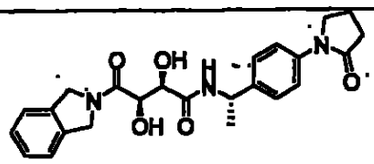
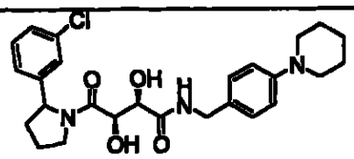
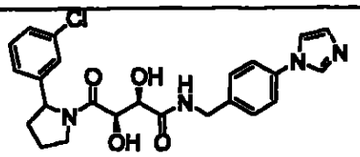
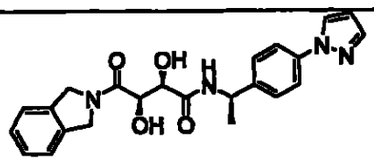
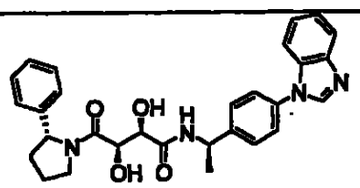
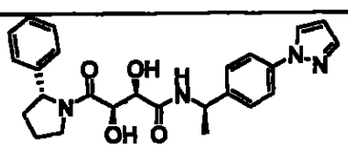
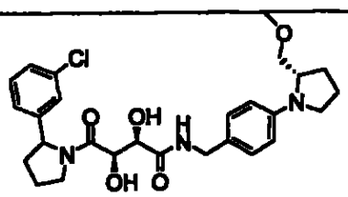
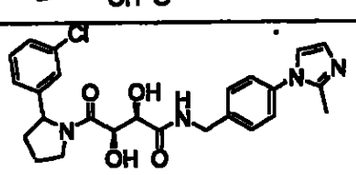
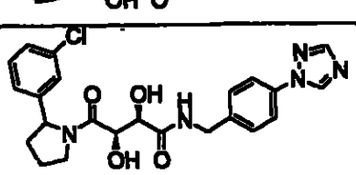
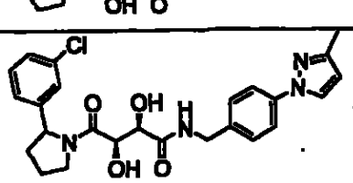
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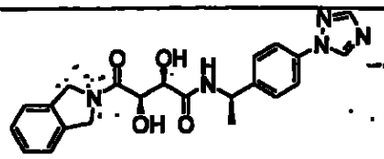
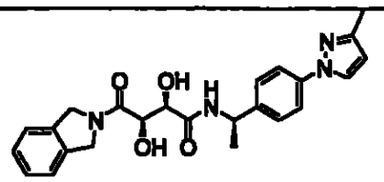
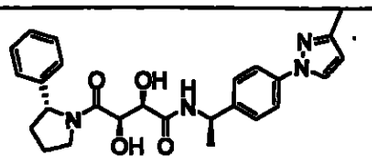
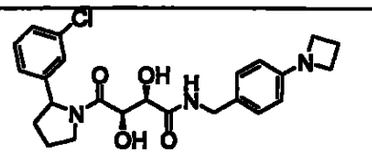
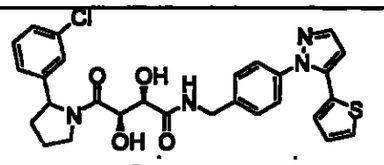
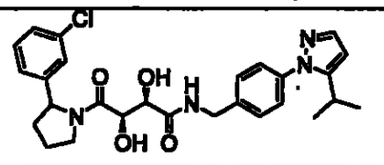
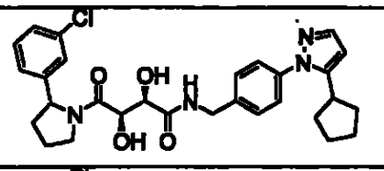
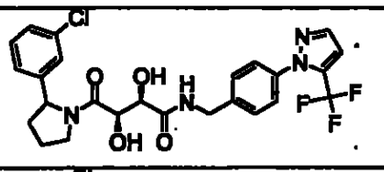
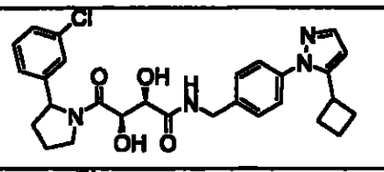
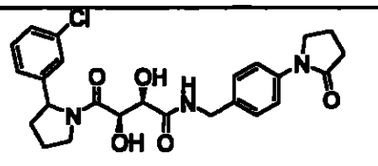
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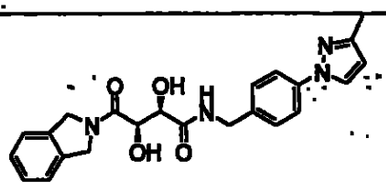
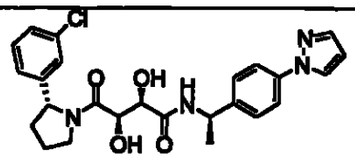
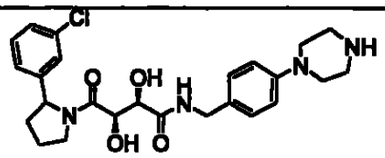
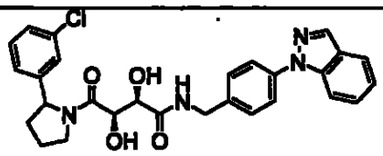
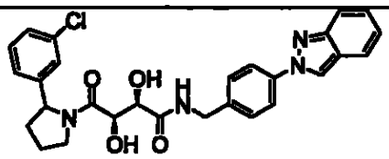
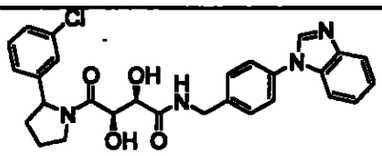
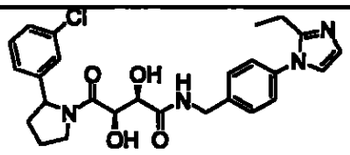
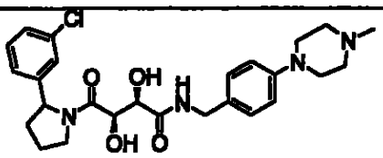
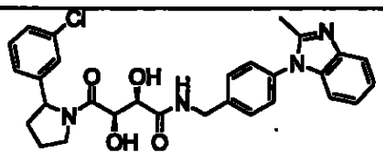
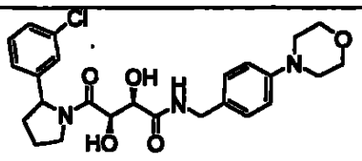
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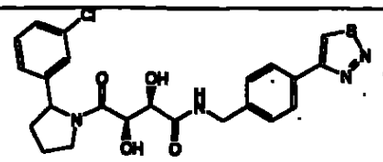
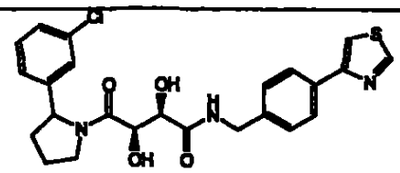
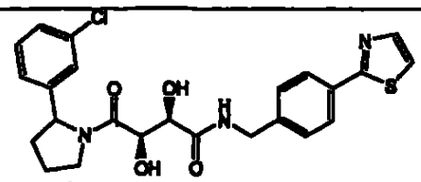
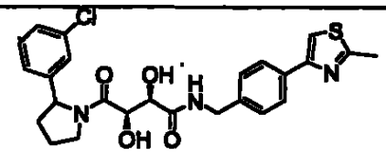
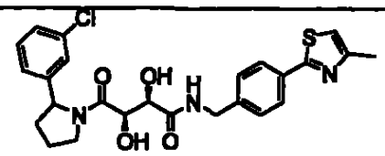
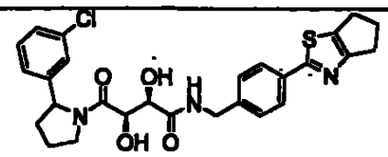
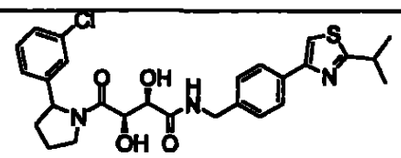
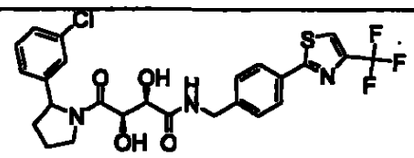
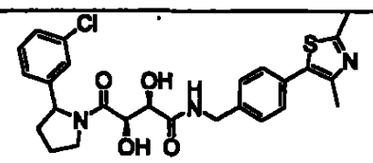
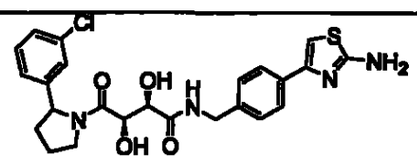
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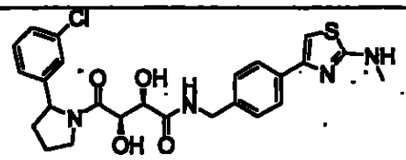
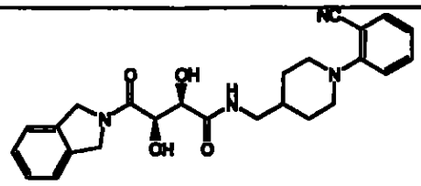
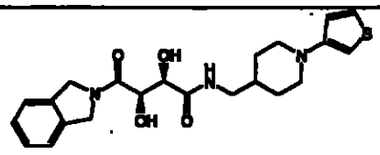
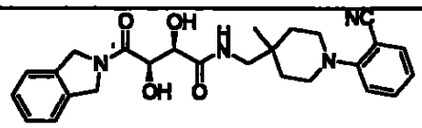
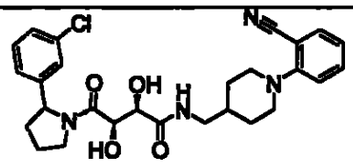
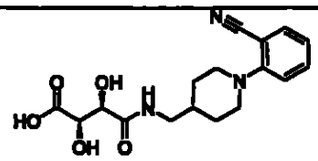
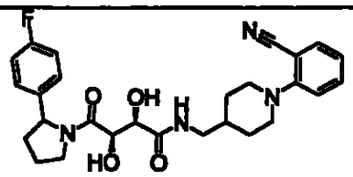
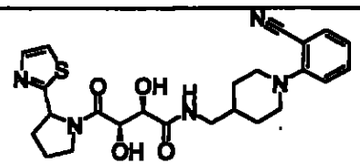
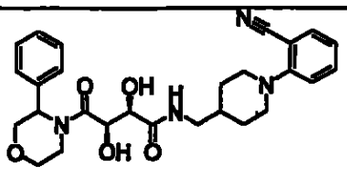
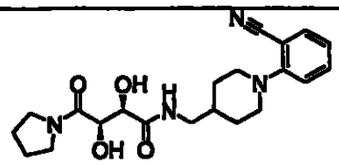
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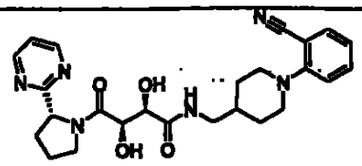
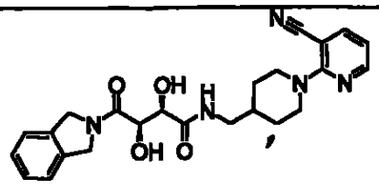
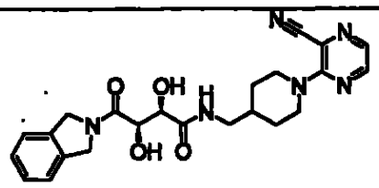
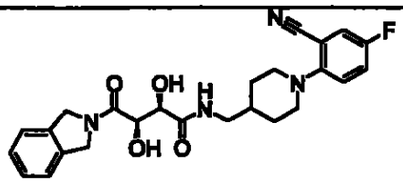
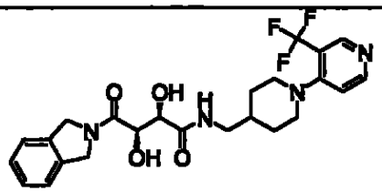
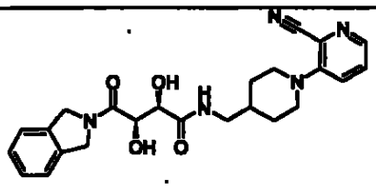
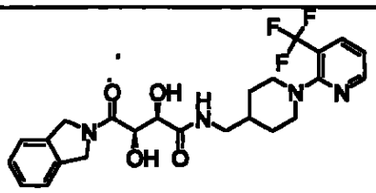
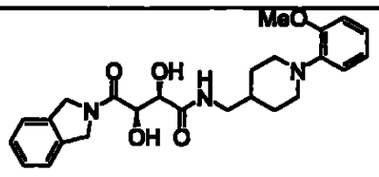
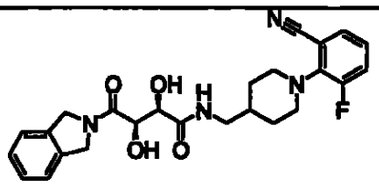
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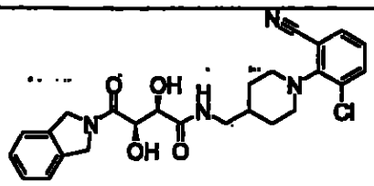
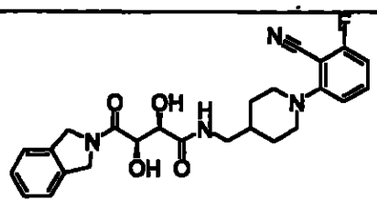
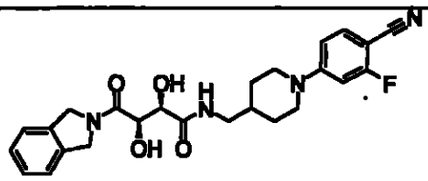
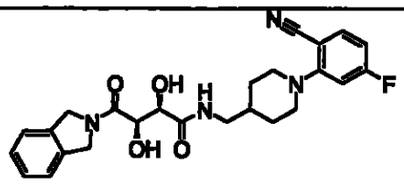
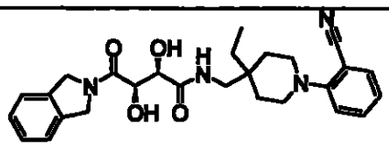
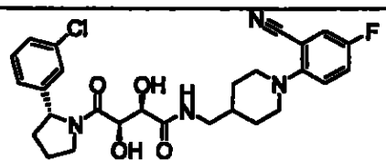
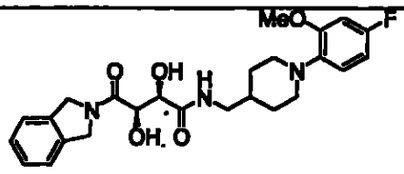
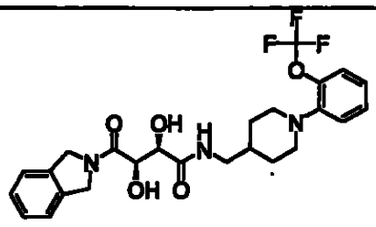
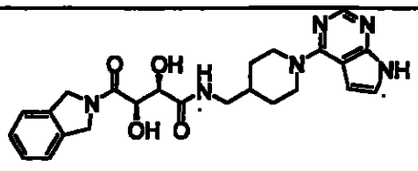
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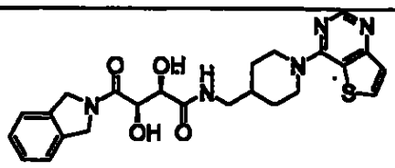
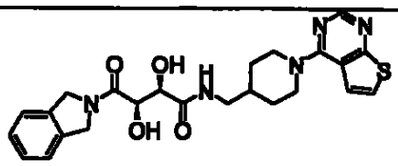
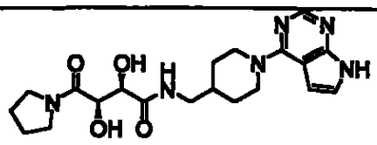
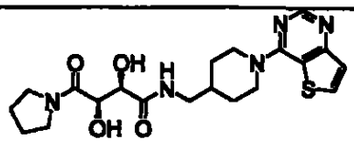
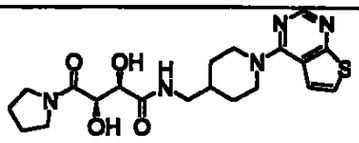
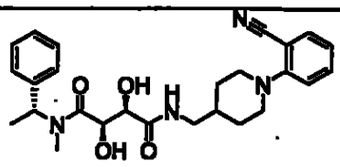
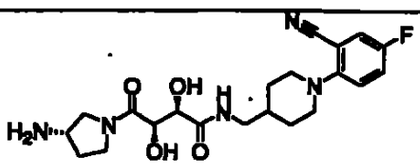
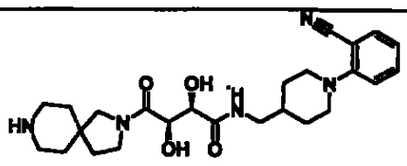
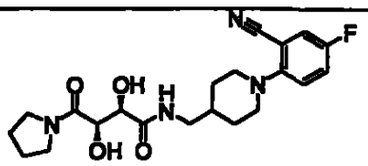
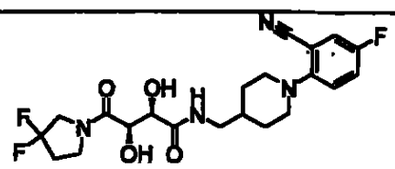
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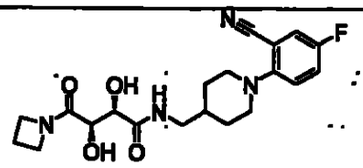
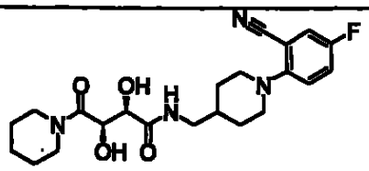
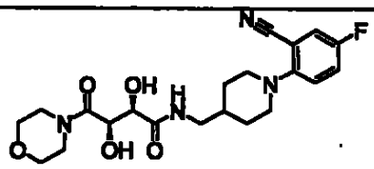
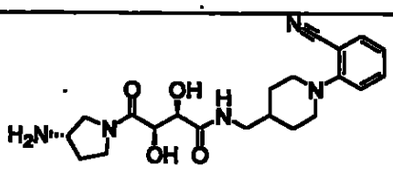
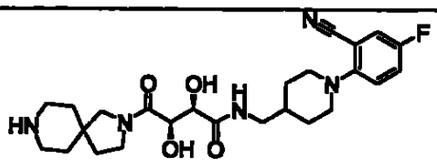
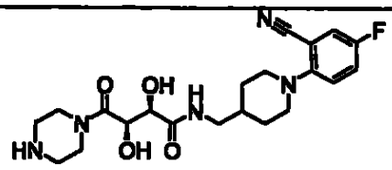
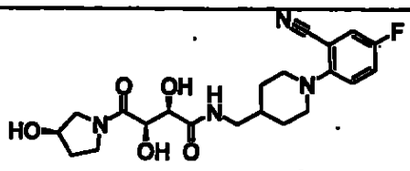
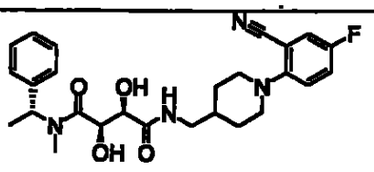
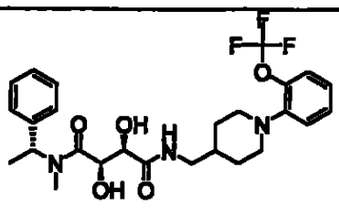
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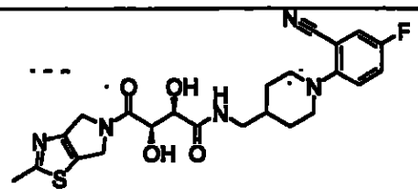
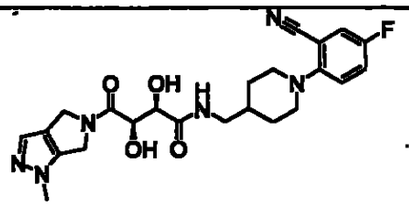
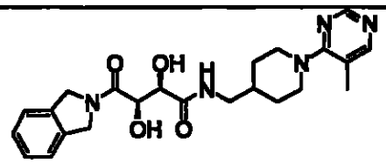
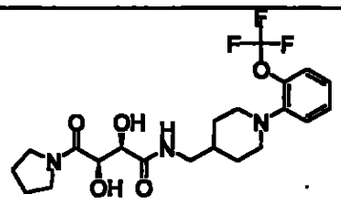
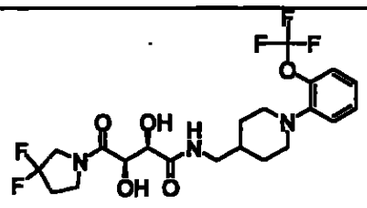
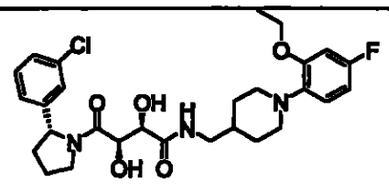
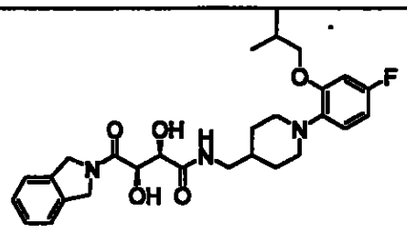
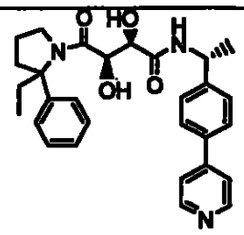
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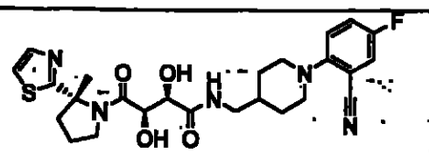
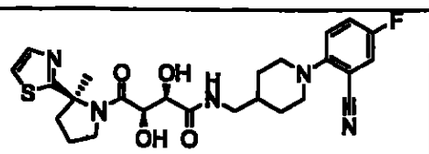
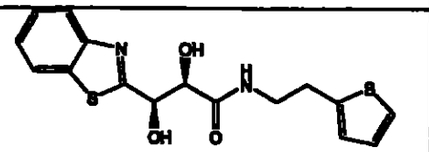
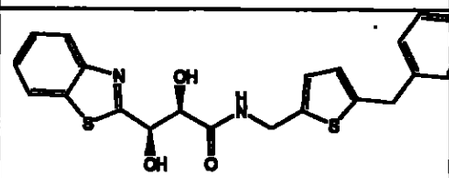
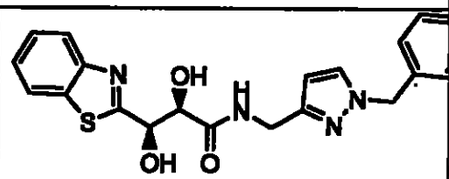
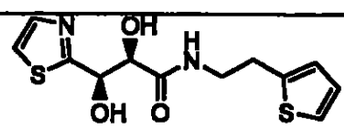
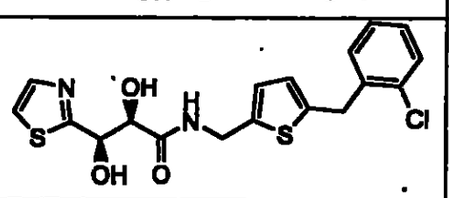
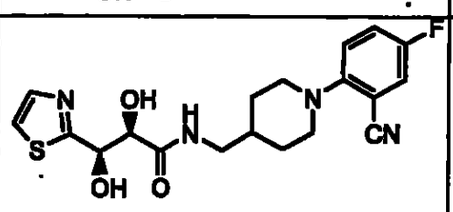
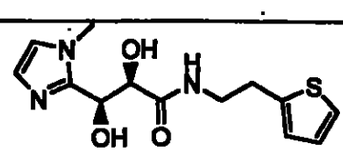
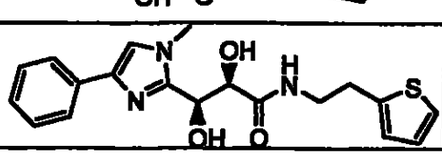
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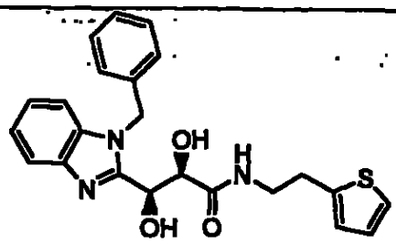
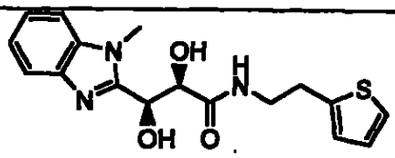
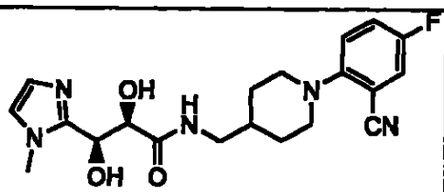
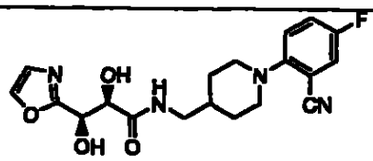
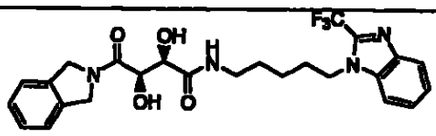
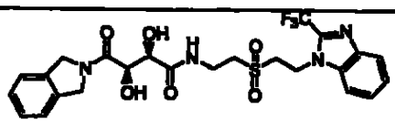
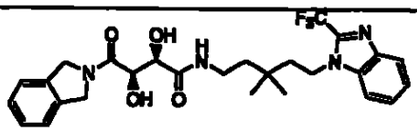
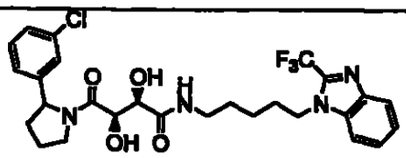
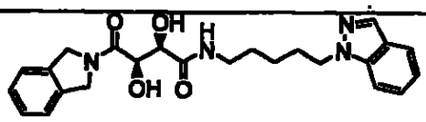
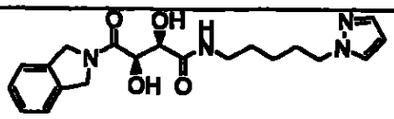
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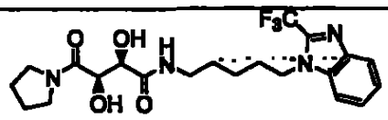
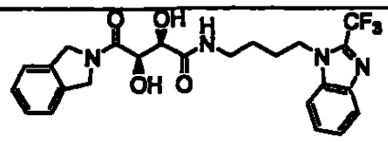
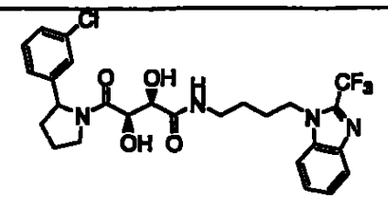
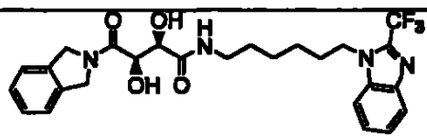
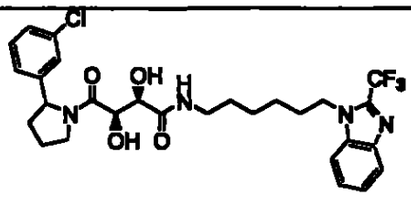
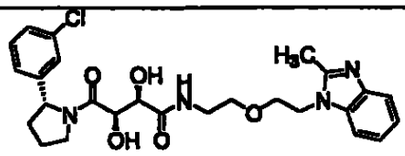
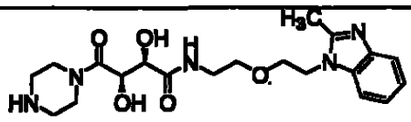
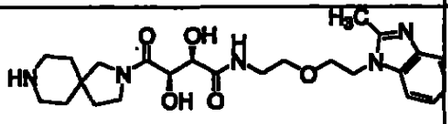
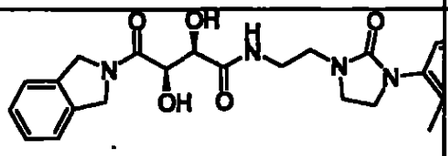
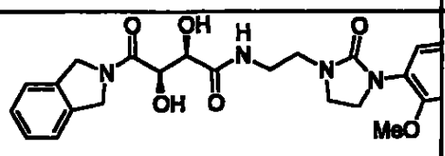
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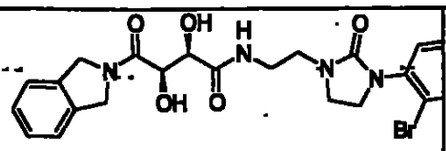
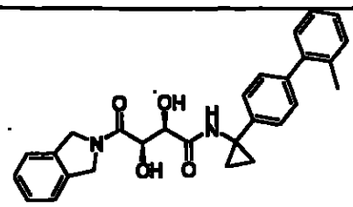
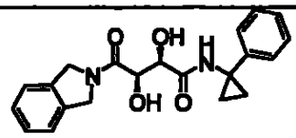
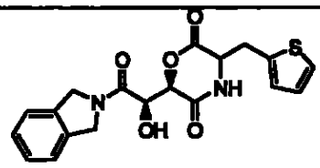
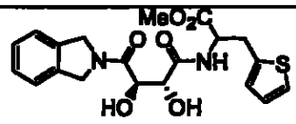
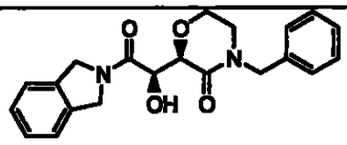
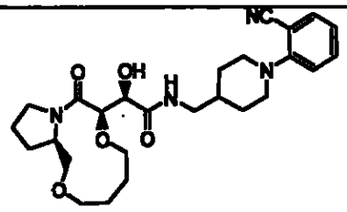
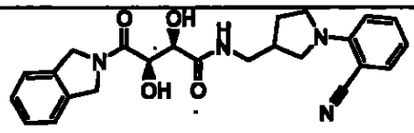
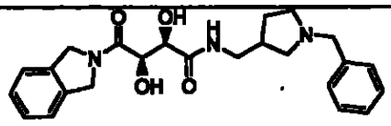
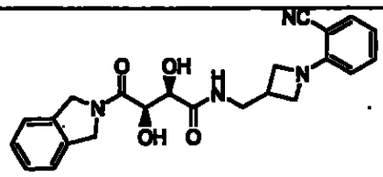
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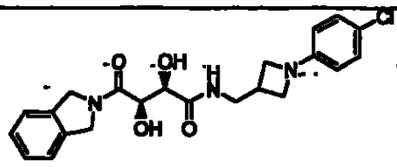
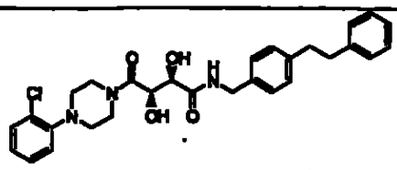
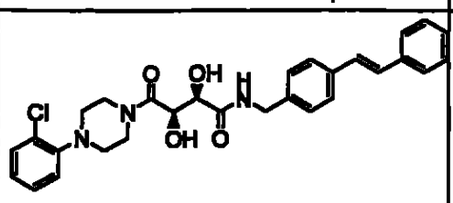
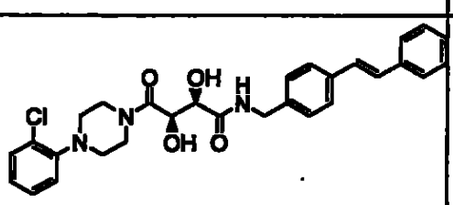
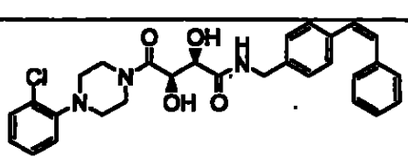
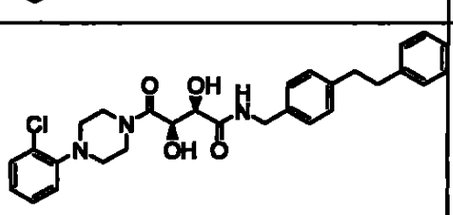
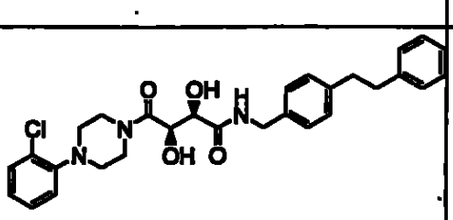
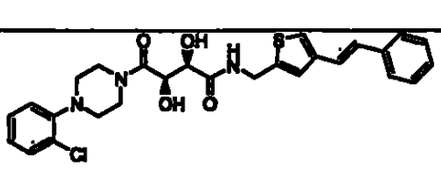
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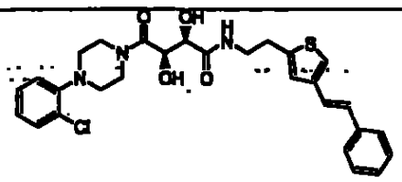
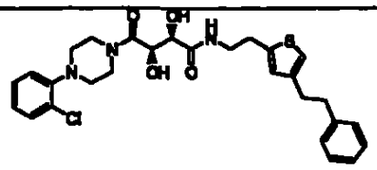
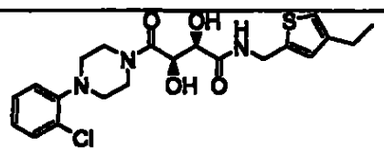
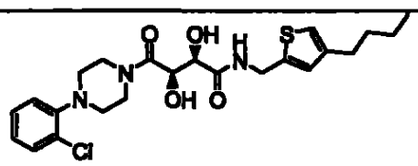
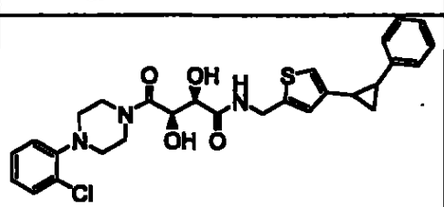
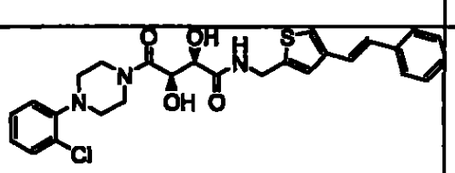
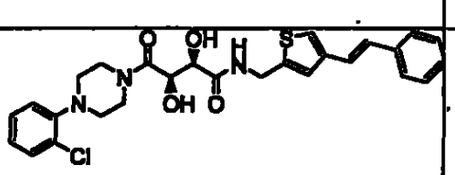
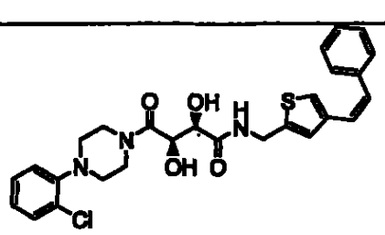
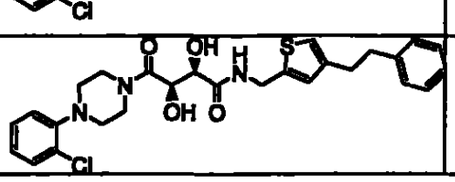
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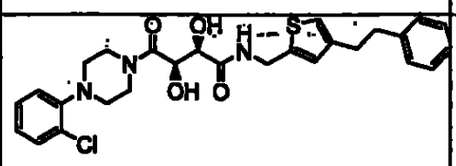
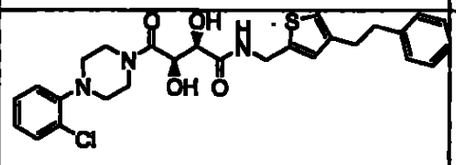
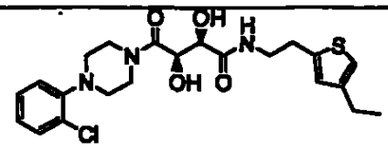
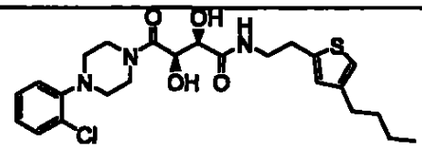
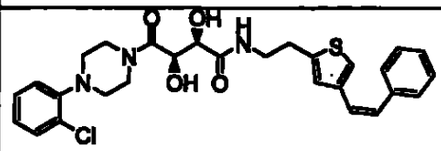
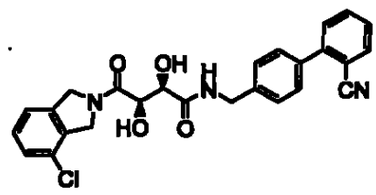
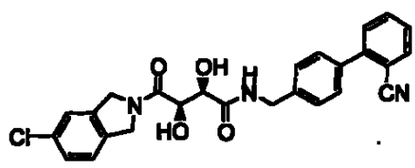
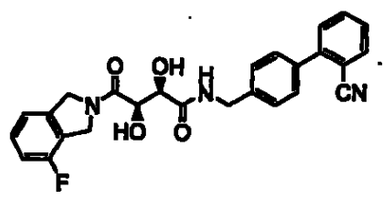
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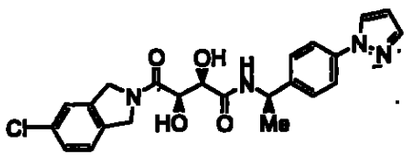
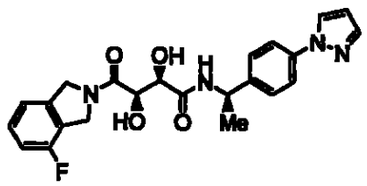
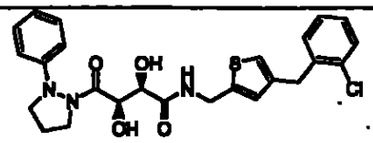
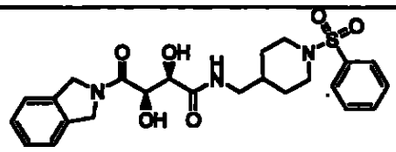
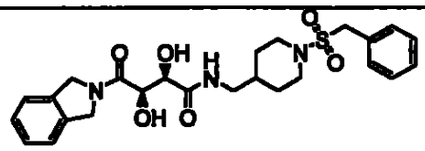
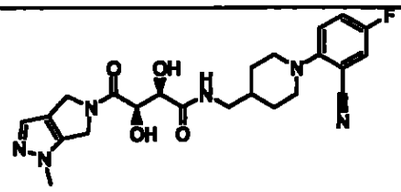
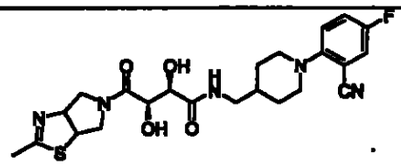
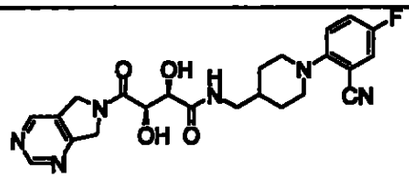
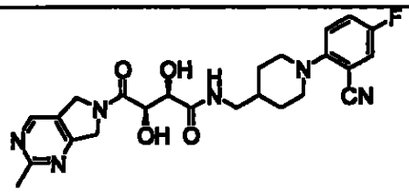
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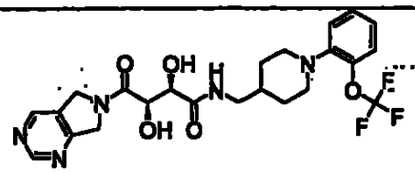
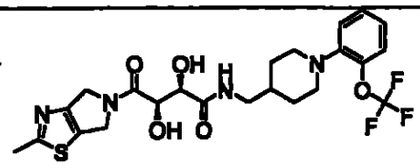
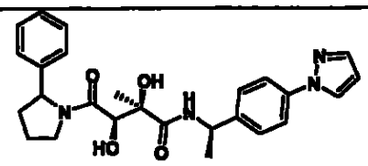
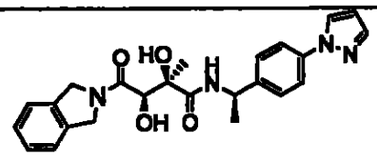
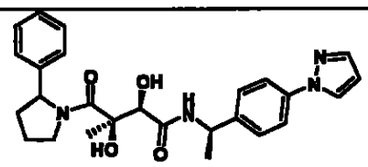
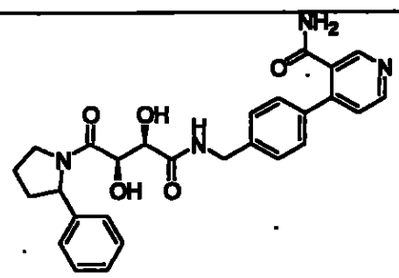
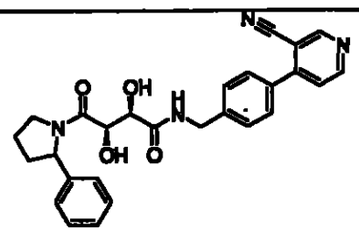
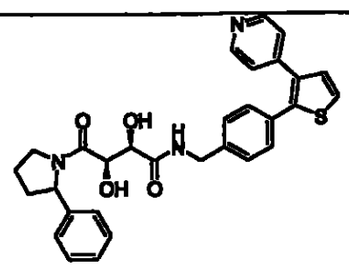
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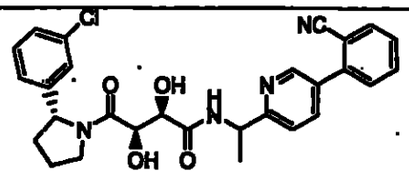
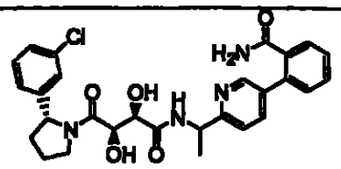
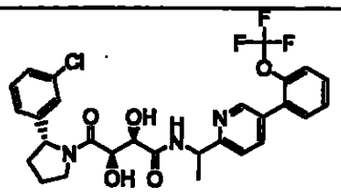
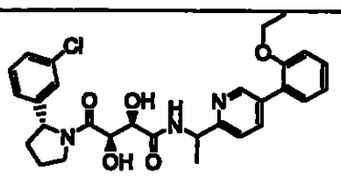
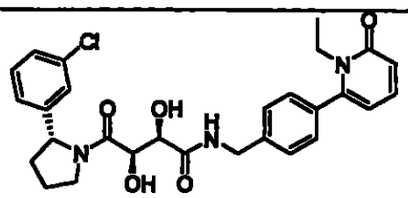
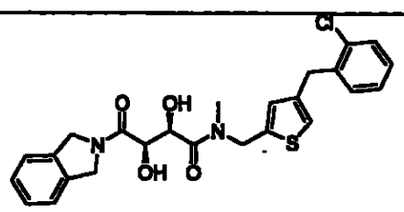
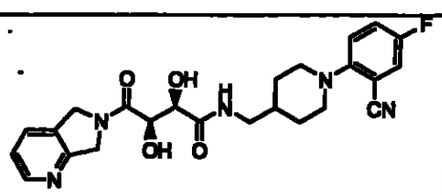
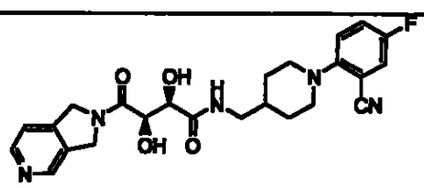
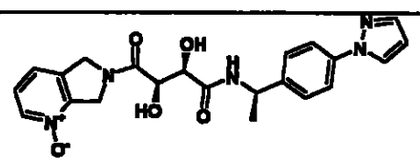
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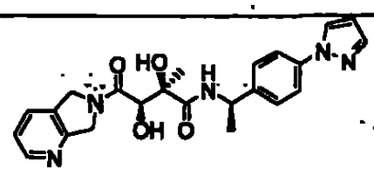
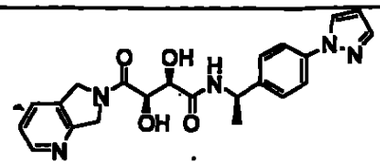
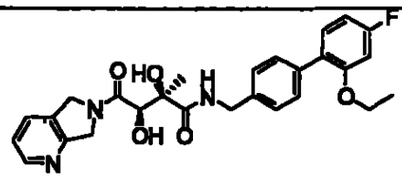
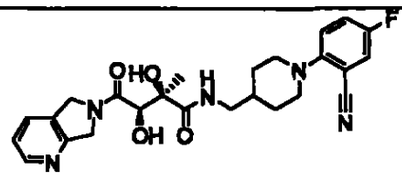
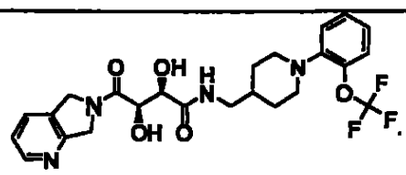
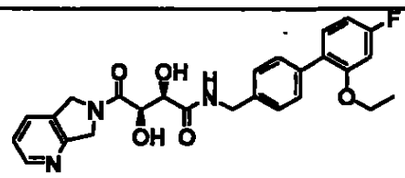
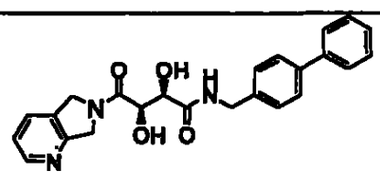
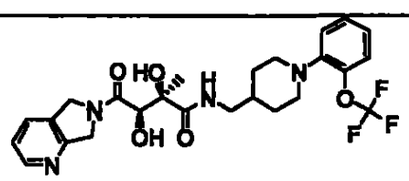
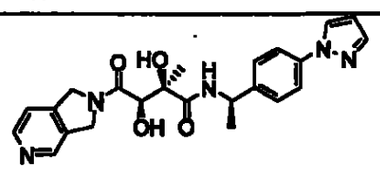
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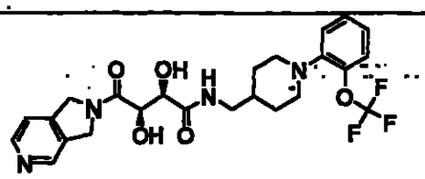
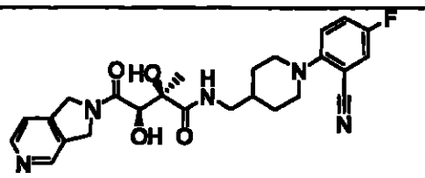
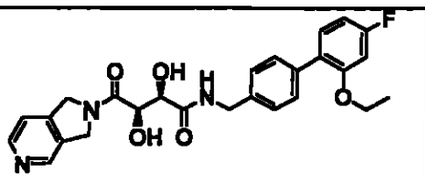
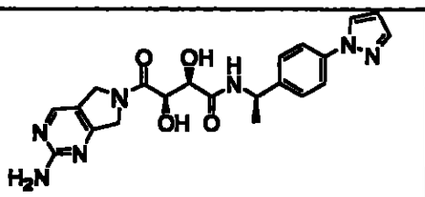
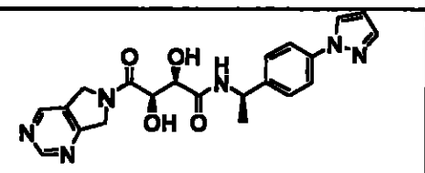
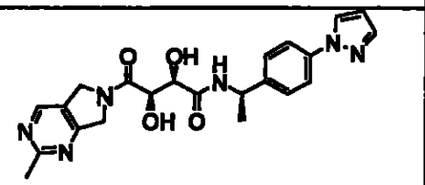
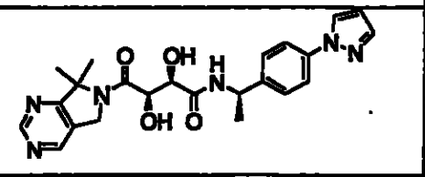
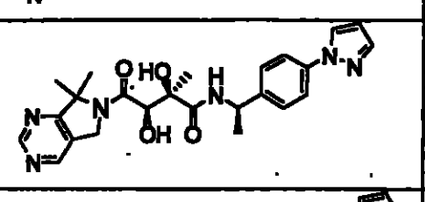
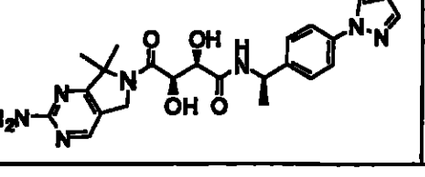
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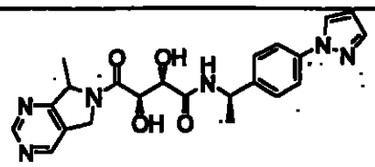
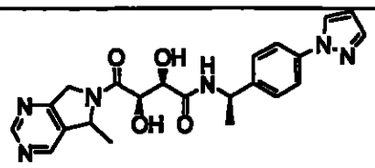
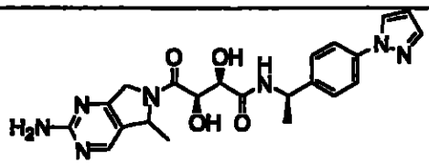
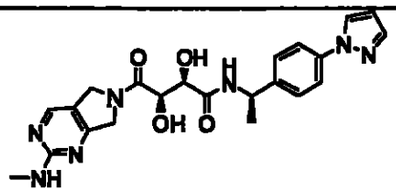
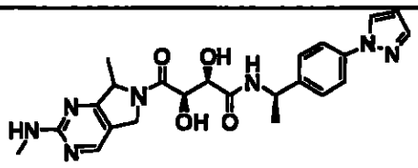
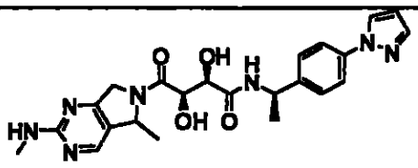
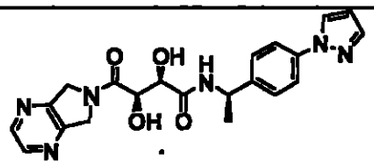
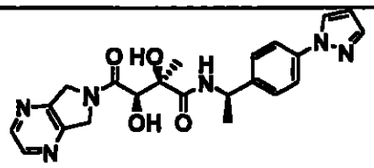
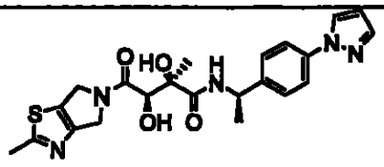
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1036		
1035		
1235A		
1235B		

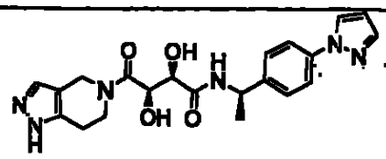
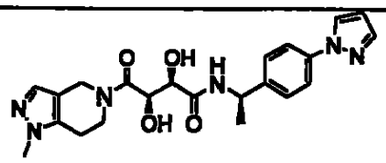
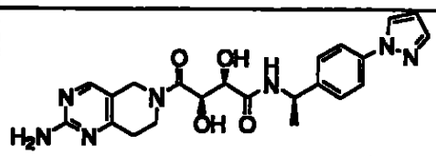
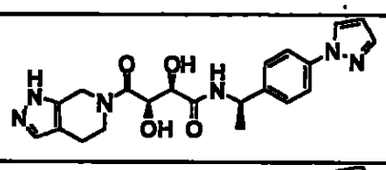
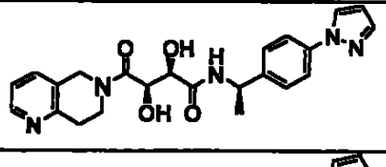
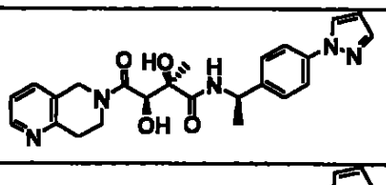
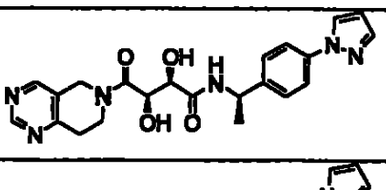
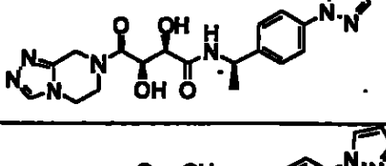
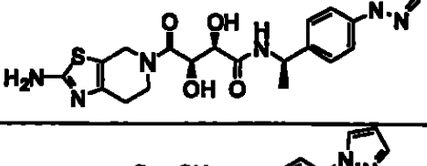
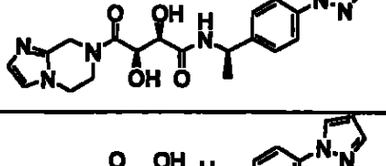
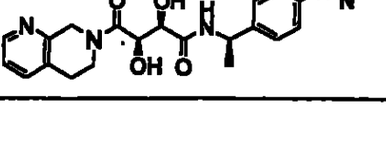
1236A		
1236B		
1243A, B (diastereomers)		
1243C		
1247A, B (diastereomers) (?)		
1255		
1256		
1261		

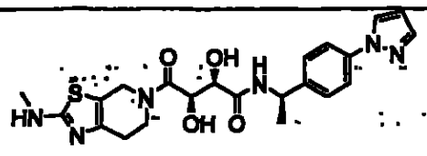
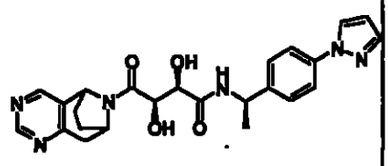
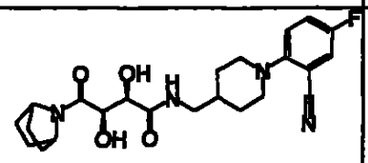
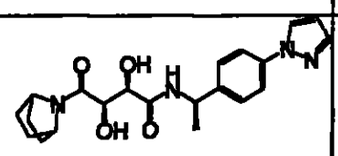
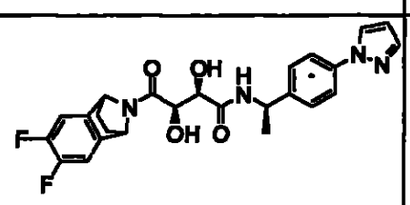
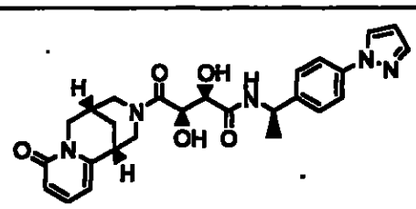
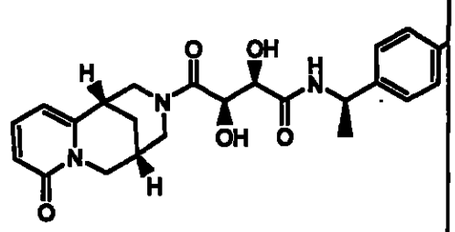
1266		
1267		
1268		
1269		
1276		
1280		
2003		B
2007		A
2030		B

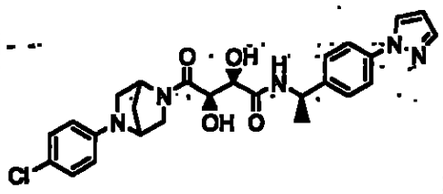
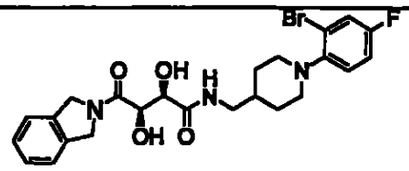
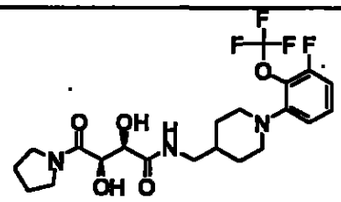
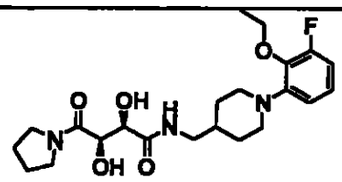
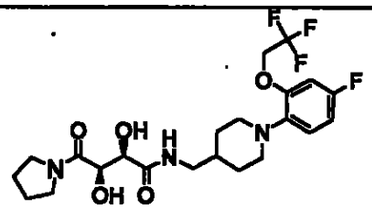
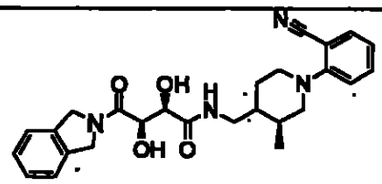
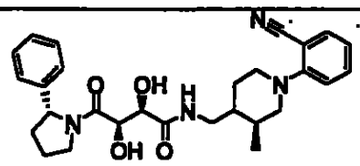
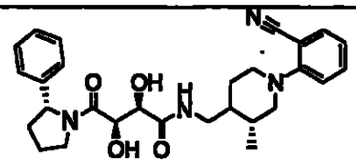
2031		A
2032		A
2033		A
2034		B
2035		A
2036		A
2037		B
2038		B
2039		A

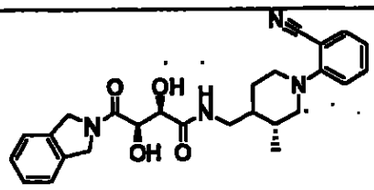
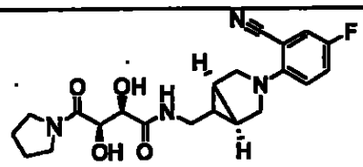
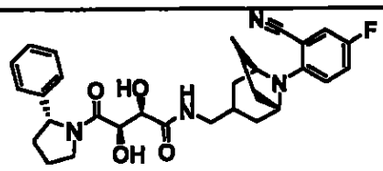
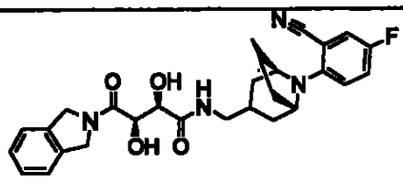
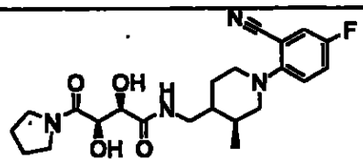
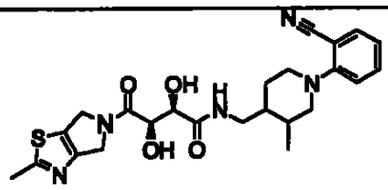
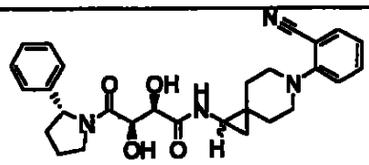
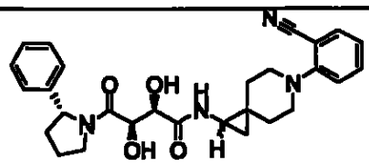
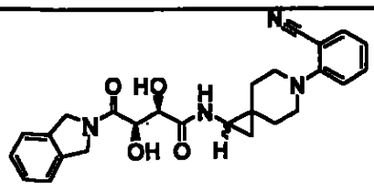
2040		A
2041		B
2042		A
2043		A
2044		A
2045		C
2046		C
2047		C
2048		B

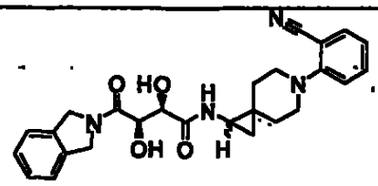
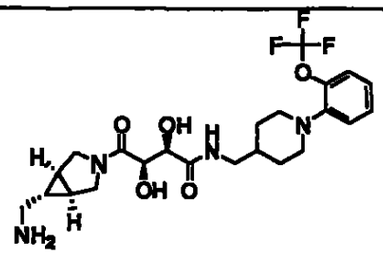
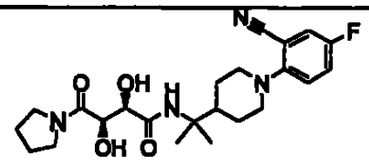
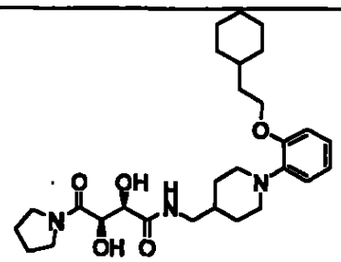
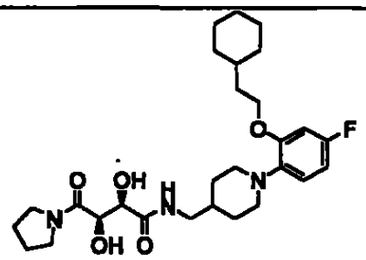
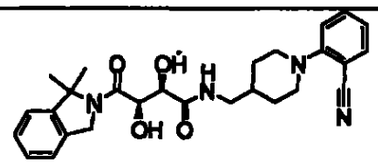
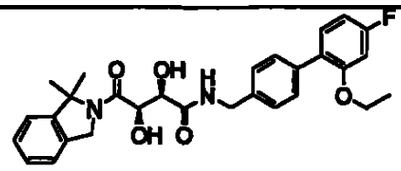
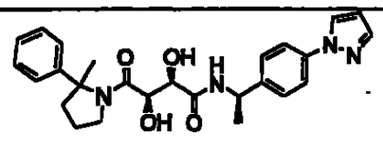
2049		B
2050		B
2051		B
2052		A
2053		B
2054		A
2055		A
2056		A
2057		A

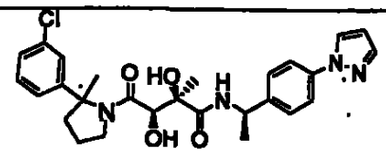
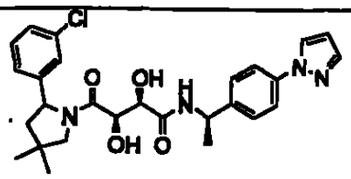
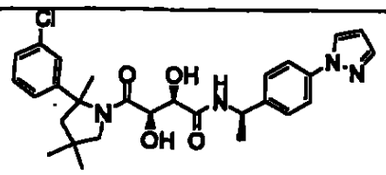
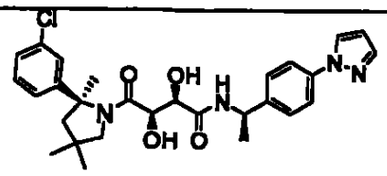
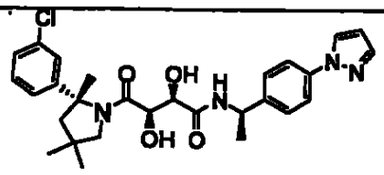
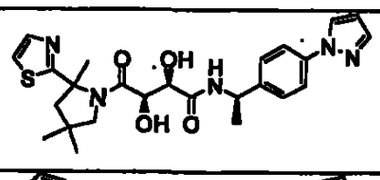
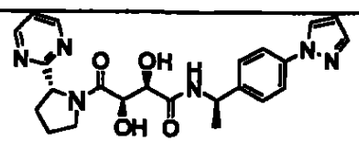
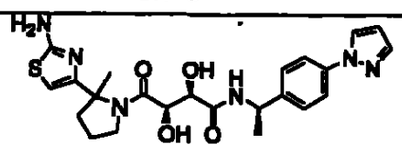
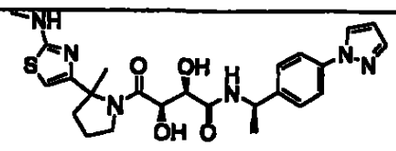
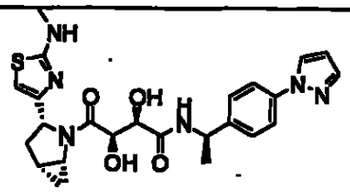
2073		B
2074		B
2075		B
2076		B
2077		B
2078		C
2079		C
2080		C
2081		A
2082		C
2083		B

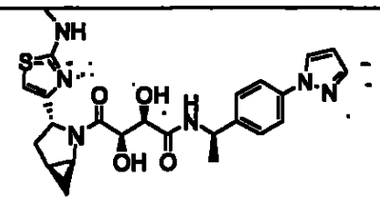
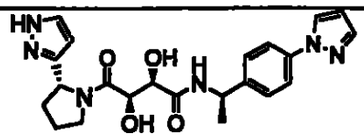
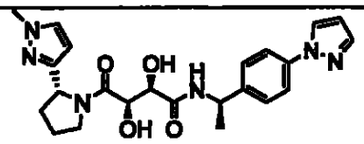
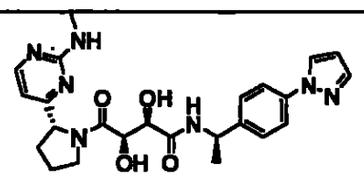
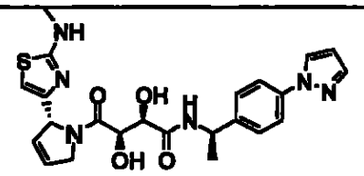
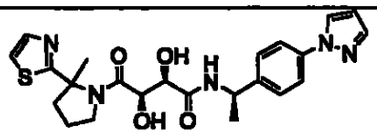
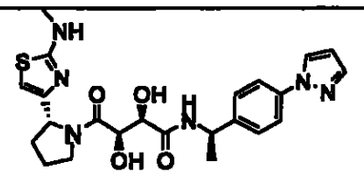
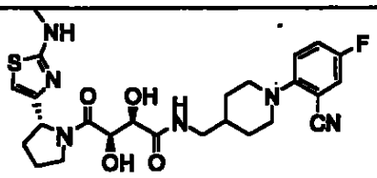
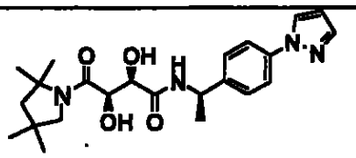
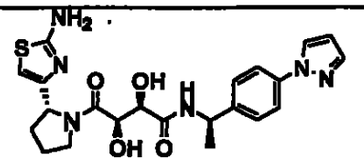
2084		B
2093		D
2094		D
2095		C
2096		C
2097		C
2098		C

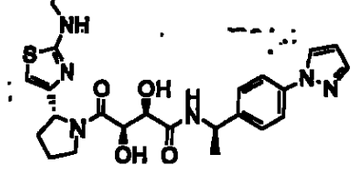
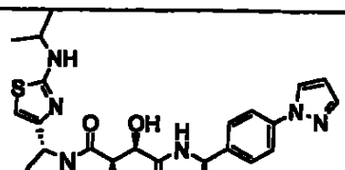
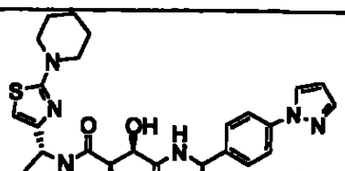
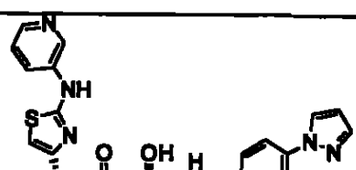
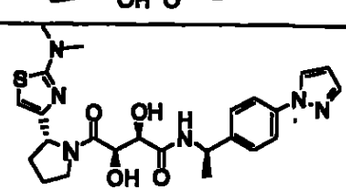
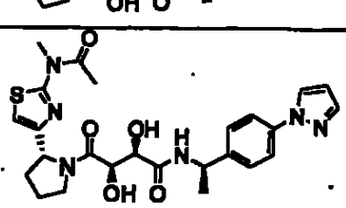
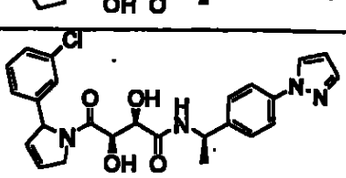
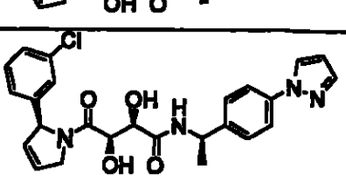
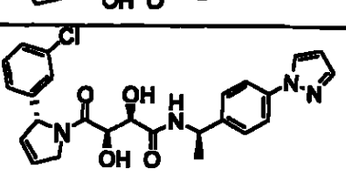
2099		C
2139		A
2140		D
2141		D
2142		B
2143		A
2144		A
2145		C

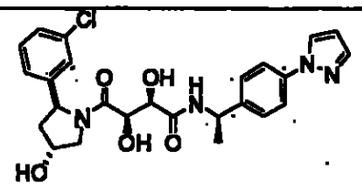
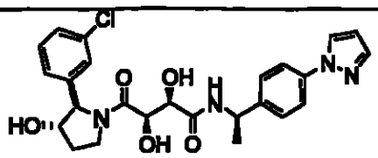
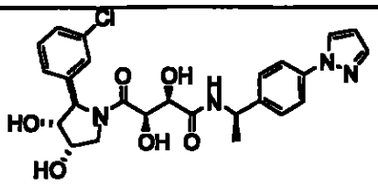
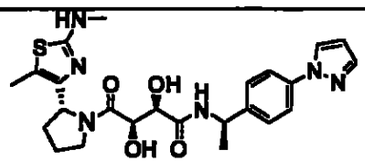
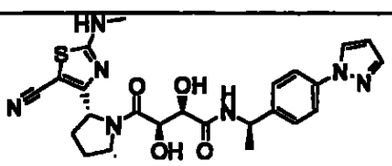
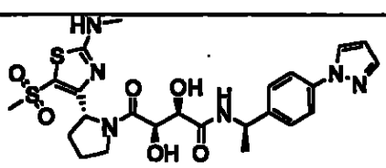
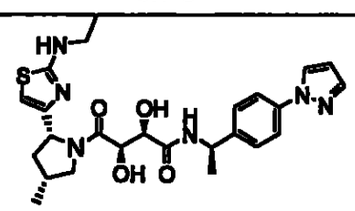
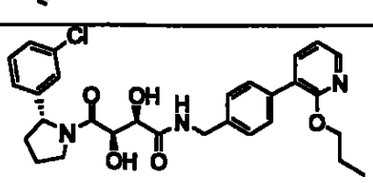
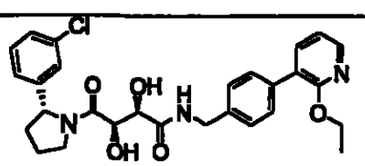
2146		C
2147		C
2148		C
2149		C
2150		B
2151		A
2152		D
2153		D
2154		D

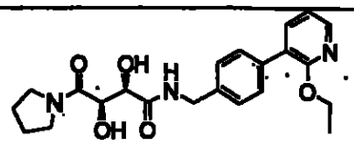
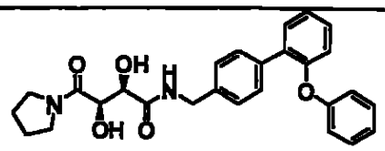
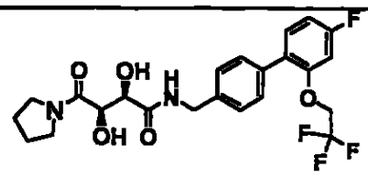
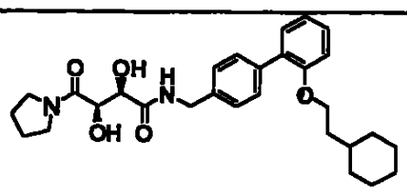
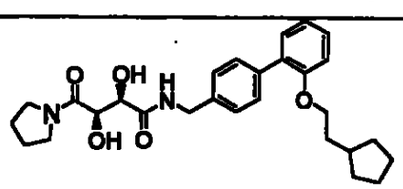
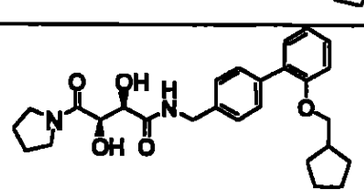
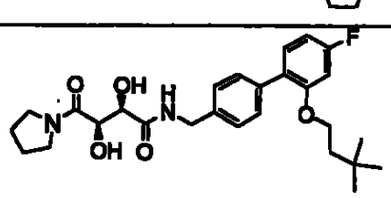
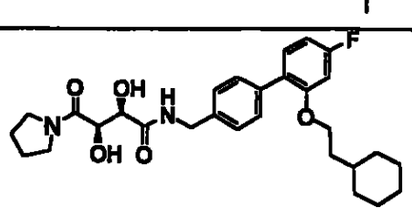
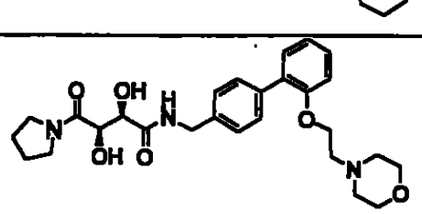
2155		D
2156		B
2157		B
2158		B
2159		B
2233		A
2234		C
2235		A

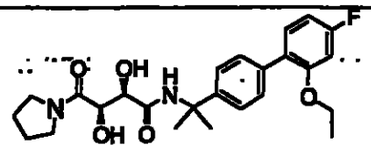
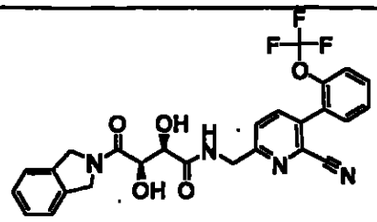
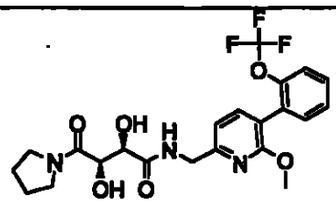
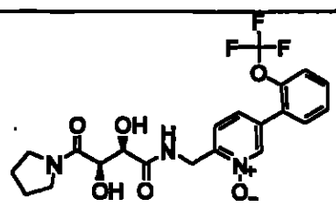
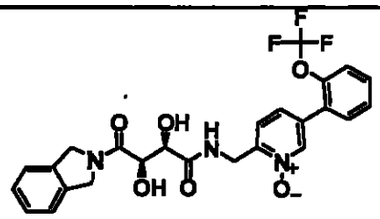
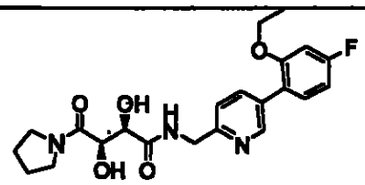
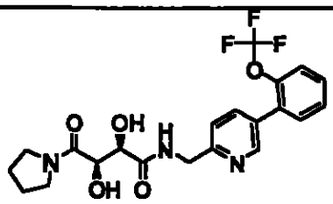
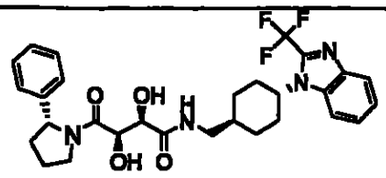
2236		D
2237		C
2238		B
2239		D
2240		B
2241		C
2242		A
2243		A
2244		A
2245		A

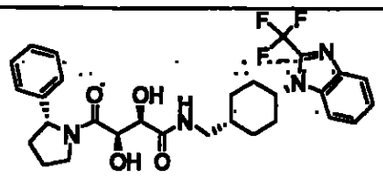
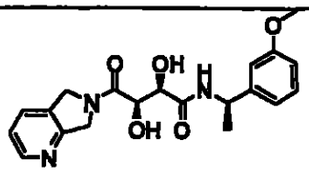
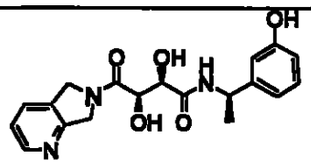
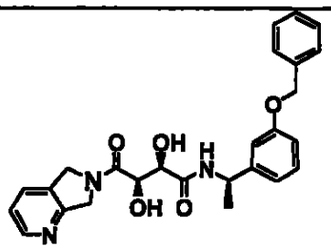
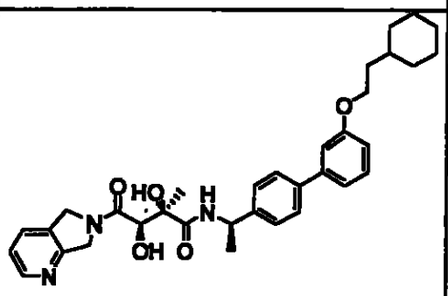
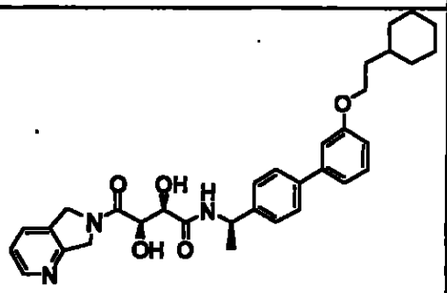
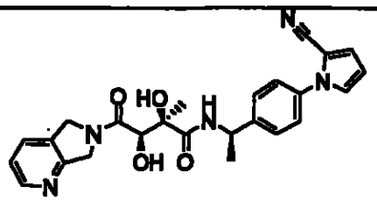
2246		B
2247		A
2248		A
2249		A
2250		A
2251		A
2252		A
2253		A
2254		C
2255		A

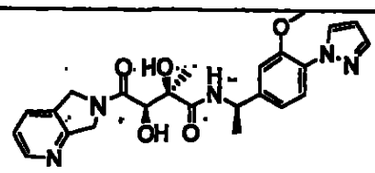
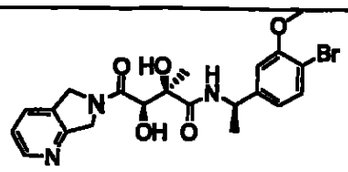
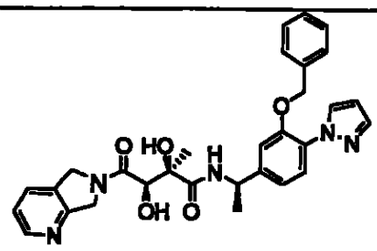
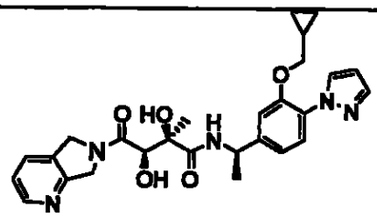
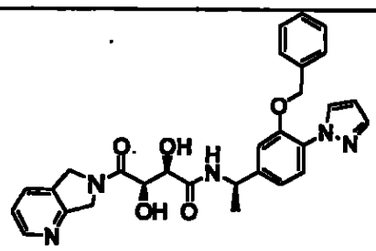
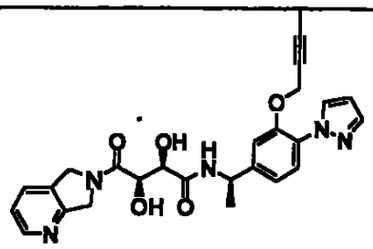
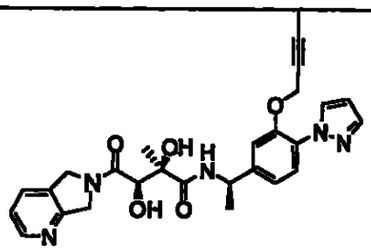
2256		A
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2258		B
2259		A
2260		B
2261		A
2262		A
2263		C
2264		A

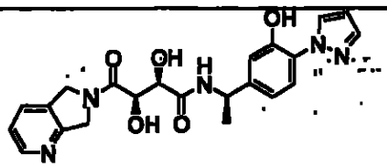
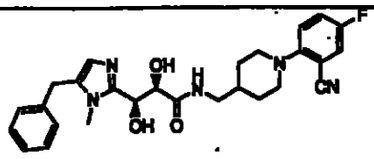
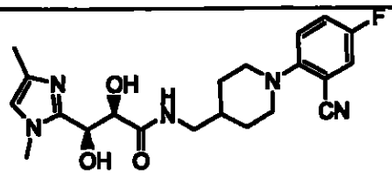
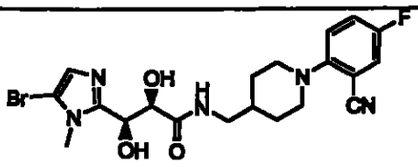
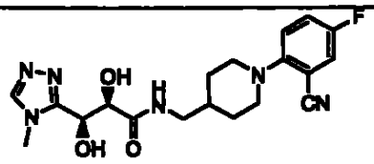
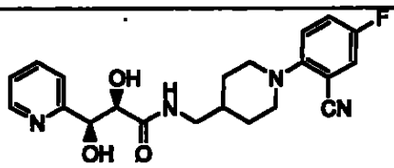
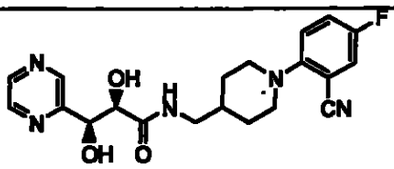
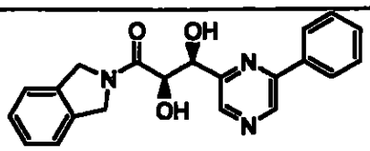
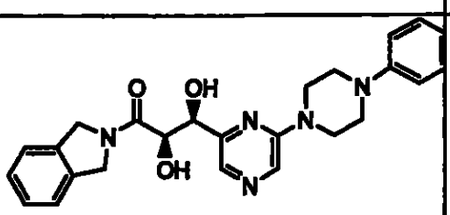
2265		A
2266		A
2267		C
2268		A
2269		A
2270		A
2271		A
2333		A
2334		A

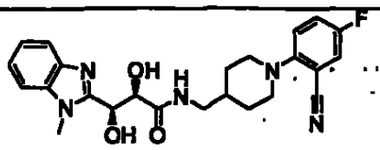
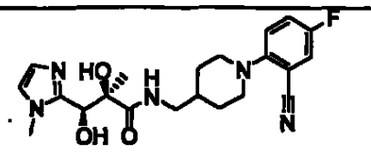
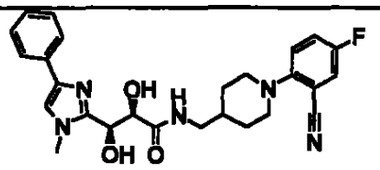
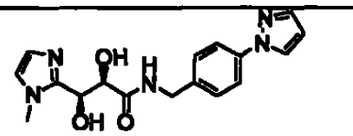
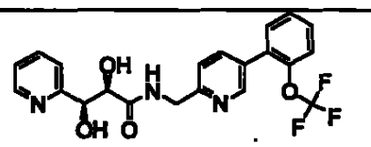
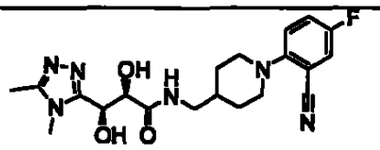
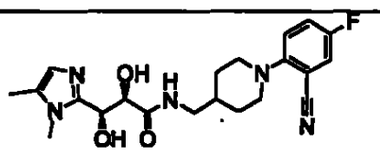
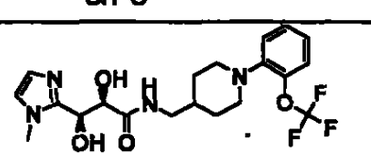
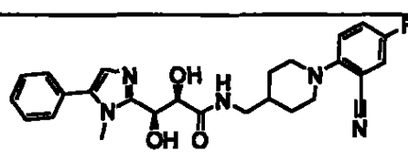
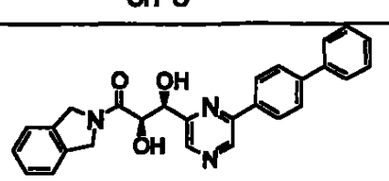
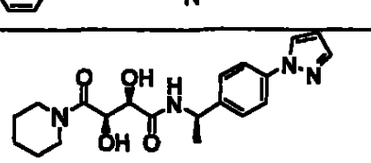
2335		C
2336		C
2337		B
2338		A
2339		B
2340		B
2341		C
2342		C
2343		D

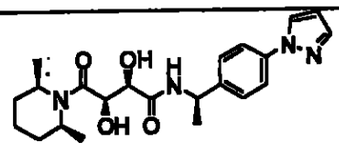
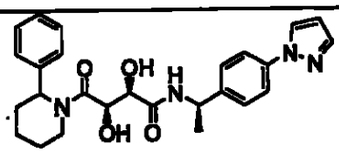
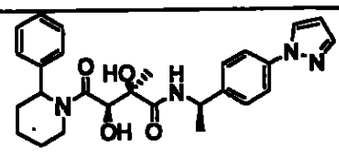
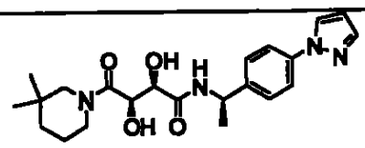
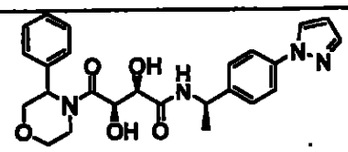
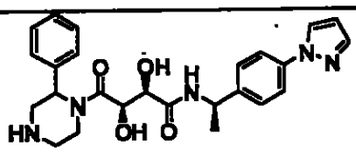
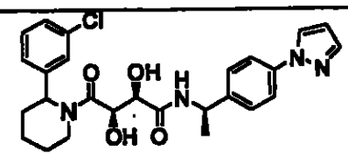
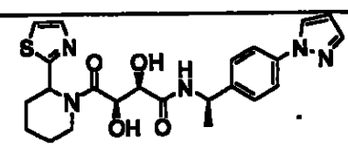
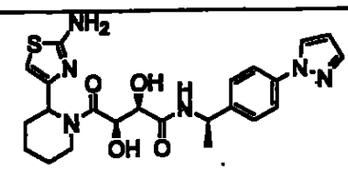
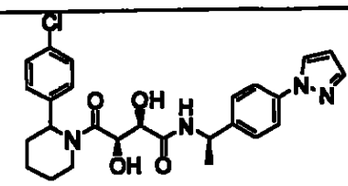
2344		D
2345		D
2346		D
2347		D
2348		C
2349		A
2350		A
2351		A

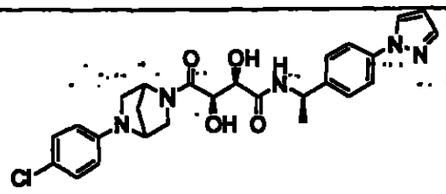
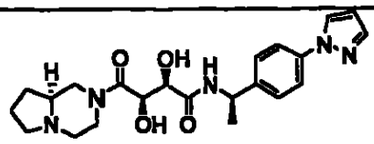
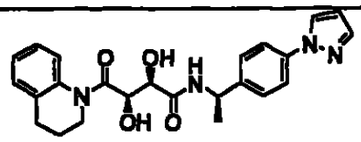
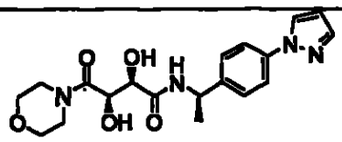
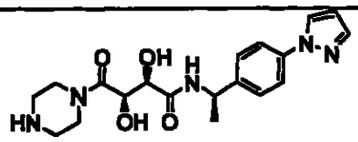
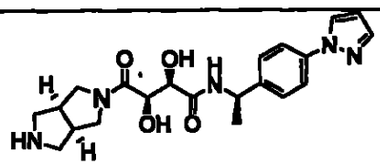
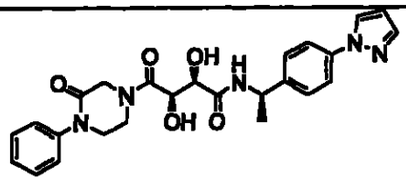
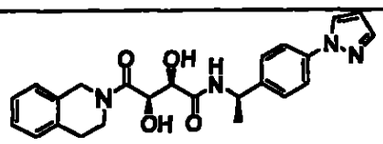
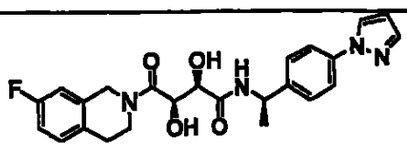
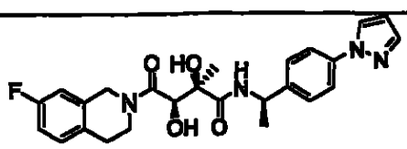
2352		A
2306		D
2307		D
2308		D
2353A		C
2353B		B
2354		B

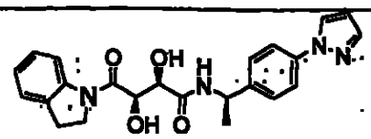
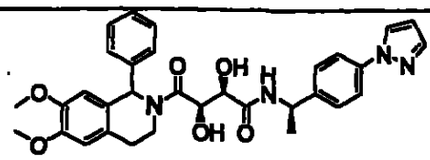
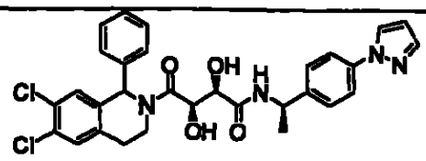
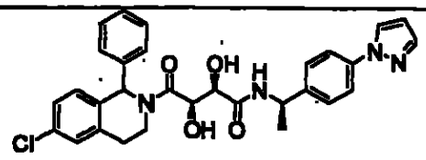
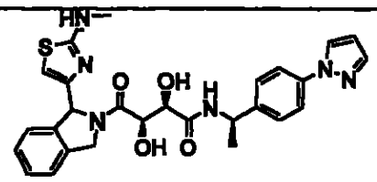
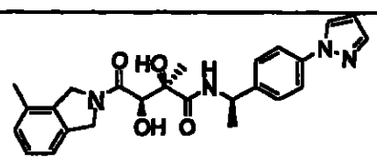
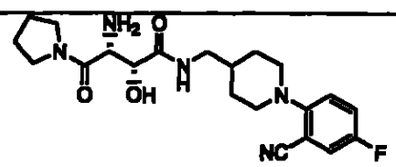
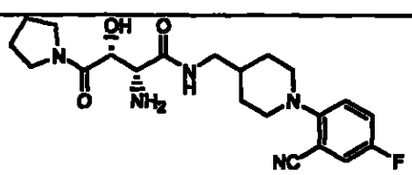
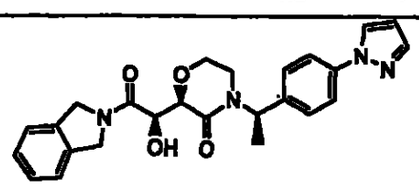
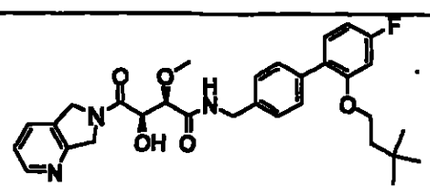
2355		A
2356		D
2357		A
2358		C
2304		A
2359		A
2360		A

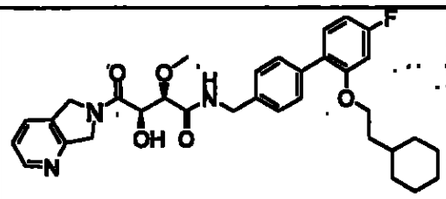
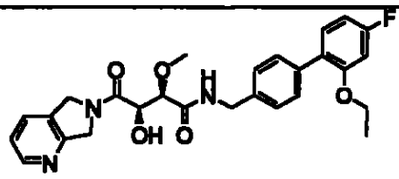
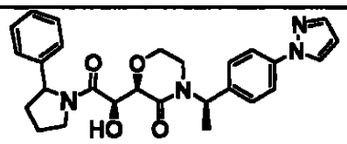
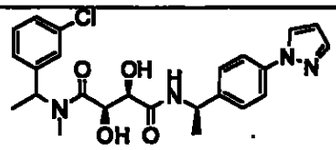
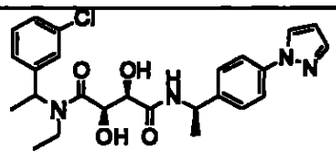
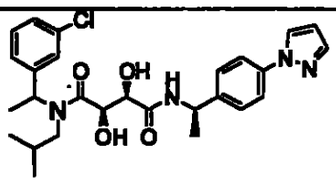
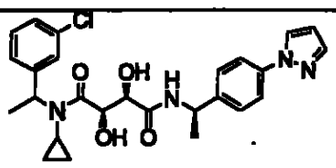
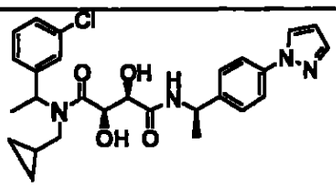
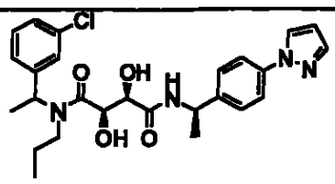
2305		A
2365		C
2369		
2372		D
2376		D
2382		D
2387		D
2391		D
2393		D

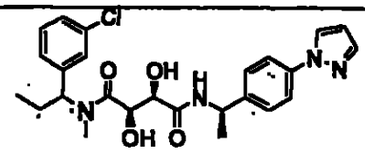
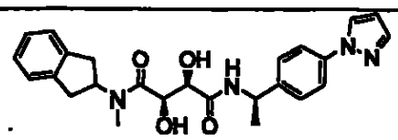
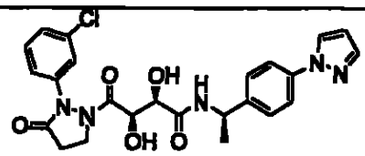
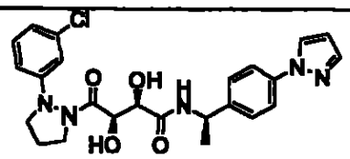
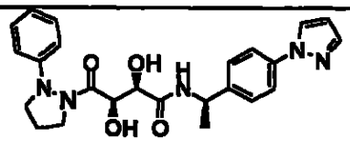
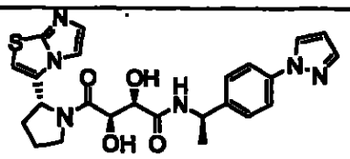
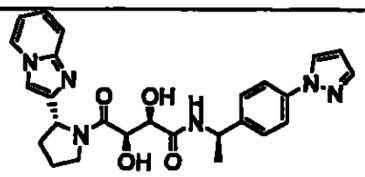
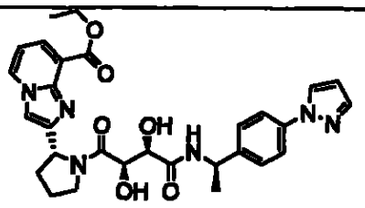
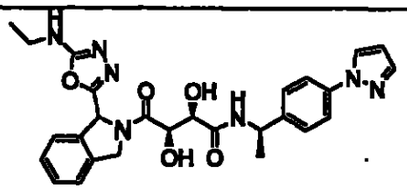
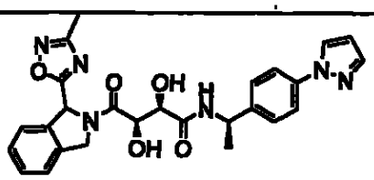
2394		D
2395		C
2396		D
2397		D
2398		D
2399		D
2400		C
2401		C
2402		D
2403		D
2408		B

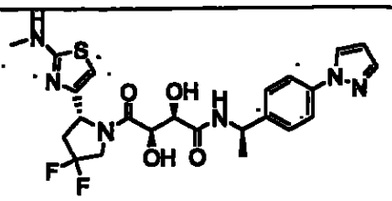
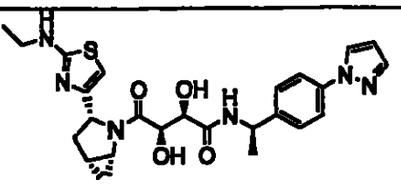
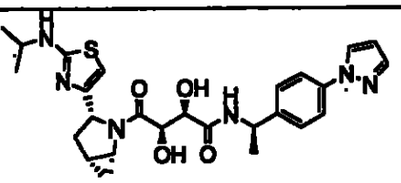
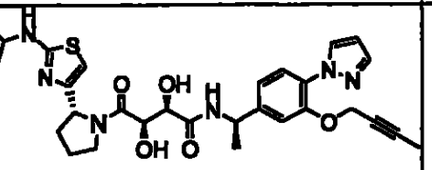
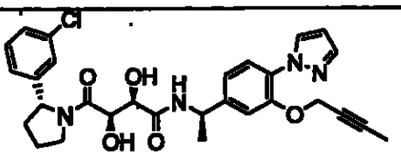
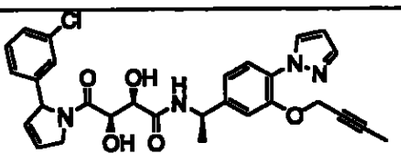
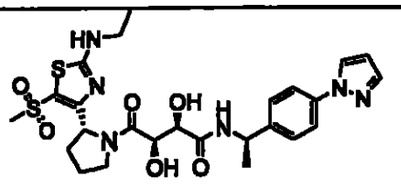
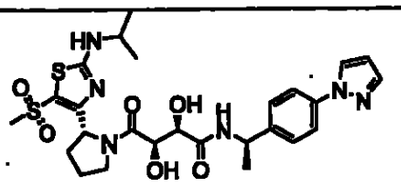
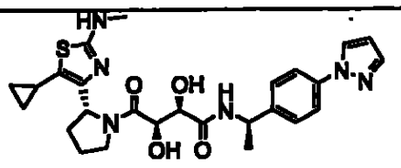
2409		C
2410		A
2411		D
2412		C
2413		A
2414		B
2415		B
2416		B
2417		B
2418		B

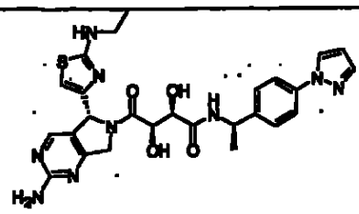
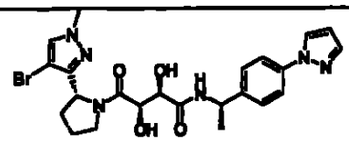
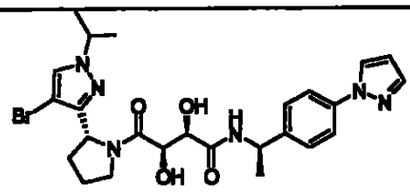
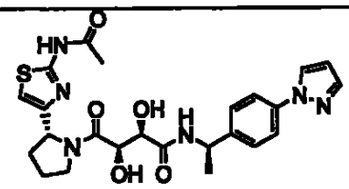
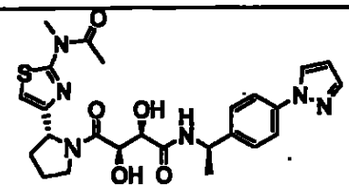
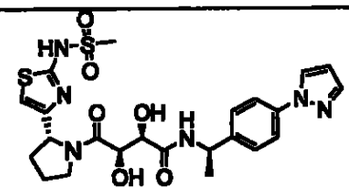
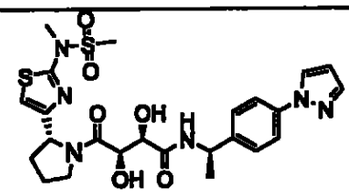
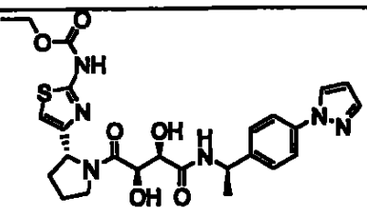
2419		C
2420		C
2421		C
2422		B
2423		C
2424		C
2425		C
2438		A
2439		A
2440		B

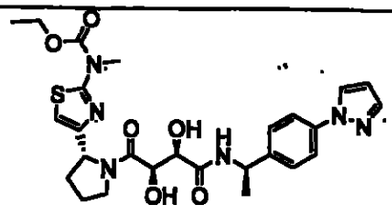
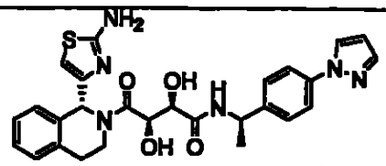
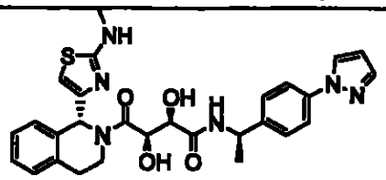
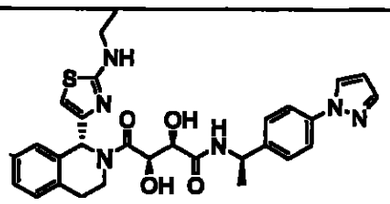
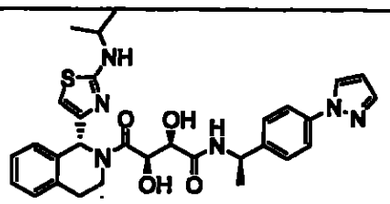
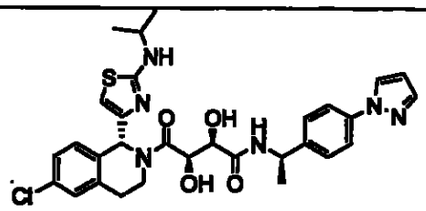
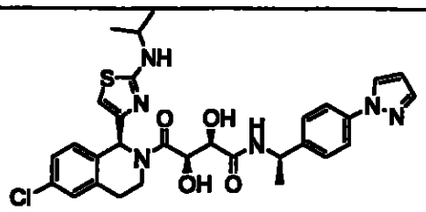
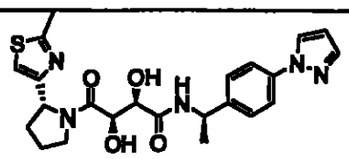
2441		B
2442		A
2443		A
2444		A
2445		A
2446		B
2456		D
2460		D
2474		D
2475		B

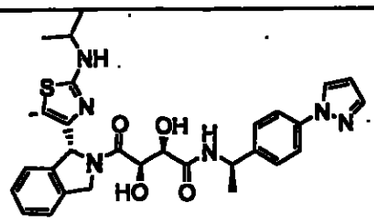
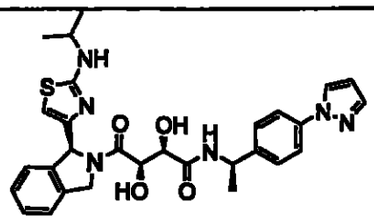
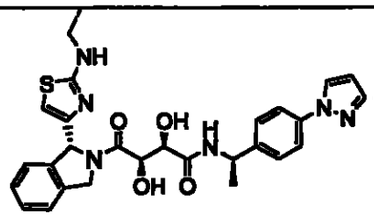
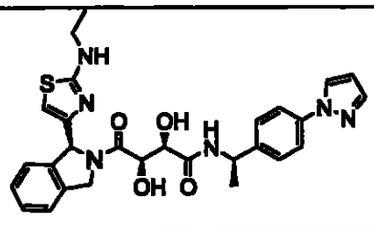
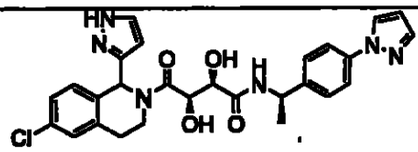
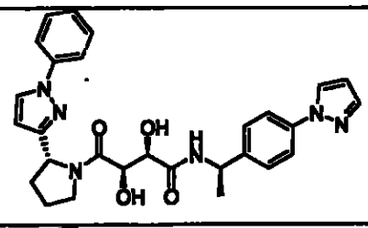
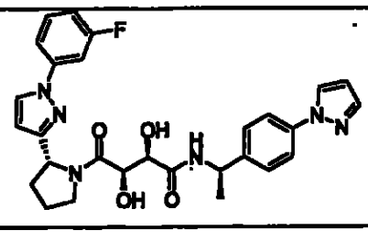
2476		B
2477		C
2478		D
2480		B
2481		C
2482		D
2483		D
2485		D
2486		D

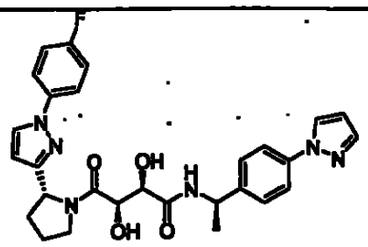
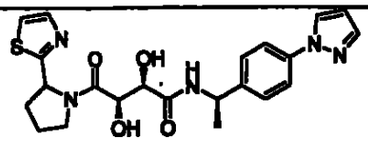
2487		B
2489		B
2494		C
2495		C
2496		C
2506		A
2507		A
2508		B
2527		A
2528		A

2567		A
2568		–
2569		–
2570		A
2571		A
2572		A
2573		–
2574		–
2575		–

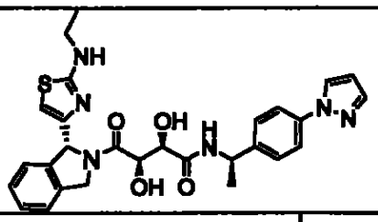
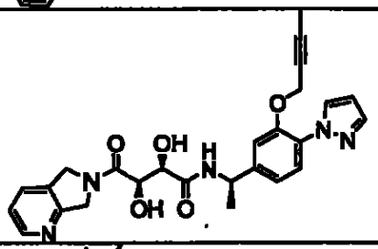
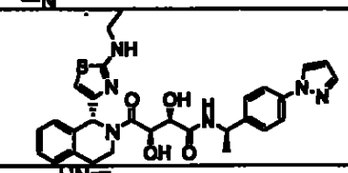
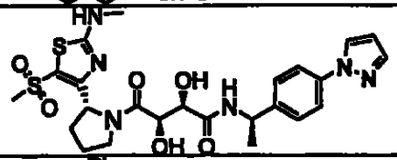
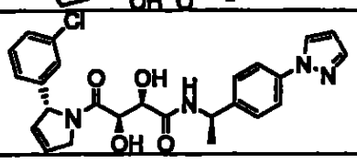
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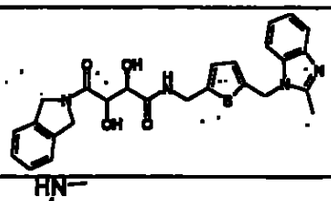
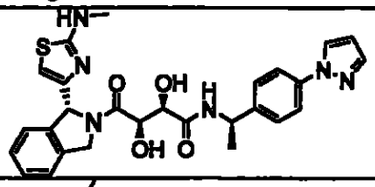
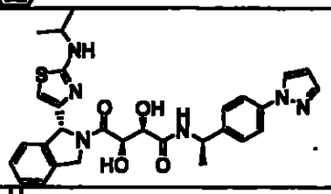
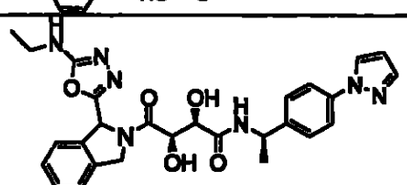
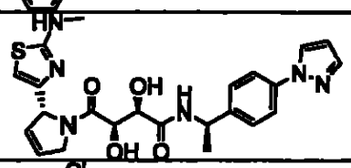
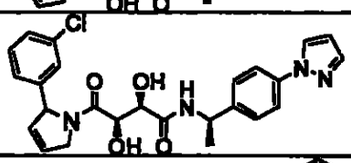
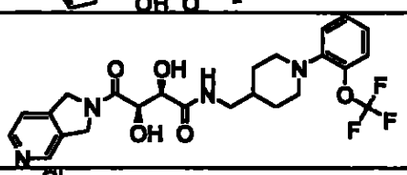
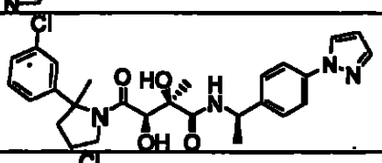
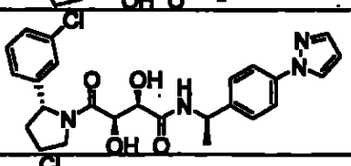
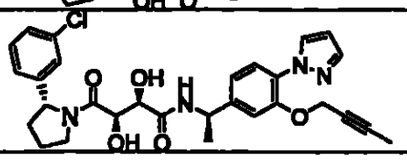
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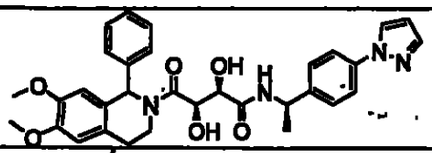
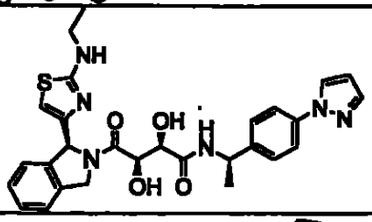
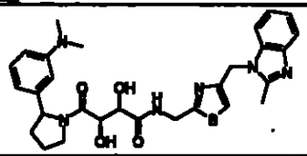
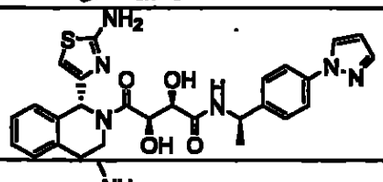
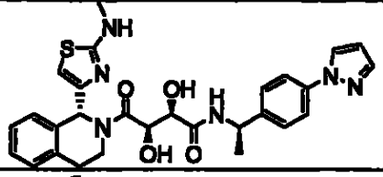
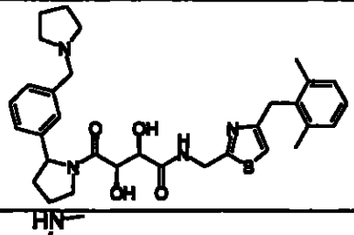
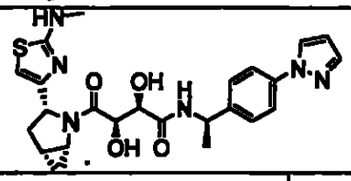
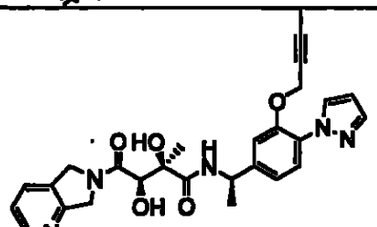
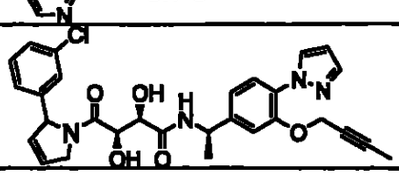
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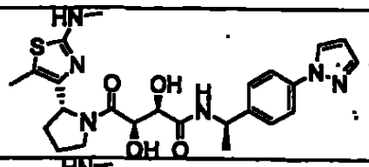
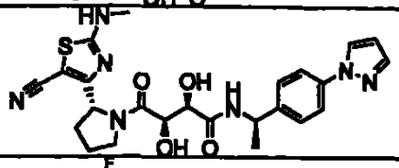
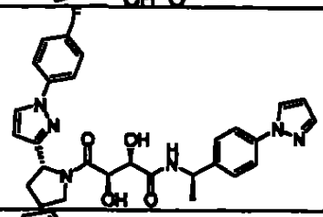
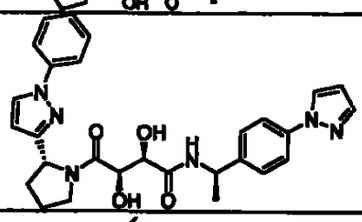
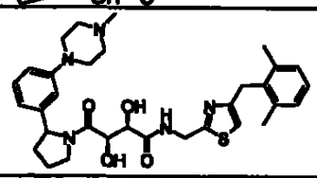
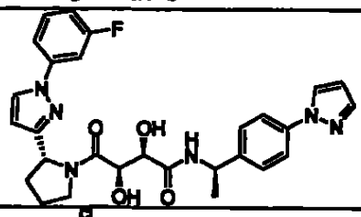
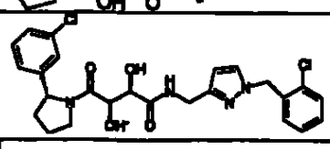
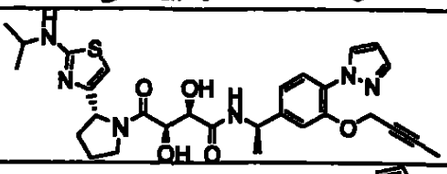
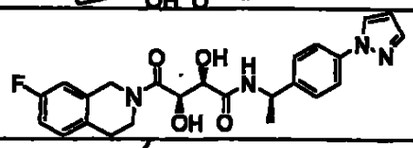
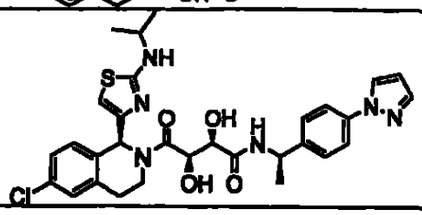
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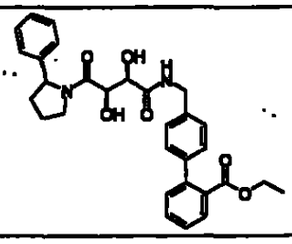
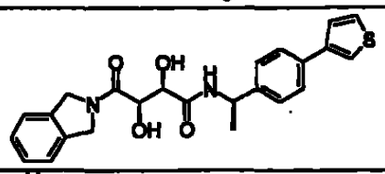
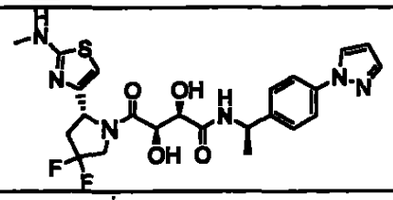
Representative examples of compounds of the Invention with their respective K_i values are listed in the table below:

	Structure	Ki (nM)
		0.16
		0.25
		0.3
		0.38
		0.49

		0.5
		0.5
		0.54
		0.56
		0.57
		0.6
		0.74
		0.75
		0.8
		0.85

		0.86
		0.89
Mixture of diastereomers		1
		1.1
		1.4
One diastereomer		1.4
		1.4
		1.44
		1.54

		2
		2
		2.0
		2.3
Mixture of diastereomers		2.5
		2.7
		2.7
		2.9
		3.0
		3.3

		3.6
		3.8
		3.9

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, lozenges, aqueous or olly suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be

337
328

coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for controlled release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or a soft gelatin capsules where in the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, e.g., sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, e.g., olive oil or arachis oil, or a mineral oil, e.g., liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, e.g., soy beans, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, e.g., polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, e.g., as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. The compositions can be

prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of The Invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles.)

The compounds for the present invention can be administered in the intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound thereof employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter, arrest or reverse the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug. Preferably, doses of the compound of Formula I useful in the method of the present invention range from 0.01 to 1000 mg per day. More preferably, dosages range from 0.1 to 1000 mg/day. Most preferably, dosages range from 0.1 to 500 mg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01 to 1000 milligrams of the active ingredient, particularly 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0,

25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.0002 mg/kg to about 50 mg/kg of body weight per day. The range is more particularly from about 0.001 mg/kg to 1 mg/kg of body weight per day.

Advantageously, the active agent of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in dividend doses of two, three or four time daily.

The amount of active ingredient that may be combined with the carrier materials to produce single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route or administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of the invention may be produced by processes known to those skilled in the art and as shown in the following reaction schemes and in the preparations and examples described below.

EXAMPLES

The following abbreviations are used in the procedures and schemes:

ACN	Acetonitrile
AcOH	Acetic acid
ADDP	1,1'-(Azodicarbonyl)dipiperidine
Anh.	Anhydrous
Aq	Aqueous
BOC	tert-Butoxycarbonyl
°C	degrees Celsius
CBZCl	Benzyl chloroformate
CDI	Carbodiimide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane

DEAD	Diethyl azodicarboxylate
(DHQ)2PHAL	Hydroquinine-1,4-phthalazinediyl diether
DIAD	Diisopropylazodicarboxylate
DIEA	Diisopropylethylamine
DMA	N,N-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMFDMA	N,N-Dimethylformamide dimethylacetal
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1h)-pyrimidinone
DMSO	Dimethyl sulfoxide
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EI	Electron ionization
Eq	Equivalents
EtOAc	Ethyl acetate
EtOH	Ethanol
g	grams
h.	hours
^1H	proton
HATU	N,N,N',N'-Tetramethyl-O-(7-Azabenzotriazol-1-yl)Uronium hexafluorophosphate
Hex	hexanes
HOBt	1-Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
M	Molar
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
min	Minutes
mg	Milligrams
MHz	Megahertz

ml	Milliliter
MS	Mass Spectroscopy
NMM	N-Methylmorpholine
NMP	1-methyl-2-pyrrolidone
ON	Overnight
$Pd(^tBu_3P)_2$	Bis-(tri-*tert*-butylophosphine)palladium
$Pd(TPP)_4$	Tetrakis-(triphenylphosphine)palladium
$Pd(Oac)_2$	Palladium(II) acetate
$PdCl_2(TPP)_2$	Bis-(triphenylphosphine)palladium(II) chloride
$PdCl_2(ddppf)$	Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
PyBrOP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
Pyr	Pyridine
RT	Room temperature
SiO_2	Silica gel 60 chromatography
sgc	Silica gel 60 chromatography
tBOC	tert-Butoxycarbonyl
TACE	TNF-alpha converting enzyme
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TPP	Triphenylphosphine
t_R	Retention time

NMR spectra were acquired on a Mercuryplus 400 MHz NMR Spectrometer (Varian), using CDCl3 or DMSO-d6 as solvents. LC-MS data was obtained using an Agilent 1100 Series LC/MSD (quadrupole, API-ES (Atmospheric Pressure Interface Electrospray)) with a capillary voltage set to 3500 V and running in positive mode. Reported analytical HPLC (LC/MS) retention times were obtained using a C18 (150 x 4.6 mm) reverse-phase column eluting with a 5 or 10 minute gradient of 0.1 % trifluoroacetic acid in water to 95:5 acetonitrile:water at a flow rate of 3 mL/min.

Purification via reverse phase chromatography was accomplished using a C18 reverse phase column with a gradient of 0.1 % trifluoroacetic acid in water to 95:5 acetonitrile:water at a flow rate of 20 mL/min. Samples were collected using a UV (Gilson, 254 nm) or mass spectra (Agilent 1100 Series LC/MSD model SL) signal.

Normal phase silica gel chromatography on a Biotage instrument was accomplished using a Quad UV System (P/N 07052) utilizing KP-SIL 32-63 um columns, 60Å with flash cartridges 12+M or 25+M.

The compounds of formula (I) may be produced by processes known to those skilled in the art and as shown in the following reaction schemes and in the preparations and examples described below. These preparations and examples should not be construed to limit the scope of the disclosure. Alternate mechanistic pathways and analogous structures may be apparent to those skilled in the art. Some of the compounds made by these processes are listed in Table 1. All kinds of isomeric forms of the compounds are considered to be within the scope of this invention.

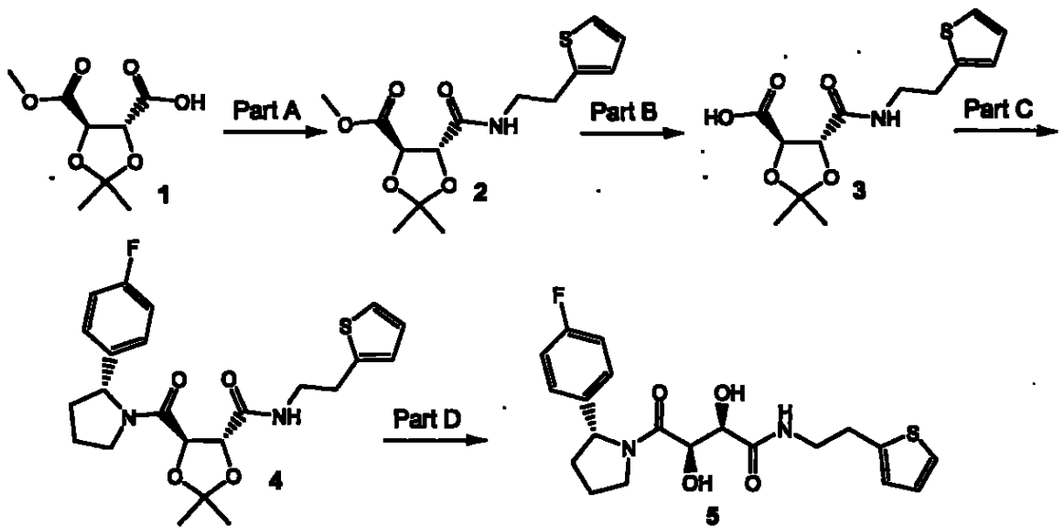
Example 1: General synthesis of tartrate inhibitors

Two general routes exist for the synthesis of tartrate diamides from amines. The first (Example 1) utilizes an acetonide-protected monoacid/monoester intermediate prepared from the commercially available acetonide dimethyl ester using a literature procedure (*J. Am. Chem. Soc.* 1978, *100*, 4865-4872). In general either Example 1 or Example 2 could be used interchangeably, although Example 2 was found to be more preferred for compounds that contained functional groups that were unstable towards acidic deprotection conditions (such as 113).

A variety of amide bond coupling reagents were acceptable, including HATU, CDI, EDC, DCC/HOBt, PyBrOP, polymer supported CDI with HOBt, polymer supported carbodiimide, and polymer supported EDC (PS-EDC) with HOBt. These coupling reagents could be used with a variety of bases, including triethylamine (TEA), diisopropylethylamine (DIEA), N-methyl morpholine, pyridine, dimethylaminopyridine (DMAP) and imidazole. In some cases the excess amines in the peptide coupling steps were removed using

liquid/liquid extraction or polymeric scavenging resins such as polymer supported isocyanate (PS-NCO) and/or polymer supported tosic acid (MP-TsOH). Unreacted acids could be removed using MP-carbonate resin or polymer resins containing basic functional groups such as trisamine (i.e. PS-trisamine), amberlite, or morpholine. Peptide couplings were conducted in a variety of solvents, including DMF, THF, dioxane, acetonitrile, NMP, and DCM. These solvents can also be combined in various proportions to optimize the reaction conditions. A less preferred but viable route using pentafluorophenyl (PFP) ester intermediates may be also utilized to prepare mono or diamides; preferred solvents for this approach should include THF. General peptide coupling strategies, including PFP-based approaches, can be found in Bodanszky & Bodanszky, *The Practice of Peptide Synthesis, second edition, Springer-Verlag, 1994.*

Cleavage (saponification) of the intermediate methyl ester could be accomplished under a variety of well-known conditions; including: a slight excess (1.1-3 equivalents) of base, KOH in methanol, LiOH in THF/water, LiOH in methanol/water, and NaOH/THF/MeOH/water. Removal of the acetonide protecting group could be afforded using a variety of acidic conditions, including TFA:water combinations (such as 80:20).



Part A:

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To 2,2-dimethyl-[1,3]dioxolane-4R,5R-dicarboxylic acid monomethyl ester (1) (Musich, J.A.; Rapoport, H.; *J. Am. Chem. Soc.* 1978, *100*, 4865-4872) (500 mg, 2.45 mmol) in DMF (5 mL) was added 2-thiopheneethylamine (316 µL, 2.70 mmol), DIEA (0.94 mL, 5.4 mmol) and HATU (989 mg, 2.60 mmol). The reaction mixture was stirred overnight and the DMF was removed in vacuo. The residue was dissolved in EtOAc, washed with water, saturated bicarbonate solution, 0.1 N HCl, and brine. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 10% EtOAc/DCM) afforded **2** as an oil (491 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, 1H , J = 1.2, 5.2 Hz), 6.95 (dd, 1H, J = 2.1, 5.2 Hz), 6.84 (d, 1H, J = 2.4 Hz), 6.66 (bs, 1H, NH), 4.72 (ABq, 2H, J = 13.2 Hz), 3.84 (s, 3H), 3.65 (m, 1H), 3.57 (m, 1H), 3.09 (t, 2H, J = 6.4 Hz), 1.47 (s, 3H), 1.40 (s, 3H); HPLC-MS t_R = 1.63 min ($UV_{254\ nm}$); Mass calculated for formula $C_{14}H_{19}NO_5S$ 313.1, observed LCMS m/z 314.2 (M+H).

Part B:

To **2** (869 mg, 2.77 mmol) in THF (10 mL) was added 1.0 M LiOH (3 mL, 3 mmol) and the reaction was stirred overnight at room temperature. The reaction mixture was diluted with water (10 mL) and the THF was removed in vacuo. The basic aqueous layer was extracted with diethyl ether and the ether wash was discarded. The aqueous layer was made acidic with 1.0 N HCl and extracted with diethyl ether. The combined organic layers were dried over sodium sulfate and concentrated to afford **3** as a yellow solid (443 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, 1H, J = 1.2, 5.2 Hz), 6.97 (dd, 1H, J = 3.6, 5.2 Hz), 6.90 (bs, 1H, NH), 6.86 (d, 1H, J = 3.2 Hz), 4.48 (ABq, 2H, J = 9.2 Hz), 3.76 (m, 1H), 3.60 (m, 1H), 3.15 (m, 2H), 1.53 (s, 3H), 1.41 (s, 3H); HPLC-MS t_R = 1.34 min ($UV_{254\ nm}$); Mass calculated for formula $C_{13}H_{17}NO_5S$ 299.1, observed LCMS m/z 300.1 (M+H).

Part C:

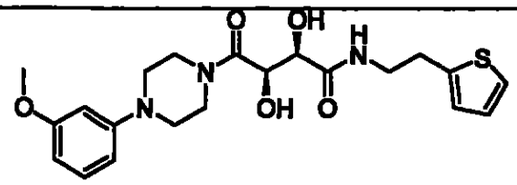
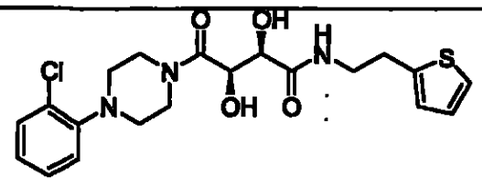
To **3** (150 mg, 0.5 mmol) in DMF (2 mL) was added racemic 2-(4-fluoro-phenyl)-pyrrolidine (99 mg, 0.6 mmol), DIEA (261 µL, 1.5 mmol), and HATU (228 mg, 0.6 mmol) and the reaction mixture was stirred overnight at room temperature. The DMF was removed in vacuo and the residue was dissolved

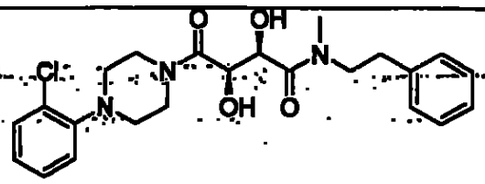
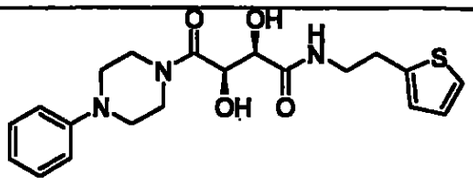
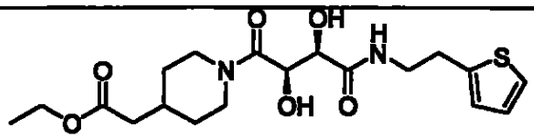
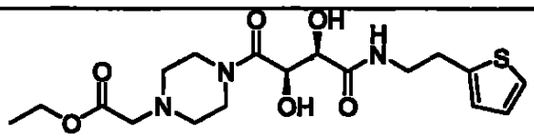
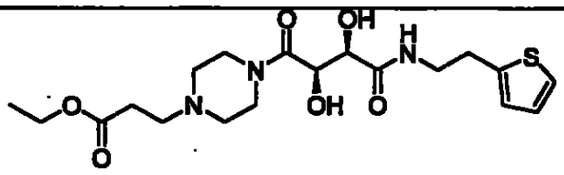
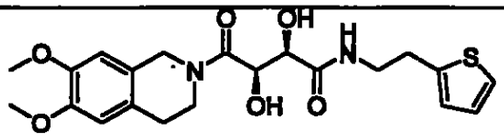
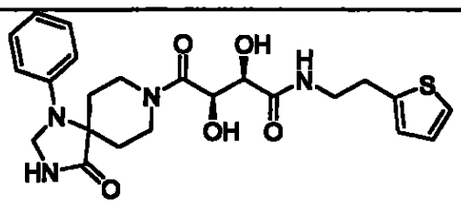
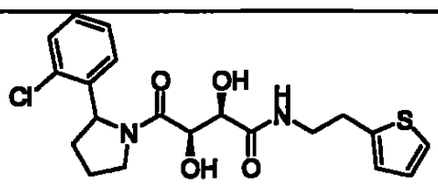
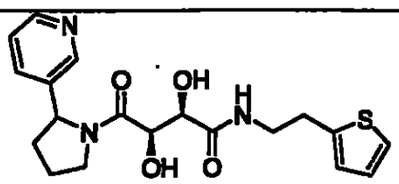
in ethyl acetate. The organic layer was washed with 0.1 N NaOH, 0.1 N HCl, water, and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2; 10% to 50% EtOAc/DCM) afforded an oil (220 mg, 99%). The diastereomers were resolved (as described in Example 18) by reverse phase HPLC to afford 4 the desired isomer (78 mg, 35%) after lypholization. HPLC-MS t_R = 1.93 min ($UV_{254\ nm}$); Mass calculated for formula $C_{23}H_{27}FN_2O_4S$ 446.2, observed LCMS m/z 447.3 (M+H).

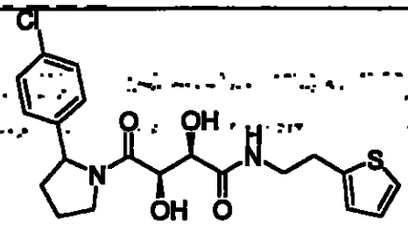
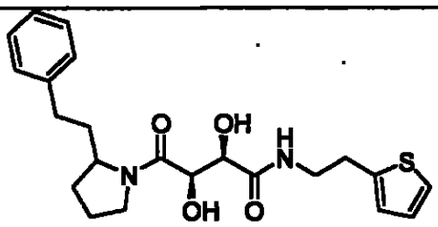
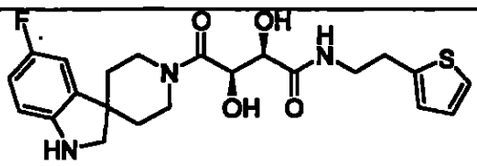
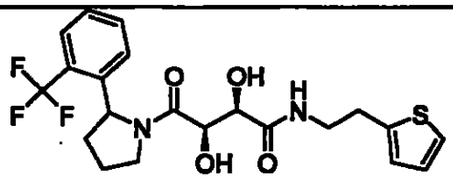
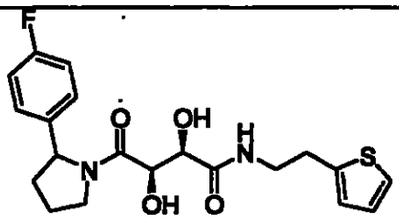
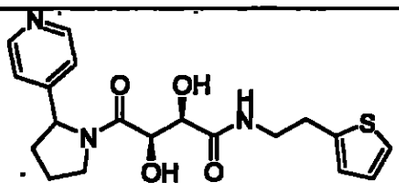
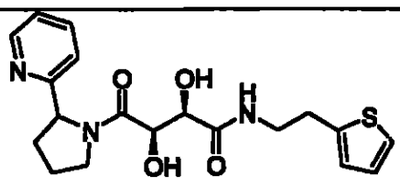
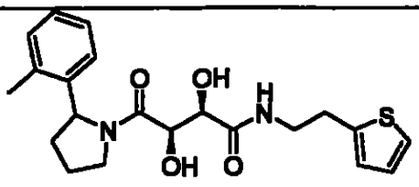
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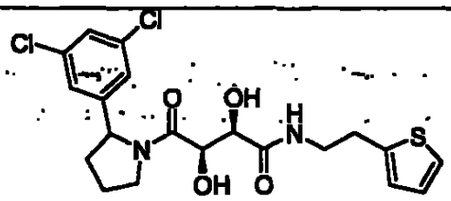
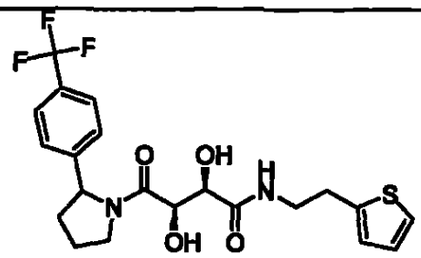
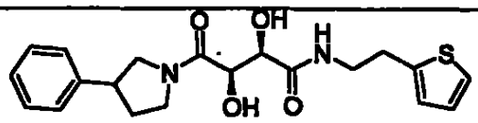
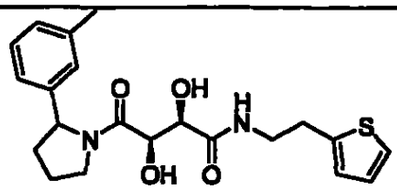
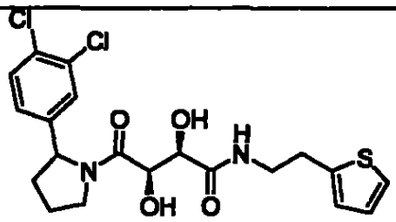
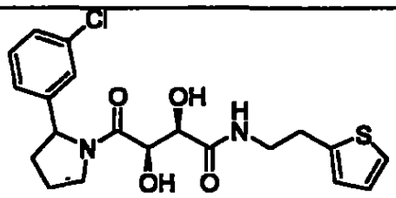
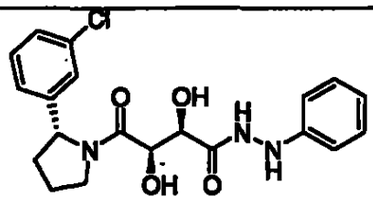
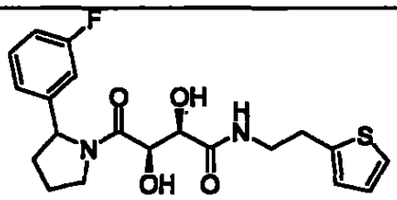
Compound 4 (78 mg, 0.17 mmol) was dissolved in 90:10 TFA:water (5 mL) and stirred for 4 hours at room temperature. The reaction mixture was quenched with 1:1 ACN:water (10 mL) and concentrated. The residue was re-dissolved in 1:1 ACN:water (10 mL) and concentrated. Lypholization afforded 5 as white solid (62 mg, 87%). ^1H NMR (400 MHz, $CDCl_3$) mixture of rotomers δ 7.16- 6.8 (m, 8H), 5.23-5.11 (m, 1H), 4.85 (m, 1H), 4.40-4.15 (m, 1H), 3.90-3.48 (m, 6H), 3.00 (m, 2H), 2.33 (m, 1H), 2.05-1.83 (m, 3H); HPLC-MS t_R = 1.50 min ($UV_{254\ nm}$); Mass calculated for formula $C_{20}H_{23}FN_2O_4S$ 406.1, observed LCMS m/z 407.2 (M+H).

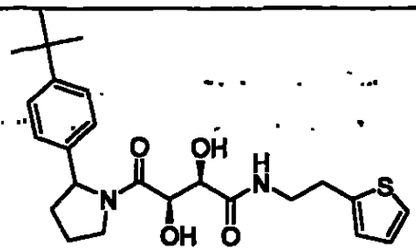
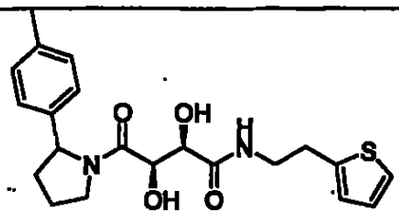
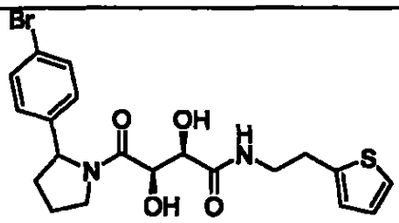
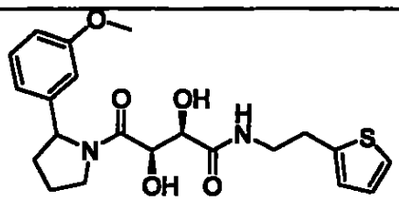
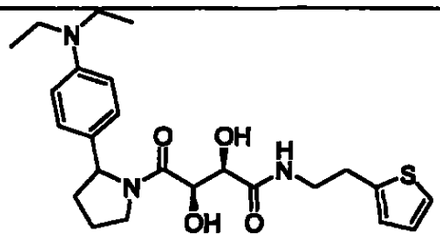
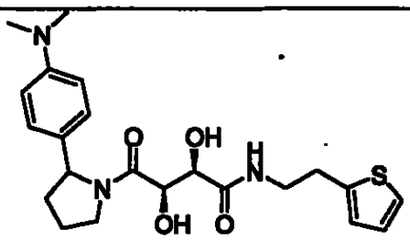
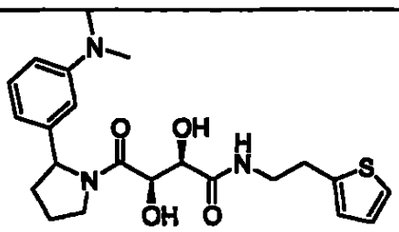
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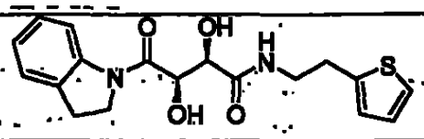
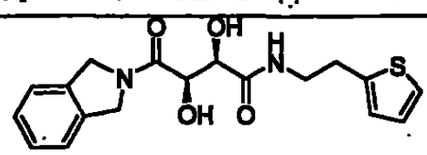
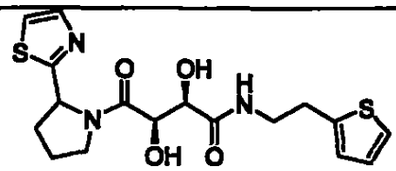
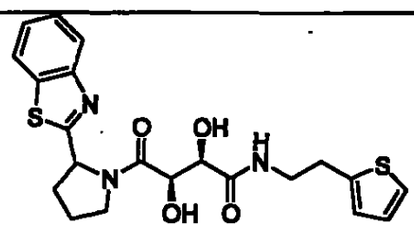
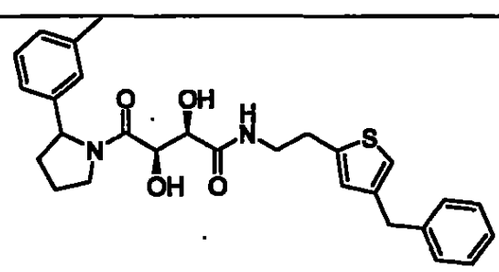
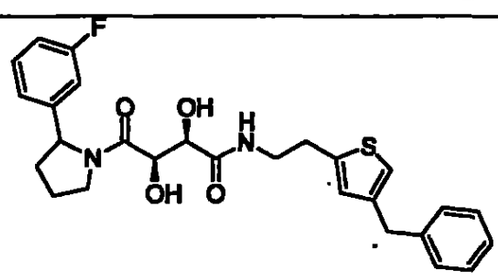
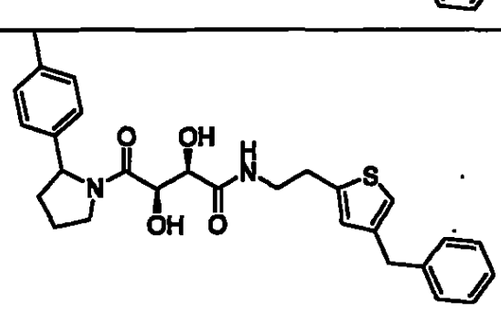
Compound #	Structure	Exact mass	MS m/z (M+H)
6		433.2	434.1
7A		437.1	438.0

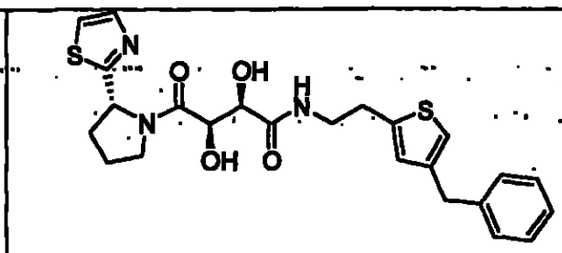
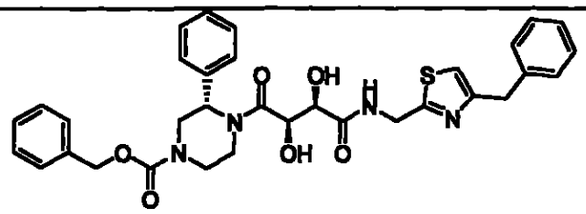
7B		445.2	446.1
8		403.2	404.1
9		412.2	413.2
10		413.2	414.0
11		427.2	428.2
12		434.2	435.1
13		472.2	473.2
14		422.1	423.4
15		389.1	390.1

16		422.1	423.3
17		416.2	417.2
18		447.2	448.1
19		456.1	457.1
20		406.1	407.2
21		389.1	390.1
22		389.1	390.1
23		402.2	403.1

24		456.1	457.0
25		456.1	457.1
26		388.2	389.2
27		402.2	403.1
28		456.1	457.0
29A		422.1	423.1
29B		403.1	404.1
30		406.1	407.2

31		444.2	445.3
32		402.2	403.1
33		466.1	467.0
34		418.2	419.2
35		459.2	460.3
36		431.2	432.2
37		431.2	432.2

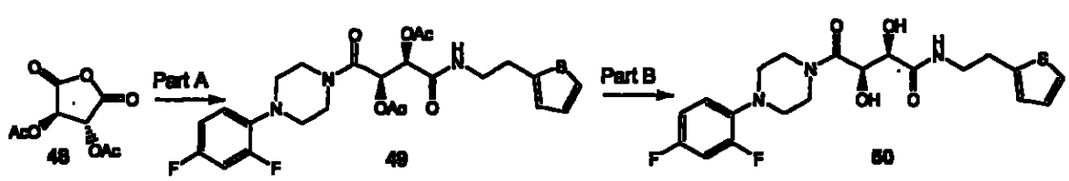
38		360.1	361.1
39		360.1	361.1
40		395.1	396.1
41		445.1	446.2
42		492.2	493.1
43		496.2	497.2
44		492.2	493.1

46		485.1	486.1
47		614.2	615.0

Example 2: Anhydride route to tartrate diamide inhibitors

A second general route to diamide compounds starting from an anhydride intermediate is delineated below in Example 2. (+)-Diacetyl –L-tartaric anhydride (48) is an article of commerce and reacts readily with a variety of amines to generate monoacid/monoamide intermediate. The preferred solvent for the ring opening is DCM; although DMF, THF or dioxane may also be compatible. The subsequent peptide coupling step proceeds under a variety of standard conditions which are given for Example 1. The acetate groups can be removed using a variety of conditions, including hydrazine/methanol, NaOMe in methanol, ammonia/methanol, lithium hydroxide/THF/water (saponification), potassium carbonate in methanol, or MP-carbonate. Often times the preferred set of conditions for parallel synthesis is to use the MP-carbonate. It has also been observed that one or both of the acetate protecting groups can be cleaved during synthetic transformations involving nucleophiles, basic reagents, heating in protic solvents or exposure to organometallic reagents.

Example 2A:



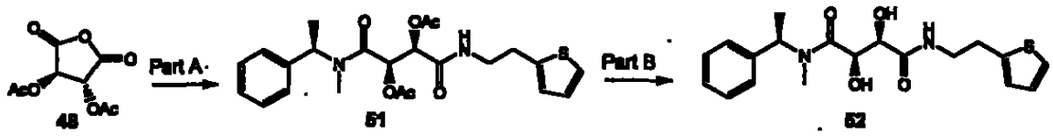
Part A:

To 48 (26 mg, 0.1 mmol) in DMF (1 mL) was added 2,4-difluorophenylpiperazine (20 mg, 0.1 mmol). The reaction mixture was stirred for 1.5 hours. To the crude mixture was added 2-thiopheneethylamine (14 µL, 0.12 mmol), DIEA (38 µL, 0.22 mmol) and HATU (42 mg, 0.11 mmol). The reaction was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with 0.1 N NaOH, 0.1 N HCl, and brine; dried over sodium sulfate and concentrated in vacuo to yield 49 as an oil (49 mg, 94%). HPLC-MS t_R = 2.10 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{27}F_2N_3O_6S$ 523.2, observed LCMS m/z 524.4 (M+H); purity > 95% (ELSD).

Part B:

To 49 (49 mg, 0.09 mmol) in MeOH (2 mL) was added anhydrous hydrazine (5 µL, 0.16 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and freeze-dried to afford 50 as a white powder (40 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, 1H, J = 5.2 Hz), 6.96 (m, 2H), 6.85 (m, 4H), 4.87 (s, 1H), 4.24 (s, 1H), 3.90 (m, 2H), 3.72 (m, 2H), 3.60 (m, 4H), 3.08 (m, 4H); HPLC-MS t_R = 1.85 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{23}F_2N_3O_4S$ 439.1, observed LCMS m/z 440.2 (M+H).

Example 2B:



Part A:

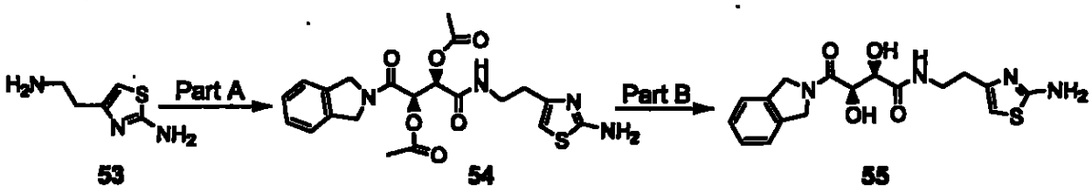
To 48 (26 mg, 0.1 mmol) in DMF (1 mL) was added N-methyl-(1*R*-phenyl-ethyl)-amine (15 µL, 0.1 mmol). The reaction mixture was stirred for 1 hour. To the crude mixture was added 2-thiopheneethylamine (47 µL, 0.4 mmol), HOBt (27 mg, 0.2 mmol), PS-carbodiimide resin (312 mg, 0.4 mmol). To the reaction mixture was added PS-TsOH resin (0.6 mmol) and MP-carbonate

resin (0.4 mmol). The reaction was tumbled overnight, filtered and concentrated. Compound 51 was used without further purification. HPLC-MS t_R = 1.82 min ($UV_{254\ nm}$); mass calculated for formula $C_{23}H_{28}N_2O_6S$ 460.2, observed LCMS m/z 461.1 (M+H).

Part B:

To 51 in MeOH (2 mL) was added anhydrous hydrazine (5 µL, 0.16 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo, purified by reverse phase prep-HPLC and freeze-dried to afford 52 as a white powder (6.7 mg, 18% overall). ^{1}H NMR (400 MHz, $CDCl_3$) major rotomer δ 7.40- 7.25 (m, 6H), 7.16 (d, 1H, J = 4.8 Hz), 6.95 (app. t, 1H, J = 4.8 Hz), 6.87 (bs, 1H, NH), 5.96 (q, 1H, J = 7.2 Hz), 4.91 (d, 1H, J = 1.2 Hz), 4.22 (d, 1H, J = 1.2 Hz), 3.60 (m, 2H), 3.08 (m, 2H), 2.79 (s, 3H), 1.56 (d, 3H, J = 5.7Hz); HPLC-MS t_R = 3.80 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{19}H_{24}N_2O_4S$ 376.2, observed LCMS m/z 377.2 (M+H).

Example 2C:



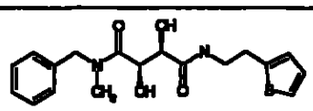
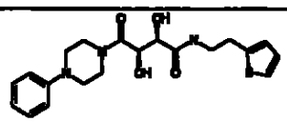
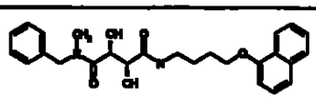
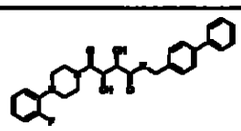
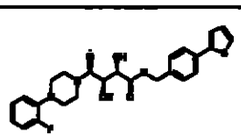
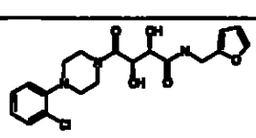
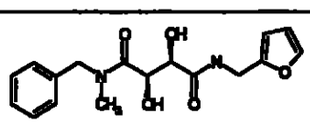
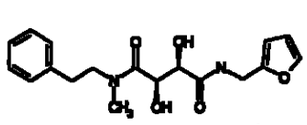
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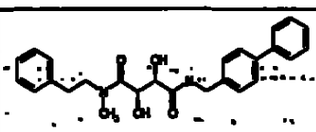
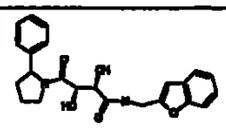
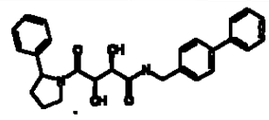
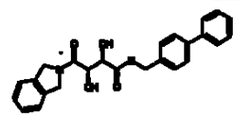
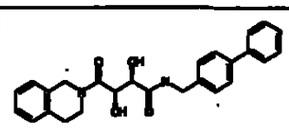
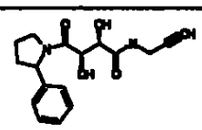
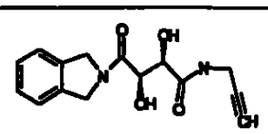
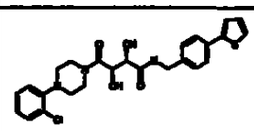
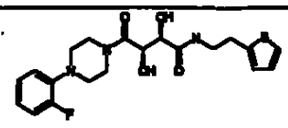
Compound 53 was prepared according to the procedure described by D. Miller et al (*J. Med. Chem.* 1999, 42, 2287).

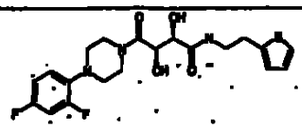
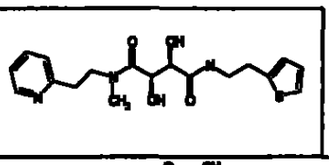
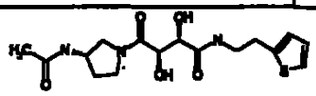
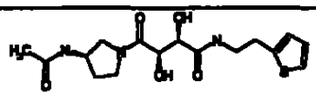
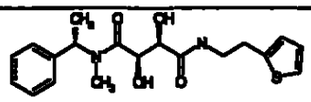
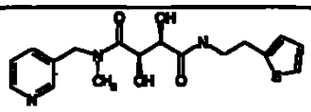
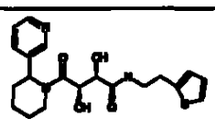
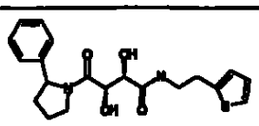
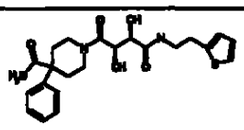
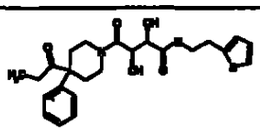
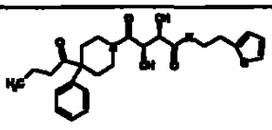
Parts A & B:

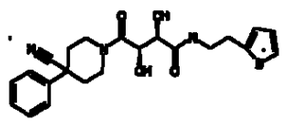
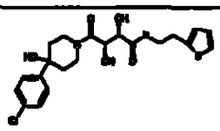
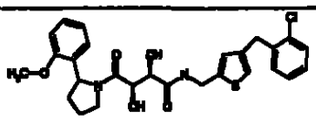
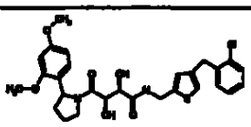
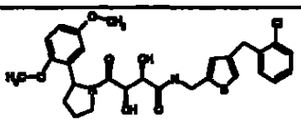
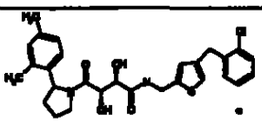
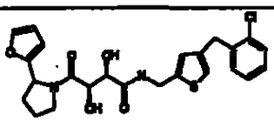
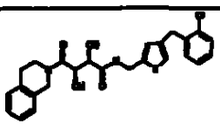
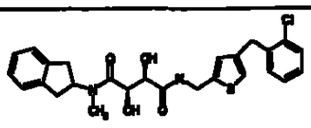
Compound 55 was prepared using procedures similar to those described in Example 14, Parts D & E.

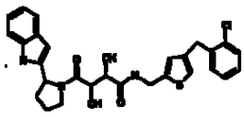
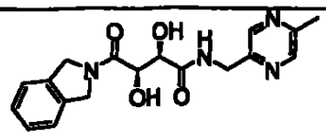
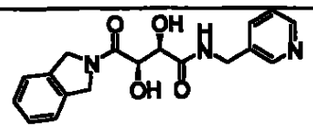
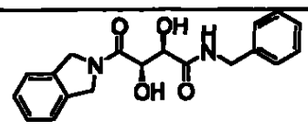
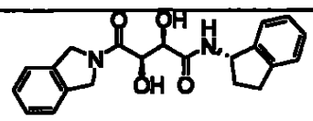
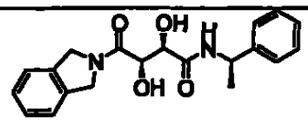
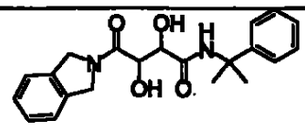
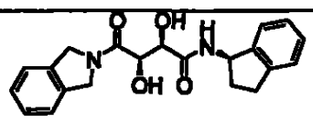
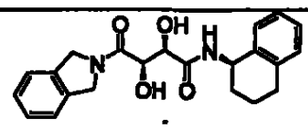
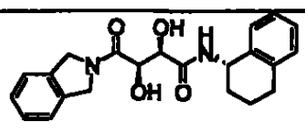
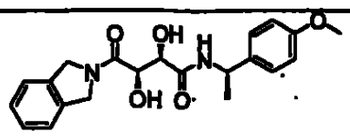
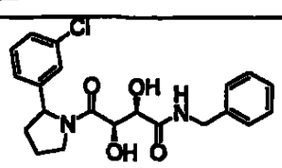
Data for 54: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.51-7.25 (m, 6H), 6.22 (s, 1H), 5.75-5.67 (m, 2H), 5.36 (s, 2H), 5.28-4.61 (m, 4H), 3.69-3.40 (m, 2H), 2.74 (s, 1H), 2.24 (s, 3H), 2.18 (s, 3H). Data for 55: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.54-7.26 (m, 6H), 6.24 (s, 1H), 5.22-5.02 (m, 2H), 4.94-4.82 (m, 3H) 4.42 (s, 1H), 3.72-3.50 (m, 2H), 2.92-2.76 (m, 2H) MS (EI) m/z M+H Obsd 377.1

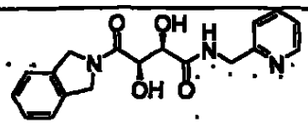
Compound #	Structure	Exact mass	MS m/z (M+H)
56		362.1	363.1
57		403.2	404.1
58		450.2	451.1
59		477.2	478.2
60		483.2	484.2
61		407.1	408.1
62		332.1	333.1
63		346.15	347.2

64		432.2	433.2
65		408.2	409.2
66		444.2	445.1
67		416.2	417.1
68		430.2	431.1
69		316.1	317.1
70		288.1	289.1
71		499.1	500.1
72		421.2	422.1
73		439.1	440.2

			
74		377.1	378.1
75		369.1	370.1
76		369.1	370.1
77		376.2	377.10
78		363.1	364.1
79		403.2	404.2
80		388.2	389.2
81		444.2	445.1
82		458.2	459.1
83		472.2	473.2

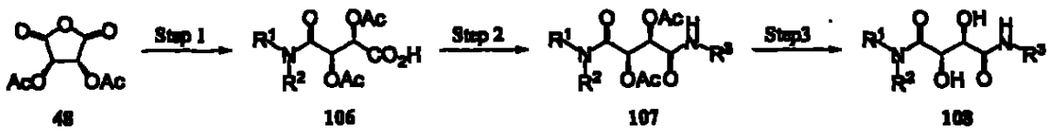
84		427.2	428.2
85		452.1	453.1
86		528.2	529.2
87		558.2	559.2
88		558.2	559.2
89		526.2	527.2
90		488.1	489.1
91		484.1	485.0
92		498.1	499.1

93		537.2	538.2
94		356.2	357.2
95		341.1	342.1
96		340.1	341.1
97		366.16	367.1
98		354.16	355.1
99		368.17	369.1
100		366.16	367.1
101		380.17	381.2
102		380.2	381.2
103		384.2	385.1
104		402.1	403.1

105		341.1	342.1

Example 2D:

Method A



48 106 107 108

Method A, Step 1:

Compound **106** (R1 = R2 = CH_2Ph) was prepared from **48** following the procedure described in Example 4A, Part C.

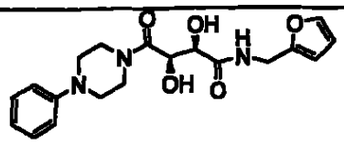
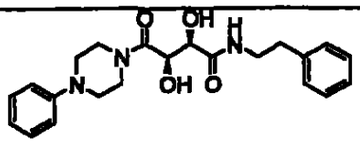
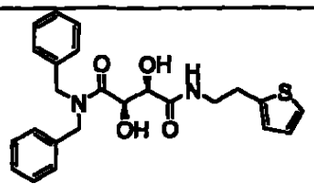
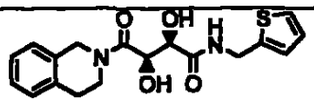
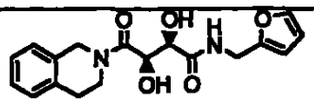
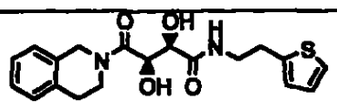
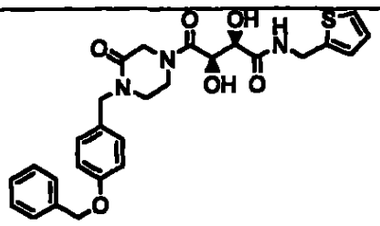
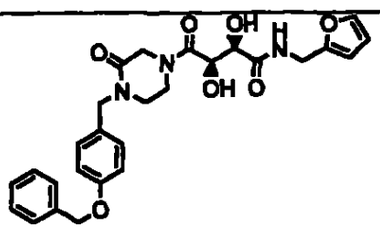
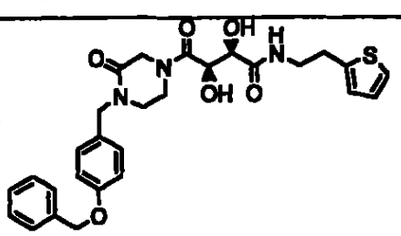
Method A, Step 2:

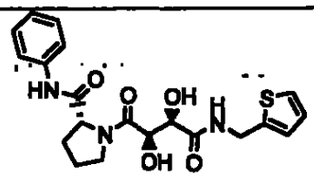
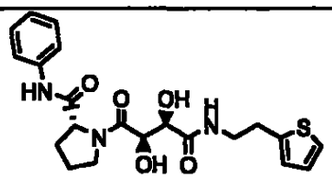
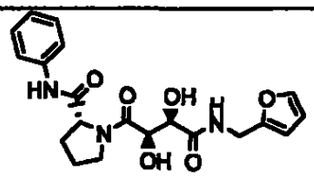
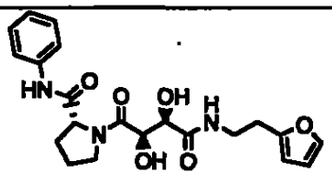
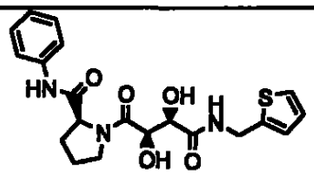
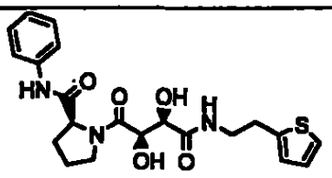
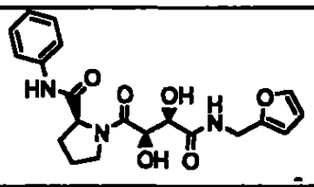
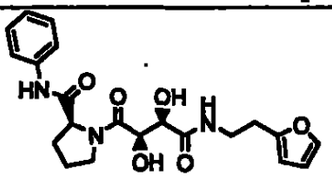
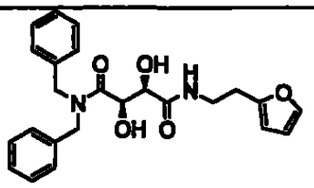
To a THF/MeCN (1:1, 0.5 mL) solution of polystyrene EDC resin (57 mg, 3 eq) in a 6 mL fritted cartridge was added a THF/MeCN (1:1) solution of **106** (0.028 mmol), a THF solution of HOBT (0.3 mL, 1.5 eq) and a 1M THF/MeCN (1:1) solution of 2-furanethylamine (0.056 mL, 2 eq). The cartridge was capped and let shake at 25°C for 20 h. Polystyrene isocyanate resin (57 mg, 3 eq) and polystyrene trisamine (39 mg, 6 eq) was added followed by 0.5 mL of THF and the mixture was shaken for 6 h. The suspension was filtered and the filtrate was concentrated to afford **107**. (R1 = R2 = CH_2Ph, R3 = $CH_2CH_2(C_4H_4O)$.

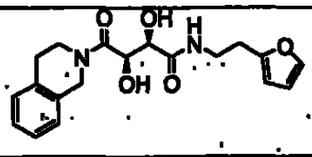
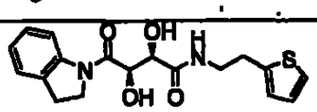
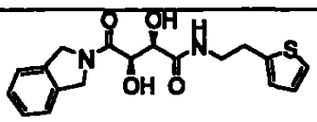
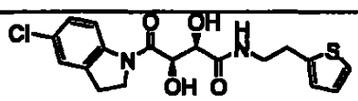
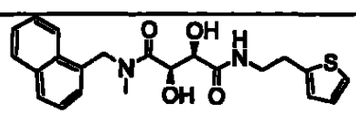
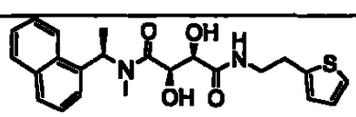
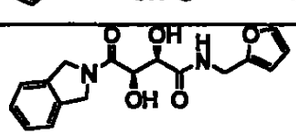
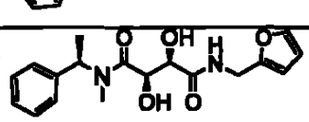
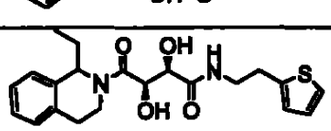
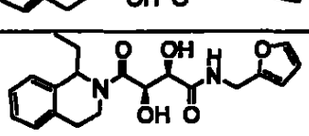
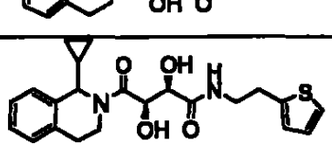
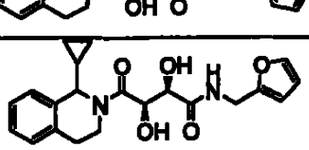
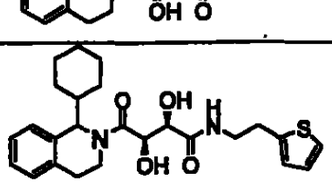
Method A, Step 3:

Compound **107** was treated with a 2N solution of NH_3 in MeOH (3 mL) for 1.5 h. The solvent was then removed in vacuo to provide **108** (R1 = R2 = CH_2Ph, R3 = $CH_2CH_2(C_4H_4O)$.

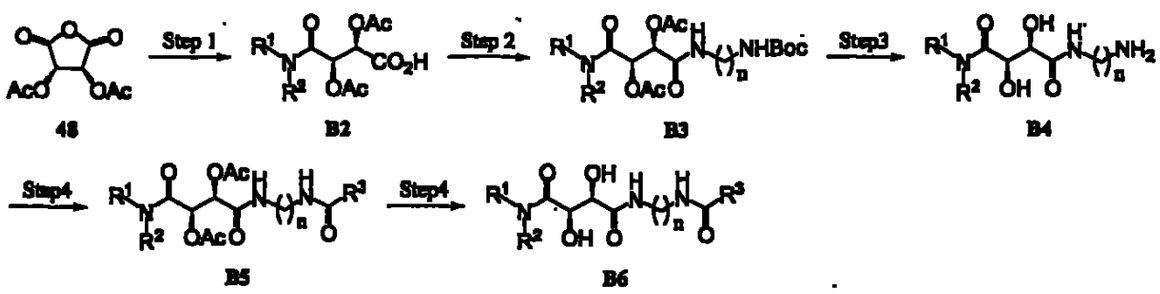
Example 2D Table A

Compound #	Structure	Exact mass	MS m/e (M+H)
109		373.2	374.2
110		397.2	398.2
111		438.2	439.1
112		360.1	361.1
113		344.1	345.1
114		374.1	375.1
115		523.2	524.1
116		507.2	508.1
117		537.2	538.1

118A		417.1	418.1
118B		431.2	432.2
119		401.2	402.1
120		415.2	416.1
121		417.1	418.1
122		431.2	432.2
123		401.2	402.1
124		415.2	416.1
108		422.2	423.1

125		358.2	359.1
38		360.1	361.2
39		360.1	361.2
126		394.1	395.2
127		412.2	413.2
128		426.2	427.2
129		330.1	331.2
130		346.2	347.2
131		402.2	403.1
132		372.2	373.1
133		414.2	415.1
134		384.2	385.1
135		456.2	457.1

Method B



Method B, Step 1:

Compound **B2** (R^1 = CH_2Ph, R^2 = CH_3) was prepared from **48** following the procedure described in Example 4A Part C.

Method B, Step 2:

To a DMF (40 mL) solution of **B2** (2.0 g, 5.93 mmol), HOBT (880 mg, 6.52 mmol), and N-Boc-1,3-propylenediamine (1.14 g, 6.52 mmol) was added EDCI (1.48 g, 7.61 mmol) at 25 °C under N_2. After stirring for 20 h, 1N HCl was added, the products were extracted with ethyl acetate (3X), combined, then washed with sat. $NaHCO_3$, water (3x), and dried over $MgSO_4$. The products were then filtered and concentrated in vacuo to give **B3** (R^1 = CH_2Ph, R^2 = CH_3, n = 3).

Method B, Step 3:

To a MeCN (30 mL) solution of **B3** (1.18 g, 2.4 mmol) at 25°C was added 20 mL of a 4N solution of HCl in dioxane. The solution was capped and stirred at 25 °C for 2.5 h. The solvent was then removed in vacuo. The product was then dissolved in 45 mL of THF/MeCN/DMF (4:4:1) and polystyrene NEt_2 resin (4.5 g, 14.4 mmol) added. After stirring for 1.5 h, the solution was filtered off and the resin washed with THF:MeCN (1:1). The filtrates were then diluted to 120 mL with additional THF/MeCN (1:1) and **B4** (R^1 = CH_2Ph, R^2 = CH_3, n = 3) was used in the preparation of the following library:

Method B, Step 4:

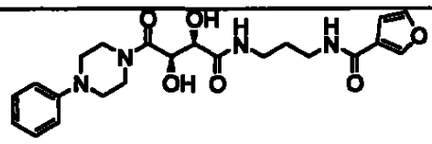
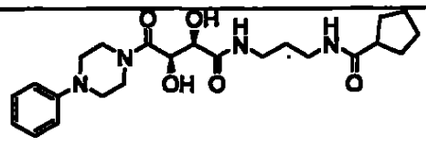
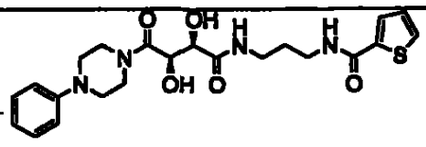
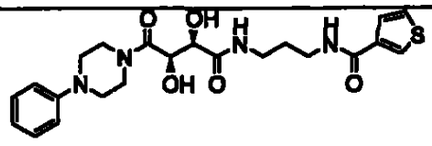
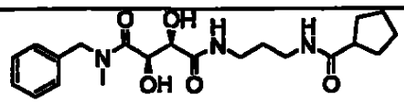
Polystyrene EDC resin (30mg, 0.045 mmol) was added to 96-wells of a deep well polypropylene microtiter plate followed by a MeCN/THF/DMF (6:6:1) stock solution (1 mL) of **B4** (0.015 mmol) and HOBT (0.0225 mmol). Then 1M

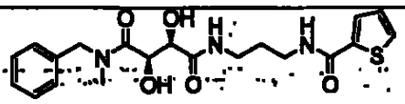
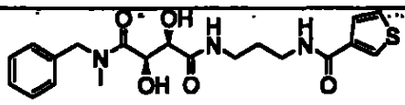
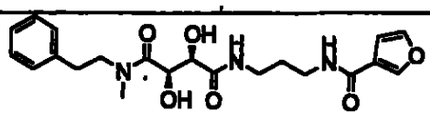
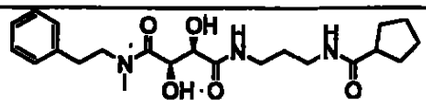
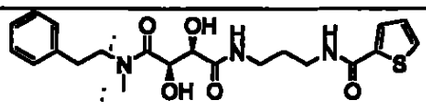
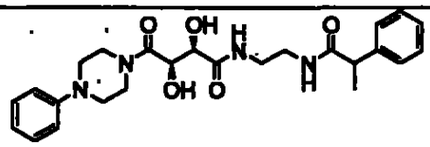
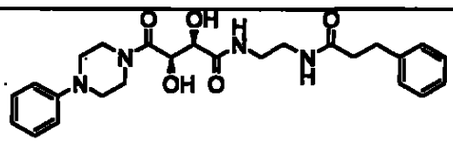
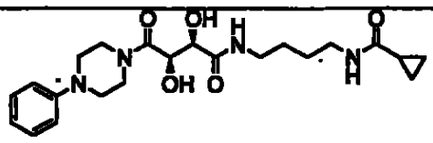
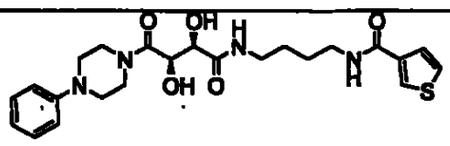
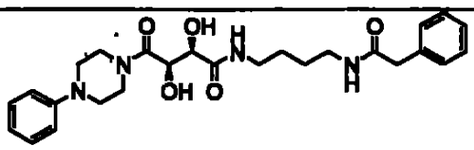
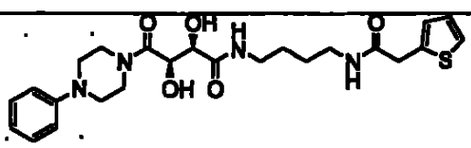
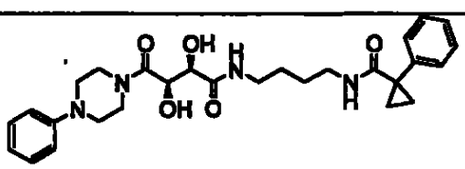
stock solutions of each of the individual acids (R^1-96COOH) (0.023 mL, 0.021 mmol) were added to the wells, which was then sealed and shaken at 25 °C for 20h. The solutions were filtered through a polypropylene frit into a 2nd microtiter plate containing polystyrene isocyanate resin (3 equivalents, 0.045 mmol) and polystyrene trisamine resin (6 equivalents, 0.09 mmol). After the top plate was washed with MeCN (0.5 mL), the plate was removed, the bottom microtiter plate sealed and shaken at 25 °C for 16h. Then the solutions were filtered through a polypropylene frit into a 96-well collection plate. The wells of the top plate were then washed with MeCN (0.5 mL), and the plate removed. Then the resultant solutions in the collection plate were transferred into vials and the solvents removed in vacuo via a SpeedVac to provide amides B5.

Method B, Step 5:

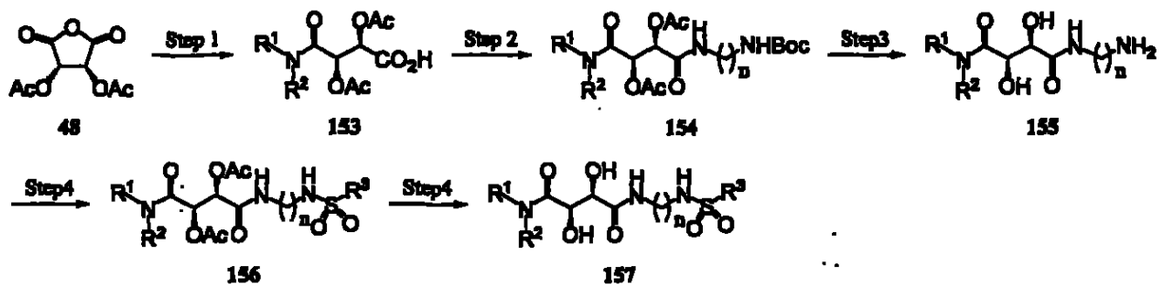
Compounds B6 were prepared from B5 following the procedure described in Method A, Step 3 (see above).

Example 2D Table B

Compound #	Structure	Exact mass	MS m/e (M+H)
136		444.2	445.2
137		446.3	447.3
138		460.2	461.3
139		460.2	461.3
140		405.2	406.2

141		419.2	420.2
142		419.2	420.2
143		417.2	418.2
144		419.2	420.2
145		433.2	434.2
146		468.2	469.3
147		468.2	469.3
148		432.2	433.2
149		474.2	475.3
150		482.3	483.3
151		488.2	489.3
152		508.3	509.3

Method C



Method C, Step 1:

Compound **153** (R^1R^2N = 4-phenylpiperazine) was prepared from **48** following the procedure described in Method B, Step 1 (see above).

Method C, Step 2:

Compound **154** (R^1R^2N = 4-phenylpiperazine, n = 3) was prepared from **153** following the procedure described in Method B, Step 2 (see above).

Method C, Step 3:

Compound **155** (R^1R^2N = 4-phenylpiperazine, n = 3) was prepared from **154** following the procedure described in Method B, Step 3 (see above) and was used in the preparation of the following library:

Method C, Step 4:

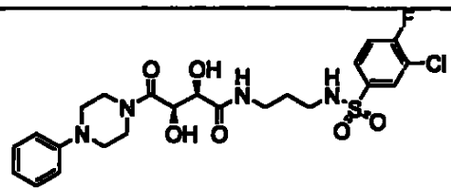
Polystyrene DIEA resin (30mg, 0.045 mmol) was added to 72-wells of a deep well polypropylene microtiter plate followed by a MeCN/THF/DMF (6:6:1) stock solution (1 mL) of **155** (0.015 mmol). Then 1M stock solutions of each of the individual sulfonyl chlorides (R^1-72SO_2Cl) (0.023 mL, 0.021 mmol) were added to the wells, which was then sealed and shaken at 25 °C for 20h. The solutions were filtered through a polypropylene frit into a 2nd microtiter plate containing polystyrene isocyanate resin (3 equivalents, 0.045 mmol) and polystyrene trisamine resin (6 equivalents, 0.09 mmol). After the top plate was washed with MeCN (0.5 mL), the plate was removed, the bottom microtiter plate sealed and shaken at 25 °C for 16h. Then the solutions were filtered through a polypropylene frit into a 96-well collection plate. The wells of the top plate were then washed with MeCN (0.5 mL), and the plate removed. Then

the resultant solutions in the collection plate were transferred into vials and the solvents removed in vacuo via a SpeedVac to provide sulfonamides 156.

Method C, Step 5:

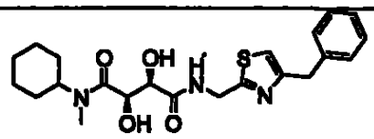
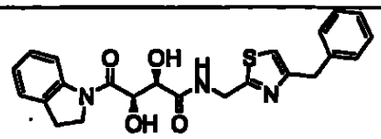
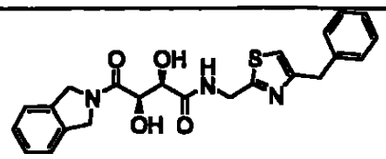
Compounds **157** were prepared from **156** following the procedure described in Method A, Step 3 (see above).

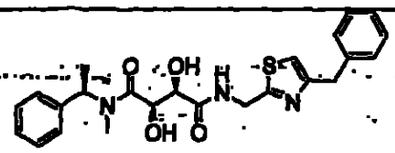
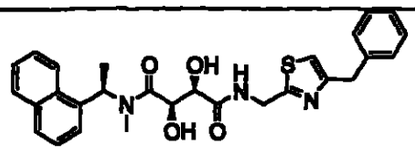
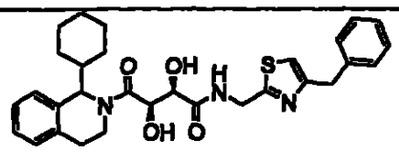
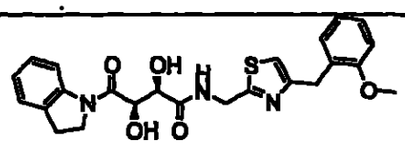
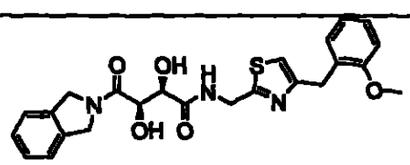
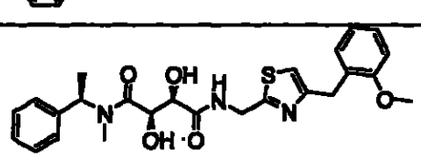
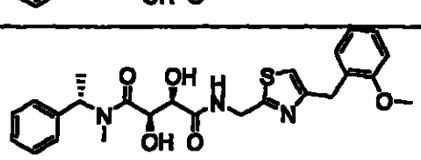
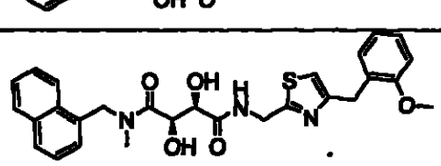
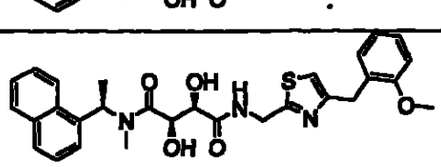
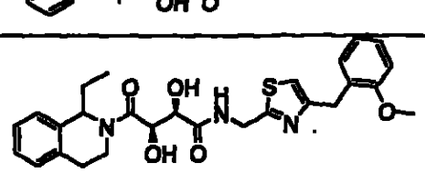
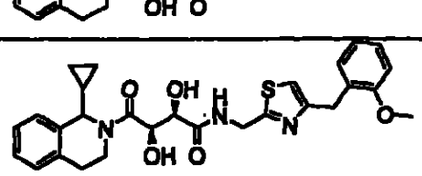
Example 2D Table C

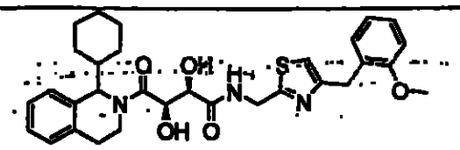
Compound #	Structure	Exact mass	MS m/e (M+H)
157		542.2	543.3

These compounds were prepared using Method A:

Example 2D Table D

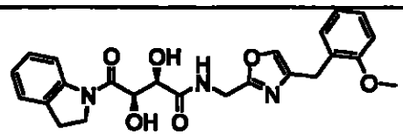
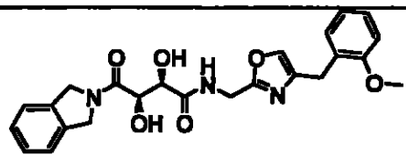
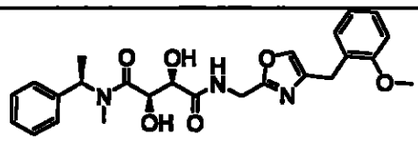
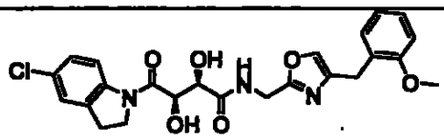
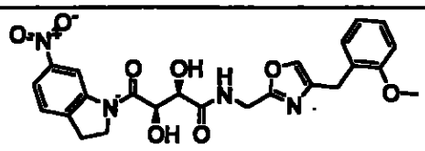
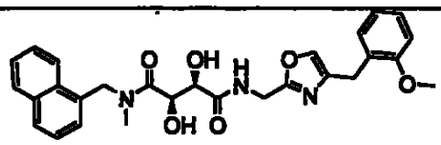
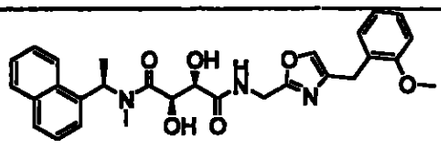
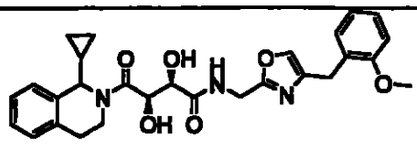
Compound #	Structure	Exact mass	MS m/e (M+H)
158		431.2	432.2
159		437.1	438.2
160		437.1	438.2

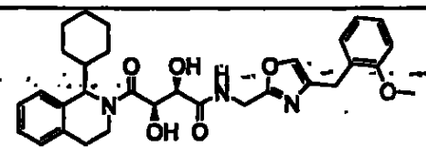
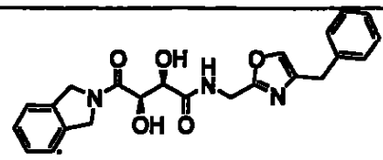
161		453.2	454.3
162		503.2	504.3
163		533.2	534.2
164		467.2	468.3
165		467.2	468.3
166		483.2	484.3
167		483.2	484.3
168		519.2	520.3
169		533.2	534.3
170		509.2	510.3
171		521.2	522.3

172		563.2	564.3

These compounds were prepared using Method A:

Example 2D Table E

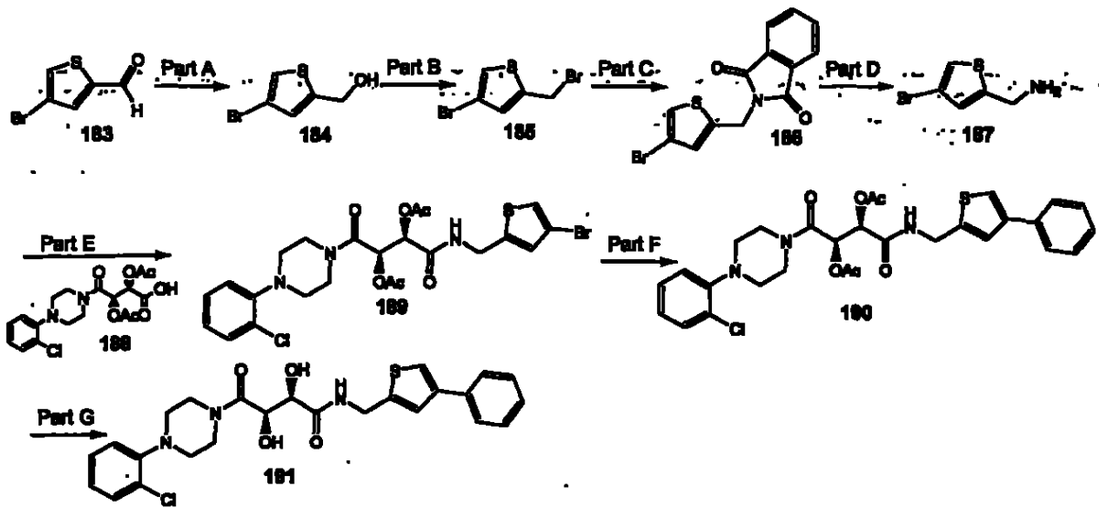
Compound #	Structure	Exact mass	MS m/e (M+H)
173		451.2	452.3
174		451.2	452.3
175		467.2	468.3
176		485.1	486.3
177		496.2	497.3
178		503.2	504.3
179		517.2	518.3
180		505.2	506.3

181		547.3	548.3
182		421.2	422.2

Example 3: Heteroaryl biaryl compounds

A compound precursor may be prepared such that the synthesis of direct analogs is facilitated. Examples of schemes for biaryl synthesis are listed below. Aryl halides and 'pseudo-halides' (i.e. triflates) are known to react with boronic acids under a variety of established conditions (*Top. Curr. Chem.* 2002, *219*, 12-49). A variety of bases for this reaction are known in the literature, including sodium carbonate, potassium carbonate, cesium carbonate, potassium t-butoxide, sodium t-butoxide, TEA, DIEA, potassium fluoride, and potassium phosphate. For most applications potassium phosphate was preferred and gave acceptable yields and chemoselectivity. A number of solvents have also been used in the literature for Suzuki reactions, including THF, dioxane, NMP, DMF, DME, DMA, toluene, and water. In general we have found that THF or dioxane are preferred solvents. Solvents may also be mixed in various proportions to enhance reactivity and/or chemoselectivity. Palladium sources for this reaction are numerous as well, including $Pd(TPP)_4$, $Pd(OAc)_2$, $PdCl_2(TPP)_2$, $PdCl_2(dppf)$, $Pd_2(dba)_3$. In general $PdCl_2(dppf)$ was found to be a preferred palladium source.

Example 3A:



Part A:

To an ice cold methanol (100 mL) solution of 4-bromo-thiophene-2-carbaldehyde (183) (90%, 11.1 g, 58.1 mmol, 1.00 equiv) was added sodium borohydride in portions (2.20 g, 58.1 mmol, 1.00 equiv) over ca. 10 minutes. The cooling bath was removed and the reaction solution was aged 30 min. The reaction was quenched at rt by the addition of acetone (until evolution of gas ceased), concentrated, and partitioned between ethyl acetate and 0.1 N HCl. The organic phase was washed with water, brine, dried (sodium sulfate), filtered, and then concentrated to give 184 as an orange oil (10.5 g, 95%) that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 6.93 (s, 1H), 4.81 (s, 2H).

Part B:

To 184 (4.38 g, 22.7 mmol) in toluene (25 mL) was added phosphorous tribromide (2.36 mL, 25 mmol). The reaction mixture was heated in an oil bath at 90 °C for 15 minutes. After cooling to room temperature the reaction mixture was poured over ice and extracted with ethyl acetate. The combined organic layer was washed with water (2x), saturated sodium bicarbonate solution (1x) and saturated sodium chloride solution, dried over magnesium sulfate and concentrated to afford 185 as a light brown oil (5.51 g, 95%). The material was used without further purification.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.03 (s, 1H), 4.66 (s, 2H).

Part C:

To **185** (5.51 g, 21.5 mmol) in DMF (20 mL) was added phthalimide (3.80 g, 25.8 mmol) and cesium carbonate (7.72 g, 23.7 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in ethyl acetate and water. The organic layer was separated, washed with saturated sodium chloride solution, dried over sodium sulfate and concentrated to afford a brown solid. Recrystallization from ~30 % ethyl acetate/hexanes afforded **186** as a peach solid (6.38 g, 2 crops, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.72 (m, 2H), 7.11 (s, 1H), 7.07 (s, 1H), 4.97 (s, 2H). HPLC-MS t_R = 2.02 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_8BrNO_2S$ 321.0, observed LCMS m/z 322.0 (M+H).

Part D:

A suspension of **186** (5.76 g, 17.8 mmol) and hydrazine hydrate (3.5 mL, 72 mmol) in ethanol (50 mL) was heated to reflux. The suspension cleared upon heating before a thick white precipitate formed. The reaction mixture was heated for 1 hour and cooled. The white precipitate was broken up by the addition of ethanol (50 mL) and sonication of the mixture. The precipitate was removed by filtration and the solids were thoroughly washed with ethanol and ethyl acetate. The filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate and water. The layers were separated. The organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate and concentrated to afford **187** as an orange-brown oil (2.66 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 1H), 6.84 (s, 1H), 4.04 (s, 2H). HPLC-MS t_R = 0.58 min ($UV_{254\ nm}$); Mass calculated for formula C_5H_6BrNS 190.9, observed LCMS m/z 192.0(M+H).

Part E:

Following the procedure described in Example 1 part A: To **188** (prepared as described in Example 4 Part C from (+)-diacetyl –L-tartaric anhydride (48) and 2-chlorophenylpiperazine) (916 mg, 2.22 mmol) in DMF (5 mL) was added **187** (502 mg, 2.61 mmol), DIEA (850 µL, 4.88 mmol) and HATU (928 mg, 2.44 mmol). Purification by column chromatography (SiO_2, 20% to 50% EtOAc/DCM) afforded **189** as an off-white foam (652 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, 1H, J = 1.2, 7.6 Hz), 7.25 (dt, 1H, J = 1.2, 7.6 Hz), 7.14 (d, 1H, J = 1.2 Hz), 7.03 (m, 2H),

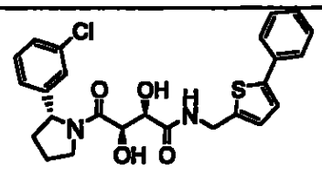
6.92 (d, 1H, J = 1.2 Hz), 6.74 (m, 1H, NH), 5.92 (d, 1H, J = 3.6 Hz), 5.70 (d, 1H, J = 4.0 Hz), 4.73 (dd, 1H, J = 6.4, 15.2 Hz), 4.50 (dd, 1H, J = 5.6, 15.6 Hz), 3.83 (m, 3H), 3.65 (m, 1H), 3.20 – 3.00 (m, 4H), 2.21 (s, 3H), 2.11 (s, 3H); Mass calculated for formula $C_{23}H_{25}BrClN_3O_6S$ 585.0, observed LCMS m/z 586.1 (M+H).

Part F:

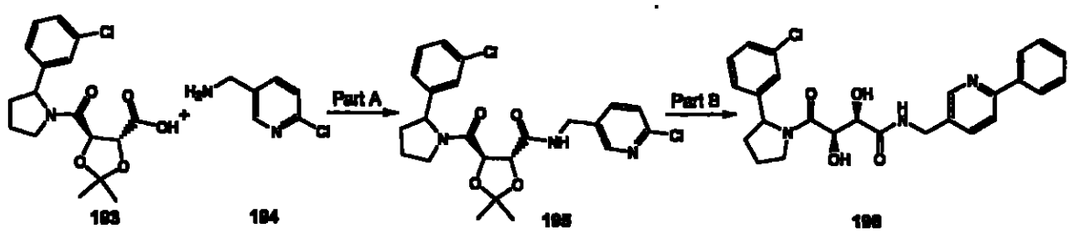
To **189** (59 mg, 0.1 mmol), phenyl boronic acid (13 mg, 0.11 mmol), potassium phosphate (42 mg, 0.2 mmol), and $PdCl_2$(dppf) (4 mg, 0.005 mmol) was added dioxane (2 mL). The reaction mixture was flushed with argon and heated to 80 °C overnight. The reaction mixture was cooled, poured into water and extracted with EtOAc. The combined organics were washed with brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% EtOAc/DCM) afforded **190** as an off-white foam (36 mg, 58%, 94% purity). HPLC-MS t_R = 5.61 min ($UV_{254\ nm}$, 10 min.); mass calculated for formula $C_{29}H_{30}ClN_3O_6S$ 583.2, observed LCMS m/z 584.2 (M+H).

Part G:

To **190** (36 mg, 0.062 mmol) in methanol was added 0.5 M sodium methoxide in methanol (6 µL, 0.003 mmol). The reaction mixture was stirred for 1.5 hours at room temperature, quenched with 0.1 N HCl and concentrated. Purification by reverse-phase prep-LC afforded **191** as a white solid (3.2 mg, 10%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, 2H, J = 1.2, 8.4 Hz), 7.40 to 7.20 (m, 9H), 7.09 (m, 1H, NH), 4.91 (d, 1H, J = 2.4 Hz), 4.70 (m, 2H), 4.33 (d, 1H, J = 2.0 Hz), 4.00 (m, 2H), 3.85 (m, 2H), 3.20 (m, 4H); HPLC-MS t_R = 1.94 min ($UV_{254\ nm}$); Mass calculated for formula $C_{25}H_{28}ClN_3O_4S$ 499.1, observed LCMS m/z 500.2 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
192		484.1	485.0

Example 3B: 3-Pyridyl-Biaryl



Part A:

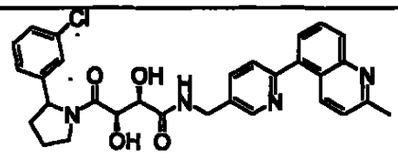
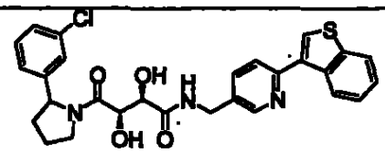
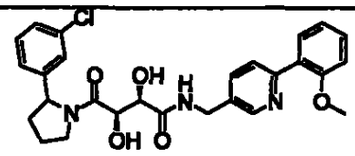
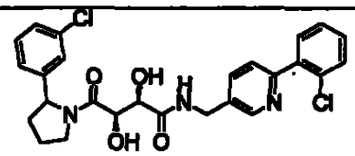
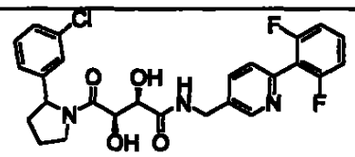
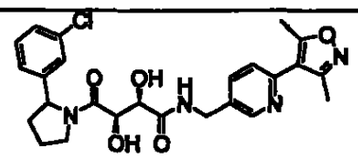
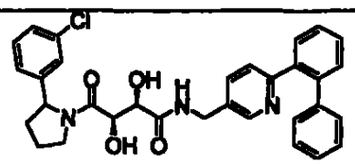
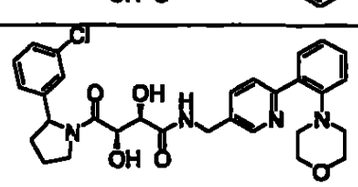
To **193** (prepared as described in Example 1) (1.5 g, 4.24 mmol) in DMF (10 mL) was added **194** (0.725 g, 5.09 mmol) and HATU (1.94 g; 5.09 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 80% ethyl acetate/hexanes) afforded **195** as a colorless oil (1.73 g, 86%). HPLC-MS t_R = 1.92 and 1.97 min ($UV_{254\ nm}$); Mass calculated for formula $C_{23}H_{25}Cl_2N_3O_4$ 477.1, observed LCMS m/z 478.1 (M+H).

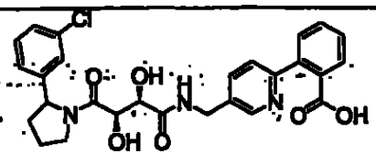
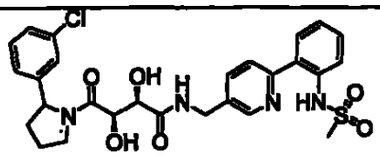
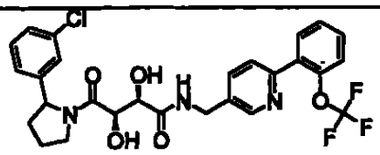
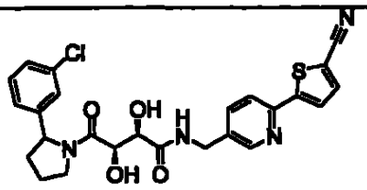
Part B:

Step1: To phenyl boronic acid (10 mg, 0.084 mmol), potassium phosphate (36 mg, 0.168 mmol) and $PdCl_2$(dppf) (3.1 mg, 10 mol%) under argon in a 4-mL vial was added **195** (20 mg, 0.042 mmol) in dioxane (0.5 mL). The reaction mixture was heated at 100 °C for 16 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through celite. The filtrate was concentrated. HPLC-MS t_R = 2.01 min ($UV_{254\ nm}$); Mass calculated for formula $C_{29}H_{30}ClN_3O_4$ 519.2, observed LCMS m/z 520.2 (M+H).

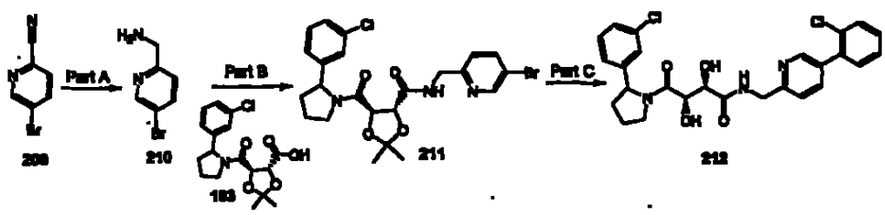
Step 2: The crude material from Step 1 was dissolved in 80:20 TFA:water (1 mL) at 0 °C and stirred at room temperature for 2 hours. The reaction mixture was quenched with 1:1 water:acetonitrile (2 mL) and concentrated.

Purification by reverse phase prep-LC afforded **196** as a solid after lypholization. HPLC-MS t_R = 3:54 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{28}H_{28}ClN_3O_4$ 479.2, observed LCMS m/z 480.2 (M+H).

Compound #	Structure	Exact mass	MS m/z (M+H)
197		544.2	454.2
198		535.1	536.2
199		509.2	510.1
200		513.1	514.2
201		515.1	516.2
202		498.2	499.2
203		555.2	556.2
204		564.2	565.2

205		523.2	524.2
206		572.2	573.2
207		563.1	564.2
208		510.0	511.1

Example 3C: 2-Pyridyl-Biaryl



Part A:

To 5-bromo-pyridine-2-carbonitrile (209) (1.0 g, 5.46 mmol) in tetrahydrofuran (10 mL) at –78 °C was added lithium aluminum hydride (1.0 M, 13.66 mL, 13.66 mmol). The reaction was stirred for 2 hours at –78 °C. The mixture was quenched at –78 °C with 10:1 THF:water. The mixture was warmed to room temperature, diluted with ethyl acetate and stirred with 1.0 N sodium hydroxide for 10 minutes. The reaction mixture was filtered through celite and the layers were separated. The organic layer was washed with 1.0 N sodium hydroxide and brine, dried over sodium sulfate and concentrated to afford 210 as an oil (600 mg). The material was used without further purification.

Part B:

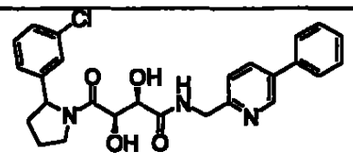
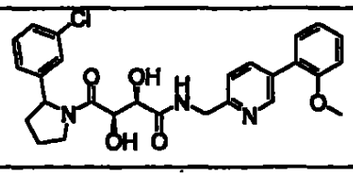
To 193 (1.13 g, 3.2 mmol) in DMF (10 mL) was added 210 (0.600 g, 3.2 mmol) and HATU (1.34 g, 3.52 mmol). The reaction mixture was stirred for 5 hours at room temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated to afford 211 as an oil (380 mg). HPLC-MS t_R = 2.00 and 2.05 min ($UV_{254\ nm}$); Mass calculated for formula $C_{23}H_{25}BrClN_3O_4$ 521.1, observed LCMS m/z 522.1 (M+H).

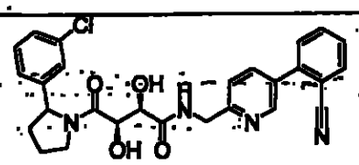
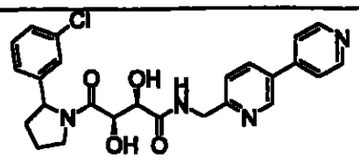
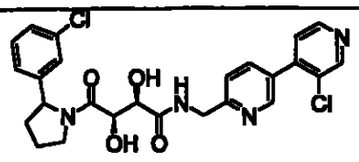
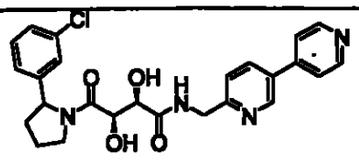
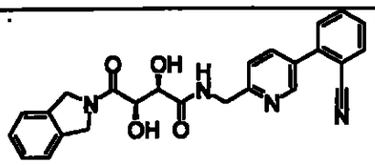
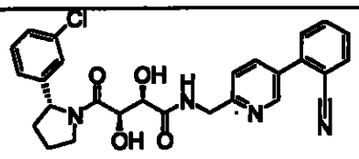
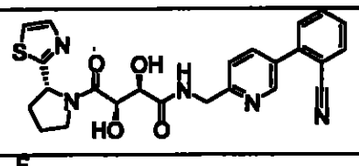
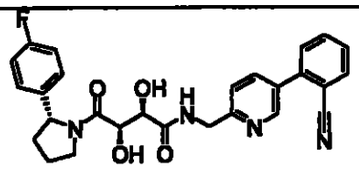
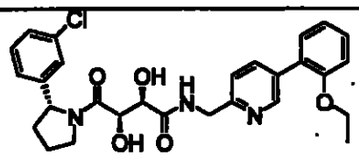
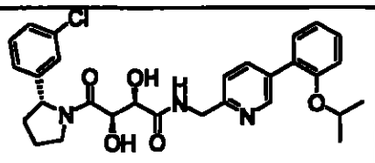
Part C:

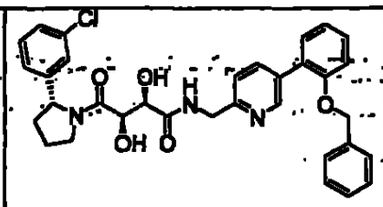
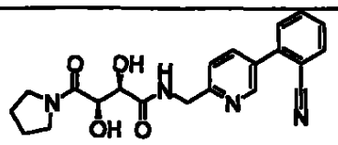
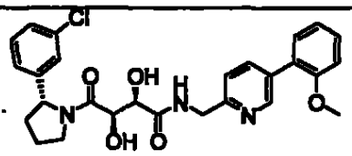
Step1: To 2-chlorophenyl boronic acid (24 mg, 0.152 mmol), potassium phosphate (65 mg, 0.306 mmol) and $PdCl_2$(dppf) (3.1 mg, 5 mol%) under argon in a 4-mL vial was added 211 (40 mg, 0.076 mmol) in dioxane (0.5 mL). The reaction mixture was heated at 100 °C for 16 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through celite. The filtrate was concentrated.

Step 2: The crude material from Step 1 was dissolved in 80:20 TFA:water (1 mL) at 0 °C and stirred at room temperature for 2 hours. The reaction mixture was quenched with 1:1 water:acetonitrile (2 mL) and concentrated. Purification by reverse phase prep-LC afforded 212 as a solid after lypholization. HPLC-MS t_R = 4.10 and 4.13 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{29}H_{25}Cl_2N_3O_4$ 513.2, observed LCMS m/z 514.2 (M+H).

The following compounds were prepared using the above procedures.

Compond #	Structure	Exact mass	MS m/z (M+H)
213		479.2	480.1
214		509.2	510.1

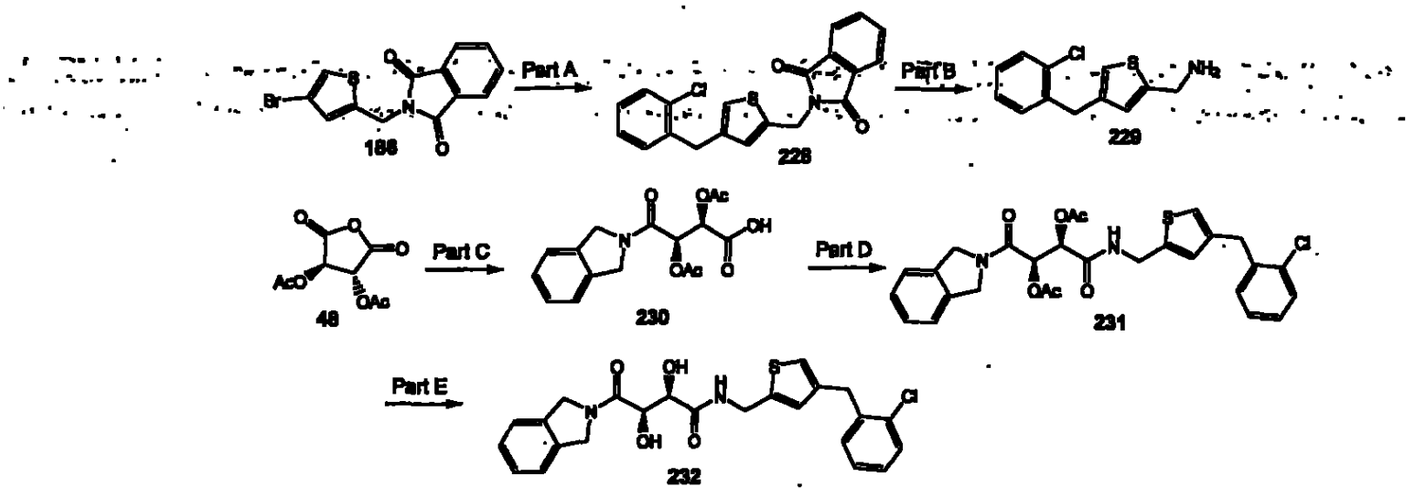
215		504.2	505.1
216		480.2	481.1
217		514.1	515.0
218		481.2	482.2
219		442.2	443.2
220		504.2	505.1
221		477.2	478.1
222		488.2	489.1
223		523.2	524.2
224		537.2	538.2

225		585.2	586.2
226		394.2	395.2
227		509.2	510.1

Example 4: Thiophene-benzyl compounds

Pd-mediated Negishi-type couplings were an efficient way to generate a set of relevant compounds for this series where Ar was a phenyl ring. While a range of palladium sources are known we found that $Pd(P^tBu_3)_2$ was preferred. The reaction can be run in a variety of solvent systems, including dioxane, THF, or DMA. A preferred method utilized the solvent from the zinc reagent, which was typically available as a THF stock solution. Removal of the t-BOC group can be completed using a range of acidic conditions including TFA/water, HCl in methanol, and HCl in dioxane; all of which proceeded equally well with most reaction substrates. The reactions are typically concentrated and freeze-dried to give HCl or TFA salts. The Negishi reactions proceed comparably, and in many cases better, when the amine was protected by a phthalimide. The phthalimide protecting group could be removed by heating in ethanol containing hydrazine hydrate.

Example 4A:



Part A:

To **186** (3.47 g, 10.8 mmol) and bis-(tri-*tert*-butyl-phosphine) palladium (0.28 g, 0.54 mmol) in a flask under argon was added 2-chlorobenzyl zinc chloride (0.5 M in THF, 54 mL, 27 mmol). The reaction was stirred at room temperature for 3 hours. The reaction mixture was diluted with EtOAc (200 mL) and washed with saturated ammonium chloride solution (100 mL), bicarbonate solution (100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% EtOAc/Hex) afforded **228** as a white solid (3.59 g, 91%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, 2H, J = 3.2, 5.6 Hz), 7.71 (dd, 2H, J = 3.2, 5.6 Hz), 7.36 (m, 1H), 7.17 (m, 3H), 6.99 (d, 1H, J = 1.0 Hz), 6.78 (d, 1H, J = 1.0 Hz), 4.95 (s, 2H), 4.00 (s, 2H).

Part B:

To **228** (3.55 g, 9.72 mmol) suspended in ethanol (35 mL) was added hydrazine monohydrate (1.9 mL, 38.9 mmol). The reaction mixture was heated at reflux for 2 hours. After cooling the solids were removed by filtration and washed with ethanol (100 mL) and ethyl acetate (50 mL). The filtrate was concentrated and the residue was dissolved in ethyl acetate (150 mL) and water (100 mL). The organic layer was separated, washed with brine (100 ml), dried over sodium sulfate and concentrated to yield **229** as a yellow oil (2.54 g, 99%).

Part C:

To **48** (2.16 mg, 10.0 mmol) in DCM (10 mL) was added isoindoline (1.13 mL, 10.0 mmol). The reaction was stirred at room temperature for 2 hours. The solvent was removed in vacuo and the residue was partitioned between ethyl acetate and 1.0 N HCl. The organic layer was separated, washed with water and brine, dried over sodium sulfate and concentrated to afford **230** as a dark solid (3.35 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.63 (bs, 1H), 7.38 – 7.28 (m, 4H), 5.01 (d, 1H, J = 13.2 Hz), 4.93 (d, 1H, J = 14.0 Hz), 4.71 (d, 1H, J = 16.4 Hz), 4.56 (d, 1H, J = 15.6 Hz), 2.12 (s, 3H), 2.07 (s, 3H); HPLC-MS t_R = 1.10 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{17}NO_7$ 335.1, observed LCMS m/z 336.1 (M+H).

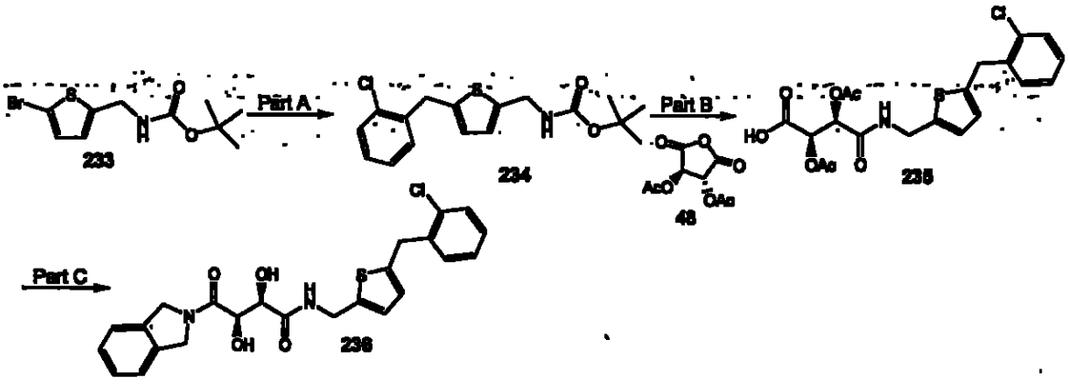
Part D:

To **230** (18 mg, 0.053 mmol) in NMP (2 mL) was added **229** (19 mg, 0.08 mmol), DIEA (26 µL, 0.148 mmol) and HATU (30 mg, 0.08 mmol). The reaction mixture was stirred overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layer was washed with 0.1 N NaOH, 0.1 N HCl and brine, dried over sodium sulfate and concentrated to afford **231**.

Part E:

To **231** (118 mg, 0.216 mmol) in methanol (3 mL) and DCM (3 mL) was added MP-carbonate resin (2.54 mmol/g, 85 mg). The reaction was stirred for 3 hours, filtered and concentrated to afford **232** as a white solid (94 mg, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (t, 1H, J = 2.0 Hz) 7.79 (dd 1H, J = 0.8, 8.0 Hz), 7.64 (dt, 1H, J =1.6, 8.0 Hz), 7.47 (d, 1H, J = 7.6 Hz), 7.40 (dt, 1H, J = 0.8, 7.6 Hz), 7.35 – 7.27 (m, 4H), 6.97 (d, 1H, J = 1.6 Hz), 6.81 (d, 1H, J = 1.2 Hz), 5.67 (d, 1H, J = 6.4 Hz), 5.05 (d, 1H, J = 12.8 Hz), 4.97 (d, 1H, J = 8.0 Hz), 4.90 (d, 1H, J = 13.2 Hz), 4.75 (d, 1H, J = 13.2 Hz), 4.60 (m, 2H), 4.36 (m, 2H, J = 6.4, 15.2 Hz) 4.24 (dd, 1H, J = 3.2, 6.8 Hz); HPLC-MS t_R = 1.85 ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{23}ClN_2O_4S$ 470.1, observed LCMS m/z 471.1

Example 4B:



Part A:

To **233** (4.00 g, 13.7 mmol) and bis-(tri-*tert*-butyl-phosphine) palladium (0.28 g, 0.54 mmol) in a flask under argon was added 2-chlorobenzyl zinc chloride (0.5 M in THF, 69 mL, 34.5 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (200 mL) and washed with saturated ammonium chloride solution (100 mL), bicarbonate solution (100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 15% EtOAc/Hex) afforded **234** as a white solid (4.5 g, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, 1H J =3.6 Hz), 7.25 – 7.18 (m, 4H), 6.74 (s, 1H), 6.64 (d, 1H, J = 3.6 Hz), 4.40 (d, 2H, J = 5.2 Hz), 4.22 (s, 2H).

Part B:

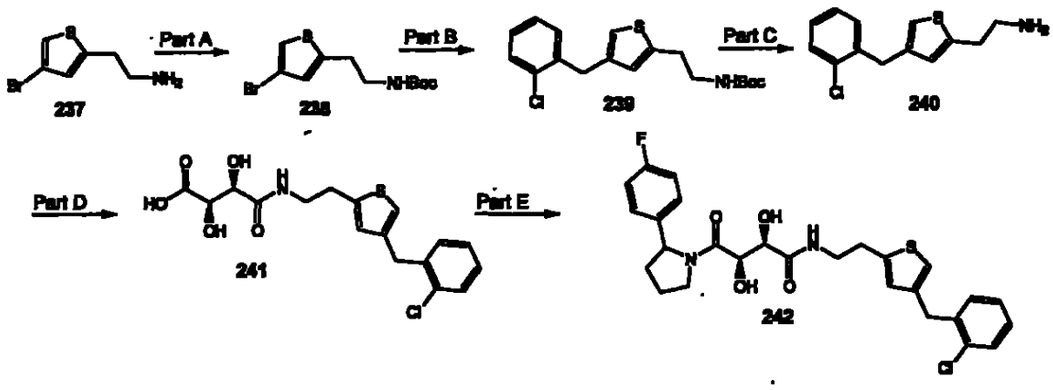
To **234** (450 mg, 1.34 mmol) was added 4M HCl in dioxane (1.5 mL) and the reaction was stirred for 30 minutes. The dioxane was removed in vacuo. The residue was dissolved in THF (10 mL) and DIEA (500 µL, 2.68 mmol) and **48** (275 mg, 1.27 mmol) were added. The reaction was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (60 mL) and washed with 1.0 N HCl. The organic layer was dried over sodium sulfate and concentrated to afford **235** as a yellow foam (505 mg, 90%).

Part C:

To **235** (40 mg, 0.09 mmol) in DMF (2 mL) were added DIEA (50 µL, 0.29 mmol), isoindoline (14 mg, 0.12 mmol), and HATU (45 mg, 0.12 mmol). The reaction mixture was stirred for 6 hours. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with 0.1 N NaOH, 0.1 N HCl and brine. The organic layer was

dried over sodium sulfate. The crude product was dissolved in methanol (3 mL) and potassium carbonate (100 mg) in water (1 mL) was added. After stirring for 30 minutes the reaction mixture was diluted with ethyl acetate (20 mL) and washed with brine. The organic layer was dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded **236** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (t, 1H, J = 6.4 Hz) 7.42 (dd, 1H, J = 1.6, 7.8 Hz), 7.37 – 7.23 (m, 7H), 6.74 (d, 1H, J = 3.6 Hz), 6.65 (d, 1H, J = 3.2 Hz), 5.66 (d, 1H, J = 5.6 Hz), 5.04 (d, 1H, J = 14.8 Hz), 4.97 (bs, 1H), 4.89 (d, 1H, J = 15.2 Hz), 4.75 (d, 1H, J = 16.4 Hz), 4.60 (m, 2H), 4.38 (dd, 1H, J = 6.4, 15.2 Hz), 4.23 (bs, 1H), 4.15 (s, 2H); HPLC-MS t_R = 4.92 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{24}H_{23}ClN_2O_4S$ 470.1, observed LCMS m/z 471.1

Example 4C: Thiophene-Benzyl



Compound **237** was prepared according to the procedure described by A. J. Hutchison et al (European Patent 0323807 A2, Dec. 7, 1989)

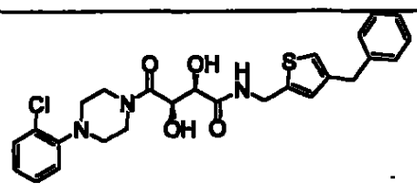
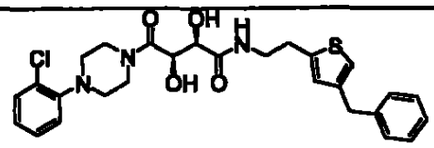
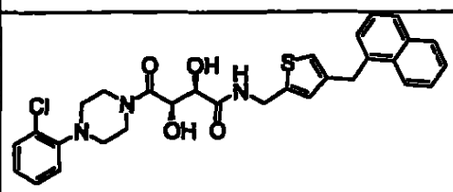
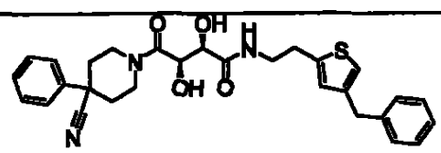
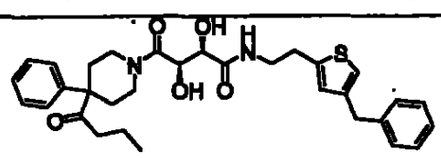
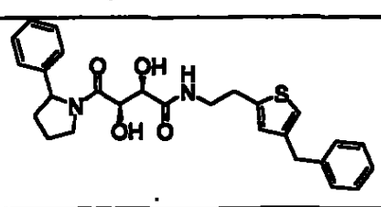
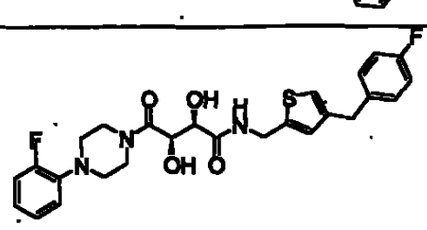
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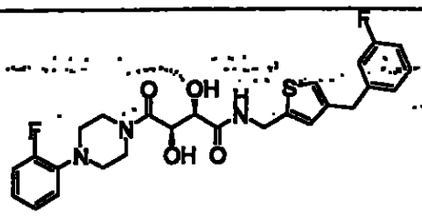
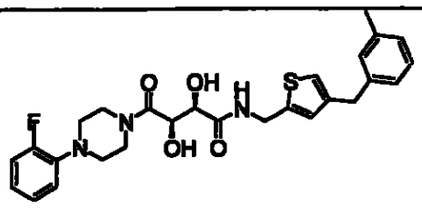
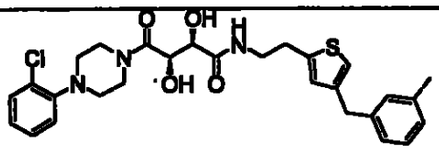
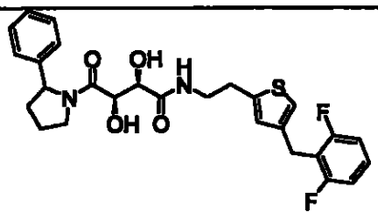
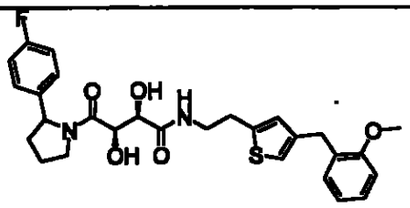
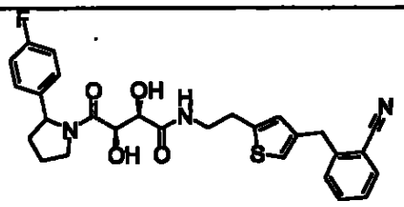
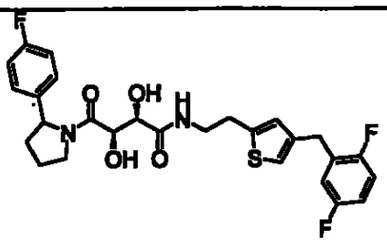
Compound **238** was prepared by procedures similar to those described in Example 5 Part A.

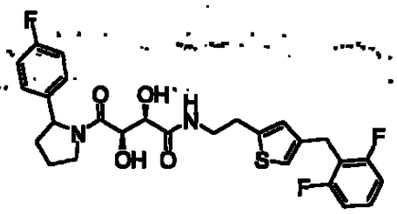
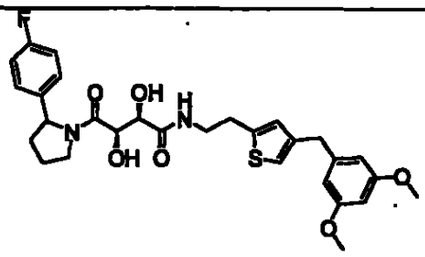
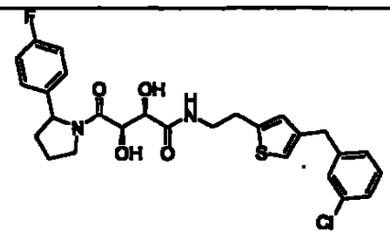
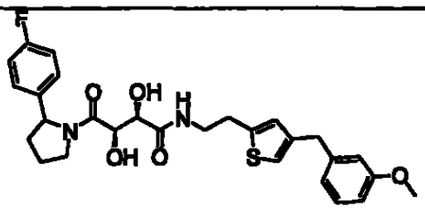
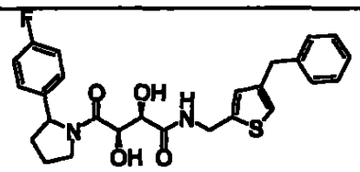
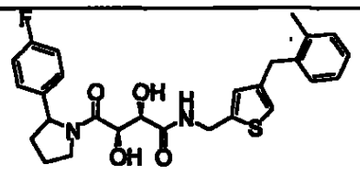
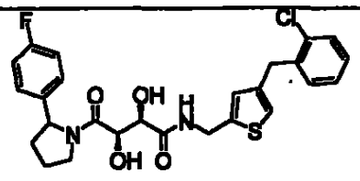
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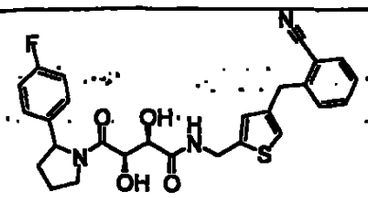
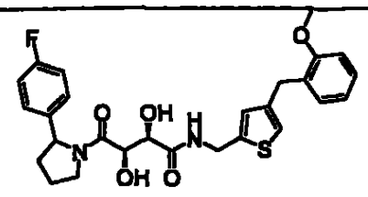
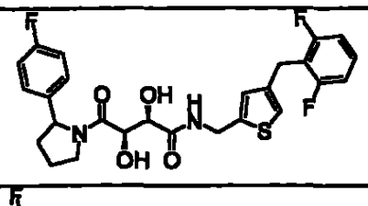
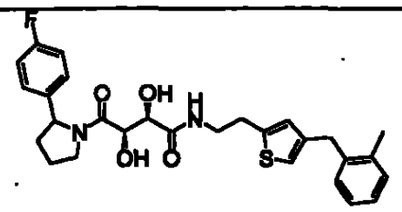
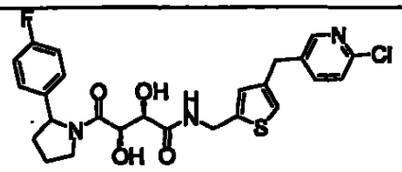
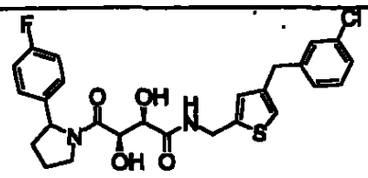
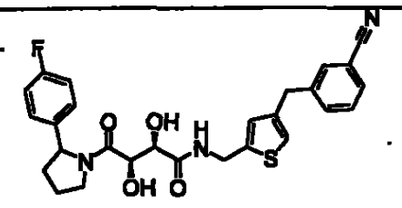
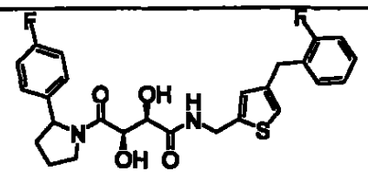
Compound **242** was prepared by procedures similar to those described in Example 4B Parts A to C. HPLC-MS t_R = 2.05 min ($UV_{254\ nm}$); mass calculated for formula $C_{27}H_{28}ClFN_2O_4S$ 530.1, observed LCMS m/z 531.1 (M+H).

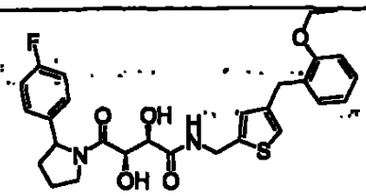
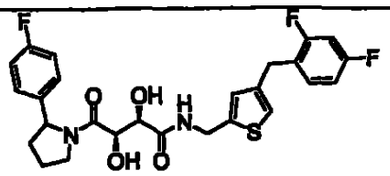
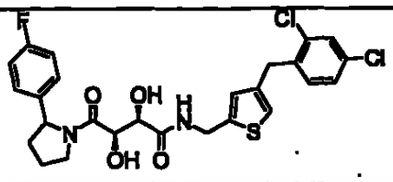
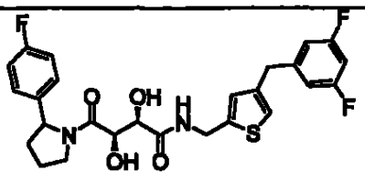
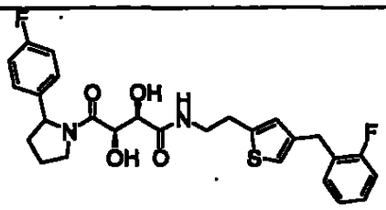
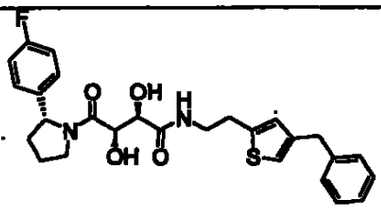
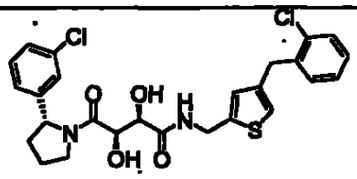
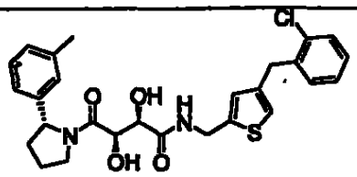
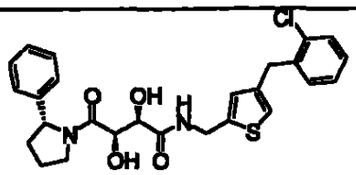
The following compounds were prepared by the procedures described in Example 4A-4C.

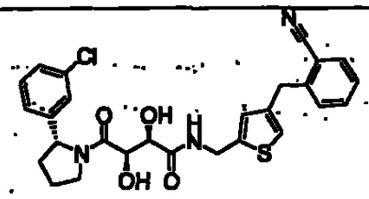
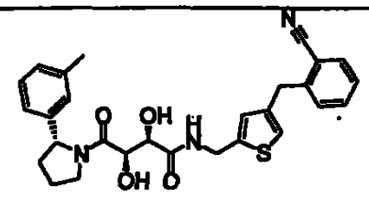
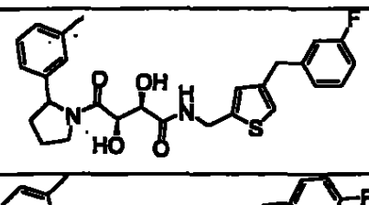
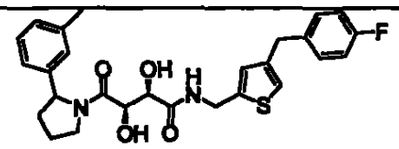
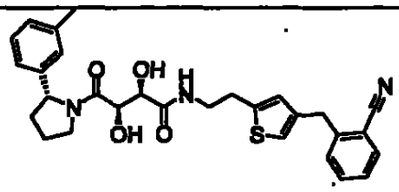
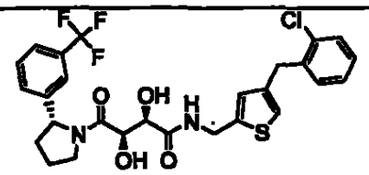
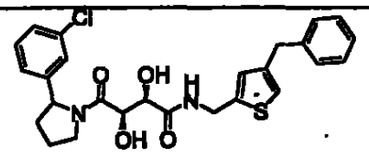
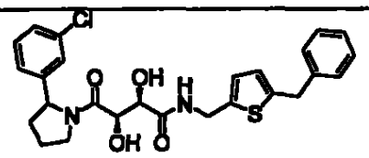
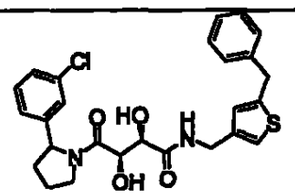
Compound #	Structure	Exact mass	MS m/z (M+H)
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244		527.2	528.1
245		563.2	564.2
246		517.2	518.2
247		562.3	563.2
248		478.2	479.2
249		515.2	516.0

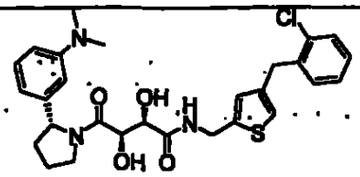
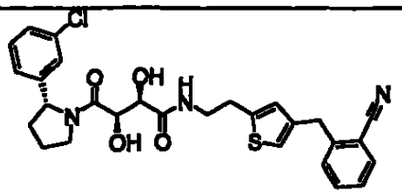
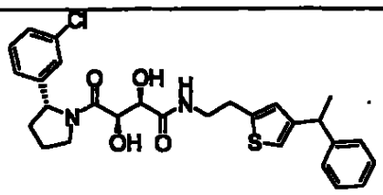
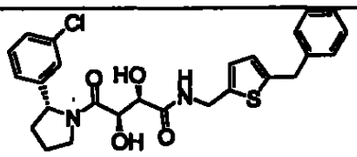
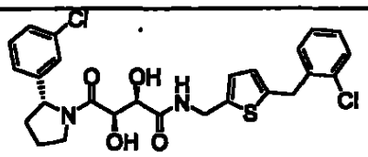
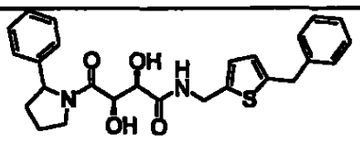
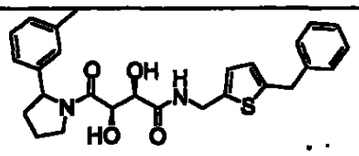
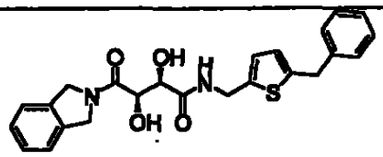
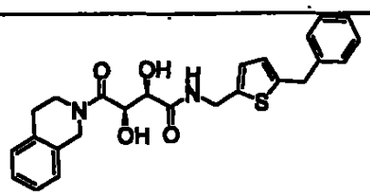
250		515.2	516.0
251		511.2	512.2
252		541.2	542.2
253		514.2	515.2
254		526.2	527.2
255		521.2	522.1
256		532.2	533.2

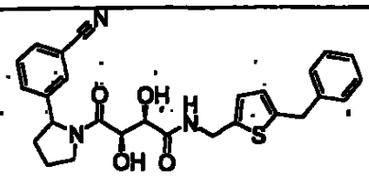
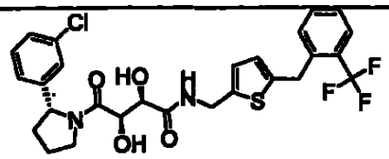
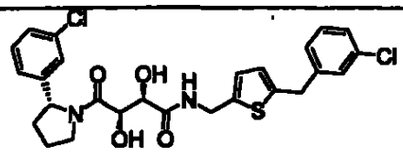
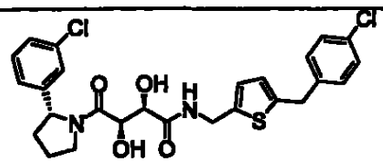
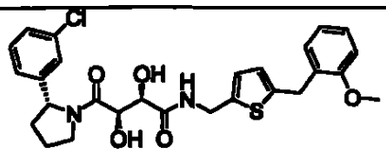
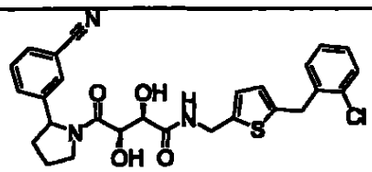
257		532.2	533.2
258		556.2	557.2
259		530.1	531.1
260		526.2	527.2
261		482.2	483.1
262		496.2	497.2
263		516.1	517.2

264		507.2	508.1
265		512.2	513.2
266		518.2	519.1
267		510.2	511.1
268		517.1	518.0
269		516.1	517.2
270		507.2	508.1
271		500.2	501.1

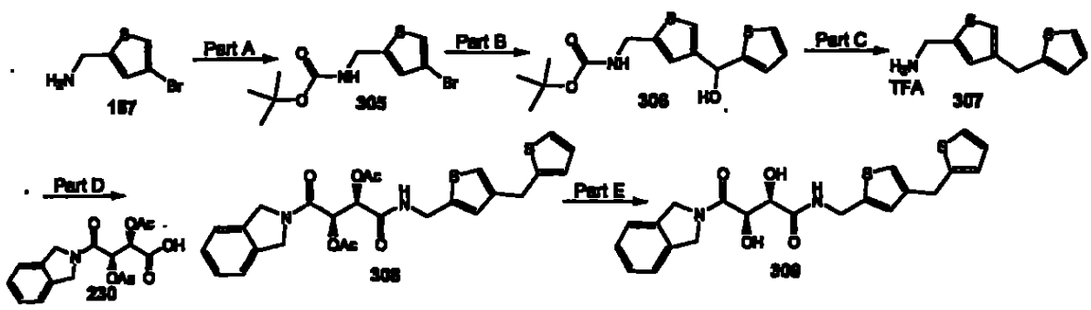
272		526.2	527.2
273		518.2	519.1
274		550.1	551.0
275		518.2	519.1
276		514.2	515.2
277		496.2	497.1
278		532.1	533.0
279		512.2	513.1
280		498.1	499.0

281		523.1	524.1
282		503.2	504.1
283		496.2	497.2
284		496.2	497.2
285		517.2	518.2
286		566.12	567.1
287		498.1	499.1
288		498.1	499.1
289		498.1	499.1

290		541.2	542.2
291		537.2	538.2
292		526.2	527.0
293		498.1	499.1
294		532.1	533.0
295		464.2	465.1
296		478.2	479.2
297		436.2	437.2
298		450.2	451.1

299		489.2	490.1
300		566.1	567.1
301		532.1	533.0
302		532.1	533.0
303		528.2	529.2
304		523.1	524.2

Example 5:



Part A:

To a solution of 187 (2.68 g, 14.0 mmol) and pyridine (2.26 mL, 28 mmol) in dichloromethane (25 mL) was added di-*tert*-butyl dicarbonate (3.21 g, 14.7 mmol).

The mixture was stirred overnight at room temperature. The reaction mixture was poured into water (25 mL) and the layers were separated. The organic layer was washed with 1.0 N HCl (20 mL), water (20 mL), and saturated sodium chloride solution (20 mL), dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, DCM) afforded **305** as a light orange solid (3.64 g, 89%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 1H), 6.87 (s, 1H), 4.01 (bs, 1H), 4.44 (d, 2H, J = 6.0 Hz), 1.48 (s, 9H).

Part B:

To *n*-butyl lithium (2.5 M, 0.31 mL, 0.78 mmol) in THF (2 mL) at –78 °C under argon was added **305** (100 mg, 0.34 mmol) in THF (1.5 mL) dropwise. The reaction mixture was stirred for 30 minutes at –78 °C. Then 2-thiophene carbaldehyde (60 µL, 0.68 mmol) was added. The reaction mixture was stirred for 30 minutes at –78 °C. The reaction mixture was quenched with saturated ammonium chloride solution and warmed to room temperature. The mixture was diluted with ethyl acetate (10 mL) and the layers were separated. The organic layer was washed with water and brine. Dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% EtOAc/hexane) afforded **306** (47 mg, 42%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 1H), 7.16 (s, 1H) 6.95 (m, 2H), 6.93 (s, 1H), 6.05 (s, 1H). 4.88 (bs, 1H), 4.43 (d, 2H, J = 5.6 Hz), 2.43 (bs, 1H), 1.48 (s, 9H).

Part C:

To **306** (47 mg, 0.14 mmol) in DCM (2 mL) was added triethylsilane (0.2 mL). The mixture was cooled in an ice bath and TFA (0.2 mL) was added. The mixture was warmed to room temperature and stirred overnight. The solvents were removed in vacuo and **307** was used without further purification. ^1H NMR (400 MHz, CD_3OD) δ 7.20 (m, 2H), 7.09 (s, 1H) 6.90 (m, 1H), 6.86 (m, 1H), 4.26(s, 2H), 4.15 (s, 2H).

Part D:

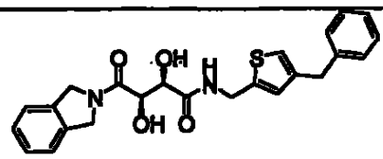
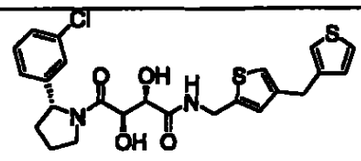
To **230** (19 mg, 0.06 mmol) in DMF (2 mL) was added **307** (18 mg, 0.06 mmol), DIEA (29 µL, 0.17 mmol) and HATU (28 mg, 0.07 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed

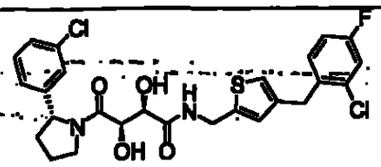
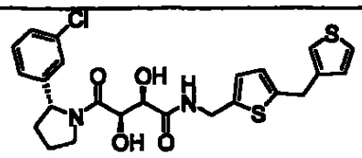
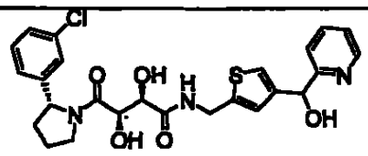
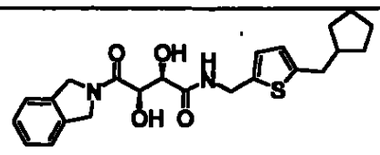
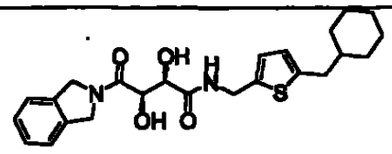
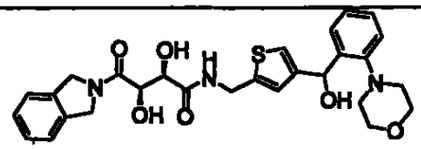
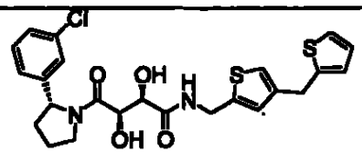
with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Compound 308 was used without further purification. HPLC-MS t_R = 1.91 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{28}N_2O_6S_2$ 526.1, observed LCMS m/z 269.9 (M+H).

Part E:

Compound 308 and potassium carbonate (20 mg) were mixed in methanol (2.5 mL) and water (0.5 mL) and were stirred for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded 309 as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (t, 1H, J = 5.6 Hz), 7.30 (m, 5H), 7.03 (s, 1H), 6.92 (s, 1H), 6.67 (s, 1H), 6.82 (s, 1H), 5.04 (d, 1H, J = 14.0 Hz), 4.90 (d, 1H, J = 14.0 Hz), 4.75 (d, 1H, J = 16.0 Hz), 4.60 (m, 2H), 4.41 (dd, 1H, J = 6.8, 14.8 Hz), 4.33 (dd, 1H, J = 5.6, 14.4 Hz), 4.25 (s, 1H), 4.04 (s, 2H); HPLC-MS t_R = 4.45 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{22}H_{22}N_2O_4S_2$ 442.1, observed LCMS m/z 443.0 (M+H).

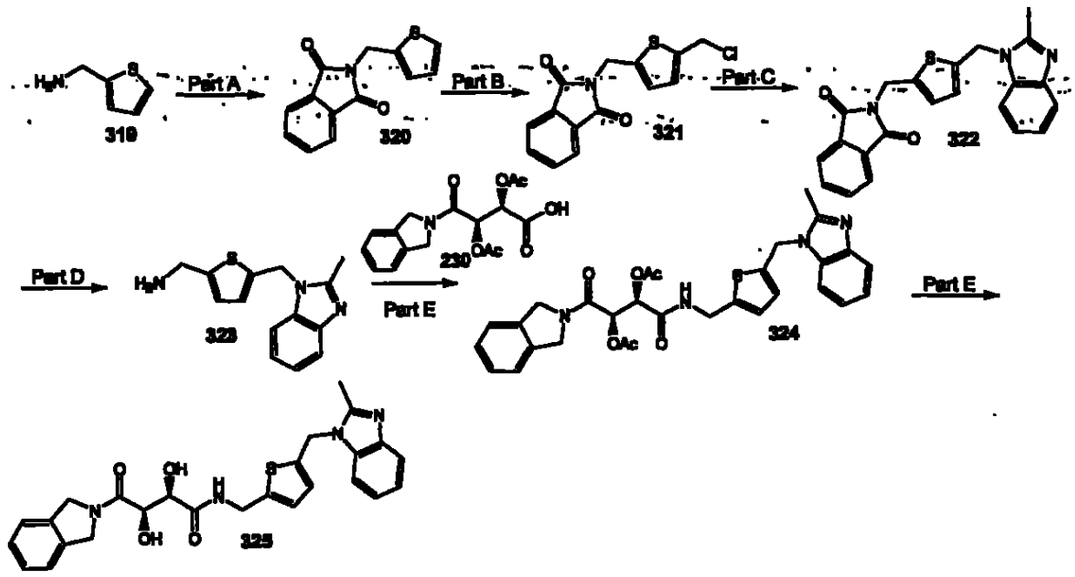
The following compounds were prepared using the procedures described above. Part C did not result in dehydration for compounds like 314 and 317.

Compound #	Structure	Exact mass	MS m/z (M+H)
310		436.2	437.3
311		504.1	505.1

312		550.1	551.0
313		504.1	505.1
314		515.1	516.1
315		428.2	429.1
316		442.2	443.0
317		537.2	538.0
318		504.09	505.0

Example 6

Example 6A:



Part A:

A mixture of 2-(aminomethyl)thiophene (**319**) (1.57 g, 13.8 mmol), monomethyl phthalate (2.75 g, 15.3 mmol), EDC (3.26 g, 16.6 mmol), HOBt (2.79 g, 20.7 mmol) and triethylamine (5 mL, 27.6 mmol) in DCM (40 mL) was stirred for 12 hours. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with 1.0 N HCl, bicarbonate solution and brine, dried over sodium sulfate and concentrated. Recrystallization of the mixture from ethyl acetate/hexanes afforded **320** as a solid (2.20 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 2H), 7.71 (m, 2H), 7.21 (m, 1H), 7.15 (m, 1H), 6.94 (m, 1H), 5.03 (s, 2H).

Part B: (Feigel, M., Lugert, G., Helchert, C.; *Liebigs Ann. Chem.* **1987**, 367) To paraformaldehyde (250 mg) in HCl (conc:, 5 mL) was added 0.5 M zinc chloride in THF (1.7 mL, 0.85 mmol). To this mixture was added **320** (235 mg, 0.85 mmol) in portions and then dioxane (3 mL). The reaction mixture was stirred at 60 °C for 45 minutes. The reaction mixture was cooled and diluted with water (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated. Recrystallization from ethyl acetate / hexane afforded **321** as a

solid (190 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, 2H, J = 3.2, 5.6 Hz), 7.72 (dd, 2H, J = 3.2, 5.6 Hz), 6.98 (d, 1H, J = 3.6 Hz), 6.90 (d, 1H, J = 3.6 Hz); 4.98 (s, 2H), 4.72 (s, 2H).

Part C:

A mixture **321** (190 mg, 0.65 mmol), 2-methylbenzimidazole (112 mg, 0.85 mmol), sodium iodide (catalytic) and cesium carbonate (275 mg, 0.85 mmol) in DMF (6 mL) were stirred overnight at room temperature. The reaction mixture was partitioned between ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Recrystallization from ethyl acetate / hexane afforded **322** (65 mg) and **322** contaminated with 2-methylbenzimidazole (120 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, 2H, J = 3.2, 5.6 Hz), 7.70 (dd, 2H, J = 3.2, 5.6 Hz), 7.68 (m, 1H), 7.29 (m, 1H), 7.23 (m, 2H), 6.95 (d, 1H, J = 3.6 Hz), 6.70 (d, 1H, J = 3.6 Hz), 5.36 (s, 2H), 4.91 (s, 2H), 2.64 (s, 3H); HPLC-MS t_R = 1.14 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{17}N_3O_2S$ 387.1, observed LCMS m/z 388.1 (M+H).

Part D:

Compound **322** (90 mg, 0.23 mmol) and hydrazine hydrate (50 µL, 0.93 mmol) in ethanol (10 mL) and DCM (5 mL) were refluxed for 1.5 hours. The reaction mixture was cooled and filtered. The filtrate was concentrated and the crude product was used without further purification.

Part E:

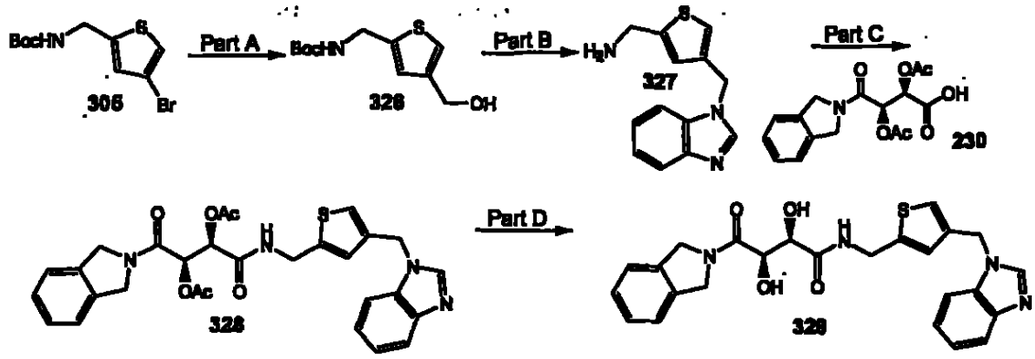
To **230** (83 mg, 0.24 mmol) in DMF (5 mL) was added **323** (82 mg, 0.32 mmol), DIEA (300 µL, 1.6 mmol) and HATU (135 mg, 0.36 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (50 mL) and water (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Compound **324** was used

without further purification. HPLC-MS t_R = 1.13 min ($UV_{254\ nm}$); mass calculated for formula $C_{30}H_{30}N_4O_6S$ 574.2, observed LCMS m/z 575.1 (M+H).

Part F:

Compound **324** (~120 mg, 0.21 mmol) and potassium carbonate (100 mg) were mixed in methanol (5 mL) and water (1 mL). After 5 minutes a solid precipitated and the reaction was stirred for 30 minutes. The solid was collected by filtration. Purification by reverse phase prep-LC afforded **325** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (t, 1H, J = 6.0 Hz), 7.93 (d, 1H, J = 8.0 Hz), 7.73 (d, 1H, J = 6.8 Hz), 7.48 (m, 2H), 7.33 (m, 1H), 7.27 (m, 3H), 7.08 (d, 1H, J = 3.6 Hz), 6.82 (d, 1H, J = 3.6 Hz), 5.80 (s, 2H), 5.02 (d, 1H, J = 14.4 Hz), 4.86 (d, 1H, J = 15.2 Hz), 4.74 (d, 1H, J = 16.8 Hz), 4.58 (d, 1H, J = 16.4 Hz), 4.57 (s, 1H), 4.33 (m, 2H), 4.22 (s, 1H), 2.84 (s, 3H); HPLC-MS t_R = 2.74 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{26}H_{28}N_4O_4S$ 490.2, observed LCMS m/z 491.2 (M+H).

Example 6B:



Part A:

To *n*-butyl lithium (2.5 M, 0.91 mL, 2.28 mmol) in THF (5 mL) at –78 °C under argon was added **305** (300 mg, 1.03 mmol) in THF (5 mL) dropwise. The reaction mixture was stirred for 30 minutes at –78 °C. Then dimethyl formamide (151 mg, 2.06 mmol) was added. The reaction mixture was stirred for 30 minutes at –78 °C. The reaction mixture was quenched with saturated ammonium chloride solution and warmed to room temperature. The mixture was diluted with ethyl acetate (10 mL) and the layers were separated. The organic layer was washed with water and brine. Dried over sodium sulfate and concentrated. The residue was dissolved in methanol and sodium borohydride (156 mg, 4.12 mmol) was added. The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and washed with 0.1 N HCl, water and brine. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% EtOAc/hexane) afforded **326** (147 mg, 58%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 1H), 6.94 (s, 1H), 4.63 (s, 2H), 4.45 (d, 2H, J = 4.7 Hz), 1.48 (s, 9H).

Part B:

To **326** (30 mg, 0.12 mmol) in THF (2 mL) was added benzimidazole (19 mg, 0.16 mmol), triphenylphosphine (42 mg, 0.16 mmol) and DIAD (32 mg, 0.16 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated. The residue was dissolved in dichloromethane (2 mL) and TFA (0.5 mL) was added. The reaction mixture was stirred for 30 minutes and

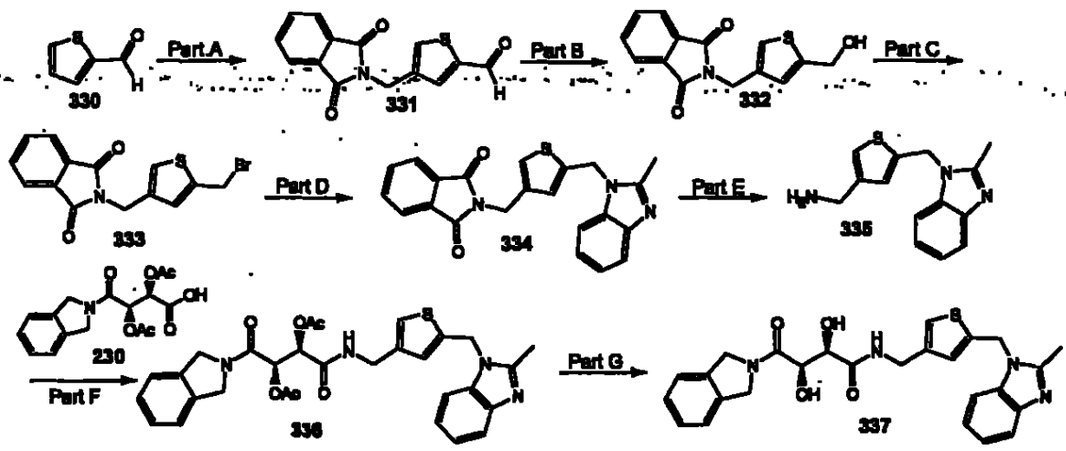
concentrated. The residue was dissolved in diethyl ether and washed twice with water. The combined aqueous layer was made basic DIEA and extracted with ethyl acetate. The combined organic layer was washed with brine, dried and concentrated to afford **327** as a film (41 mg). The material was used without further purification.

Part C:

To **230** (20 mg, 0.06 mmol) in DMF (2 mL) was added **327** (19 mg, 0.08 mmol), DIEA (31 µL, 0.18 mmol), DMAP (1 mg) and HATU (30 mg, 0.08 mmol). The reaction mixture was stirred overnight. The mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with 0.1 N NaOH, water and brine, dried over sodium sulfate and concentrated. Compound **328** was used without further purification.
Mass calculated for formula $C_{29}H_{28}N_4O_6S$ 560.2, observed LCMS m/z 561.2 (M+H).

Part D:
Compound **328** and potassium carbonate (20 mg) were mixed in methanol (2.5 mL) and water (0.5 mL) and were stirred for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded **329** as a white solid (8 mg). HPLC-MS t_R = 2.77 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{25}H_{24}N_4O_4S$ 476.2, observed LCMS m/z 477.1 (M+H).

Example 6C



Part A:

N-(Hydroxymethyl)phthalimide (1.0 g, 5.6 mmol) was dissolved in 1% triflic acid in trifluoroacetic acid (10 mL) at 0 °C. To this mixture was added 330 (0.52 mL, 5.6 mmol). The reaction mixture was warmed to room temperature slowly and stirred overnight. The reaction mixture was poured into ice water (100 mL) and extracted with DCM. The combined organic layers were washed with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 30% EtOAc/Hex) afforded 331 (619 mg, 41%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.85 (d, 1H, J = 1.6 Hz), 7.86 (m, 2H), 7.81 (d, 1H, J = 1.6 Hz), 7.76 (s, 1H), 7.73 (m, 2H), 4.87 (s, 2H).

Part B:

Compound 331 (315 mg, 1.16 mmol) was dissolved in 1:1 methylene chloride:methanol (10 mL) and cooled in an ice bath. To this solution was added sodium borohydride (11 mg, 0.29 mmol) and the reaction was stirred for 30 minutes. Additional sodium borohydride (3 mg, 0.08 mmol) was added and the reaction was stirred for 30 minutes. The reaction mixture was diluted with methylene chloride and washed with saturated ammonium chloride solution, water and brine. The reaction mixture was dried over sodium sulfate and concentrated to afford 332 as a white solid (310 mg, 98%). ^1H NMR (400 MHz, CD_3OD) δ 7.83 (m, 2H), 7.79 (m, 2H), 7.24 (s, 1H), 6.97 (s, 1H), 4.76 (s, 2H), 4.65 (s, 2H).

Part C:

A mixture of **332** (97 mg, 0.36 mmol) and phosphorous tribromide (34 µL, 0.39 mmol) in DCM (5 mL) was stirred for 30 minutes at room temperature. The reaction mixture was poured into ice water and extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated to afford **333** as a white solid (104 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, 2H, J = 2.8, 5.2 Hz), 7.72 (dd, 2H, J = 2.8, 5.2 Hz), 7.32 (s, 1H), 7.15 (s, 1H), 4.77 (s, 2H), 4.66 (s, 2H).

Part D:

A mixture of **333** (450 mg, 1.34 mmol), 2-methyl-benzimidazole (355 mg, 2.69 mmol) and cesium carbonate (875 mg, 2.69 mmol) in DMF (5 mL) was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and washed with water and brine, dried over sodium sulfate and concentrated. Recrystallization from ethyl acetate / hexanes afforded **334** as a white solid (252 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, 2H, J = 2.8, 5.2 Hz), 7.72 (dd, 2H, J = 2.8, 5.2 Hz), 7.68 (m, 1H), 7.23 (m, 3H), 7.19 (s, 1H), 7.05 (s, 1H), 5.38 (s, 2H), 4.75 (s, 2H), 2.66 (s, 3H).

Part E:

A mixture of **334** (225 mg, 0.58 mmol) and hydrazine hydrate (113 µL, 2.32 mmol) in ethanol (4 mL) was refluxed for 4 hours. The reaction mixture was cooled and filtered. The filtrate was concentrated and the residue was dissolved in ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated to afford a **335** as yellow solid (148 mg, 99%).

Part F:

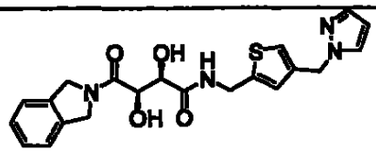
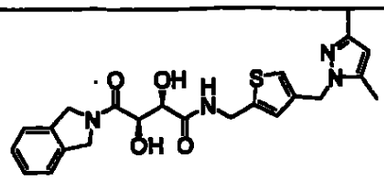
To **230** (12 mg, 0.036 mmol) in DMF (2 mL) was added **335** (12 mg, 0.045 mmol), DIEA (18 µL, 0.11 mmol) and HATU (17 mg, 0.045 mmol). The reaction mixture was stirred overnight at room temperature. The reaction

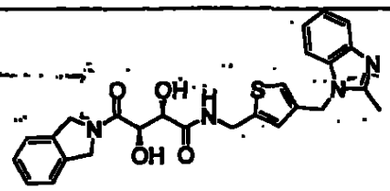
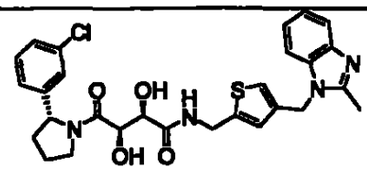
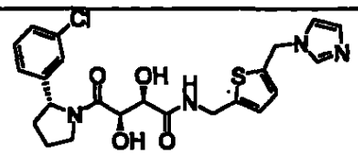
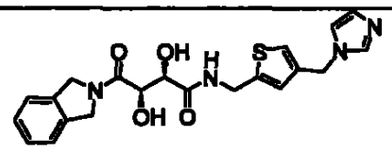
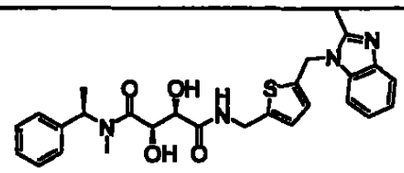
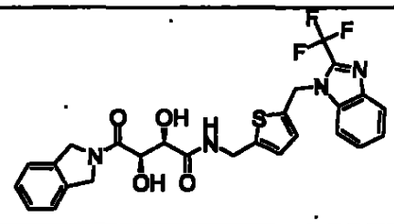
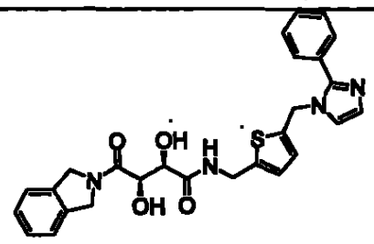
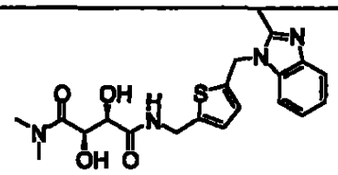
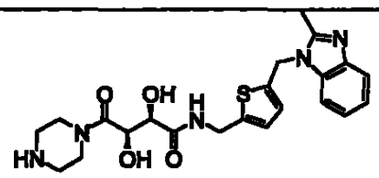
mixture was diluted with ethyl acetate (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Compound **336** was used without further purification. HPLC-MS t_R = 1.22 min (UV_{254} nm); mass calculated for formula $C_{30}H_{30}N_4O_6S$ 574.2, observed LCMS m/z 575.0 (M+H).

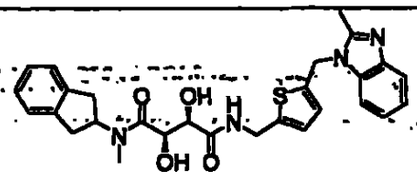
Part G:

Compound **336** and potassium carbonate (20 mg) were mixed in methanol (1.5 mL) and stirred for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded **337** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (t, 1H, J = 6.4 Hz), 7.89 (m, 1H), 7.70 (m, 1H), 7.44 (m, 2H), 7.33 (m, 1H), 7.27 (m, 3H), 7.20 (s, 1H), 7.14 (s, 1H), 5.80 (s, 2H), 5.04 (d, 1H, J = 13.2 Hz), 4.88 (d, 1H, J = 15.2 Hz), 4.73 (m, 2H), 4.60 (m, 2H), 4.25 (m, 2H), 2.83 (s, 3H); HPLC-MS t_R = 2.04 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{28}H_{26}N_4O_4S$ 490.2, observed LCMS m/z 491.1 (M+H).

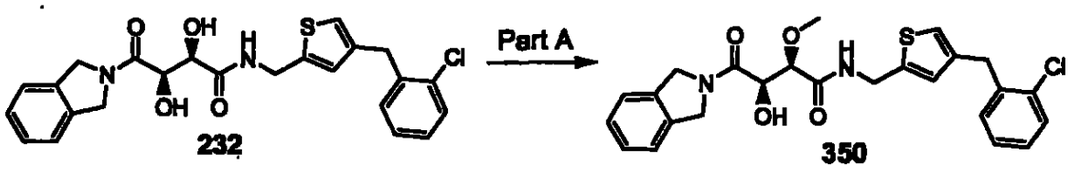
The following compounds were prepared using the procedures described in Example 6A to 6C.

Compound #	Structure	Exact mass	MS m/z (M+H)
338		426.1	427.1
339		454.2	455.2

340		490.2	491.2
341		552.2	553.2
342		488.1	489.0
343		426.1	427.1
344		506.2	507.2
345		544.1	545.1
346		502.2	503.2
347		416.2	417.2
348		457.2	458.1

349		518.2	519.2

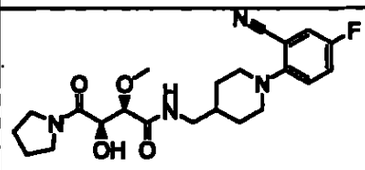
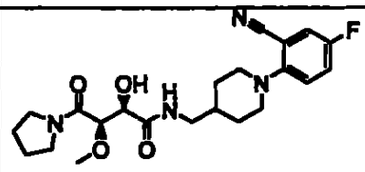
Example 7:



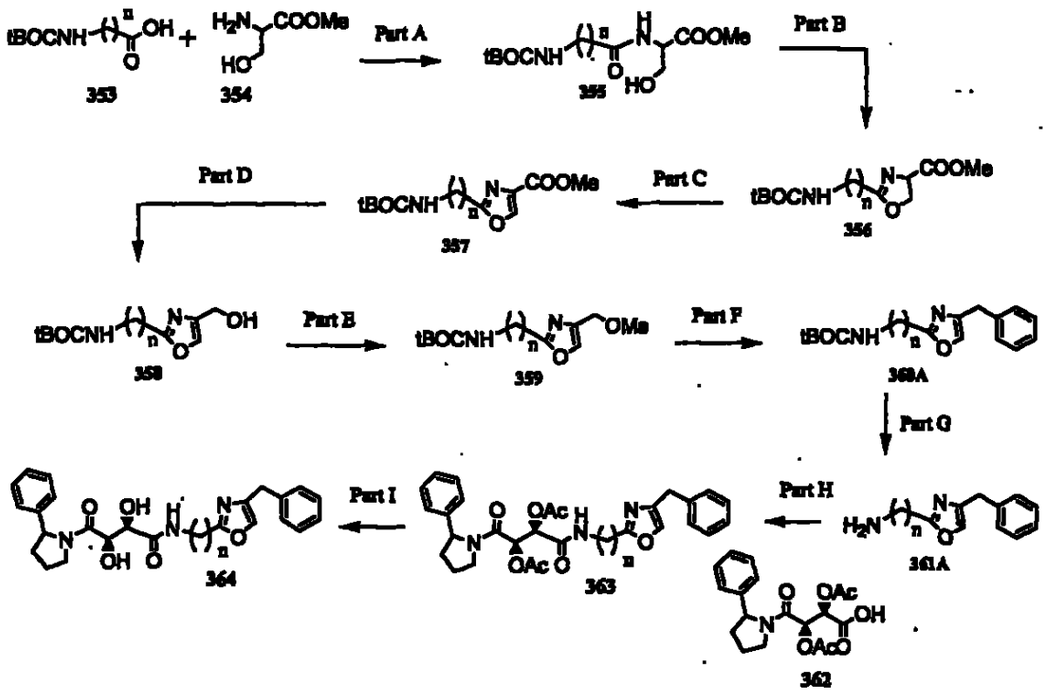
232 350

Part A:

To **232** (26 mg, 0.056 mmol) in toluene (5 mL) was added dibutyltin oxide (20 mg, 0.08 mmol). The mixture was heated for 3 hours at reflux with a Dean Stark trap. The mixture was concentrated. The residue was dissolved in NMP (3 mL) and treated with cesium fluoride (8.5 mg, 0.056 mmol) and iodomethane (14 µL, 0.224 mmol). The reaction mixture was heated at 50 °C overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. Purification by prep-HPLC afforded **350** (3.4 mg, 13%). HPLC-MS t_R = 5.26 min (UV_{254} nm, 10 min.); mass calculated for formula $C_{25}H_{25}ClN_2O_4S$ 484.1, observed LCMS m/z 485.0 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
351		432.2	433.2
352		432.2	433.2

Example 8:



Part A:

To BOC-glycine (353) (25.0 g, 0.143 mol) dissolved in dry THF (100 mL) and cooled to -20 °C under a nitrogen atmosphere was added Hunig's base (23.1 g, 31.1 mL, 0.357 mol) then isobutylchloroformate (21.4 g, 20.4 mL, 0.157 mol). Stirred at -20 °C for 60 mins. Serine methyl ester (354) (24.4 g, 0.157 mol) then Hunig's base (23.1 g, 31.1 mL, 0.357 mol) was added. The reaction mixture was warmed to room temperature, stirred for 18 h and concentrated. The residue was partitioned between 0.5 N NaOH (300 mL) CH_2Cl_2. The layers were separated and the acqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over magnesium sulfate and concentrated. Purified by silica gel chromatography (eluant: 1% MeOH-CH_2Cl_2 to 3% MeOH-CH_2Cl_2) to give 20.5 g (52%) of the product 355 as a yellow oil. MS m/e: 277 (M+H).

For n=2: MS m/e: 291 (M+H)

Part B:

To compound **355** (4.55g, 16.5 mmol) dissolved in CH_2Cl_2 (200 mL) and cooled to -50 °C under a nitrogen atmosphere was added diethylaminosulfur trifluoride (3.19 g, 2.4 mL, 19.8 mmol) dropwise via syringe. Stirred at -50 °C for 2 h, added potassium carbonate (3.88 g, 28.1 mmol), and warmed slowly to room temperature over 2 h. Added 0.2 N NaOH (100 mL) and separated layers. Extracted aqueous layer with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 2% MeOH-CH_2Cl_2 to 4% MeOH-CH_2Cl_2) to give 3.06 g (72%) of the product **356** as a yellow oil. MS m/e: 259 (M+H).
For n=2: MS m/e: 273 (M+H)

Part C:

To compound **356** (6.10 g, 23.6 mmol) dissolved in CH_2Cl_2 (250 mL) and cooled to 0 °C was added DBU (12.59 g, 12.4 mL, 82.7 mmol) and bromotrichloromethane (16.40 g, 8.1 mL, 82.7 mmol). Warmed slowly to room temperature over 2 h and stirred for 16 h. Added 0.1 N NaOH (200 mL) and separated layers. Extracted aqueous layer with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 2% MeOH-CH_2Cl_2 to 3% MeOH-CH_2Cl_2) to give 4.27 g (71%) of the product **357** as an orange oil. MS m/e: 257 (M+H).
For n=2: MS m/e: 271 (M+H)

Part D:

To compound **357** (4.25 g, 16.6 mmol) dissolved in Et_2O (100 mL) was added lithium borohydride (1.44 g, 66.3 mmol) and MeOH (2.13 g, 2.7 mL, 66.3 mmol). Refluxed for 3 h, cooled to room temperature, and concentrated. Added water (100 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 5% MeOH-CH_2Cl_2 to 10% MeOH-CH_2Cl_2) to give 2.43 g (64%) of the product **358** as a yellow oil. MS m/e: 229 (M+H).
For n=2: MS m/e: 243 (M+H)

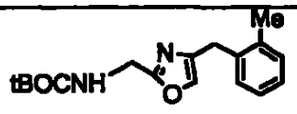
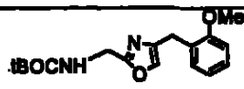
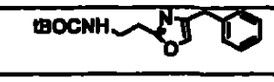
Part E:

To compound **358** (1.41 g, 6.18 mmol) dissolved in CH_2Cl_2 (35 mL) and cooled to -25 °C was added triethylamine (1.25 g, 1.7 mL, 12.4 mmol) then mesyl chloride (0.85 g, 0.57 mL, 7.41 mmol) dropwise. Warmed to 0 °C slowly over 60 mins. Added water (50 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated to give 1.89 g (100%) of the product **359** as a yellow oil. MS m/e: 251 (M+2-tBu).
For n=2: MS m/e: 265 (M+2-tBu)

Part F:

Suspended copper cyanide (1.66 g, 18.5 mmol) in dry THF (70 mL) under a nitrogen atmosphere and cooled to -25 °C. Added phenyl magnesium bromide (3.0 M in Et_2O, 12.3 mL, 37.0 mmol) dropwise via syringe such that internal temperature < -20 °C. Stirred at -20 °C for 30 mins then at 0 °C for 30 mins. Warmed to 15 °C internal temperature then recooled to -25 °C. Added compound **359** (1.89 g, 6.18 mmol) dissolved in dry THF (20 mL) dropwise via syringe. Stirred at -25 °C internal temperature for 2 h then at 0 °C for 16 h. Concentrated, added 2 N NH_4OH (100 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 5% EtOAc-hexane to 20% EtOAc-hexane) to give 0.82 g (46%) of the product **360A** as a yellow oil. MS m/e: 289 (M+H).

The following intermediates were prepared according to the above procedure:

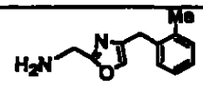
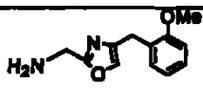
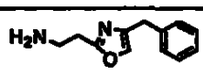
Compound #	Intermediate Structure	MS
360B		303 (M+H)
360C		319 (M+H)
360D		303 (M+H)

Part G:

To compound **360A** (1.00 g, 3.47 mmol) dissolved in 1:1 CH_2Cl_2:MeOH (30 mL) was added 4 N HCl in dioxane (7.8 mL, 31.2 mmol). Stirred at room

temperature for 4 h then concentrated to give 0.78 g (100%) of the product **361A** (hydrochloride salt) as a yellow solid. MS m/e: 189 (M+H).

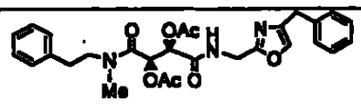
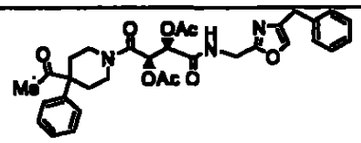
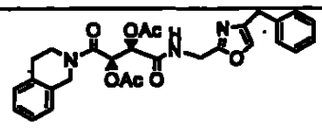
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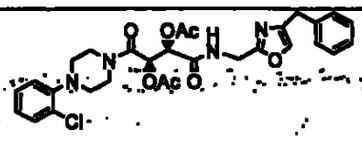
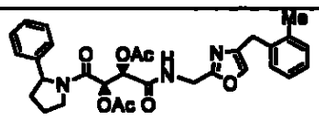
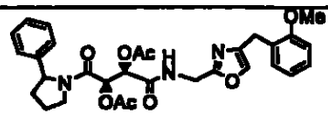
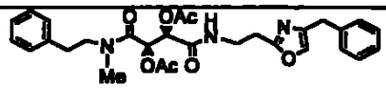
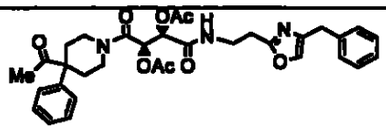
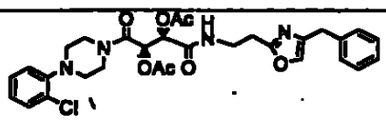
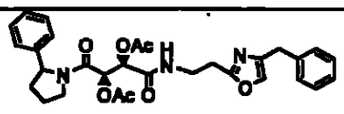
Compound #	Intermediate Structure	MS
361B		303 (M+H)
361C		219 (M+H)
361D		203 (M+H)

Part H: (JFL 80324-023)

Combined compound **361A** (0.20 g, 0.677 mmol), compound **362** (0.30 g, 0.812 mmol), HATU (0.51 g, 1.35 mmol), and triethylamine (0.21 g, 0.28 mL, 2.03 mmol) in dry DMF (8 mL). Stirred at room temperature for 16 h. Concentrated, added 0.5 N NaOH (15 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 3% MeOH-CH_2Cl_2) to give 0.25 g (70%) of the product **363** as a beige oil. MS m/e: 534 (M+H).

The following intermediates were prepared according to the above procedure:

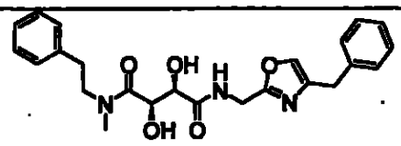
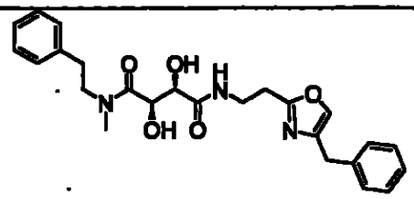
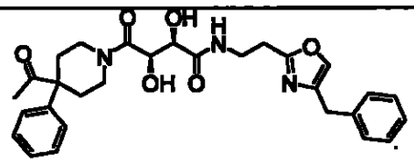
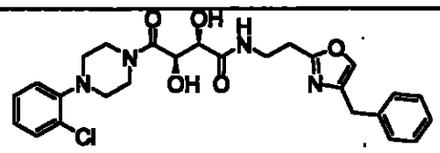
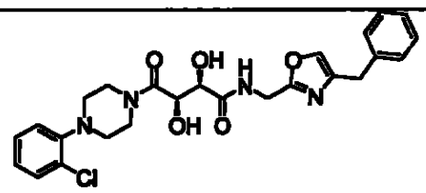
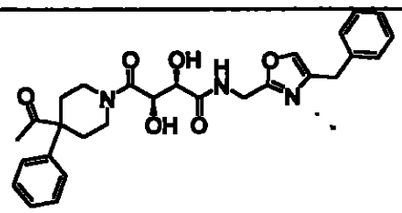
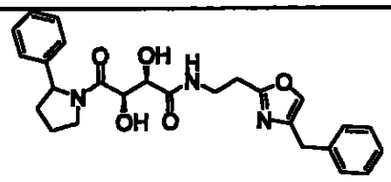
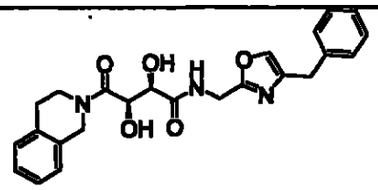
Compound #	Intermediate Structure	MS
365		522 (M+H)
366		590 (M+H)
367		520 (M+H)

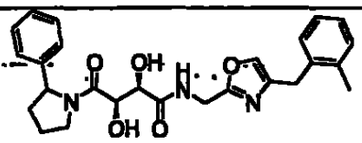
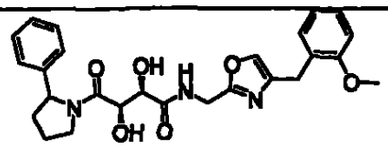
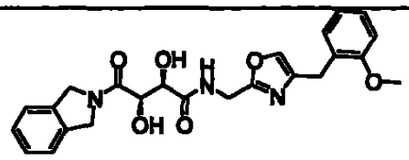
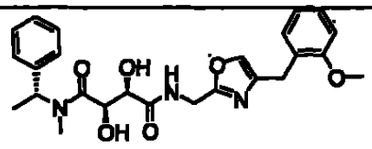
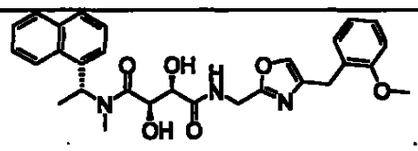
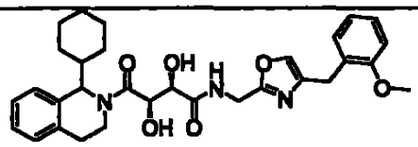
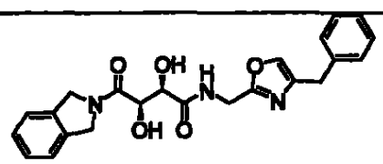
368		583 (M+H)
369		548 (M+H)
370		564 (M+H)
371		536 (M+H)
372		604 (M+H)
373		597 (M+H)
374		548 (M+H)

Part I:

To compound **363** (0.24 g, 0.450 mmol) dissolved in MeOH (10 mL) was added 0.5 M NaOMe in MeOH (0.09 mL, 0.045 mmol). Stirred at room temperature for 60 mins. Added 4 N HCl in dioxane (0.11 mL, 0.450 mmol) and concentrated to give 0.20 g (100%) of the product **364** as a brown foam. MS m/e: 450 (M+H).

The following compounds were prepared according to Example 8:

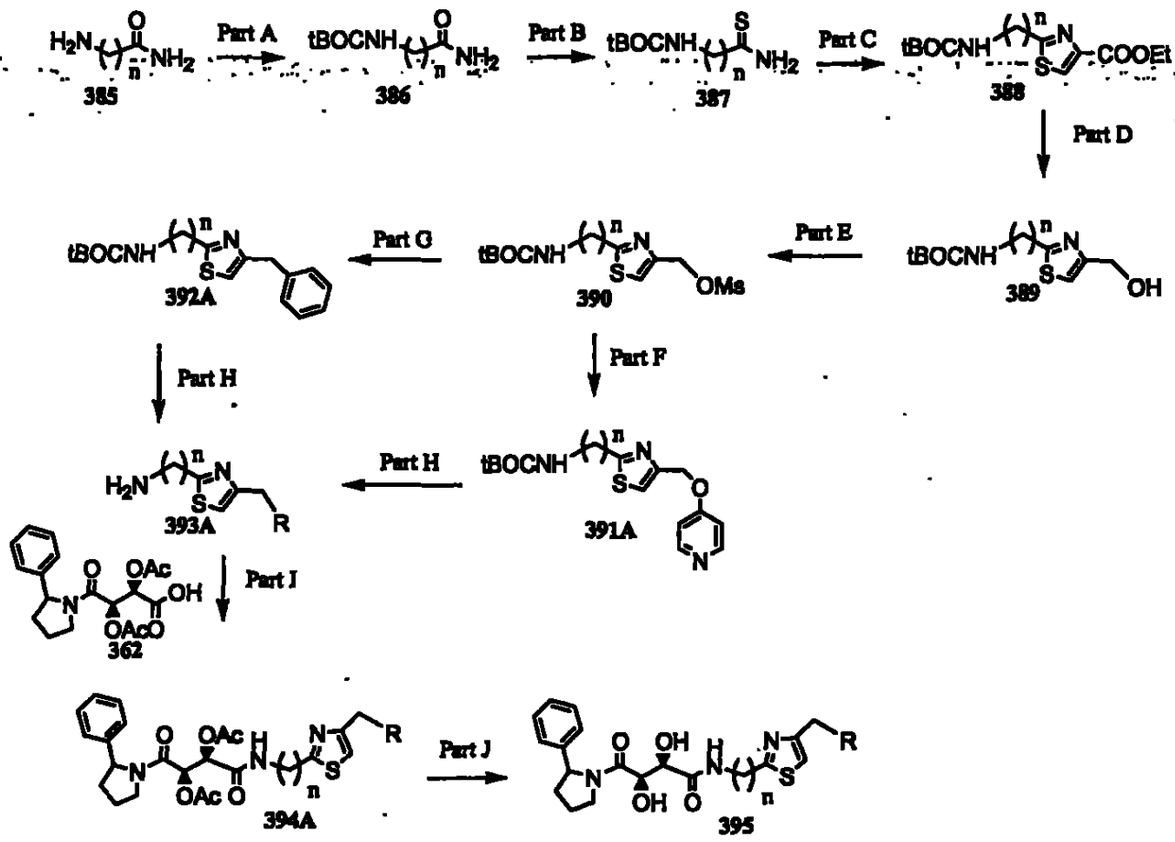
Compound #	Structure	Exact mass	MS, m/z (M+H)
375		437.2	438.0
376		451.2	452.0
377		519.2	520.0
378		512.2	513.0
379		498.2	499.2
380		505.2	506.3
381		463.2	464.2
382		435.2	436.2

383		463.2	464.2
384		479.2	480.2
174		451.2	452.2
175		467.2	468.3
179		517.2	518.3
181		547.3	548.3
182		421.2	422.2

Example 9: Thiazole-benzyl inhibitors

Example 9A:

Scheme 1



Part A:

To glycinamide HCl **385** (60.0 g, 0.543 mol) suspended in MeOH (1000 mL) and cooled to 0 °C was added triethylamine (109.9 g, 151.4 mL, 1.09 mol) and tBOC anhydride (148.0 g, 0.678 mol) portionwise. Warmed to room temperature and stirred for 24 h. Concentrated, added 1 N NaOH (600 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated to give 53.0 g (56%) of the product **396** as a white solid. MS m/e: 175 (M+H).

For n=2: MS m/e: 189 (M+H)

Part B:

To compound **386** (21.63 g, 0.124 mol) dissolved in THF (400 mL) was added Lawesson reagent (30.13 g, 0.074 mol). Stirred at room temperature for 16 h then concentrated. Purified by silica gel chromatography (eluant: 3% MeOH-CH_2Cl_2) then re-purified by silica gel chromatography (eluant: 2% MeOH-

CH_2Cl_2) to give 23.59 g (100%) of the product **387** as a light green solid. MS m/e: 135 (M+2-tBu).

For n=2: MS m/e: 149 (M+2-tBu)

Part C:

To compound **387** (6.00 g, 31.5 mmol) dissolved in CH_2Cl_2 (150 mL) was added ethyl bromopyruvate (6.76 g, 4.4 mL, 34.7 mmol). Stirred at room temperature for 5 h then concentrated. Added 3 A sieves (6 g) and EtOH (150 mL) and refluxed for 16 h. Filtered and concentrated to give a dark foam. Dissolved foam in 1:1 CH_2Cl_2:EtOH (100 mL) and added triethylamine (6.40 g, 8.8 mL, 63.1 mmol) and tBOC anhydride (7.60 g, 34.7 mmol). Stirred at room temperature for 5 h then concentrated. Added 0.25 N NaOH (100 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 10% EtOAc-CH_2Cl_2 to 30% EtOAc-CH_2Cl_2) to give 6.00 g (67%) of the product **388** as a brown oil. MS m/e: 287 (M+H).

For n=2: MS m/e: 301 (M+H)

Part D:

To compound **388** (4.70 g, 16.4 mmol) dissolved in Et_2O (140 mL) was added lithium borohydride (1.43 g, 65.7 mmol) and MeOH (2.10 g, 2.7 mL, 65.7 mmol). Refluxed for 16 h, cooled to room temperature, and concentrated. Added water (100 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 2% MeOH-CH_2Cl_2 to 5% MeOH-CH_2Cl_2) to give 3.70 g (92%) of the product **389** as a yellow solid. MS m/e: 245 (M+H).

For n=2: MS m/e: 259 (M+H)

Part E:

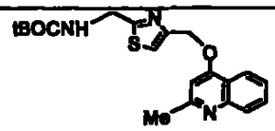
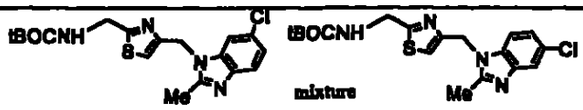
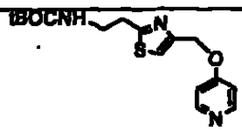
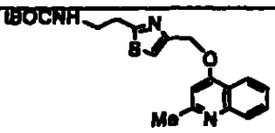
To compound **389** (5.30 g, 21.7 mmol) dissolved in CH_2Cl_2 (130 mL) and cooled to -25 °C was added triethylamine (4.40 g, 6.0 mL, 43.4 mmol) then mesyl chloride (3.00 g, 2.0 mL, 26.0 mmol) dropwise. Warmed to 0 °C slowly over 60 mins. Added water (100 mL), extracted with CH_2Cl_2, dried combined

organic extracts ($MgSO_4$), filtered, and concentrated to give 7.00 g (100%) of the product **390** as a yellow oil. MS m/e: 223 (M+2-tBOC).
For n=2: MS m/e: 237 (M+2-tBOC)

Part F:

To compound **390** (0.60 g, 1.86 mmol) dissolved in dry DMF (25 mL) was added 4-hydroxypyridine (0.22 g, 2.30 mmol) and cesium carbonate (1.20 g, 3.72 mmol). Stirred at room temperature for 16 h then concentrated. Added water (25 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 10% MeOH with NH_3-CH_2Cl_2) to give 0.40 g (68%) of the product **391A** as a colorless oil. MS m/e: 322 (M+H).

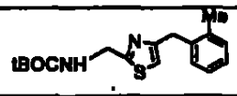
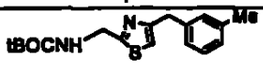
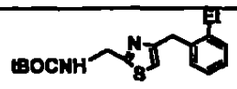
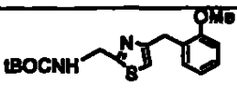
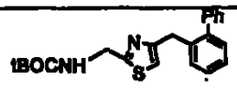
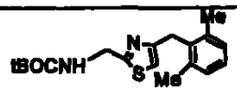
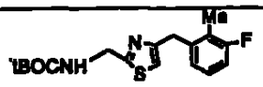
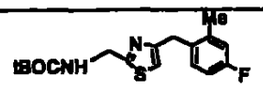
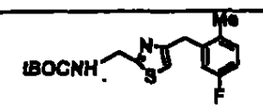
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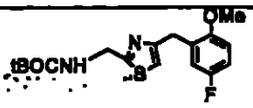
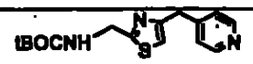
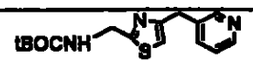
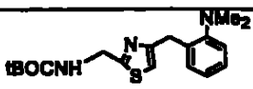
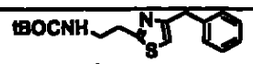
Compound #	Intermediate Structure	MS
391B		386 (M+H)
391C		359 (M+H)
391D		413 (M+H)
391E		373 (M+H)
391F		393 (M+H)
391G		336 (M+H)
391H		400 (M+H)

Part G:

Suspended copper cyanide (1.65 g, 18.4 mmol) in dry THF (70 mL) under a nitrogen atmosphere and cooled to -25 °C. Added phenyl magnesium bromide (3.0 M in Et_2O, 12.3 mL, 37.0 mmol) dropwise via syringe such that internal temperature < -20 °C. Stirred at -20 °C for 30 mins then at 0 °C for 30 mins. Warmed to 15 °C internal temperature then recooled to -25 °C. Added compound **390** (1.98 g, 6.14 mmol) dissolved in dry THF (20 mL) dropwise via syringe. Stirred at -25 °C internal temperature for 2 h then at 0 °C for 16 h. Concentrated, added 2 N NH_4OH (100 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 5% EtOAc-hexane to 20% EtOAc-hexane) to give 1.14 g (66%) of the product **392A** as a yellow oil. MS m/e: 305 (M+H).

The following intermediates were prepared according to the above procedure:

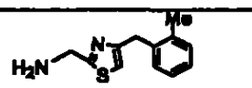
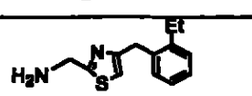
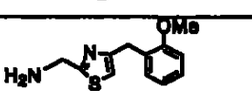
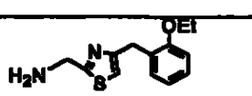
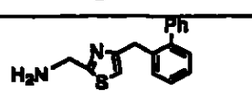
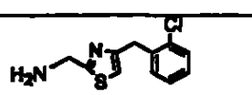
Compound #	Intermediate Structure	MS
392B		319 (M+H)
392C		319 (M+H)
392D		333 (M+H)
392E		335 (M+H)
392F		381 (M+H)
392G		333 (M+H)
392H		337 (M+H)
392I		337 (M+H)
392J		337 (M+H)

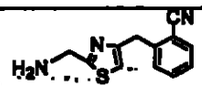
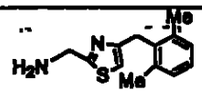
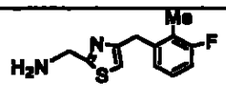
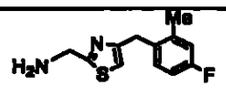
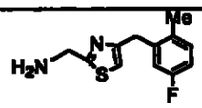
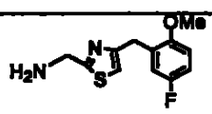
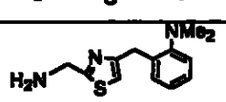
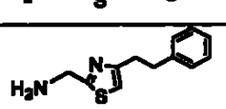
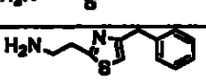
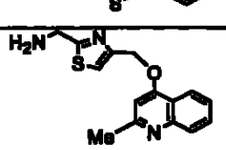
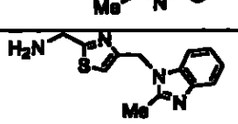
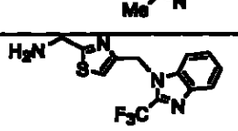
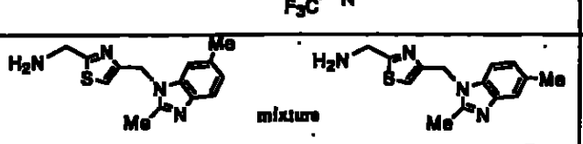
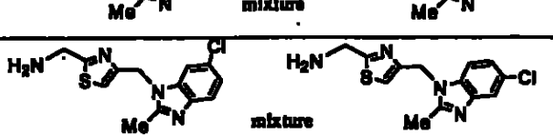
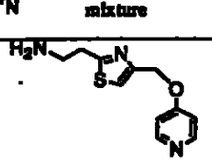
392K		353 (M+H)
392L		306 (M+H)
392M		306 (M+H)
392N		348 (M+H)
392O		319 (M+H)

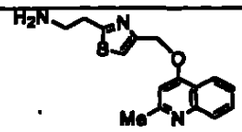
Part H:

To compound **392A** (0.30 g, 0.986 mmol) dissolved in 1:1 CH_2Cl_2:MeOH (10 mL) was added 4 N HCl in dioxane (2.4 mL, 9.86 mmol). Stirred at room temperature for 16 h then concentrated to give 0.23 g (100%) of the product **393A** (hydrochloride salt) as a beige foam. MS m/e: 205 (M+H).

The following intermediates were prepared according to the above procedure:

Compound #	Intermediate Structure	MS
393B		219 (M+H)
393C		219 (M+H)
393D		233 (M+H)
393E		235 (M+H)
393F		249 (M+H)
393G		281 (M+H)
393H		239 (M+H)

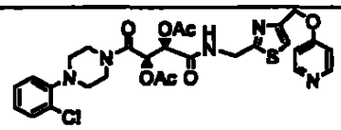
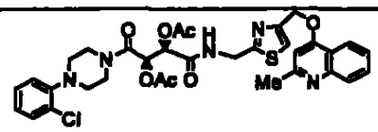
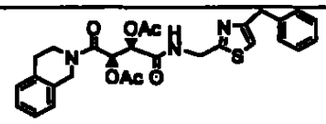
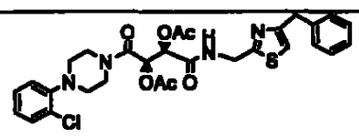
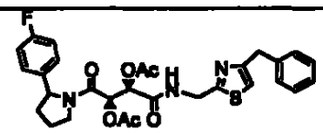
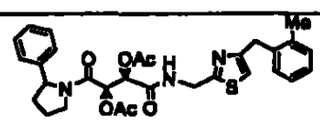
393I		230 (M+H)
393J		233 (M+H)
393K		237 (M+H)
393L		237 (M+H)
393M		237 (M+H)
393N		253 (M+H)
393O		206 (M+H)
393P		206 (M+H)
393Q		248 (M+H)
393R		219 (M+H)
393S		219 (M+H)
393T		286 (M+H)
393U		259 (M+H)
393V		313 (M+H)
393W		273 (M+H)
393X		293 (M+H)
393Y		236 (M+H)

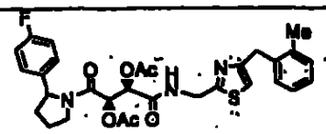
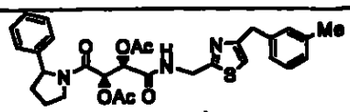
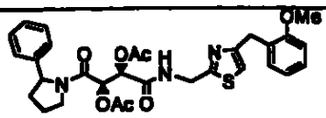
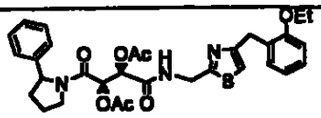
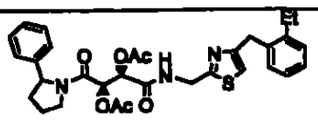
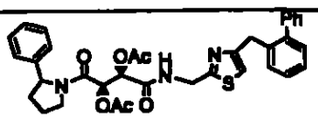
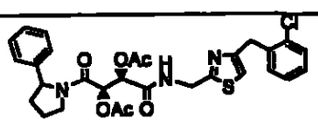
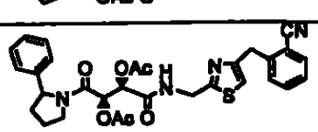
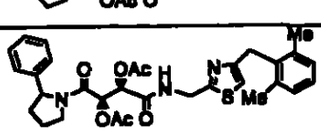
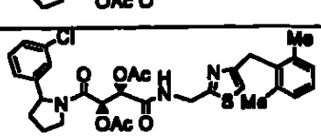
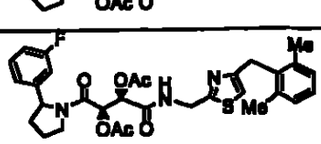
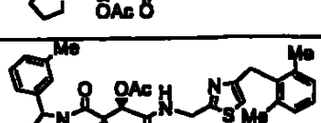
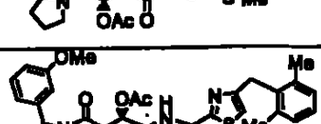
393Z		300 (M+H)

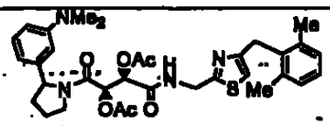
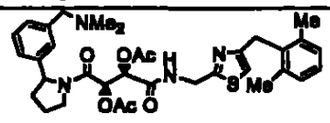
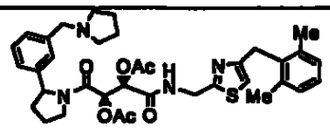
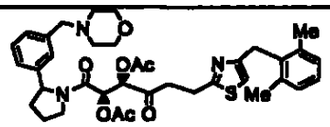
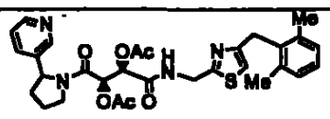
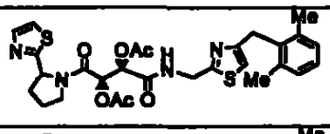
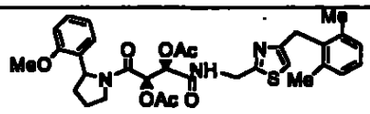
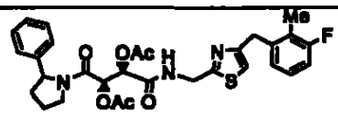
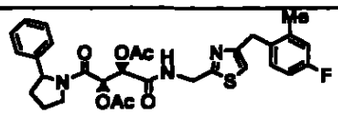
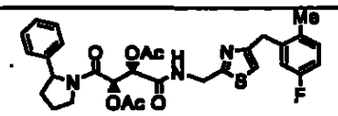
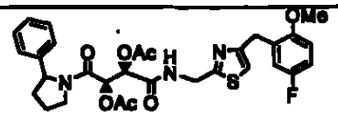
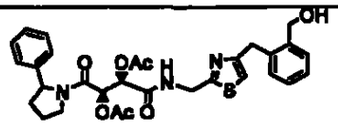
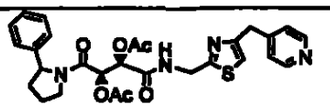
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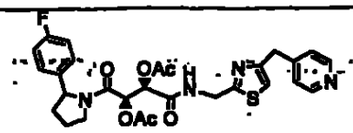
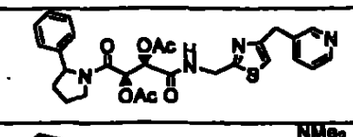
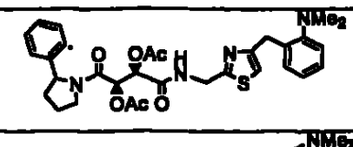
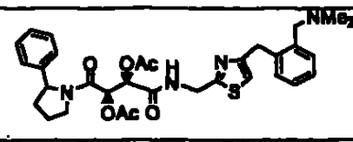
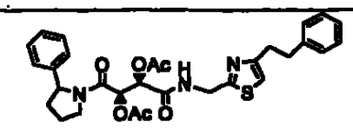
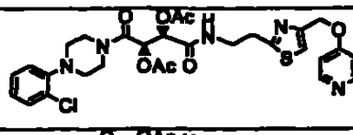
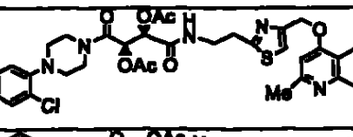
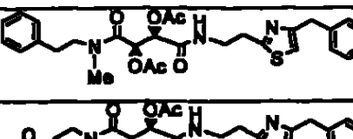
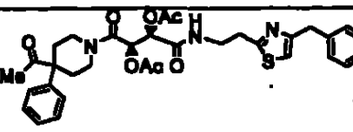
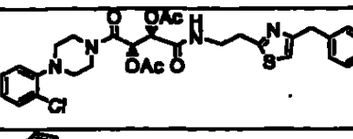
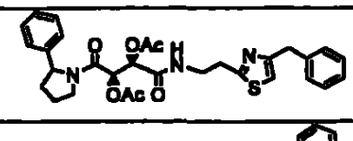
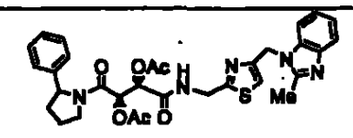
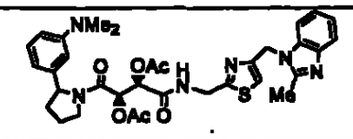
Combined compound **393A** (100 mg, 0.416 mmol), compound **362** (181 mg, 0.499 mmol), HATU (316 mg, 0.832 mmol), and triethylamine (126 mg, 0.17 mL, 1.25 mmol) in dry DMF (6 mL). Stirred at room temperature for 16 h. Concentrated, added 0.5 N NaOH (15 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 3% MeOH-CH_2Cl_2) to give 120 mg (52%) of the product **394A** as a colorless oil. MS m/e: 550 (M+H).

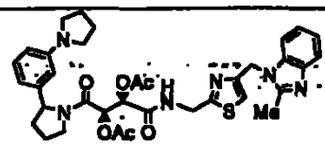
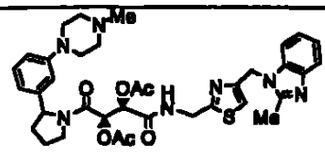
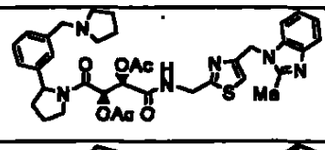
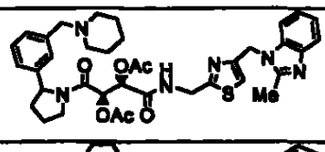
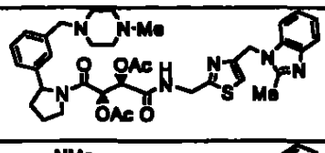
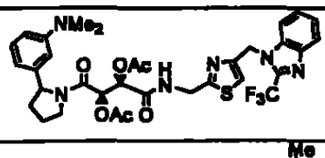
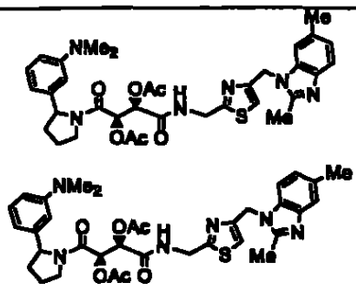
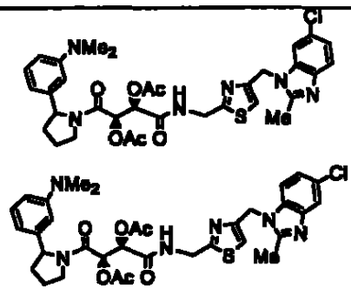
The following intermediates were prepared according to the above procedure:

Compound #	Intermediate Structure	MS
394B		616 (M+H)
394C		680 (M+H)
394D		536 (M+H)
394E		600 (M+H)
394F		568 (M+H)
394G		564 (M+H)

394H		582 (M+H)
394I		564 (M+H)
394J		580 (M+H)
394K		594 (M+H)
394L		578 (M+H)
394M		626 (M+H)
394N		584 (M+H)
394O		575 (M+H)
394P		578 (M+H)
394Q		612 (M+H)
394R		596 (M+H)
394S		592 (M+H)
394T		608 (M+H)

394U		621 (M+H)
394V		635 (M+H)
394W		661 (M+H)
394X		677 (M+H)
394Y		579 (M+H)
394Z		585 (M+H)
394AA		608 (M+H)
394BB		582 (M+H)
394CC		582 (M+H)
394DD		582 (M+H)
394EE		598 (M+H)
394FF		580 (M+H)
394GG		551 (M+H)

394HH		569 (M+H)
394II		551 (M+H)
394JJ		593 (M+H)
394KK		607 (M+H)
394LL		564 (M+H)
394MM		630 (M+H)
394NN		694 (M+H)
394OO		552 (M+H)
394PP		620 (M+H)
394QQ		613 (M+H)
394RR		564 (M+H)
394SS		604 (M+H)
394TT		647 (M+H)

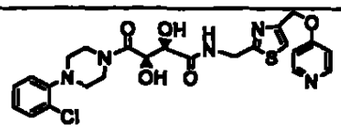
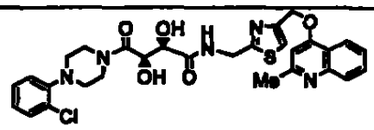
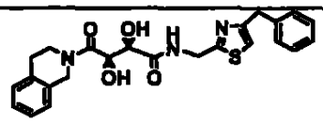
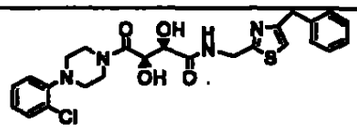
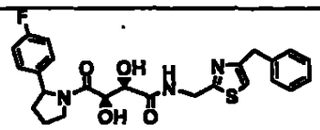
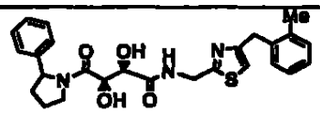
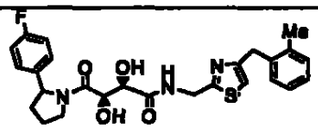
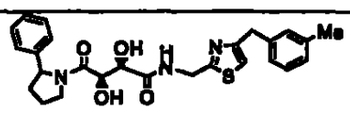
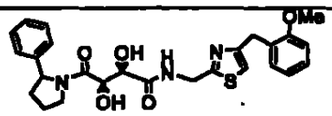
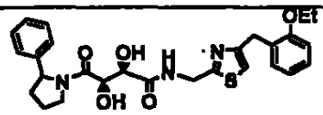
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394VV		702 (M+H)
394WW		687 (M+H)
394XX		701 (M+H)
394YY		716 (M+H)
394ZZ		701 (M+H)
394AAA		661 (M+H)
394BBB		682 (M+H)

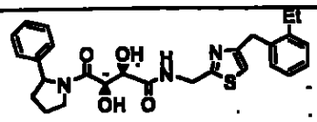
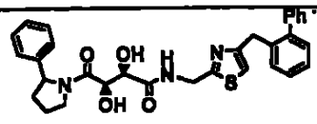
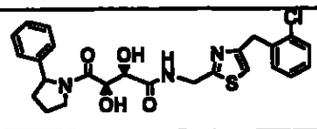
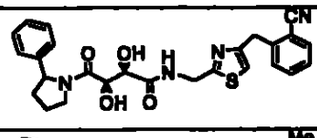
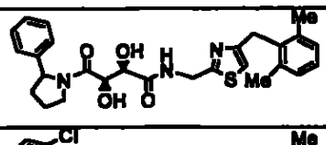
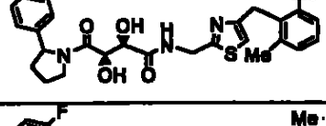
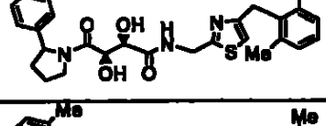
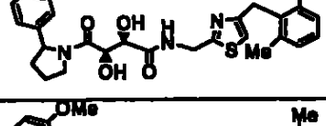
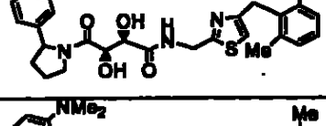
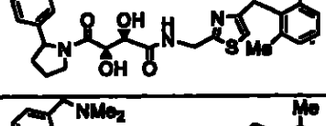
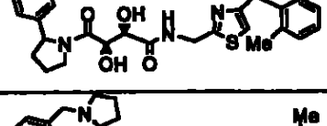
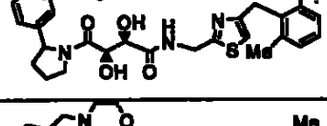
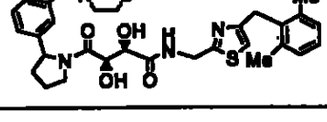
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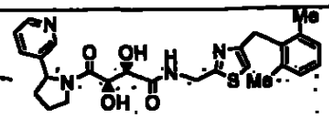
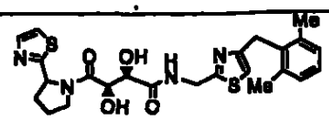
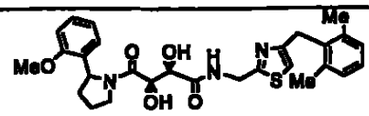
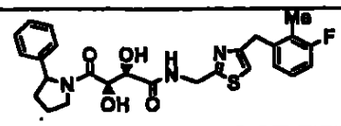
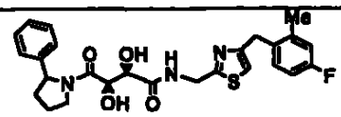
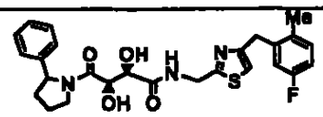
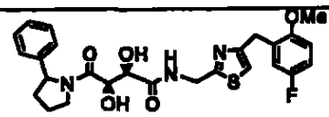
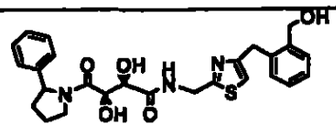
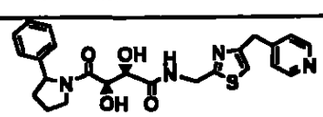
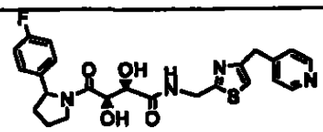
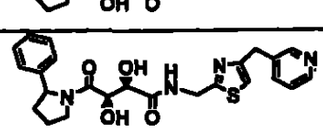
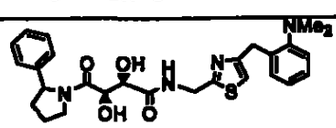
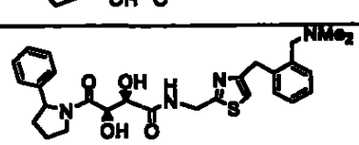
To compound 394A (0.12 g, 0.218 mmol) dissolved in MeOH (6 mL) was added 0.5 M NaOMe in MeOH (0.044 mL, 0.0218 mmol). Stirred at room temperature for 60 mins. Added 4 N HCl in dioxane (0.055 mL, 0.218 mmol)

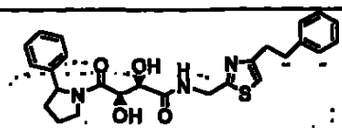
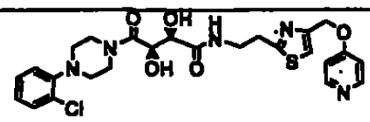
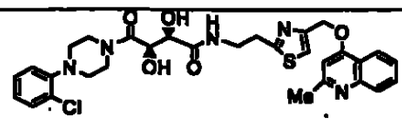
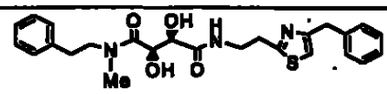
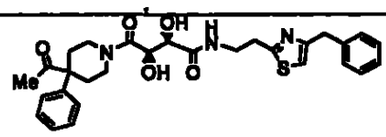
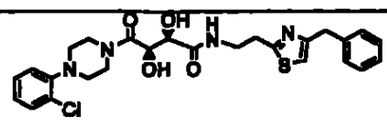
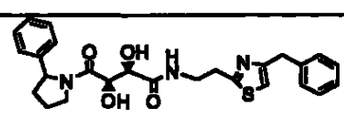
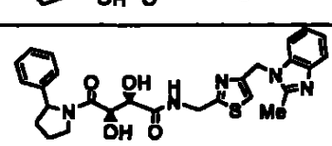
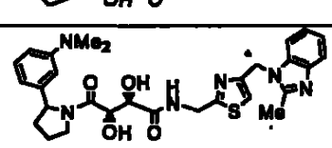
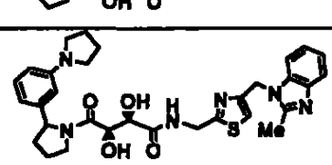
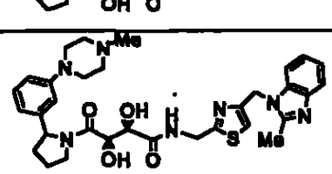
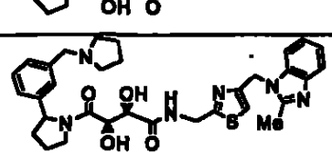
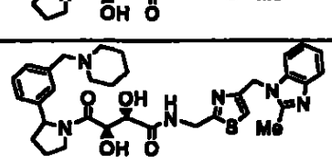
and concentrated to give 0.10 g (100%) of the product 395 as a light yellow foam: MS m/e: 466 (M+H).

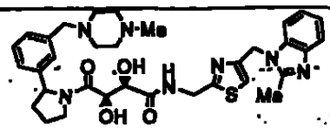
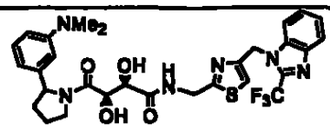
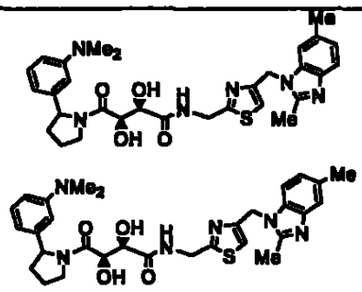
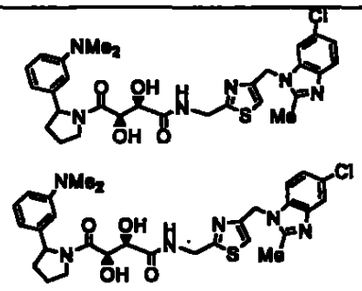
The following compounds were prepared according to the above procedure:

Compound #	Compound	MS
396		532 (M+H)
397		596 (M+H)
398		452 (M+H)
399		515 (M+H)
400		484 (M+H)
401		480 (M+H)
402		498 (M+H)
403		480 (M+H)
404		496 (M+H)
405		510 (M+H)

406		494 (M+H)
407		542 (M+H)
408		500 (M+H)
409		491 (M+H)
410		494 (M+H)
411		528 (M+H)
412		512 (M+H)
413		508 (M+H)
414		524 (M+H)
415		537 (M+H)
416		551 (M+H)
417		577 (M+H)
418		593 (M+H)

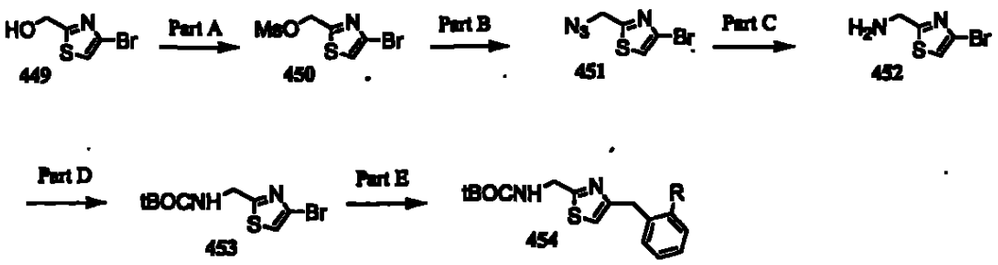
419		495 (M+H)
420		501 (M+H)
421		524 (M+H)
422		498 (M+H)
423		498 (M+H)
424		498 (M+H)
425		514 (M+H)
426		496 (M+H)
427		467 (M+H)
428		485 (M+H)
429		467 (M+H)
430		509 (M+H)
431		523 (M+H)

432		480 (M+H)
433		546 (M+H)
434		610 (M+H)
435		468 (M+H)
436		536 (M+H)
437		529 (M+H)
438		480 (M+H)
439		520 (M+H)
440		563 (M+H)
441		589 (M+H)
442		618 (M+H)
443		603 (M+H)
444		617 (M+H)

445		632 (M+H)
446		617 (M+H)
447		577 (M+H)
448		597 (M+H)

Example 9B

Scheme 1



Reference for compound **449**:

K. C. Nicolaou, N. P. King, M. R. V. Finlay, Y. He, F. Roschangar, D. Vourloumis, H. Vallberg, F. Sarabia, S. Ninkovic, D. Hepworth; *Bioorg. Med. Chem.* **1999**, 7, 665-697.

Part A:

To compound **449** (4.86 g, 25.0 mmol) dissolved in CH_2Cl_2 (200 mL) and cooled to -30 °C was added triethylamine (5.07 g; 7.0 mL; 50.1 mmol) and then mesyl chloride (3.44 g, 2.3 mL, 30.1 mmol) dropwise via syringe. Warmed slowly to 0 °C over 60 mins. Added water (200 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated to give 6.80 g (100%) of the product **450** as an orange oil. MS m/e: 272 (M+H).

Part B:

To compound **450** (6.80 g, 25.0 mmol) dissolved in DMF (100 mL) was added sodium azide (3.25 g, 50.0 mmol) and heated at 80 °C for 2 h. Cooled to room temperature and concentrated. Added water (200 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 5% EtOAc-hexane to 10% EtOAc-hexane) to give 4.18 g (76%) of the product **451** as an orange oil. MS m/e: 219 (M+H).

Part C:

To compound **451** (4.18 g, 19.1 mmol) dissolved in 10:1 THF:water by volume (150 mL) was added triphenylphosphine (20.0 g, 76.3 mmol) and refluxed for 2 h. Cooled to room temperature and concentrated. Purified by silica gel chromatography (eluant: 3% MeOH with NH_3-CH_2Cl_2) to give 6.18 g of the product **452** (with triphenylphosphine oxide) as a yellow solid. 100% yield of product **452** would be 3.68 g. MS m/e: 194 (M+H).

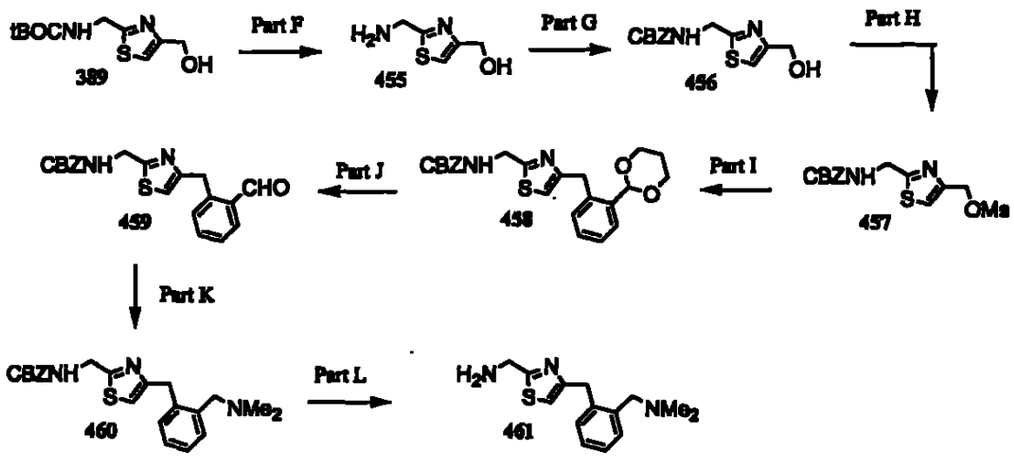
Part D:

To compound **452** (3.68 g, 19.1 mmol) dissolved in CH_2Cl_2 (100 mL) was added tBOC anhydride (5.21 g, 23.9 mmol). Stirred at room temperature for 2 h then concentrated. Purified by silica gel chromatography (eluant: 3% MeOH-CH_2Cl_2) to give 3.97 g (71%) of the product **453** as a yellow oil. MS m/e: 293 (M+H).

Part E:

To compound **453** (1.07 g, 3.65 mmol) dissolved in dry THF (10 mL) under a nitrogen atmosphere was added 2-chlorobenzylzinc chloride (0.5 M in THF; 14.6 mL, 7.30 mmol) and bis(tri-t-butylphosphine)palladium (0.14 g, 0.274 mmol). Heated at 60 °C for 2 h. Cooled to room temperature and concentrated. Added 0.2 N HCl (30 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 5% EtOAc-hexane to 15% EtOAc-hexane) to give 0.61 g (49%) of the product **454** as a yellow oil. MS m/e: 339 (M+H).

Scheme 2



Part F:

To compound **389** (2.00 g, 8.18 mmol) dissolved in MeOH (40 mL) was added 4 N HCl in dioxane (20.5 mL, 81.8 mmol). Stirred at room temperature for 3 h. Concentrated to give 1.48 g (100%) of the product **455** as a white solid. MS m/e: 145 (M+H).

Part G:

To compound **455** (1.48 g, 8.18 mmol) suspended in CH_2Cl_2 (50 mL) was added triethylamine (2.48 g, 3.4 mL, 24.5 mmol) and cooled to 0 °C. Added CBZCl (1.54 g, 1.3 mL, 9.00 mmol) dissolved in CH_2Cl_2 (10 mL) dropwise via addition funnel. Stirred at 0 °C for 30 mins then at room temperature for 2 h. Added 0.2 N NaOH (100 mL), extracted with CH_2Cl_2, dried combined organic

extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 5% MeOH-CH_2Cl_2 to 10% MeOH-CH_2Cl_2) to give 1.41 g (62%) of the product **456** as a white solid. MS m/e: 279 (M+H).

Part H:

To compound **456** (1.40 g, 5.03 mmol) dissolved in CH_2Cl_2 (40 mL) and cooled to -30 °C was added triethylamine (1.02 g, 1.4 mL, 10.1 mmol) and then mesyl chloride (0.69 g, 0.47 mL, 6.04 mmol) dropwise via syringe. Warmed slowly to 0 °C over 60 mins. Added water (50 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated to give 1.79 g (100%) of the product **457** as a yellow oil. MS m/e: 357 (M+H).

Part I:

To 2-(1,3-dioxan-2-yl)phenylmagnesium bromide (0.25 M in THF, 100 mL, 25.0 mmol) under a nitrogen atmosphere and cooled to -25 °C internal temperature was added copper cyanide (1.12 g, 12.5 mmol). Stirred at -25 °C for 1 h then at 0 °C for 1 h. Warmed to 15 °C internal temperature then recooled to -25 °C. Added compound **457** (1.78 g, 4.99 mmol) dissolved in dry THF (15 mL) dropwise via syringe. Stirred at -25 °C internal temperature for 1 h then at 0 °C for 16 h. Concentrated, added 2 N NH_4OH (100 mL) and CH_2Cl_2 (100 mL), and filtered through celite. Separated layers of filtrate, extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 10% EtOAc-hexane to 40% EtOAc-hexane) to give 1.35 g (64%) of the product **458** as a white solid. MS m/e: 425 (M+H).

Part J:

To compound **458** (1.34 g, 3.16 mmol) dissolved in CH_2Cl_2 (10 mL) was added water (2 mL) and TFA (8 mL). Stirred at room temperature for 5 h then concentrated. Added 1 N NaOH (50 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 20% EtOAc-CH_2Cl_2 to 30% EtOAc-CH_2Cl_2) to give 1.05 g (91%) of the product **459** as a yellow oil. MS m/e: 367 (M+H).

Part K:

To compound 459 (0.74 g, 2.02 mmol) dissolved in CH_2Cl_2 (20 mL) was added dimethylamine (2 M in THF, 2.0 mL, 4.04 mmol), 3A sieves (0.60 g), glacial acetic acid (0.12 g, 0.12 mL, 2.02 mmol), then sodium triacetoxyborohydride (0.64 g, 3.03 mmol). Stirred at room temperature for 16 h. Added 0.5 N NaOH (25 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 5% MeOH with NH_3-CH_2Cl_2 to 15% MeOH with NH_3-CH_2Cl_2) to give 0.65 g (81%) of the product 460 as a yellow oil. MS m/e: 396 (M+H).

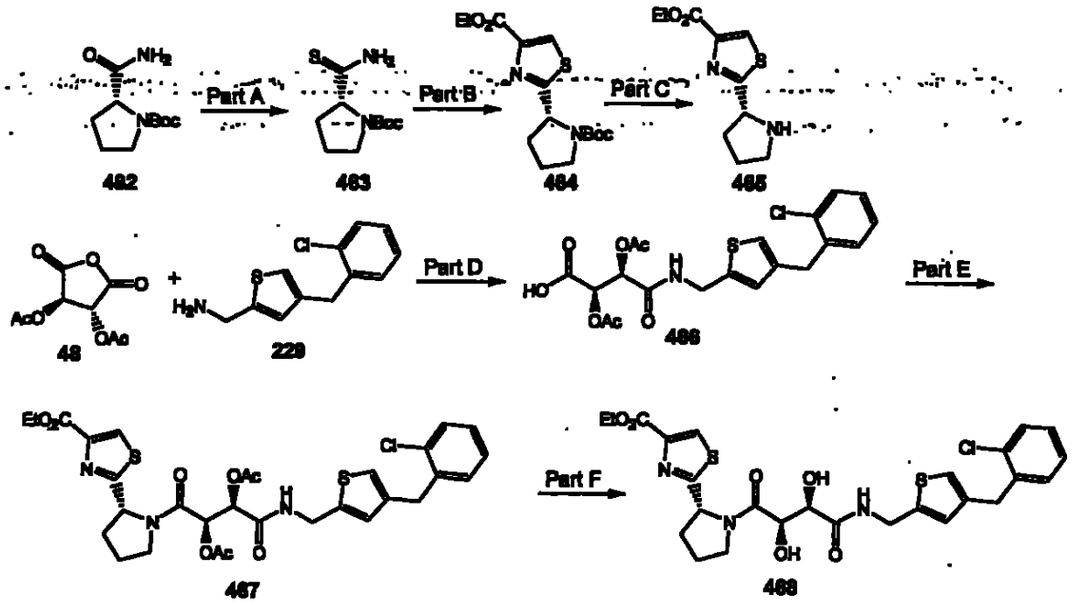
Part L:

To compound 460 (0.64 g, 1.62 mmol) dissolved in MeOH (5 mL) was added THF (2 mL) and 6.25 N NaOH (5 mL). Refluxed for 3 h. Cooled to room temperature and concentrated. Purified by silica gel chromatography (eluant: 10% MeOH with NH_3-CH_2Cl_2 to 15% MeOH with NH_3-CH_2Cl_2) to give 0.31 g (74%) of the product 461 as an orange oil. MS m/e: 262 (M+H).

Select compounds prepared using the procedures from Example 9B are exemplified in the preceding table.

Example 10: 2-Heteroaryl pyrrolidines & derivatives

Example 10A:



Part A:

To D-1-N-Boc-prolinamide (**462**) (2.5 g, 11.7 mmol) in THF (15 mL) was added Lawesson's reagent (2.36 g, 5.8 mmol) portionwise at room temperature. The reaction mixture was stirred for 3.5 hours under argon atmosphere. The solvents were removed in vacuo. Purification by column chromatography (SiO_2, 5% MeOH/DCM) afforded **463** as a light yellow solid (2.5 g, 93%).

Part B:

A mixture of **463** (500 mg, 2.15 mmol) and potassium hydrogencarbonate (1.74 g, 17.35 mmol) in DME (12 mL) was stirred for 10 minutes. Ethyl bromopyruvate (0.81 mL, 6.45 mmol) was added dropwise via a syringe to the reaction mixture. The reaction mixture was stirred for 30 minutes. The reaction mixture was cooled to 0 °C and a mixture of trifluoroacetic anhydride (1.21 mL, 8.6 mmol) and 2,6-lutidine (2.12 mL, 18.3 mmol) was added dropwise via syringe over 10 minutes. The reaction mixture was stirred for 30 minutes at 0 °C. The solvents were removed in vacuo. The residue was dissolved in chloroform, washed with 1.0 N HCl, bicarbonate solution and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 30% EtOAc/hexane) afforded **464** as a light yellow

solid (520 mg, 74%). HPLC-MS t_R = 1.88 min ($UV_{254\ nm}$); Mass calculated for formula $C_{15}H_{22}N_2O_4S$ 326.1, observed LCMS m/z 327.1 (M+H).

Part C:

To **464** (486 mg, 1.49 mmol) in dioxane (1 mL) was added 4 N HCl in dioxane (1 mL). The reaction mixture was stirred for 1 hour at room temperature and concentrated. HPLC-MS t_R = 0.60 min ($UV_{254\ nm}$); Mass calculated for formula $C_{10}H_{14}N_2O_2S$ 226.1, observed LCMS m/z 227.1 (M+H).

Part D:

To **48** (216 mg, 1.0 mmol) in THF (2 mL) was added material from **229** (238 mg, 1 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated and freeze-dried to afford a white powder (410 mg, 90%). HPLC-MS t_R = 1.74 min ($UV_{254\ nm}$); Mass calculated for formula $C_{20}H_{20}ClNO_7S$ 453.0, observed LCMS m/z 454.0 (M+H).

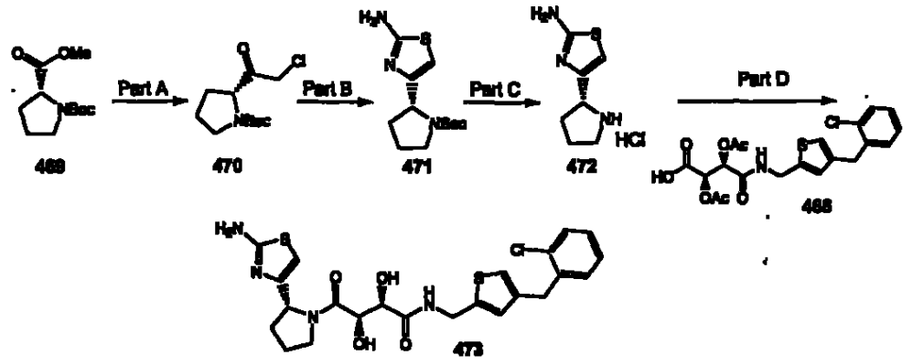
Part E:

To **465** (26 mg, 0.1 mmol) in DMF (0.5 mL) was added DIEA (35 µL, 0.2 mmol), **466** (54 mg, 0.12 mmol) in DMF (1 mL) and then HATU (57 mg, 0.15 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL) and the layers were separated. The organic layer was washed with 0.1 N NaOH, 0.1 N HCl and brine, dried over sodium sulfate and concentrated. Compound **467** was used without further purification. HPLC-MS t_R = 2.06 min ($UV_{254\ nm}$); Mass calculated for formula $C_{30}H_{32}ClN_3O_8S_2$ 661.1, observed LCMS m/z 662.0 (M+H).

Part F:

To **467** in methanol (1 mL) was added 7.0 M ammonia in methanol (1 mL). The reaction mixture was stirred for 1 hour at room temperature and concentrated. Purification by reverse phase prep-LC afforded **468** as a white powder (2 mg). HPLC-MS t_R = 5.04 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{28}H_{28}ClN_3O_8S_2$ 577.1, observed LCMS m/z 578.0 (M+H).

Example 10B:



Part A:

A solution of LDA was formed by the addition of 1.6 M *n*-butyl lithium (34 mL, 54.5 mmol) to diisopropylamine (8.47 mL, 60 mmoL) in THF (20 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 20 minutes and warmed to 0 °C gradually. The LDA solution was added dropwise to a mixture of N-Boc-D-proline methyl ester (469) (2.5 g, 10.9 mmol) and chloroiodomethane (3.17 mL, 43.6 mmol) in THF (20 mL) at – 78 °C via a cannula over 30 minutes. The reaction mixture was stirred at –78 °C for 30 minutes. A solution of acetic acid (15 mL) in THF (15 mL) was added slowly over 20 minutes at –78 °C. The reaction mixture was stirred for 20 minutes and then warmed to room temperature. The reaction mixture was diluted with ethyl acetate and washed with water, sodium bicarbonate solution and brine. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% EtOAc/hexane) afforded 470 as a light brown solid (2.0 g, 74%). HPLC-MS t_R = 1.80 min ($UV_{254\ nm}$); Mass calculated for formula $C_{11}H_{18}ClNO_3$ 247.1, observed LCMS m/z 248.1 (M+H).

Part B:

A mixture of 470 (250 mg, 1.0 mmol) and thiourea (152 mg, 2 mmol) were stirred for 72 hours. The reaction mixture was diluted with ethyl acetate and washed with sodium bicarbonate solution and brine. The organic layer was dried over sodium sulfate and concentrated. Purification by column

chromatography (SiO_2, 80% EtOAc/hexane) afforded **471** as a white solid (201 mg, 75%). HPLC-MS t_R = 0.67 min ($UV_{254\ nm}$); Mass calculated for formula $C_{12}H_{19}N_3O_2S$ 269.1, observed LCMS m/z 270.1 (M+H).

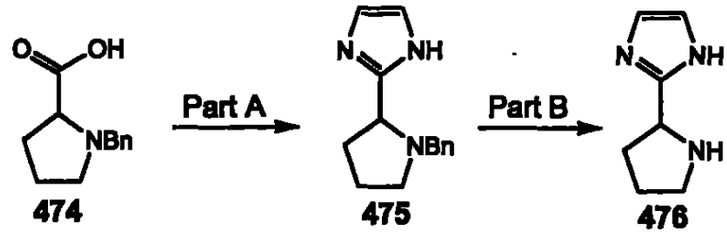
Part C:

To **471** (201 mg, 0.75 mmol) in dioxane (1 mL) was added 4 N HCl in dioxane (1 mL). The reaction mixture was stirred for 1 hour at room temperature and concentrated.

Part D:

A mixture of **466** (45 mg, 0.1 mmol), **472** (29 mg, 0.12 mmol), DIEA (50 µL, 0.28 mmol) and HATU (57 mg, 0.15 mmol) in DMF (2 mL) was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL) and the layers were separated. The organic layer was washed with 0.1 N NaOH, 0.1 N HCl and brine, dried over sodium sulfate and concentrated. The residue was dissolved in methanol (1 mL) and 7.0 M ammonia in methanol (1 mL) was added. The reaction mixture was stirred for 1 hour at room temperature and concentrated. Purification by reverse phase prep-LC afforded **473** as a white powder. HPLC-MS t_R = 1.42 min ($UV_{254\ nm}$); Mass calculated for formula $C_{23}H_{25}ClN_4O_4S_2$ 520.1, observed LCMS m/z 521.1 (M+H).

Example 10C:



474 **475** **476**

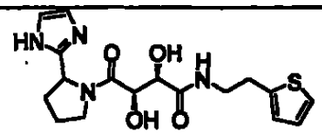
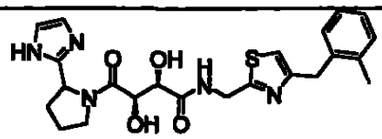
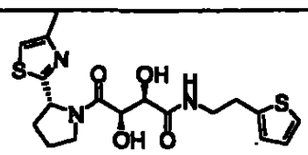
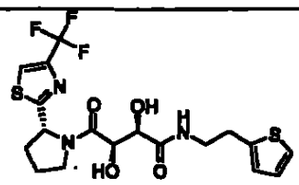
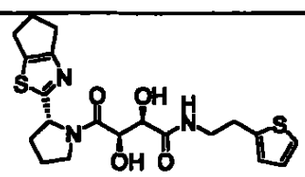
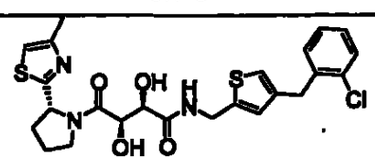
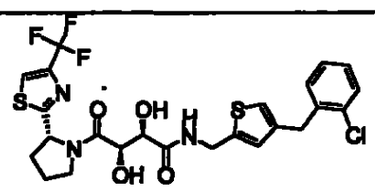
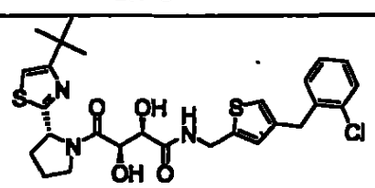
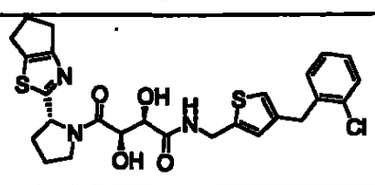
Part A:

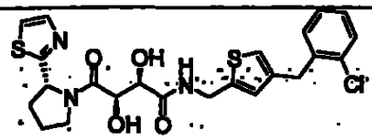
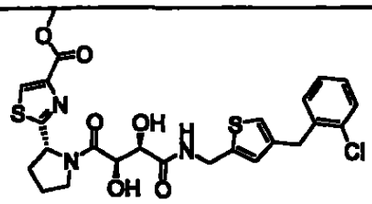
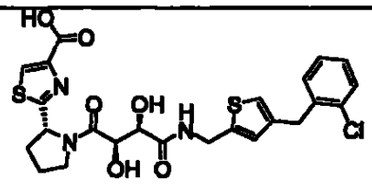
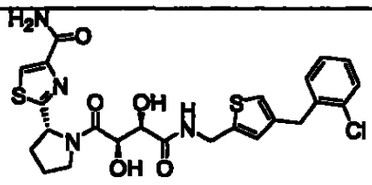
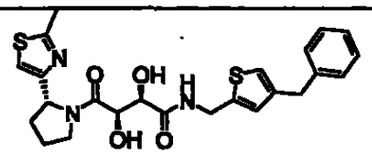
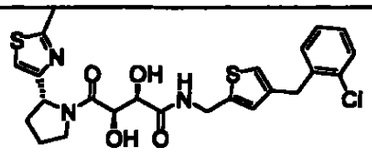
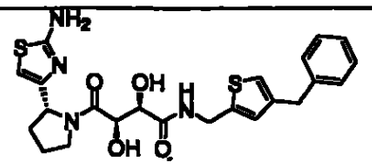
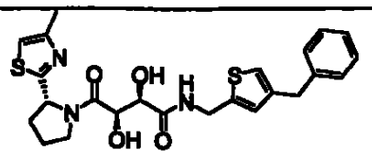
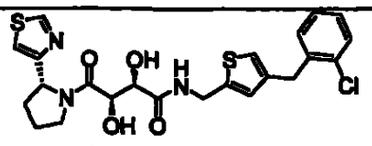
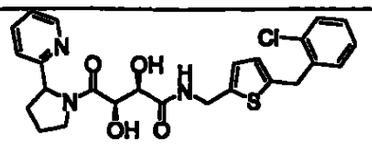
To 1-Benzyl-pyrrolidine-2-carboxylic acid (**474**) (Belokon, Y. N. at al; Tetrahedron Asymmetry **1998**, *9*, 4249-4252) in CH_2Cl_2 (20 mL) was added 2,2-dimethoxy-ethylamine (614 mg, 5.84 mmol), EDCI (1.12 g, 5.84 mmol),

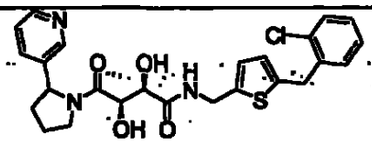
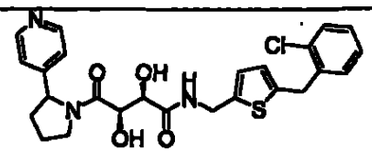
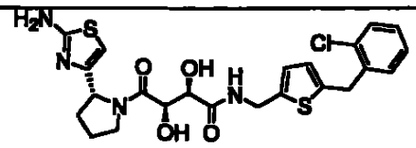
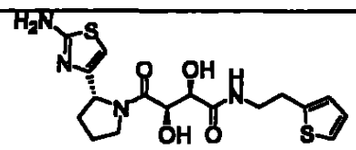
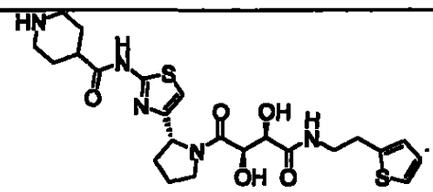
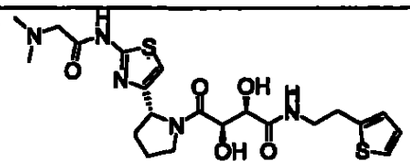
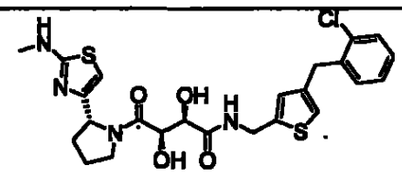
HOBT (658 mg, 4.87 mmol), and NMM (1.08 mL, 9.8 mmol). The reaction mixture was stirred overnight at 25 °C. Saturated aqueous $NaHCO_3$ solution (50 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (50 mL x3). The combined organic layers was washed with brine (50 mL), dried over Na_2SO_4, and concentrated by rotary evaporator to give 1-benzyl-pyrrolidine-2-carboxylic acid (2,2-dimethoxy-ethyl)-amide as yellow oil. To 1-benzyl-pyrrolidine-2-carboxylic acid (2,2-dimethoxy-ethyl)-amide was added acetic acid (10 mL) and ammonium acetate (11 g). The reaction mixture was heated to 140 °C overnight. After it was cooled down, it was poured into 100 mL ice-water with stirring. Solid $NaHCO_3$ was added in small portion with stirring to adjust the pH of the solution to 8~9. The aqueous solution was extracted with EtOAc (100 mL x2). The combined organic layers was washed with brine, dried over Na_2SO_4, and concentrated with rotary evaporator. Compound **475** (110 mg) was isolated by SiO_2 chromatography (CH_2Cl_2/MeOH/NH_3: 40:1:0.1 to 20:1:0.1). MS: m/z 228.3 $[M+H]^+$.

Part B: 5-Pyrrolidine-2-yl-1*H*-imidazole:
To **475** (110 mg) in 10 mL EtOH was added Pd/C (10%, 50 mg). The reaction mixture was hydrogenated under hydrogen (50 psi) for 24 hours. The solid was filtrated and the solution was evaporated by rotary evaporator to give 5-Pyrrolidine-2-yl-1*H*-imidazole (476) (67 mg). MS m/z 138.2 $[M+H]^+$.^{1}H-NMR (300 MHz, $CDCl_3$): δ ppm: 6.95 (s, 2H), 4.35 (t, 1H, J = 7.4 Hz), 3.00 (m, 2H), 2.22~2.03 (m, 2H), 1.85 (m, 3H).

The following compounds were prepared by procedures described in Example 11. The 2-(pyridyl)-pyrrolidines are commericial amines (entries **495 - 497**). The amino-thiazole of **471** was further functionalized via acylation chemistry to afford **500 – 501**.

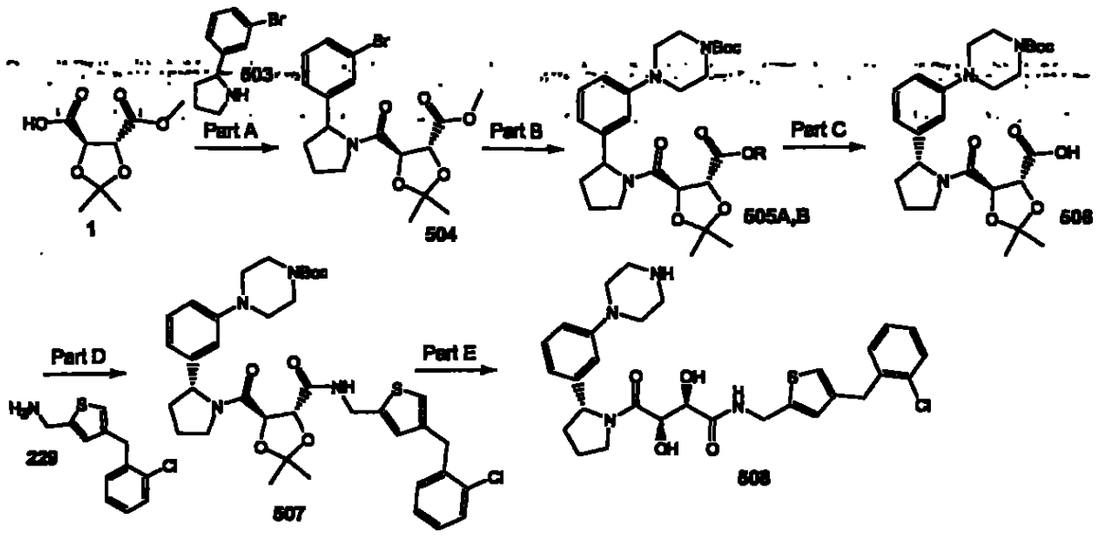
Compound #	Structure	Exact mass	MS m/z (M+H)
477		378.1	379.1
478		469.2	470.1
479		409.1	410.1
480		463.1	464.0
481		435.1	436.1
482		519.1	520.0
483		573.1	574.0
484		561.2	562.2
485		545.1	546.1

486		505.1	506.0
487		563.1	564.1
488		549.1	550.0
489		548.1	549.1
490		485.1	486.1
491		519.1	520.0
492		486.1	487.1
493		485.1	486.1
494		505.1	505.9
495		499.1	499.9

496		499.1	499.9
497		499.1	499.9
498		520.1	520.9
499		521.2	522.1
500		522.2	522.1
501		495.2	496.1
502		534.1	535.0

Example 11: 2-Phenyl pyrrolidines & derivatives

Example 11A:



Part A:

To 1 (925 mg, 4.53 mmol) in DMF (5 mL) was added 2-(3-bromophenyl)-pyrrolidine (503) (prepared by the method of Sorgi, K.L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E.; *J. Am. Chem. Soc.* 1990, *112*, 3567) (1.12 g, 4.95 mmol), DIEA (1.75 mL, 10.0 mmol) and HATU (1.88 g, 4.95 mmol). The reaction mixture was stirred overnight at room temperature. The DMF was removed in vacuo and the residue was partitioned between ethyl acetate (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate solution, 1.0 N HCl and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 10 - 20% EtOAc/DCM) afforded 504 (1.22 g, 65%). HPLC-MS t_R = 2.00 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{22}BrNO_5$ 411.1, observed LCMS m/z 412.2 (M+H).

Part B:

To piperazine-1-carboxylic acid tert-butyl ester (279 mg, 1.5 mmol), potassium phosphate (530 mg, 2.5 mmol), $Pd_2(dba)_3$ (23 mg, 0.025 mmol) and 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.1 mmol) under argon atmosphere was added the material from Part A (414 mg, 1.0 mmol). The reaction mixture was evacuated and flushed with argon. The mixture was heated overnight at 90 °C. The reaction mixture was diluted with ethyl acetate, filtered through

celite and concentrated to give a mixture of methyl ester **505A** and acid **505B** as an orange film (679 mg). The material was used without further purification. **505A**: HPLC-MS t_R = 2.08 & 2.14 min (ester, UV_{254} nm); mass calculated for formula $C_{27}H_{39}N_3O_7$ 517.3, observed LCMS m/z 518.0 (M+H). **505B**: HPLC-MS t_R = 1.83 & 1.91 min (acid, UV_{254} nm); mass calculated for formula $C_{26}H_{37}N_3O_7$ 503.3, observed LCMS m/z 504.1 (M+H)

Part C:

To the mixture of **505A** and **505B** (~1 mmol) in THF (4 mL) and water (1 mL) was added 1.0 M lithium hydroxide (1.2 mL, 1.2 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with water (10 mL) and the THF was removed in vacuo. The aqueous layer was washed with diethyl ether (3 x 10 mL), made acidic with 1.0 N HCl and extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate layers were dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded the desired isomer **506** (107 mg, 96% purity). HPLC-MS t_R = 1.83 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{37}N_3O_7$ 503.3, observed LCMS m/z 504.1 (M+H).

Part D:

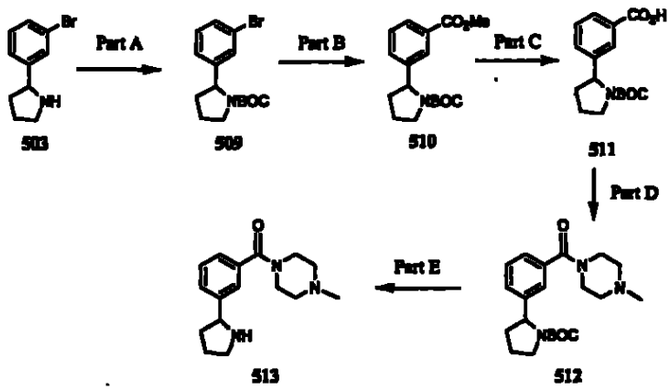
To **506** (107 mg, 0.21 mmol) in DMF (5 mL) was added **229** (55 mg, 0.23 mmol), DIEA (80 µL, 0.46 mmol) and HATU (87 mg, 0.23 mmol). The reaction mixture was stirred overnight at room temperature. The DMF was removed in vacuo and the residue was partitioned between ethyl acetate and water. The layers were separated. The organic layer was washed with 0.1 N NaOH, 0.1 N HCl, and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% EtOAc/hexane) afforded **507** (98 mg, 64%). HPLC-MS t_R = 2.49 min ($UV_{254\ nm}$); mass calculated for formula $C_{38}H_{47}ClN_4O_6S$ 722.2, observed LCMS m/z 723.1 (M+H).

Part E:

To **507** (98 mg, 0.14 mmol) was added 80:20 TFA:water (4 mL) and the mixture was stirred for 4 hours at room temperature. The reaction was quenched with 1:1 acetonitrile:water (10 mL) and concentrated. The residue

was dissolved in ethyl acetate and washed with sodium bicarbonate solution. To the aqueous layer was added sodium chloride and it was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate and concentrated. The residue was dissolve in acetonitrile (2 mL) and 1.0 N HCl (0.3 mL) and concentrated. The material was lyophilized to afford **508** as the HCl salt as a white powder (75 mg, 86%). HPLC-MS t_R = 1.27 min ($UV_{254\ nm}$); mass calculated for formula $C_{30}H_{35}ClN_4O_4S$ 582.2, observed LCMS m/z 583.2 (M+H).

Example 11B



Part A

To a solution of compound **503** (5.0 g, 22.1 mmol) in dry CH_2Cl_2 (80 mL) was added di-tert-butyl dicarbonate (5.55 g, 25.4 mmol). The solution was stirred at room temperature for 2 hours. The solvent was removed by rotary evaporator. The product was isolated by silica gel chromatography (Hexane/EtOAc 5:1 to 3:1) to give compound **509** (5.7 g, 79%).

Part B

To a two neck flask was charged with compound **509** (1.0 g, 3.06 mmol), MeOH (8 mL), triethylamine (6 mL), DMF (6 mL), and $Pd(PPh_3)_2Cl_2$. A condenser with a three-way-valve on the top was attached to the flask. A balloon and a carbon monoxide tank were attached to the three-way-valve. The balloon was filled with CO and flashed the system twice. Then the balloon was filled with CO and was connected to the flask system. The flask

was heated in a 80 °C oil bath for 36 hours. After cooling down to room temperature, water (50 mL) and EtOAc (100 mL) were added. The organic phase was separated, washed with water (50 mL) twice and brine; dried over Na_2SO_4, concentrated with rotary evaporator, the product was isolated with silica gel chromatography (Hexane/EtOAc 10:1 to 5:1) to give compound **510** (610 mg, 65%).

Part C

Compound **510** (384 mg, 1.26 mmol) was dissolved in dioxane/water (3:1, 4 mL) and LiOH (100 mg. 2.38 mmol) was added. The solution was stirred at room temperature for four hours. Saturated NH_4Cl solution (20 mL) was added. The aqueous phase was extracted with EtOAc (25 mL) twice. The organic phases were combined, washed with brine, dried over Na_2SO_4, concentrated by rotary evaporator, and dried under vacuum to give compound **511** (368 mg, 100%).

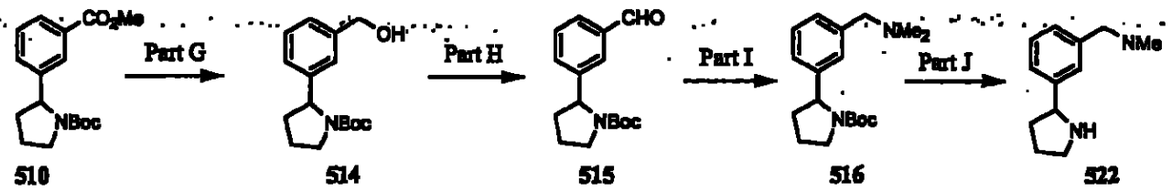
Part E

Compound **511** (76 mg, 0.26 mmol) was dissolved in dry CH_2Cl_2 (1.5 mL). N-methyl piperazine (0.035 mL, 0.31 mmol), EDCI (75 mg, 0.39 mmol), HOBT (43 mg, 0.31 mmol), and NMM (0.086 mL, 0.78 mmol) were added. The solution was stirred at room temperature for 16 hours. Saturated $NaHCO_3$ solution (5 mL) and CH_2Cl_2 (5 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (5 mL) twice. The organic phases were combined, dried over Na_2SO_4, concentrated by rotary evaporator. The product was isolated by silica gel chromatography to give compound **512** (90 mg, 92%).

Part F

Compound **512** (90 mg, 0.24 mmol) was dissolved in MeOH (1 mL) and HCl (4M in dioxane, 0.25 mL, 1 mmol) was added. The solution was stirred at room temperature for overnight. The solvent was removed by rotary evaporator to give compound **513** (83 mg, 100%).

Example 11C:



510 514 515 516 522

Part G:

Compound **510** (3.68 g, 12.0 mmol) was dissolved in dry THF (60 mL), and lithium borohydride (0.78 g, 36.2 mmol) was added. The solution was heated at reflux for 16 h then cooled to room temperature. MeOH (4 mL) was added, and the solvent was removed by rotary evaporator. Water (75 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (75 mL) three times. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel chromatography (eluant: 5% MeOH-CH_2Cl_2 to 10% MeOH-CH_2Cl_2) to give 3.28 g (98%) of compound **514**. MS (m/e for M+1): 278.

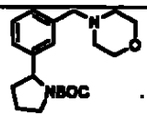
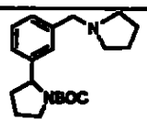
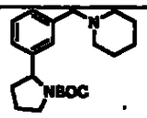
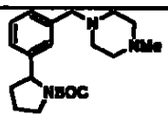
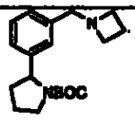
Part H:

Oxalyl chloride (1.87 g, 1.3 mL, 14.7 mmol) was dissolved in dry CH_2Cl_2 (35 mL) and cooled to -78° C under a nitrogen atmosphere. DMSO (2.30 g, 2.1 mL, 29.5 mmol) dissolved in dry CH_2Cl_2 (5 mL) was added dropwise via addition funnel. The solution was stirred at -78° C for 15 mins then compound **514** (3.27 g, 11.8 mmol) dissolved in CH_2Cl_2 (15 mL) was added. The reaction mixture was stirred at -78° C for 60 mins then triethylamine (3.58 g, 4.9 mL, 35.4 mmol) was added. The reaction mixture was stirred at -78° C for 15 mins then warmed to 0° C. Water (75 mL) was added, and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (75 mL) two times. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel chromatography (eluant: 5% EtOAc-CH_2Cl_2 to 10% EtOAc-CH_2Cl_2) to give 2.94 g (90%) of the product **515**. MS (m/e for M+1): 276.

Part I:

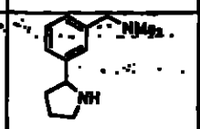
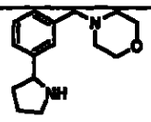
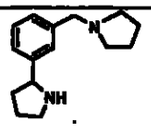
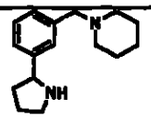
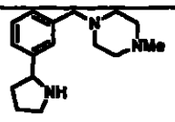
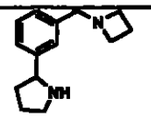
Compound **515** (0.50 g, 1.82 mmol) was dissolved in CH_2Cl_2 (10 mL), and 3A sieves (0.50 g), dimethylamine in THF (2 M, 1.8 mL, 3.64 mmol), glacial acetic acid (0.109 g, 1.82 mmol), and sodium triacetoxyborohydride (0.579 g, 2.73 mmol) were added. The reaction mixture was stirred at room temperature for 24 h. 1 N NaOH (25 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (25 mL) four times. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel chromatography (eluant: 5% MeOH-CH_2Cl_2 to 15% MeOH-CH_2Cl_2) to give 0.396 g (72%) of the product **516**. MS (m/e for M+1): 305.

The following intermediates were also prepared.

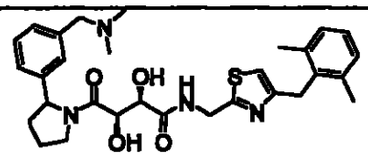
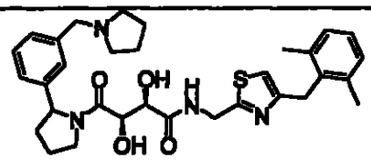
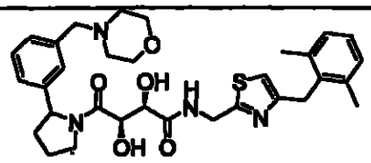
Compound #	Intermediate	MS (m/e for M+1)
517		347
518		331
519		345
520		360
521		317

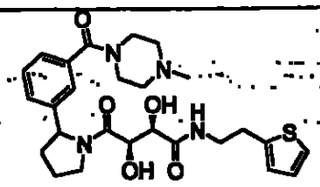
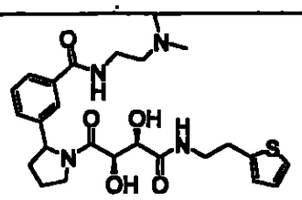
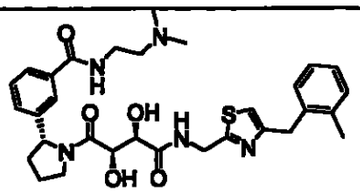
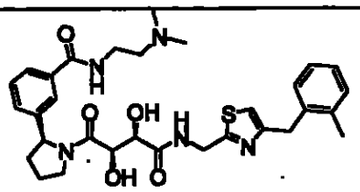
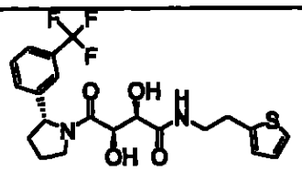
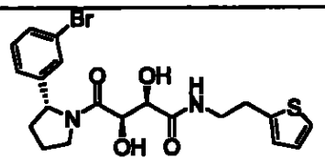
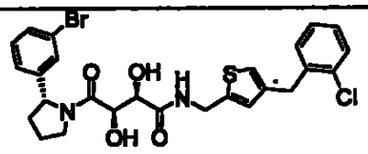
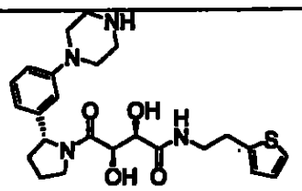
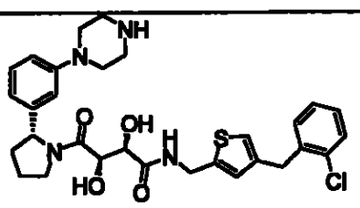
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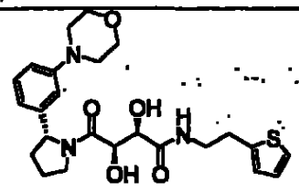
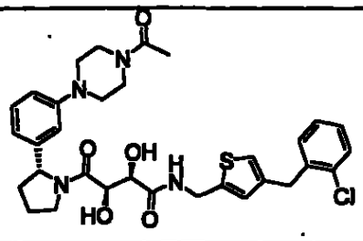
The following compounds were prepared using procedure described in Example 11B Part F.

Compound #	Intermediate	MS (m/e for M+1)
522		205
523		247
524		231
525		245
526		260
527		217

The following compounds were prepared using the procedures described in Example 11.

Compound #	Structure	Exact mass	MS m/e (M+H)
416		550.3	551.3
417		576.3	577.3
418		592.3	593.3

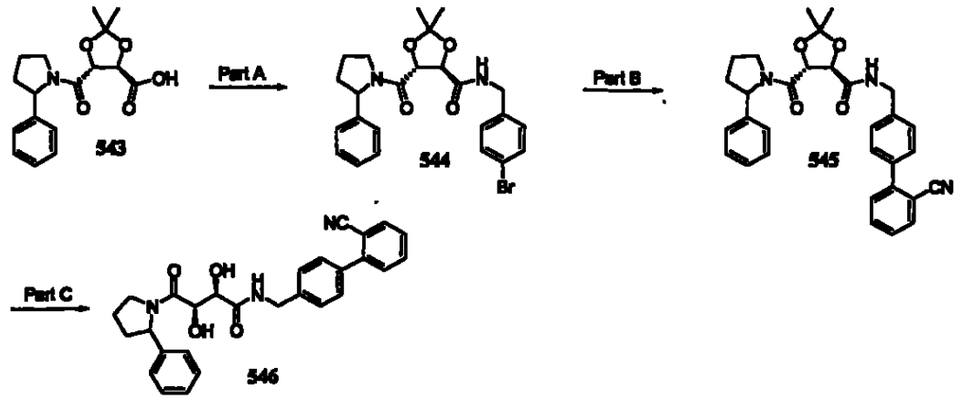
529		514.2	515.0
530		502.2	503.1
531		593.3	594.1
532		593.3	594.1
536		456.1	457.1
537		466.1	467.0
538		576.1	577.0
539		472.2	473.2
540		582.2	583.2

541		473.2	474.2
542		624.2	625.1

Example 12: Suzuki Aryl-Aryl couplings

Example 12A:

Scheme 1 Biaryl Preparation (preferred method)



Compound **543** was prepared by procedures described in Example 1.

Part A:

To a solution of **543** (1.01 g, 3.17 mmol) and 4-bromobenzyl amine (0.71 g, 3.83 mmol) in CH_2Cl_2 (10 mL) cooled to 0 °C was added DIEA (1.10 mL, 6.31 mmol) followed by PyBrOP (1.10 g, 3.43 mmol). The reaction was warmed to room temperature and stirred for 16 hours. The liquid was concentrated, and the thick oil was taken up in EtOAc. The organic layer was washed with 0.5 N $KHSO_4$ (1x), sat. $NaHCO_3$ (1x), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (eluting 0% to 100%

EtOAc/hexanes) to furnish **544** (1.27 g, 2.61 mmol, 82% yield) as a tan oil. MS m/e: 487.1 (M+H).

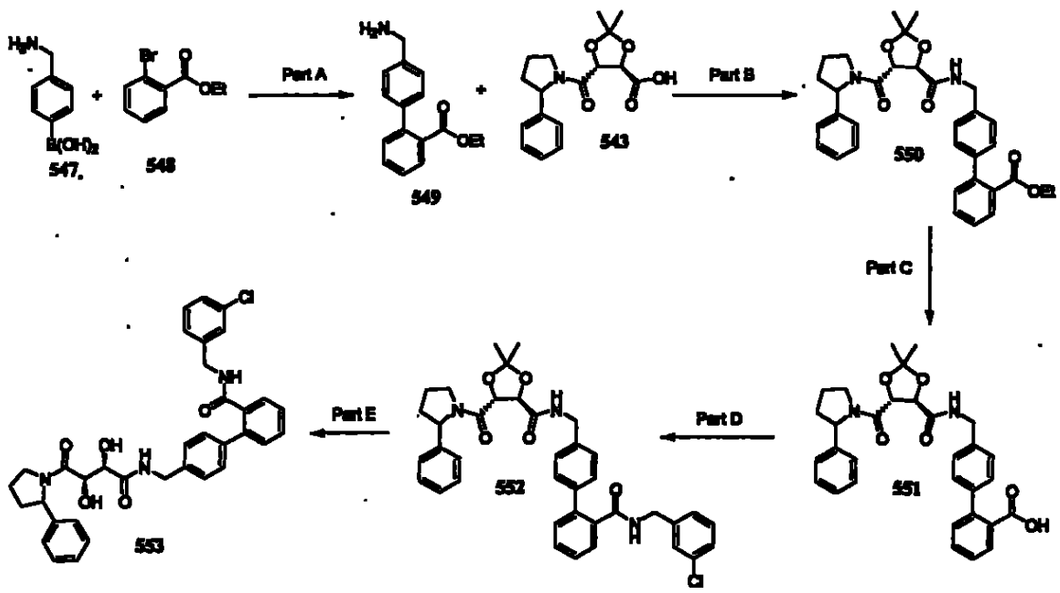
Part B:

A solution of **544** (0.105 g, 0.215 mmol), 2-cyanophenyl boronic acid (0.032 g, 0.215 mmol), and $Pd(dppf)Cl_2$ (0.016 g, 0.021 mmol) in CH_3CN (1 mL) and 1 N K_2CO_3 (1 mL) was heated in a SmithCreator microwave (2-5 mL vessel, 150 °C for 10 minutes). The mixture was concentrated and the residue was purified by silica gel chromatography (eluting 0% to 100 % EtOAc/hexanes) to furnish **545** (0.062 g, 0.12 mmol, 56% yield) as a tan oil. MS m/e: 510.1 (M+H).

Part C:

A solution of **545** (0.049 g, 0.096 mmol) in a 70% TFA/20% CH_2Cl_2/10% H_2O mixture was stirred at room temperature for 2 hours. The mixture was concentrated, and the residue was purified by reverse phase HPLC (eluting 5:95 to 95:5 CH_3CN/H_2O (0.1% HCO_2H)) to provide **546** (0.023 g, 0.049 mmol, 51% yield) as a white solid. MS m/e: 470.1 (M+H).

Example 12B:



Part A:

A solution of ethyl 2-bromobenzoate (548) (0.25 g, 1.1 mmol), (4-aminomethylphenyl)boronic acid (547) (0.20 g, 1.1 mmol), and $Pd(dppf)Cl_2$ (0.040 g, 0.055 mmol) in CH_3CN (1 mL) and 1 N K_2CO_3 (1 mL) was heated in a SmithCreator microwave (2-5 mL vessel, 100 °C for 5 minutes). The reaction was diluted with H_2O and EtOAc. The organic layer was removed, and the aqueous phase was extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (eluting 0% to 20% CH_2Cl_2/MeOH) to furnish 549 (0.14 g, 0.55 mmol, 50 % yield) as a brown oil. MS m/e: 256.1 (M+H).

Part B:

To a solution of 549 (0.21 g, 0.82 mmol) and 543 (0.19 g, 0.59 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C was added DIEA followed by PyBrOP. The reaction was stirred for 20 hours gradually warming to room temperature. The mixture was concentrated, and the brown oil was taken up in EtOAc. The organic phase was washed with 0.5 N $KHSO_4$ (1x), sat. $NaHCO_3$ (1x), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (eluting 0% to 100% EtOAc/hexanes) to furnish 550 (0.29 g, 0.51 mmol, 87% yield) as a brown oil. MS m/e: 557.1 (M+H).

Part C:

To a solution of 550 (0.26 g, 0.47 mmol) in a THF (2 mL)/MeOH (2 mL)/H_2O (1 mL) mixture was added $LiOH \cdot H_2O$ (0.052 g, 1.24 mmol) in one solid portion. The reaction was stirred overnight and then acidified to pH ~ 3 with 1N HCl. After dilution with EtOAc, the organic layer was removed, and the aqueous phase was extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by reverse phase HPLC (eluting 10:90 to 100:0 CH_3CN/H_2O (0.1% HCO_2H) to furnish 551 (0.22 g, 0.38 mmol, 88 % yield). MS m/e: 529.1 (M+H).

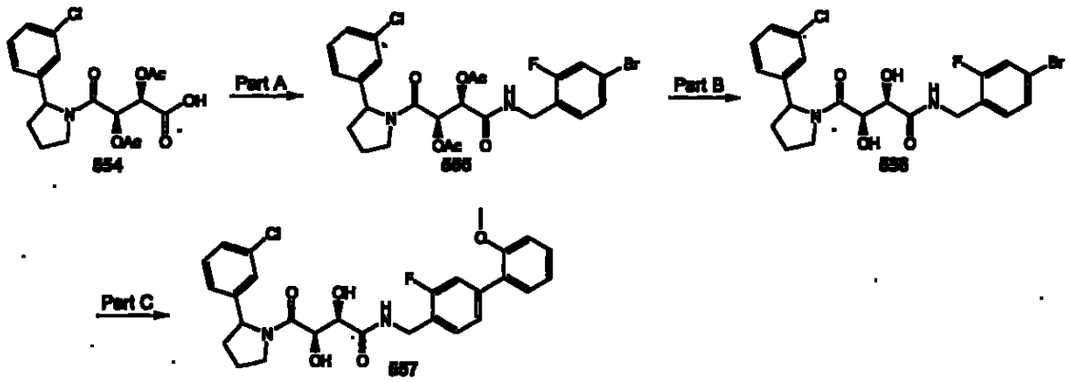
Part D:

To a solution of **551** (55 mg, 0.104 mmol) in CH_2Cl_2 (1 mL) was added polystyrene-bound HOBt (109 mg, 0.095 mmol), DIC (0.067 mL, 0.427 mmol), and DMAP (7 mg, 0.057 mmol) and was shaken overnight. The mixture was filtered, then washed with DMF (3 x 3 mL), CH_2Cl_2 (3 x 3 mL), DMF (3 x 3 mL), and THF (3 x 3 mL). The resin was dried under vacuum overnight. To the dried resin-bound acid (82 mg, 0.034 mmol) was added 3-chlorobenzylamine (8.33 μL, 0.068 mmol) in CH_2Cl_2 (1 mL) and the mixture was shaken overnight. To the mixture was added polystyrene-bound isocyanate resin (70 mg, 0.102 mmol) and shaken for 5 hours. Filter the desired product and wash the filtrate with CH_2Cl_2 (3 x 3 mL) and THF (3 x 3 mL). Concentrate the organic portions *in vacuo* to afford **552** (14.6 mg, 0.022 mmol, 66 % yield). MS m/e: 652.2 (M+H).

Part E:

To **552** (14.6mg, 0.022 mmol) was added a 2 mL of a mixture of TFA/CH_2Cl_2/H_2O (7/2/1) and stirred at room temperature for 2 h. The mixture was concentrated *in vacuo*. The mixture was purified via reverse-phase HPLC to furnish **553** (3.7 mg, 0.006 mmol, 27 % yield). MS m/e: 612.1 (M+H).

Example 12C:



Compound **554** was prepared by the procedure desribed in Example 4 Part C. HPLC-MS t_R = 1.39 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{16}ClNO_5$ 397.1, observed LCMS m/z 398.1 (M+H).

Part A:

To **554** (355 mg, 0.89 mmol) in DMF (5 mL) was added 2-fluoro-4-bromobenzylamine hydrochloride (257 mg, 1.07 mmol), DIEA (530 uL, 3.03 mmol) and HATU (407 mg, 1.07 mmol). The reaction was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with 0.1 N NaOH, 0.1 N HCl, and brine; dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 80% ethyl acetate/hexanes) afforded **555** as a foam (320 mg, 62%). HPLC-MS t_R = 2.03 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{25}BrClFN_2O_6$ 582.1, observed LCMS m/z 583.0 (M+H).

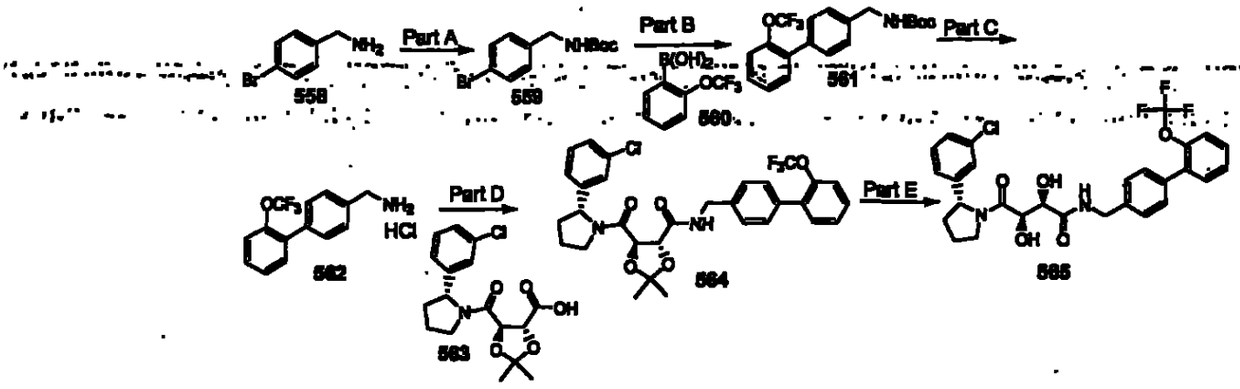
Part B:

To **555** (320 mg, 0.55 mmol) in MeOH (5 mL) was added anhydrous hydrazine (28 µL, 0.88 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and lypholized to afford **556** as a white powder (275 mg, 100%). HPLC-MS t_R = 1.81 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{21}BrClFN_2O_4$ 498.0, observed LCMS m/z 499.0 (M+H).

Part C:

Compound **556** (46 mg, 0.092 mmol) in dioxane (1 mL) was added to a solution of 2-methoxyphenyl boronic acid (22 mg, 0.14 mmol), potassium phosphate (42 mg, 0.2 mmol), and $PdCl_2$(dppf) (4 mg, 0.005 mmol) under argon atmosphere. The reaction mixture was heated to 80 °C overnight. After cooling the mixture was filtered through celite and the pad was rinsed with ethyl acetate. The filtrate was concentrated. Purification by reverse phase prep-LC afforded **557** as a white solid (26 mg) after lypholization. HPLC-MS t_R = 1.97 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{28}ClFN_2O_5$ 526.2, observed LCMS m/z 527.0 (M+H).

Example 12D:



Part A:

A mixture of 4-bromo-benzylamine hydrochloride (558) (1.0 g, 4.5 mmol), di-*tert*-butyl dicarbonate (1.48 g, 6.8 mmol) and DIEA (2.4 mL, 13.8 mmol) in chloroform (40 mL) was stirred overnight at room temperature. The reaction mixture was washed with 1.0 N HCl, water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% ethyl acetate/hexane) afforded a mixture of 559 (1.17 g, 91%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, 2H, J = 8.8 Hz), 7.15 (d, 2H, J = 8.8 Hz), 4.85 (bs, 1H), 4.27 (d, 2H, J = 5.7 Hz), 1.48 (s, 9H).

Part B:

A mixture of 559 (100 mg, 0.35 mmol), 560 (107 mg, 0.52 mmol) potassium phosphate (223 mg, 1.05 mmol) and $PdCl_2$(dppf) (14 mg, 0.018 mmol) in dioxane (5 mL) was under argon atmosphere was heated to 80 °C overnight. The reaction mixture was cooled and filtered through celite. The celite pad was washed with ethyl acetate. The filtrate was washed with saturated sodium bicarbonate, water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% ethyl acetate/hexane) afforded slightly impure 561 (146 mg). HPLC-MS t_R = 2.35 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{20}F_3NO_3$ 367.1, observed LCMS m/z 390.1 (M+Na).

Part C:

Compound 561 (129 mg, 0.35 mmol) in 3:1 DCM:TFA (4 mL) was stirred for 1 hour. The residue was dissolved in DCM (5 mL) and concentrated. The residue was dissolved in diethyl ether (20 mL) and treated with 1.0 M HCl in

diethyl ether (2 mL). The resulting white solid was collected by filtration and washed with diethyl ether to afford **562** (90 mg, 85% 2 steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.3 (bs, 3H), 7.50 (m, 8H), 4.09 (s, 2H).

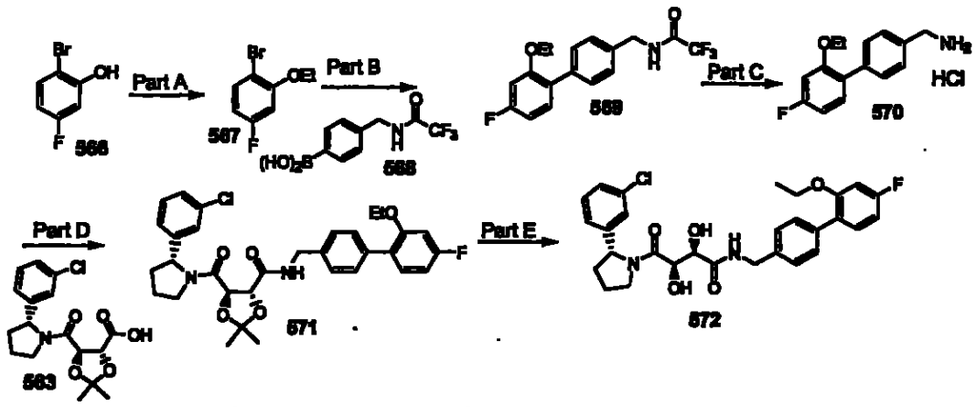
Part D:

Compound **563** was prepared using procedures similar to those described in Example 11A. Compound **564** was prepared from **562** and **563** using procedures similar to those described in Example 1 Part A. HPLC-MS t_R = 2.49 min ($UV_{254\ nm}$); mass calculated for formula $C_{31}H_{30}ClF_3N_2O_5$ 602.2, observed LCMS m/z 603.2 (M+H).

Part E:

Compound **565** was prepared using the procedures described in Example 1 Part B. HPLC-MS t_R = 2.16 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{26}ClF_3N_2O_5$ 562.2, observed LCMS m/z 563.0 (M+H).

Example 12E:



Part A:

To 2-bromo-5-fluoro-phenol (**566**) (2.28 g, 11.94 mmol) in DMF (15 mL) was added iodoethane (1.16 mL, 14.32 mmol) and cesium carbonate (4.28 g, 13.13 mmol). The reaction mixture was stirred for 72 hours. The mixture was filtered and the DMF was removed in vacuo. The residue was partitioned in ethyl acetate and water. The layers were separated and the organic layer was washed with water and brine, dried over sodium sulfate and concentrated to afford **567** (1.76 g, 67%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.46 (dd, 1H, J = 6.3, 8.8 Hz), 6.62 (dd, 1H, J = 2.7, 10.5 Hz), 6.57 (m, 1H, J = 2.7), 4.08 (q, 2H, J = 6.9 Hz), 1.50 (t, 3H, J = 7.0 Hz).

Part B:

Compound **569** (607 mg, 58%) was prepared from **567** and **568** (prepared by the procedures of Maku, S. et. al. (*J. Comb. Chem.* 2003, *5*, 379)) using the procedures described in Example 12D Part B. HPLC-MS t_R = 2.13 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{15}F_4NO_2$ 341.1, observed LCMS m/z 342.1 (M+H).

Part C:

To **569** (607 mg, 1.78 mmol) in methanol (6 mL) was added 10% potassium carbonate in 2:1 methanol:water (20 ml). To obtain a clear solution additional water (5 mL) was added. The reaction mixture was stirred overnight at room temperature. The methanol was removed in vacuo. The residue was portioned between water and ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The residue was dissolved in diethyl ether (20 mL) and treated with 1.0 M HCl in diethyl ether (5 mL). The resulting white solid was collected by filtration and washed with diethyl ether to afford **570** (377 mg, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (bs, 3H), 7.49 (m, 4H), 7.29 (dd, 1H, J = 6.9, 8.3 Hz), 7.00 (dd, 1h J = 2.5, 11.4 Hz), 6.83 (dt, 1H, J = 2.8, 8.6, 10.8Hz) 4.05 (m, 4H), 1.27 (t, 3H, J = 6.5 Hz).

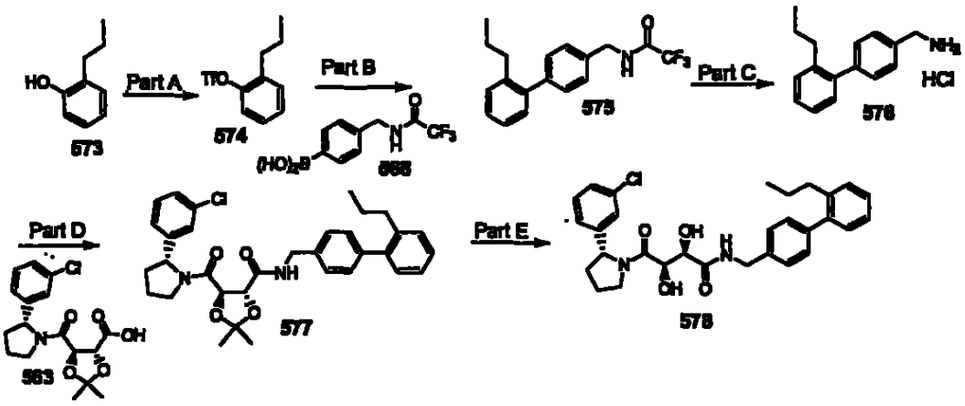
Part D:

Compound **571** was prepared using procedures described in Example 12E Part D. Purification by column chromatography (SiO_2, 20% ethyl acetate/hexane) afforded **571** (104 mg, 95%). HPLC-MS t_R = 2.40 min ($UV_{254\ nm}$); mass calculated for formula C32H34ClFN2O5 580.2, observed LCMS m/z 581.2 (M+H).

Part E:

Compound **572** was prepared using the procedures described in Example 12D Part E. HPLC-MS t_R = 2.06 min ($UV_{254\ nm}$); mass calculated for formula $C_{29}H_{30}ClFN_2O_5$ 540.2, observed LCMS m/z 541.2 (M+H).

Example 12F:



Part A:

To a mixture of 2-propyl phenol (**573**) (0.5 mL, 3.63 mmol) and DIEA (0.950 mL, 5.45 mmol) in DCM (20 mL) at 0 °C was added triflic anhydride (0.734 mL, 4.36 mmol) in DCM (10 mL) via an addition funnel. The reaction mixture was stirred for 45 minutes. The mixture was poured into water. The layers were separated and the organic layer was washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 5% ethyl acetate/hexane) afforded **574** (916 mg, 100%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.26 (m, 2H), 2.70 (m, 2H), 1.68 (m, 2H), 1.00 (t, 3H, J = 7.3 Hz).

Part B:

Compound **575** (288 mg, 89%) was prepared using the procedures described in Example 12D Part B and a reaction temperature of 100 °C. HPLC-MS t_R = 2.30 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{18}F_3NO$ 321.1, observed LCMS m/z 322.2 (M+H).

Part C:

Compound **576** (203 mg, 86%) was prepared using the procedure described in Example 12E Part C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (bs, 3H), 7.52 (d, 2H, J = 8.0 Hz), 7.32 (d, 2H, J = 8.1 Hz), 7.31 (m, 2H), 7.22 (m, 1H), 7.10 (d, 1H, J = 7.1 Hz), 4.08 (s, 2H,) 2.54 (m, 2H), 1.44 (m, 2H), 0.75 (t, 3H, J = 7.7 Hz).

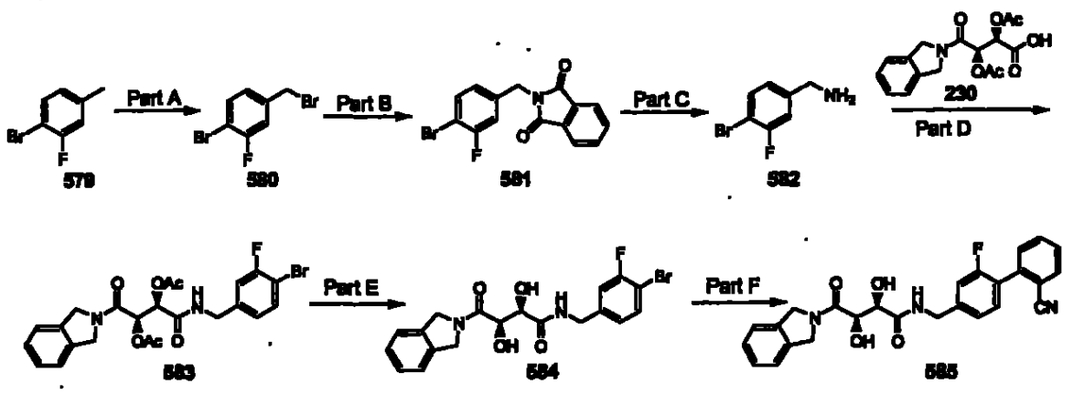
Part D:

Compound **577** (62 mg, 92%) was prepared according to the procedure described in Example 12D Part D. HPLC-MS t_R = 2.55 min ($UV_{254\ nm}$); mass calculated for formula $C_{33}H_{37}ClN_2O_4$ 560.2, observed LCMS m/z 561.2 (M+H).

Part E:

Compound **578** (53 mg, 93%) was prepared according to the procedure described in Example 12D Part E. . HPLC-MS t_R = 2.21 min ($UV_{254\ nm}$); mass calculated for formula $C_{30}H_{33}ClN_2O_4$ 520.2, observed LCMS m/z 521.2 (M+H).

Example 12G:



Part A:

A mixture of 4-bromo-3-fluoro-toluene (**579**) (2.0 mL, 15.8 mmol), N-bromosuccinimide (3.38 g; 19.0 mmol) and benzoylperoxide (48 mg, 0.2 mmol) in carbon tetrachloride (50 mL) was heated to reflux under a nitrogen atmosphere for 16 hours. The reaction mixture was cooled and filtered. The filtrate was washed with water (2x), saturated sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated to afford a mixture of **580** and dibromonated product (4.02 g). The material was used without

further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, 1H, J = 6.6, 7.6 Hz), 7.17 (dd, 1H, J = 2.0, 8.9 Hz), 7.11 (dd, 1H, J = 2.0, 8.2 Hz), 4.42 (s, 2H).

Part B:

A mixture of **580** (4.02 g, 15.0 mmol), phthalimide (2.65 g, 18 mmol) and cesium carbonate (5.38 g, 16.5 mmol) in DMF (30 mL) was stirred for 72 hours. The reaction mixture was poured into water (100 mL) and extracted with ethyl acetate. The combined organic layers were washed with water (3X) and brine, dried over sodium sulfate and concentrated. Recrystallization from 30% ethyl acetate/hexanes afforded slightly impure **581** (3.28 g) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.74 (m, 2H), 7.49 (dd, 1H, J = 7.3, 8.4 Hz), 7.20 (dd, 1H, J = 1.9, 9.3 Hz), 7.06 (dd, 1H, J = 2.0, 7.9 Hz), 4.80 (s, 2H).

Part C:

A mixture of **581** (1.00 g, 3.0 mmol) and hydrazine monohydrate (580 uL, 12.0 mmol) in ethanol (25 mL) was heated to reflux for 1 hour. The reaction mixture was diluted with ethyl acetate and filtered. The precipitate was washed with ethyl acetate. The filtrate was concentrated and the residue was dissolved in water and ethyl acetate. The layers were separated. The organic layer was washed with saturated sodium bicarbonate solution, water and brine, dried over sodium sulfate and concentrated to afford **582** (375 mg) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, 1H, J = 8.5 Hz), 7.12 (dd, 1H, J = 2.2, 9.5 Hz), 6.99 (dd, 1H, J = 1.6, 8.2 Hz), 3.86 (s, 2H).

Part D:

Compound **583** was prepared using procedures similar to those described in Example 12C Part A. HPLC-MS t_R = 1.82 min ($UV_{254\ nm}$); mass calculated for formula $C_{23}H_{22}BrFN_2O_6$ 520.0, observed LCMS m/z 521.0 (M+H).

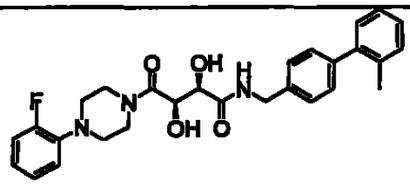
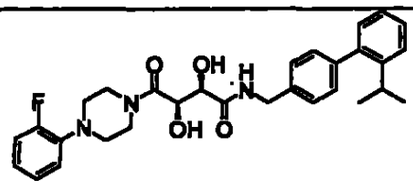
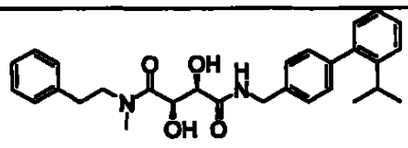
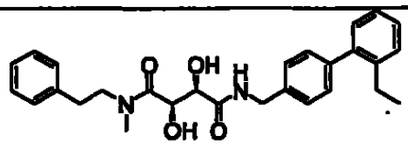
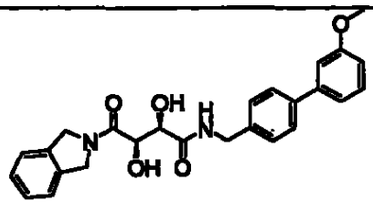
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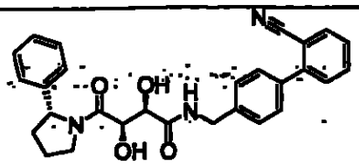
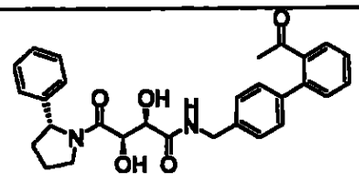
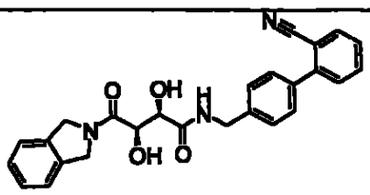
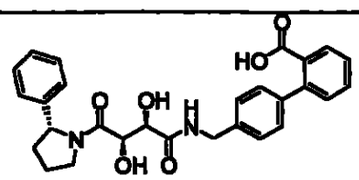
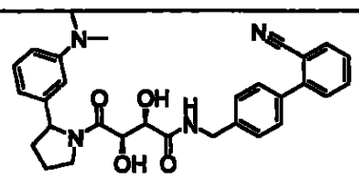
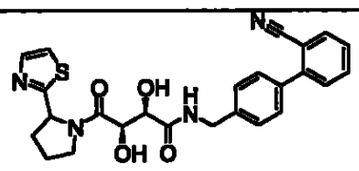
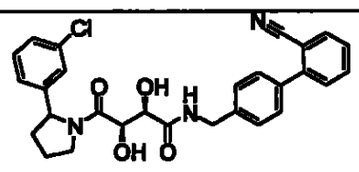
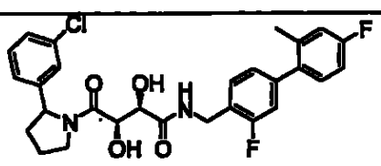
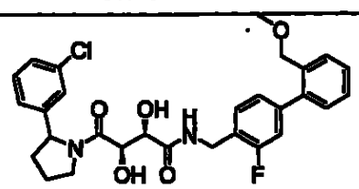
Compound **584** was prepared using the procedures described in Example 12C Part B. HPLC-MS t_R = 1.81 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{18}BrFN_2O_4$ 436.0, observed LCMS m/z 437.0 (M+H).

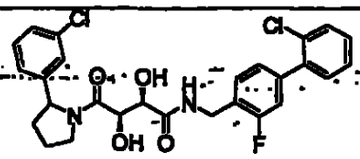
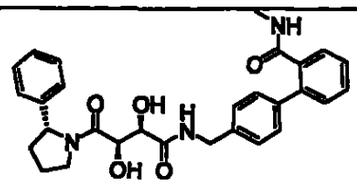
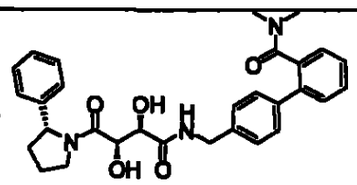
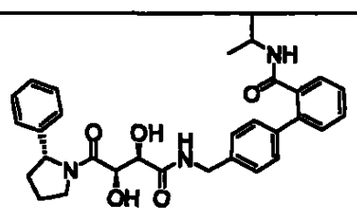
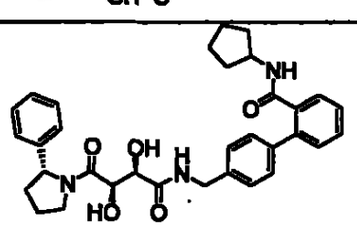
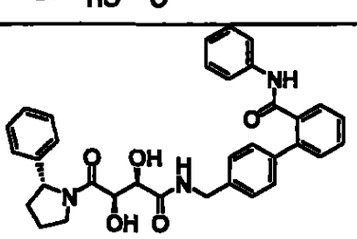
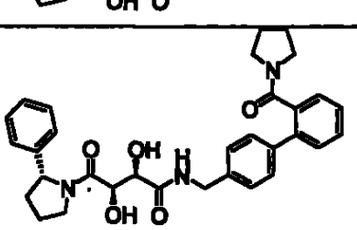
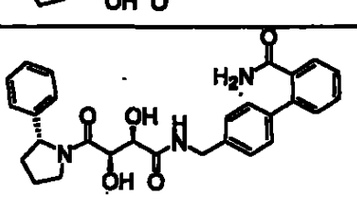
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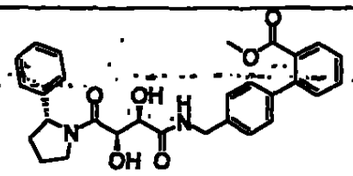
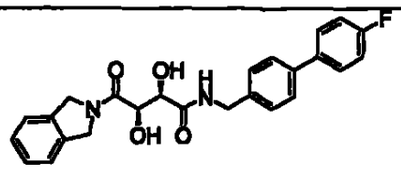
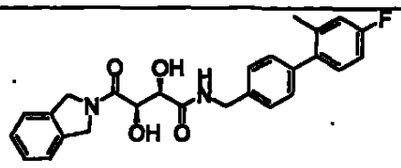
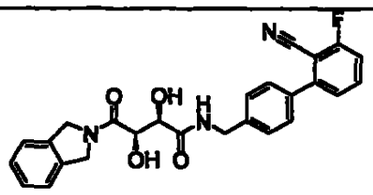
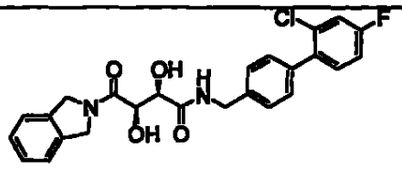
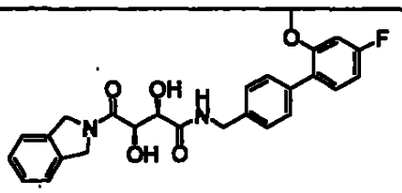
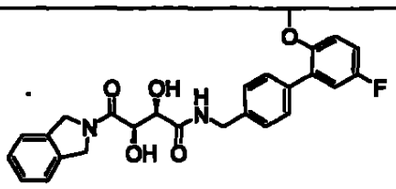
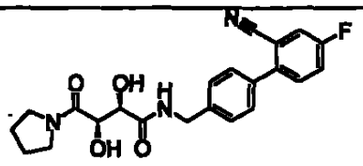
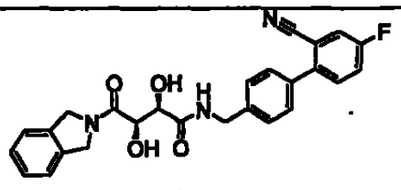
Compound **585** was prepared using procedures similar to those described in Example 12C Part C. HPLC-MS t_R = 4.12 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{28}H_{22}FN_3O_4$ 459.2, observed LCMS m/z 460.1 (M+H).

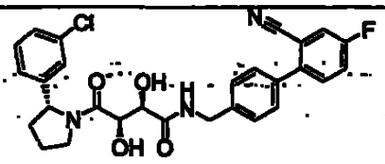
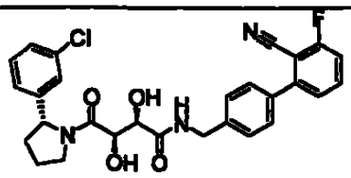
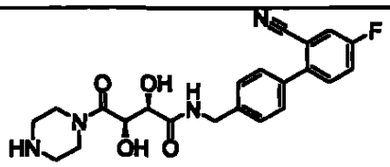
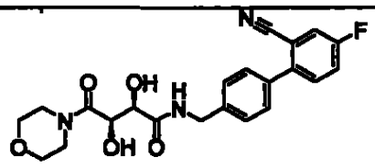
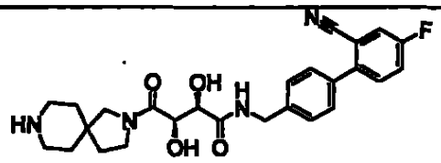
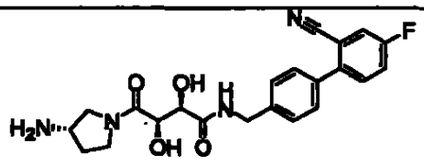
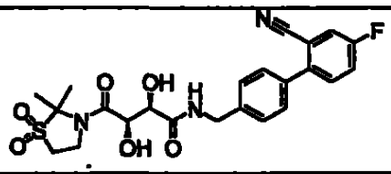
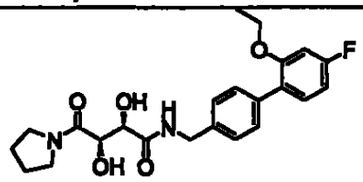
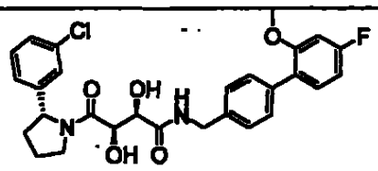
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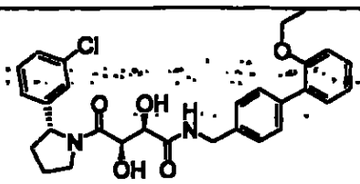
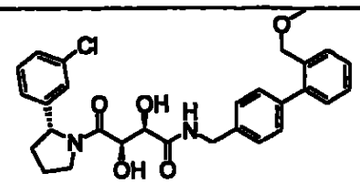
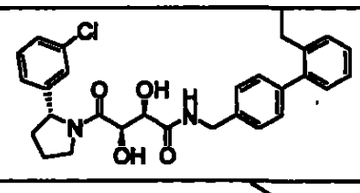
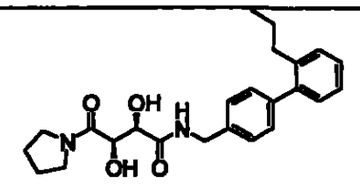
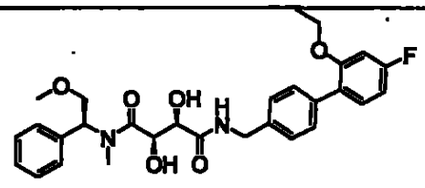
Compound #	Structure	Exact mass	MS m/e (M+H)
586		491.2	492.2
587		519.3	520.3
588		474.3	475.3
589		460.2	461.2
590		446.2	447.2

591		469.2	470.1
592		486.2	487.1
593		441.2	442.1
594		488.2	489.1
595		512.2	513.3
596		476.2	477.2
597		503.2	504.2
598		528.2	529.2
599		540.2	541.2

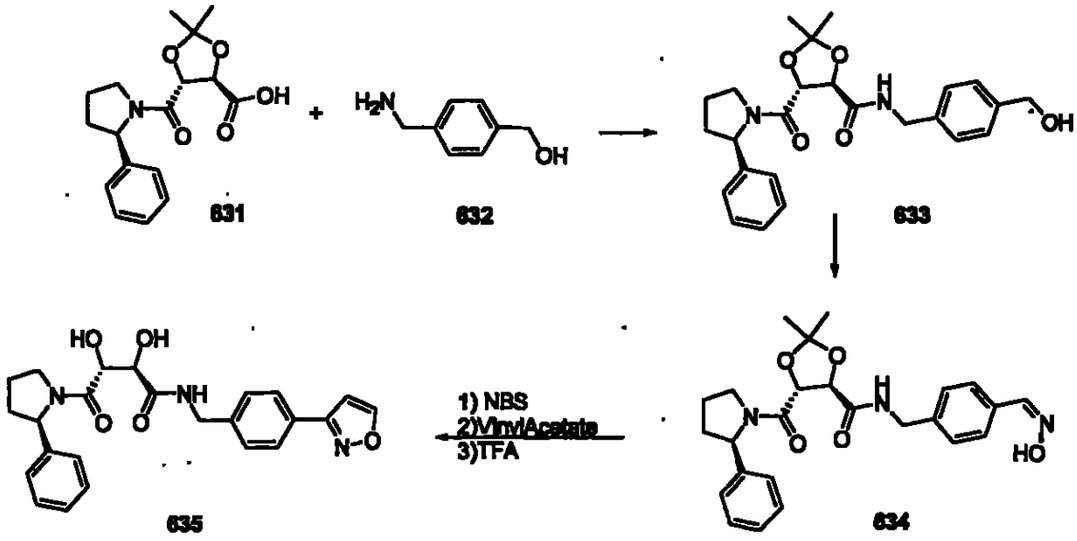
600		530.1	531.0
601		501.2	502.3
602		515.2	516.3
603		529.3	530.3
604		555.3	556.3
605		563.2	564.3
606		541.3	542.3
607		487.2	488.1

608		502.2	503.1
609		434.2	435.2
610		448.2	449.2
611		459.2	460.1
612		468.1	469.1
613		464.2	465.1
614		464.2	465.1
615		411.2	412.1
616		459.2	460.1

617		521.2	522.1
618		521.2	522.1
619		426.2	427.1
620		427.2	428.1
621		480.2	481.2
622		426.2	427.1
623		489.1	490.1
624		430.2	431.2
625		526.2	527.2

626		522.2	523.2
627		522.2	523.2
628		506.2	507.2
629		410.2	411.2
630		524.2	525.2

Example 13



Compound **631** was prepared by the procedures described in Example 11A.

Part A.

To a solution of **631** (0.46 g) and **632** (1.2 eq) in 10 ml DMF at 0C were added HATU (1.5 eq) and HOBt (1.5 eq). The reaction was stirred at r.t. overnight before the solvent was removed in vacuo and residue chromatographed using Ethyl Acetate in Hexane (0 - 100 %) to give 0.46 gram of desired product **633**.

Part B.

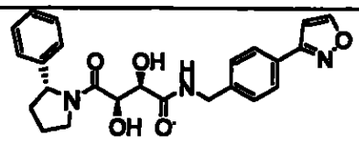
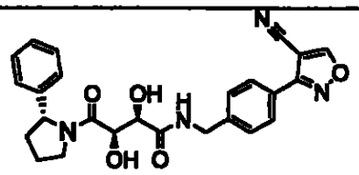
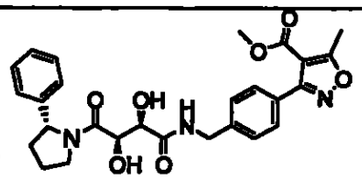
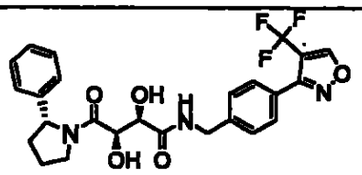
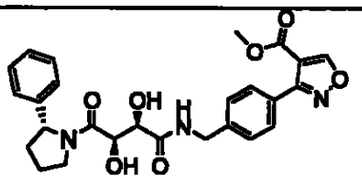
To a solution of 0.46 g of **633** in 10 ml of DCM was added Dess-Martin Reagent (1.1 eq) and the reaction was stirred at r.t. for 30 min before it was treated with sat. aqueous solution of sodium bicarbonate and sodium thiosulfate 7:1 (w/w). The aqueous layer was extracted with DCM (2X) and the combined organic layers was dried over anhydrous sodium sulfate. After removal of solvent, the crude reaction product was dissolved in 2 ml pyridine. To the solution was added 1.5 eq of hydroxylamine hydrochloride and the solution was heated to reflux for 30 min before the solvent was removed in vacuo and residue chromatographed using Ethyl Acetate in Hexane (0 - 100 %) to give 0.4 gram of product **634**.

Part C

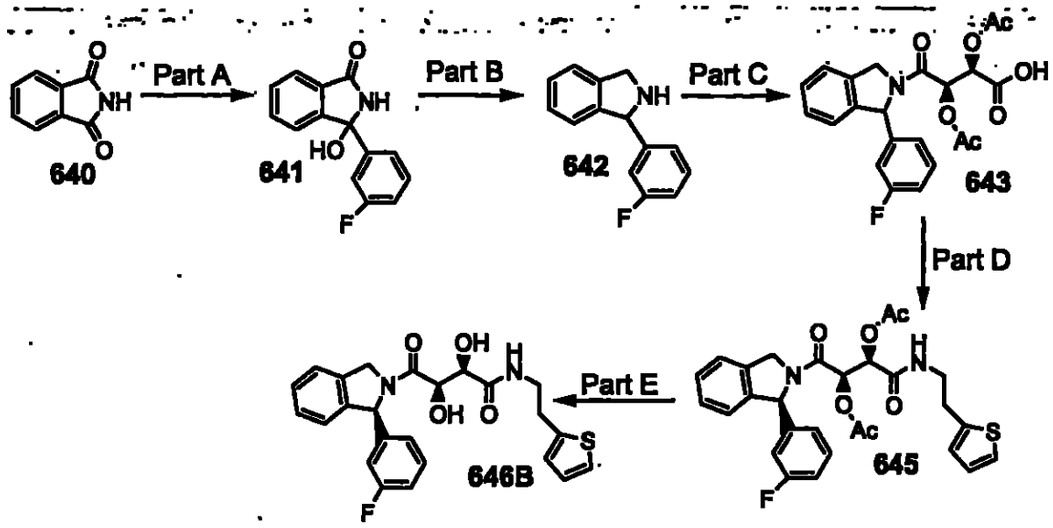
To a flask containing **634** (0.42 g) in anhydrous DMF at 0 °C was added NBS (1 eq) and the solution was allowed to warm up to r.t. overnight before another equivalent of NBS was added and solution stirred for another overnight. The final reaction mixture was poured over ice and extracted with DCM. The organic phase was washed with water and brine, dried over sodium sulfate. After removal of the solvent, the residue was chromatographed using Ethyl Acetate in Hexane (0 - 100 %) to give 0.38 gram of desired product.

To a solution of 0.035 gram of above compound in 2 ml DCM was added vinylacetate (2 eq) and DIEA (3.5 eq) and the solution was stirred at r.t. overnight. After removal of solvent, the residue was chromatographed using Ethyl Acetate in Hexane (0 - 100 %) to give 20 mg product which was treated with 50% TFA in DCM for 2h. before it was purified using a RP HPLC system to give 10 mg of desired product **635**.

The following compounds were generated using similar procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
635		435.2	436.0
636		460.2	461.0
637		507.2	508.0
638		503.2	504.0
639		493.2	494.0

Example 14:



Part A:

A Schlenck flask was flame dried under N_2 flow, capped with a septum, and allowed to cool to rt. Phthalimide (640) (4.13 g, 28.1 mmol) was added followed by anhydrous THF (100 mL). After the phthalimide had dissolved, the flask was placed in an ice water bath and allowed to cool for 20 min. A 1 M solution of 3-fluorophenyl magnesium bromide in THF (25 mL) was added causing a precipitate to form. DMPU (5 mL) was added, causing the reaction mixture to become clear again. Additional 3-fluorophenyl magnesium bromide was added (35 mL) over 10 min. The reaction mixture was stirred at 0 °C for 3.5 h, then quenched with 1.0 M pH 6.5 sodium phosphate buffer. The resulting mixture was diluted with EtOAc and the layers were separated. The organic layer was washed with water and brine, then dried with $MgSO_4$. Evaporation of the solvent gave and off white solid (7.4 g). This material was triturated in CH_2Cl_2/hexanes to give 4.0 g of pure 641. MS (EI) m/z Obsd. M+H 244.0

Part B:

A Schlenck flask was flame dried under N_2 flow, capped with a septum, and allowed to cool to rt. $LiAlH_4$ (1.26 g, 33.2 mmol) and $AlCl_3$ (1.47 g, 11.0 mmol) were added to the flask, followed by anhydrous THF. The flask was placed in

an ice-water bath immediately and allowed to cool with stirring. Compound **641** was added to the flask in portions. The reaction mixture was stirred for 3 h during which time it warmed to 15 °C. The reaction was recooled to 0 °C and water (3 mL) was added. Aqueous 3.0 N sodium hydroxide was added (6 mL) followed by water (9 mL). The reaction mixture was filtered through a pad of Celite which was rinsed with EtOAc. The resulting filtrate was concentrated to dryness giving a green solid. The crude product was partially purified via flash sgc using a 40%-50% EtOAc/hexanes gradient, followed by 98%EtOAc/2% Et_3N. The fractions containing the impure desired product were combined to give a blue oil. This material was dissolved in CH_2Cl_2 (6 mL). TFA (4 mL) and triethyl silane (2 mL) were added and the reaction mixture was left stirring ON. The reaction mixture was concentrated to give a green oil. This material was purified via flash sgc using 2:1 hexanes:EtOAc, followed by 98%EtOAc/2% Et_3N as the mobile phase. Compound **642** was isolated as a yellow oil (0.56 g). MS (EI) m/z Obsd M+H 214.2.

Part C:

Compound **642** (0.56 g, 2.6 mmol) was dissolved in CH_2Cl_2 (8 mL). Triethyl amine was added (1 mL) followed by (+)-diacetyl-(L)-tartaric anhydride (0.65 g, 3.00 mmol). The reaction mixture was left stirring at rt ON. The reaction mixture was concentrated to dryness and purified via sgc using 2%-5% MeoH/ CH_2Cl_2 mobile phase with 1% acetic acid added to it. After evaporating the solvent and azeotopic removal of the acetic acid with heptane, compound **643** was obtained as a white solid (0.33 g). MS (EI) m/z Obsd M+H 430.1

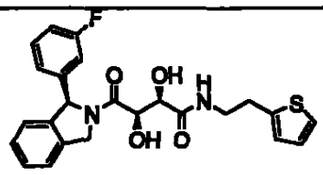
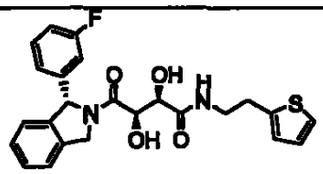
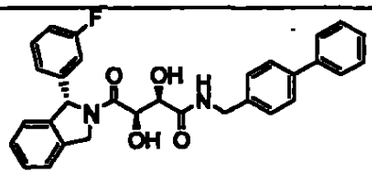
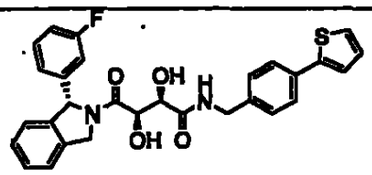
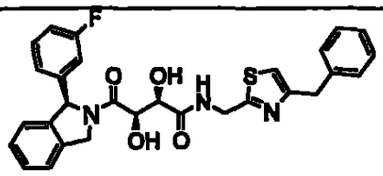
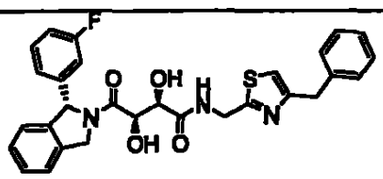
Part D:

Compound **643** (92 mg, 0.214 mmol), HOBT (36 mg, 0.26 mmol), DMF(1.5 mL), 2-thiophene ethylamine (44 mg, 0.34 mmol), and N-methylmorpholine (50 µL) were added to a flask. EDC was added and the reaction mixture was left stirring ON at rt. The reaction mixture was diluted with EtOAc and washed with aqueous $NaHCO_3$, citric acid, water, and brine. The organic layer was dried with $MgSO_4$ and concentrated to give a brown oil. The crude product was purified via flash sgc using a 10%-80% EtOAc/Hexanes gradient. Two diastereomeric compounds were isolated-**644** Diastereomer A (0.02 g) MS

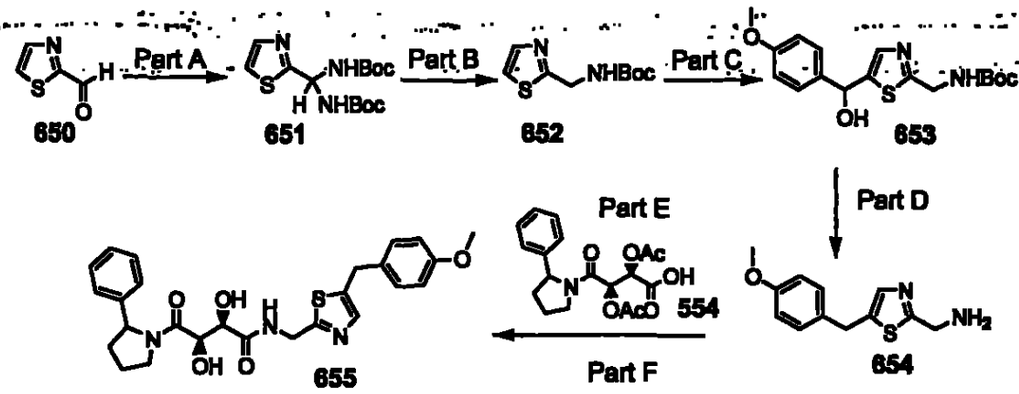
(EI) m/z Obsd M+H 539.06 and **645** Diastereomer B (0.03 g) MS (EI) m/z Obsd M+H 539.03.

Part E:

Compound **645** was dissolved in 2 M methanolic ammonia and stirred at rt for 30 m. The reaction was purified to dryness. The crude product was purified via prep TLC on silica plates using 1:1 EtOAc: Hexanes as the mobile phase. **646B:** MS (EI) m/z Obsd M+H 455.1.

Compound #	Structure	Exact mass	MS m/z (M+H)
646A		454.1	455.1
646B		454.1	455.1
647		510.2	511.1
648		516.2	517.1
649A		531.2	532.1
649B		531.2	532.1

Example 15:



Part A:

Compound **650** (8.36 g, 73.9 mmol) and tert-butyl carbamate (25.96 g, 222 mmol) were dissolved in acetonitrile (300 mL) and trifluoroacetic acid was added. The reaction was stirred overnight at rt under N_2, then concentrated. The resulting mixture was dissolved in EtOAc and washed with water. The organic layer was dried with Na_2SO_4 and concentrated to dryness. The crude product was purified via flash sgc using 1:3 EtOAc: Hexanes as the mobile phase to give 30.27 g of product **651**. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.40 (s, 1H), 6.38-6.30 (m, 1H), 1.51 (s, 18H) MS (EI) m/z Obsd M+H 330.1

Part B:

Compound **651** (30.27 g, 91.89 mmol) was dissolved in 2-propanol (1500 mL) and sodium borohydride (17.0 g, 46 mmol) was added. The reaction mixture was refluxed for 3 h, then concentrated on the rotovap. The resulting material was diluted with EtOAc, washed with water, and dried with Na_2SO_4. The solvents were evaporated and the crude product was purified via flash sgc using 1:2 EtOAc: Hexanes as the mobile phase to give 11.58 g of **652**. Yield = 73% over steps one and two. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.33 (s, 1H), 5.35 (s, 1H), 4.69 (s, 2H), 1.53 (s, 9H); MS (EI) MS (EI) m/z Obsd M+H 215.0

Part C:

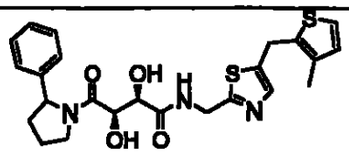
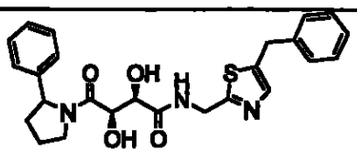
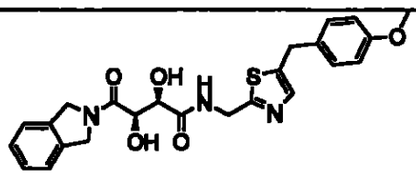
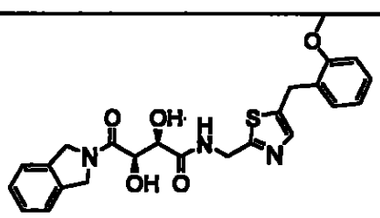
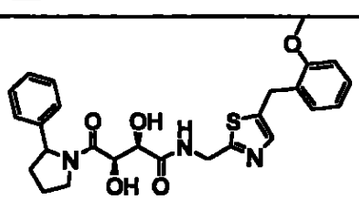
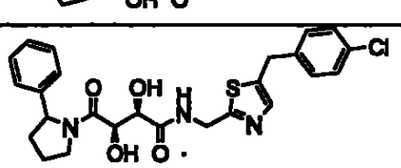
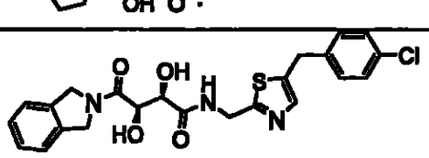
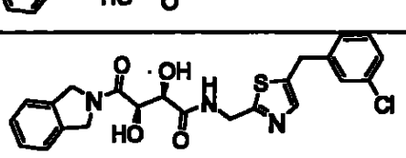
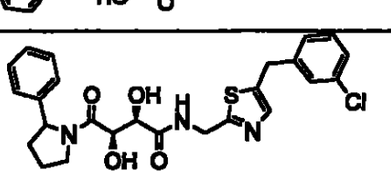
Compound **652** (0.30 g, 1.40 mmol) was dissolved in 5 mL of anhydrous THF (5 mL). The flask was capped with a septum, placed under N_2 blanket, and cooled in a dry ice/2-propanol bath. A solution of LDA (1.71 mL, 1.8 M) was added via syringe and the reaction mixture was stirred for 0.5 h. A solution of 4-methoxy benzaldehyde (0.21 g, 1.54 mmol) in 5 mL of anhydrous THF was added via syringe. The reaction mixture was stirred for 1 h. The ice bath was removed and the reaction was left stirring overnight at rt. Water was added and the reaction mixture was diluted with EtOAc. The layers were separated. The organic layer was washed with water and dried with Na_2SO_4. The solvent was evaporated and the crude product was purified via flash sgc using 1:1 EtOAc: Hexanes to give 0.28 g of **653**. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.37-7.32 (m, 2H), 6.89-6.94 (m, 2H), 6.02 (s, 1H), 5.38 (broad s, 1H), 4.55 (s, 2H), 3.86 (s, 3H) 3.28 (s, 1H), 1.49 (s, 9H).

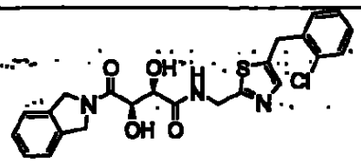
Part D:

Compound **653** (0.28 g, 0.80 mmol) was dissolved in triethylsilane (2 mL) and TFA (0.6 mL). The reaction mixture was refluxed for 3 h then allowed to cool to rt and stirred overnight. The reaction mixture was concentrated. Methanol was added and the reaction mixture was concentrated. Lithium hydroxide (10 mL, 1.0 M aq) and dioxane (10 mL) were added. The reaction mixture was stirred for 3 h then partially concentrated. EtOAc was added and the layers were separated. The organic layer was washed with water and dried with Na_2SO_4. The reaction mixture was concentrated to give 0.23 g of compound **654**. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.19 (d, J=9 Hz, 2 H), 6.89 (d, J=9 Hz, 2H), 4.16 (s, 2H), 4.11 (s, 2H), 3.84 (s, 3H), 1.77 (broad s, 2H).

Parts E and F:

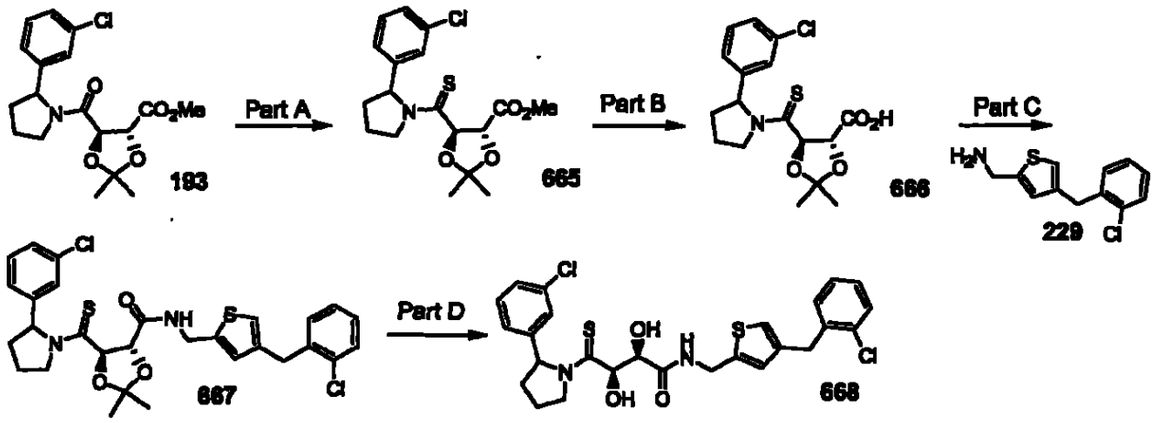
Compound **654** was converted to compound **655** using procedures described in Example 2. Data for **655**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.41-7.26 (m, 5H), 7.22-7.14 (M, 4H), 6.89-6.81 (m, 2H), 5.50-5.17 (m, 1H), 4.98-4.54 (m, 4H), 4.53-4.31 (m, 2H), 4.06-3.98 (m, 2H), 3.84 (s, 3H), 2.47-2.27 (m, 1H), 2.12-1.75 (m, 1H). MS (EI) m/z Obsd M+H 496.1.

Compound #	Structure	Exact mass	MS m/z (M+H)
656A		485.1	486.3
656B		465.2	466.1
657		467.2	468.1
658		467.2	468.1
659		495.2	496.1
660		499.1	500.1
661		471.1	472.1
662		471.1	472.1
663		499.1	500.1

664		471.1	472.1

Example 16: Thioamides

Example 16A:



Part A:

To a solution of compound **193** (200 mg, 0.54 mmol) in THF (5 mL) was added portionwise of Lawesson's reagent (203 mg, 0.5 mmol). The reaction mixture was stirred overnight under argon at room temperature, and diluted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. Column chromatography over silica gel (EtOAc/hexane, 20:80) afforded compound **665**. Mass calculated for formula $C_{18}H_{22}ClNO_4S$ 383.1, observed LCMS m/z 384.1 (M+H).

Part B:

To compound **665** in MeOH (5 mL) was added powdered K_2CO_3 (50 mg). Mixture was stirred at room temperature for 1 h and the solvent was removed in vacuo. The residue was dissolved in water and acidified with 1 N HCl. It was extracted with EtOAc, the combined organic layers was washed with 1N HCl, brine, dried over Na_2SO_4, and concentrated to afford compound **666** as

an oil (45 mg). Mass calculated for formula $C_{17}H_{20}ClNO_4S$ 369.1, observed LCMS m/z 370.1 (M+H).

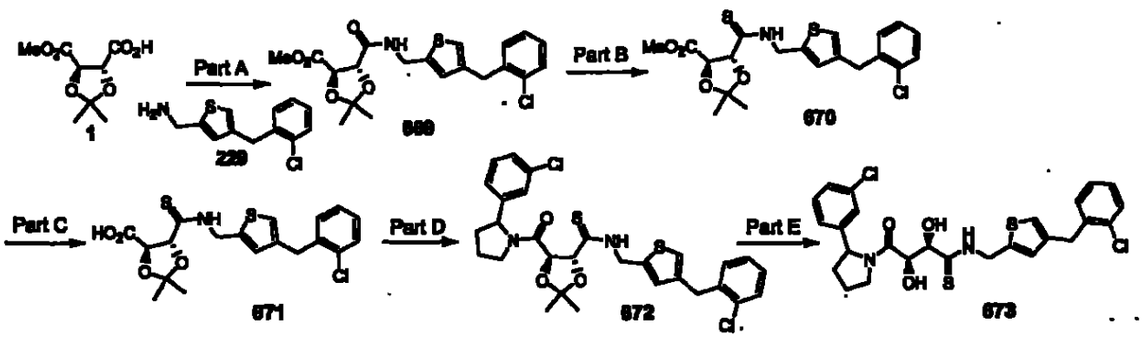
Part D:

To compound **666** (10 mg, 0.027 mmol) in DMF (0.5 mL) was **229** (11 mg, 0.041 mmol) and HATU (20.5 mg, 0.054 mmol). The reaction mixture was stirred at room temperature for 4 h, and diluted with ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in compound **667** as an oil. Mass calculated for formula $C_{28}H_{30}Cl_2N_2O_3S_2$ 588.1, observed LCMS m/z 589.1 (M+H).

Part E:

Compound **667** was dissolved in 0.5 mL of TFA/H_2O (80:20) and stirred at room temperature for 2 h. The reaction mixture was quenched with ACN/H_2O (50:50) and concentrated in vacuo. Purification by reverse phase prep-LC afforded compound **668** as a white solid. HPLC-MS t_R = 6.97 min ($UV_{254\ nm}$, 10 min), Mass calculated for formula $C_{28}H_{28}Cl_2N_2O_3S_2$ 548.1, observed LCMS m/z 549.1 (M+H).

Example 16B:



Part A:

To **1** (204 mg, 1mmol) in DMF (2 mL) was added **229** (320 mmol, 1.2 mmol) and HATU (570 mg, 1.5 mmol). The reaction mixture was stirred overnight at room temperature, and diluted with ethyl acetate and water. The organic

layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in **669** as a slightly yellow oil (280 mg, 66%).

Part B:

To a solution of **669** (280 mg, 0.54 mmol) in THF (5 mL) was added portionwise of Lawesson's reagent (202 mg, 0.5 mmol). The reaction mixture was stirred overnight under argon at room temperature, and diluted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. Column chromatography over silica gel (EtOAc/hexane, 20:80) afforded compound **670**. Mass calculated for formula $C_{20}H_{22}ClNO_4S$ 439.1, observed LCMS m/z 440.1 (M+H).

Part C:

To **670** in MeOH (5 mL) was added powdered K_2CO_3 (50 mg). The mixture was stirred at room temperature for 1 h and the solvent was removed in vacuo. The residue was dissolved in water and acidified with 1 N HCl. It was extracted with EtOAc, the combined organic layers was washed with 1N HCl, Brine, dried over Na_2SO_4, and concentrated to afford compound **671** as an oil (80 mg). Mass calculated for formula $C_{17}H_{20}ClNO_4S$ 425.1, observed LCMS m/z 426.1 (M+H).

Part D:

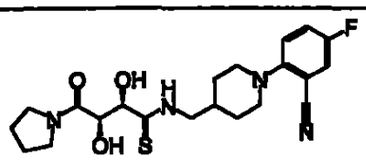
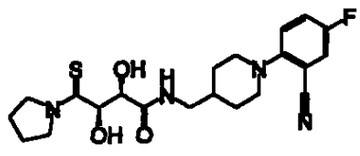
To compound **671** (10 mg, 0.027 mmol) in DMF (0.5 mL) was added racemic 2-(3-chlorophenyl)pyrrolidine (6.5 mg, 0.035 mmol) and HATU (17.5 mg, 0.046 mmol). The reaction mixture was stirred at room temperature for 4 h, and diluted with ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in compound **672** as an oil. Mass calculated for formula $C_{29}H_{30}Cl_2N_2O_3S_2$ 588.1, observed LCMS m/z 589.1 (M+H).

Part E:

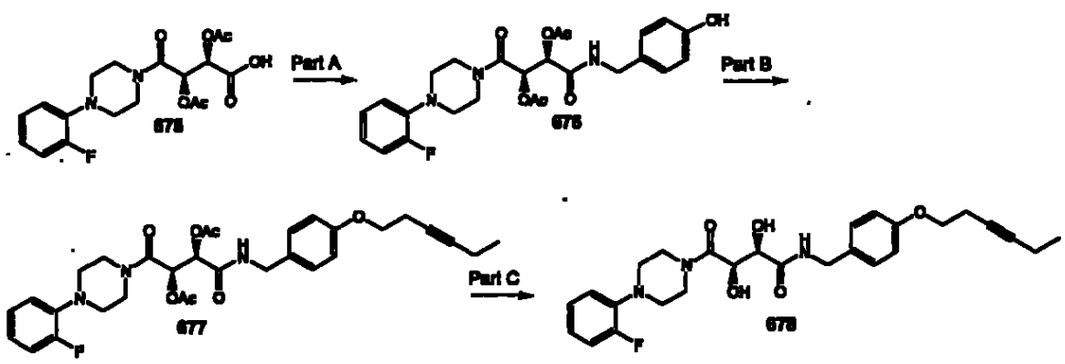
Compound **672** was dissolved in 0.5 mL of TFA/H_2O (80:20) and stirred at room temperature for 2 h. The reaction mixture was quenched with ACN/H_2O

(50:50) and concentrated in vacuo. Purification by reverse phase prep-LC afforded compound **673** as a white solid. HPLC-MS t_R = 7.04 min ($UV_{254\ nm}$, 10 min), Mass calculated for formula $C_{28}H_{28}Cl_2N_2O_3S_2$ 548.1, observed LCMS m/z 549.1 (M+H).

The following compounds were prepared by the methods described above. Belleau's reagent was substituted for Lawesson's reagent.

Compound #	Structure	Exact mass	MS m/e (M+H)
673		434.2	435.2
674		434.2	435.1

Example 17



Compound **675** was prepared as described in Example 4A Part C.

Part A:

To **675** (1.34 g, 3.38 mmol) in DMF (20 mL) was added 4-hydroxybenzylamine (0.5 g, 4.06 mmol), DIEA (0.71 mL, 4.06 mmol) and HATU (1.54 g, 4.06 mmol). The reaction mixture was stirred overnight at

room temperature. The reaction mixture was diluted with water and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 80% EtOAc/hexane) afforded **676** (1.41 g, 83%). HPLC-MS t_R = 1.56 min ($UV_{254\ nm}$); Mass calculated for formula $C_{25}H_{28}FN_3O_7$ 501.2, observed LCMS m/z 502.1 (M+H).

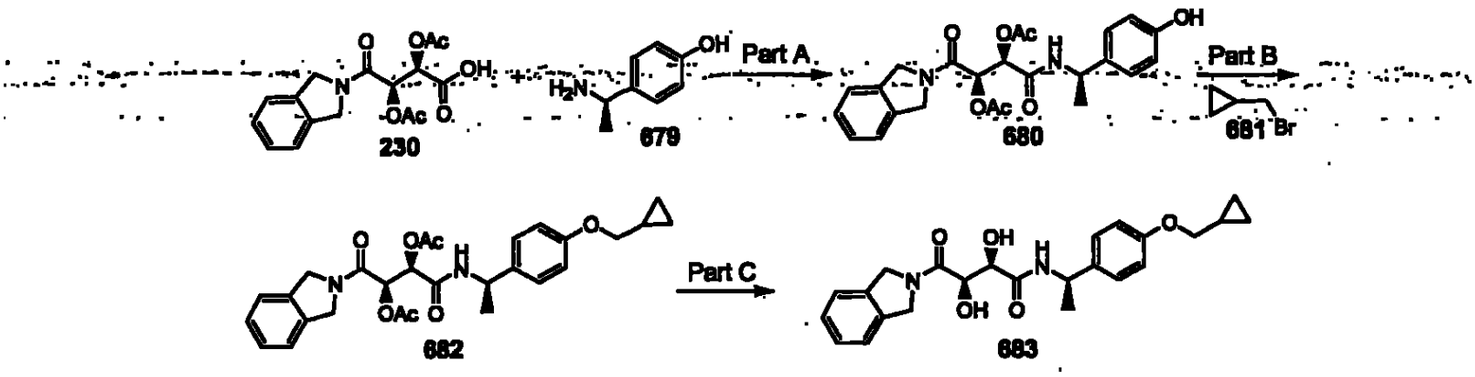
Part B:

To a mixture of **676** (50 mg, 0.1 mmol), triphenylphosphine (79 mg, 0.3 mmol), 3-hexyn-1-ol (33 µL, 0.3 mmol) in THF (0.5 mL) at 0 °C was added DEAD (47 µL, 0.3 mmol). The reaction mixture was warmed to room temperature and stirred for 5 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% EtOAc/hexane to 100% EtOAc) afforded **677** (9 mg, 15%). HPLC-MS t_R = 2.09 min ($UV_{254\ nm}$); Mass calculated for formula $C_{31}H_{38}FN_3O_7$ 581.3, observed LCMS m/z 582.2 (M+H).

Part C:

To **677** (9 mg, 0.02 mmol) in methanol (0.5 mL) was added anhydrous hydrazine (2 µL, 0.04 mmol). The reaction mixture was stirred overnight at room temperature. The solvents were removed in vacuo and the material was freeze-dried to yield **678** as a white powder (2 mg). HPLC-MS t_R = 1.89 min ($UV_{254\ nm}$); Mass calculated for formula $C_{27}H_{32}FN_3O_5$ 497.2, observed LCMS m/z 498.2 (M+H).

Example 17B:



Part A:

Compound **680** was prepared from compounds **230** & **679** using procedures described in Example 17A Part A. HPLC-MS t_R = 1.37 min ($UV_{254\ nm}$); Mass calculated for formula $C_{24}H_{28}N_2O_7$ 454.2, observed LCMS m/z 455.2 (M+H).

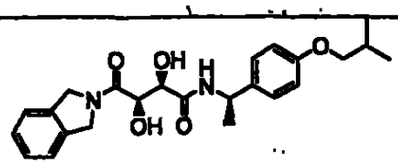
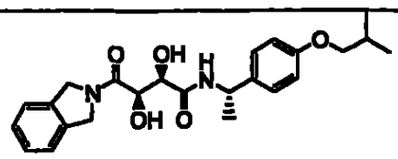
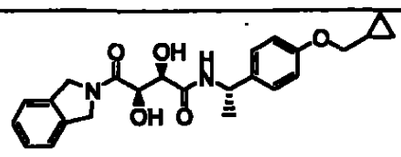
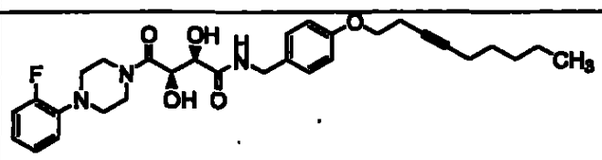
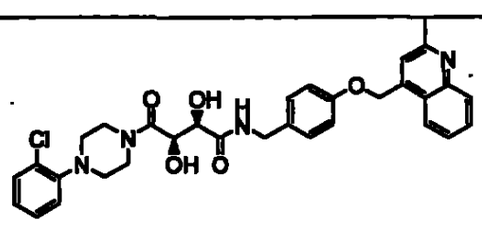
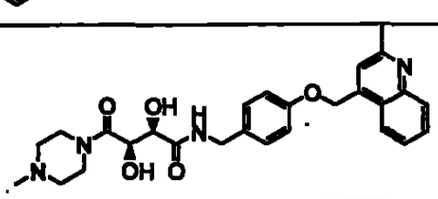
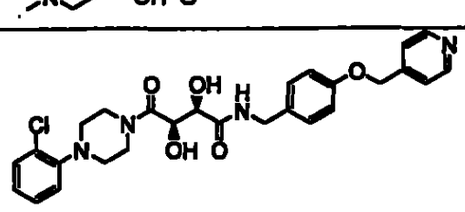
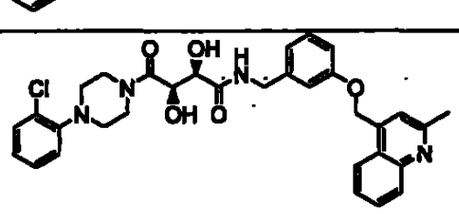
Part B:

A mixture of **680** (49 mg, 0.11 mmol), **681** (14 uL, 0.14 mmol) and cesium carbonate (46 mg, 0.14 mmol) in DMF (2 mL) was stirred 24 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated to afford **682** (33 mg). The material was used without further purification. HPLC-MS t_R = 1.91 min ($UV_{254\ nm}$); Mass calculated for formula $C_{28}H_{32}N_2O_7$ 508.2, observed LCMS m/z 509.2 (M+H).

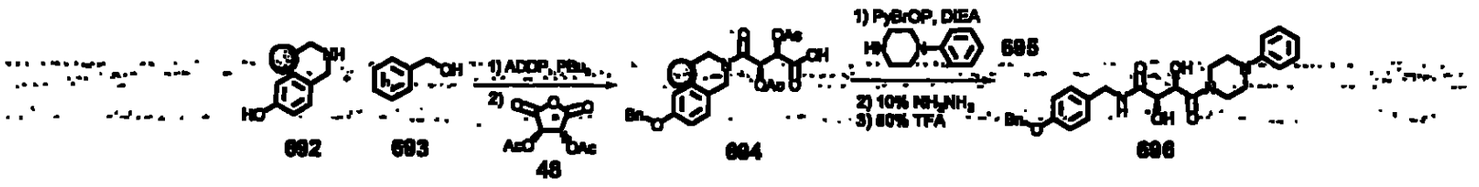
Part C:

To compound **682** (33 mg, 0.06 mmol) in methanol (2 mL) was added 7.0 M ammonia in methanol (2 ml). The reaction mixture was stirred for 1 hour and concentrated. Purification by reverse phase prep-HPLC afforded **683** (8 mg). HPLC-MS t_R = 4.28 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{24}H_{28}N_2O_5$ 424.2, observed LCMS m/z 425.2 (M+H).

The following compounds were prepared using procedures described in Example 17A & 17B.

Compound #	Structure	Exact Mass	Mass Obsvd
684		426.2	427.1
685		426.2	427.1
686		424.2	425.2
687		539.3	540.3
688		588.2	589
689		492.2	493
690		524.1	525
691		588.2	589

Example 17C:



Step A1:

To pre-swelled MB-CHO resin (5.0 g, 1.0 mmol/g) in 40 ml DCE was added 4-hydroxybenzylamine (1.5 eq) and triacetoxyborohydride (2 eq) and the mixture was agitated overnight before the solution was drained and resin washed with MeOH, DCM and THF 5 cycles to give resin **692** after drying in vacuo overnight.

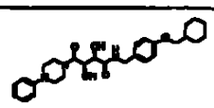
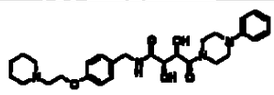
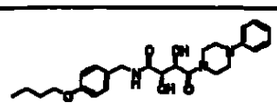
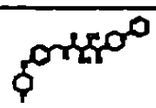
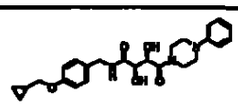
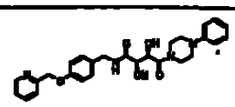
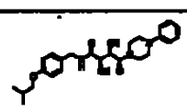
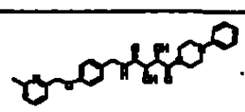
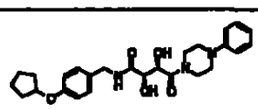
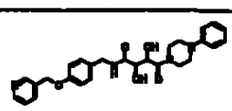
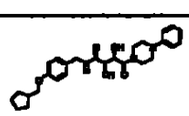
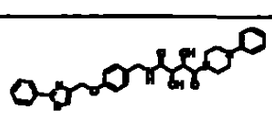
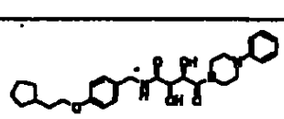
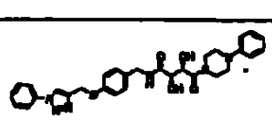
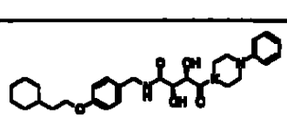
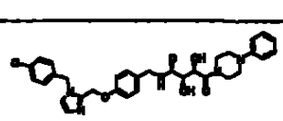
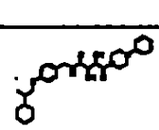
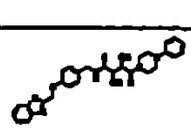
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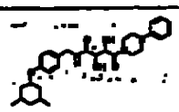
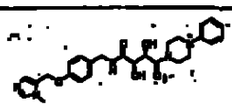
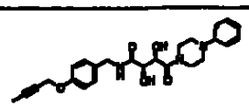
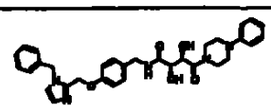
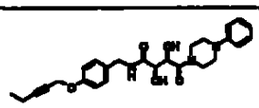
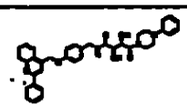
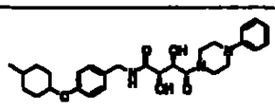
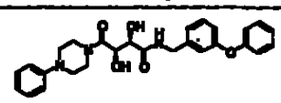
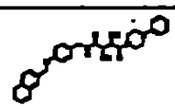
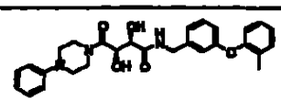
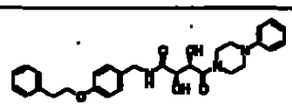
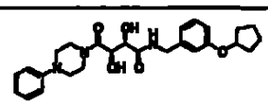
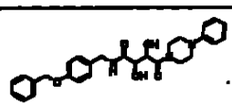
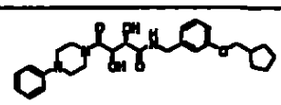
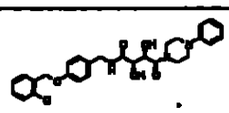
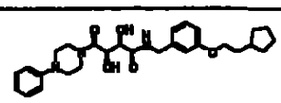
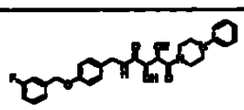
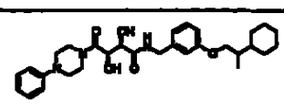
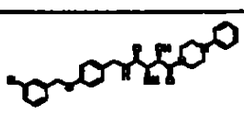
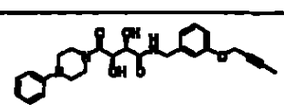
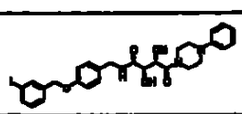
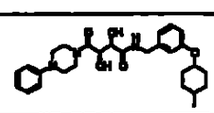
To a pre-swelled resin **692** (150 mg, 1 mmol/g) in anhydrous THF was added benzylalcohol (5 eq) and PPh_3 (7 eq) in 1.5 ml of THF and ADDP (5 eq) in 0.5 ml of DCM. The reaction was agitated at room temperature over the weekend. The reaction solution was drained and resin washed with 5 cycles of MeOH, DCM and THF and dried in vaccuo before it was swelled in NMP followed by addition of 1.5 ml 1M NMP solution of compound **48**. The reaction mixture was agitated overnight before the solution was drained and resin washed with 5 cycles of MeOH, DCM and THF and dried in vacuo to give resin **694**.

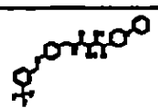
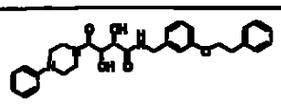
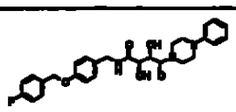
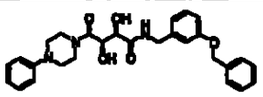
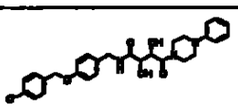
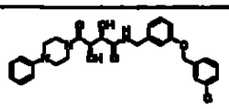
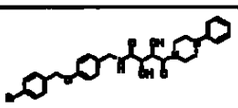
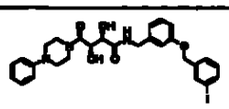
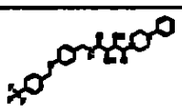
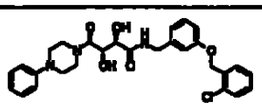
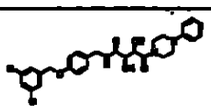
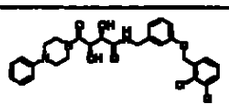
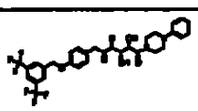
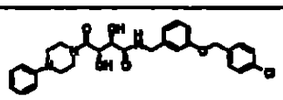
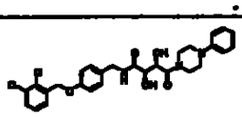
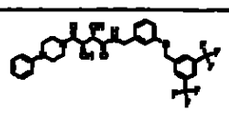
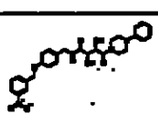
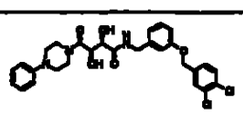
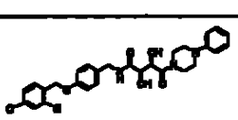
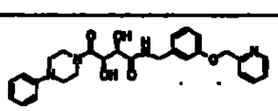
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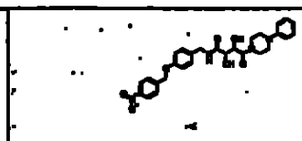
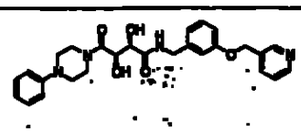
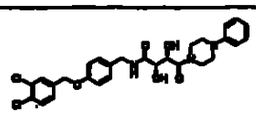
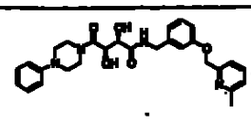
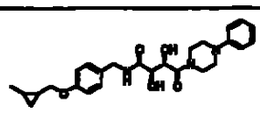
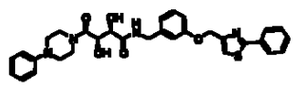
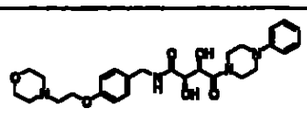
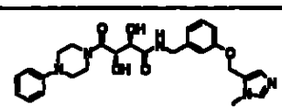
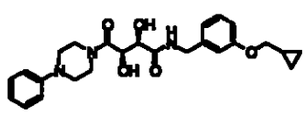
Resin **694** was pre-swelled in DCM, before 1-phenylpiperazine hydrochloric salt (695)(6 eq) was added followed by addition of PyBrop (3 eq) and DIEA (9 eq) in 3 ml of DCM. The reaction solution was agitated overnight before it was drained and resin washed with 5 cycles of MeOH, DCM and THF before it was treated with 10% hydrazine in methanol for 2h. The resin was then further washed with 5 cycles of MeOH, DCM and THF followed by cleavage using 50% of TFA in DCM. The cleavage solution was evaporated and residue purified with a RP-HPLC system to give 5 mg of desired product **696**.

The following compounds were generated using similar methods.

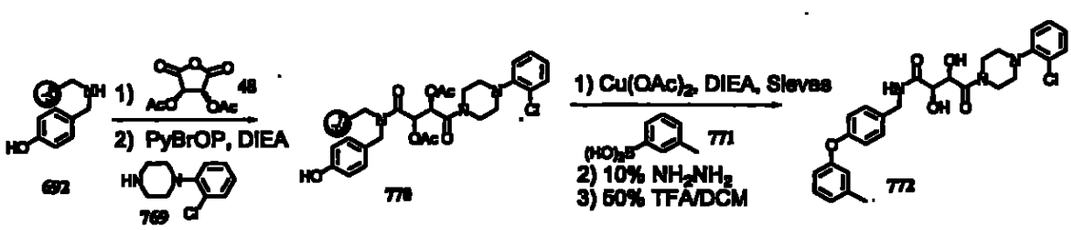
Compound #	Structure	Obs. MS	Compound #	Structure	Obs. MS
697		496	698		511
699		456	700		497
701		454	702		491
703		456	704		505
705		468	706		491
707		482	708		573
709		496	710		557
711		510	712		604
713		524	714		547

715		510	716		494
717		452	718		570
719		466	720		617
721		496	722		476
723		540	724		490
725		504	726		468
696		490	728		482
729		524	730		496
731		508	732		524
733		524	734		452
735		616	736		496

737		558	738		504
739		508	740		490
741		524	742		524
743		569	744		616
745		558	746		524
747		558	748		558
749		626	750		524
751		558	752		626
753		535	754		558
755		558	756		491

757		535		758		491
759		558		760		505
761		468		762		573
763		513		764		494
765		454				

Example 17D:



Step A.

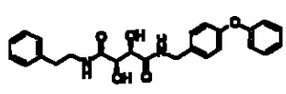
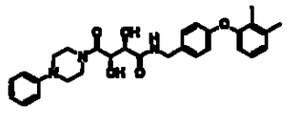
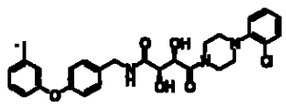
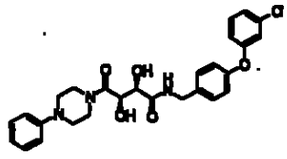
To resin **692** (2.6 g, 1mmol/g), preswelled in NMP was added **48** (5 eq) and the mixture was agitated for 48 h. before the solution was drained and resin washed with 5 cycles of MeOH, DCM and THF and dried in vacuo. The resin was then swelled in anhydrous DCM (25 ml) before **769** (6 eq, HCl salt) and DIEA (9 eq) were added followed by addition of PyBrop. The reaction was

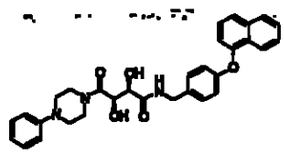
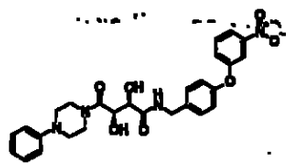
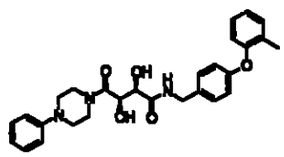
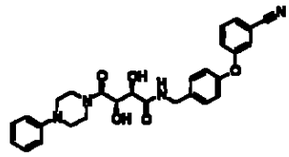
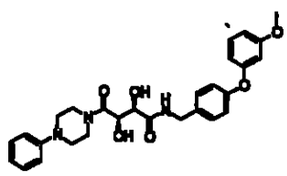
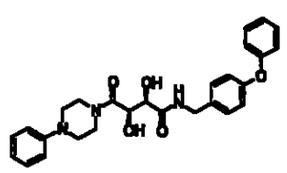
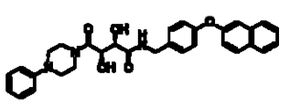
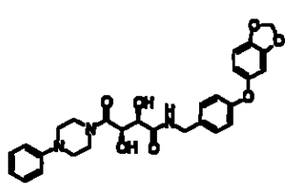
agitated at r.t. overnight before the solution was drained and resin washed with 5 cycles of MeOH, DCM and THF and dried in vacuo to give resin 770 (0.9 mmol/g loading).

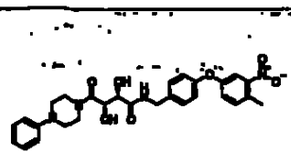
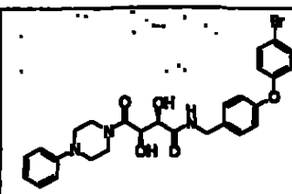
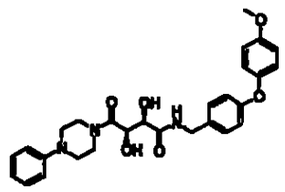
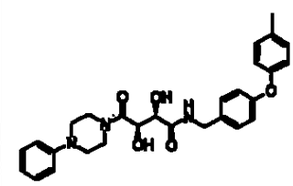
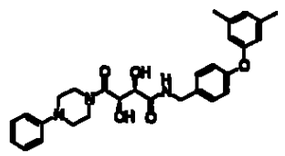
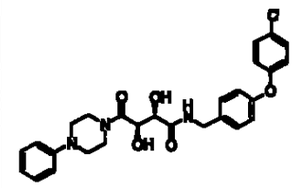
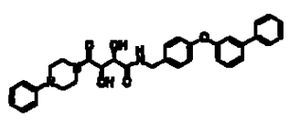
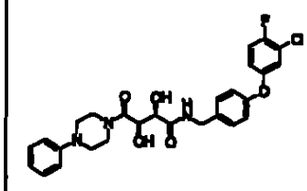
Step B.

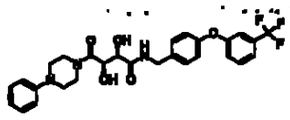
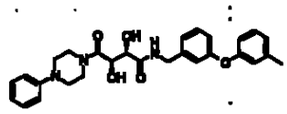
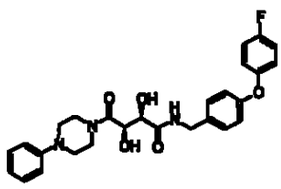
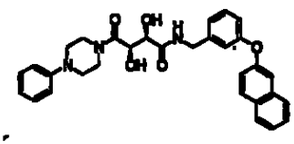
To a pre-swelled resin 770 (0.095 g, 0.9 mmol/g) in anhydrous DCM was added anhydrous $Cu(OAc)_2$ (3 eq), 771 (5 eq), 4 A molecular sieves (5micron particle size, 100 mg) and DIEA (7eq) in 2 ml anh. DCM. The reaction was agitated for 48 h. before the mixture was drained and resin washed with 5 cycles of H_2O, MeOH, DCM and THF before it was treated with 10% hydrazine in Methanol for 2h. The resin was then further washed with 5 cycles of MeOH, DCM and THF followed by cleavage using 50% of TFA in DCM. The cleavage solution was evaporated and residue purified with a RP-HPLC system to give 5 mg of desired product 772.

The following compounds were synthesized in similar fashion.

Comound #	Structure	OBS. Mass		Compound #	Structure	OBS. Mass
773		435		774		504
772		524		776		510

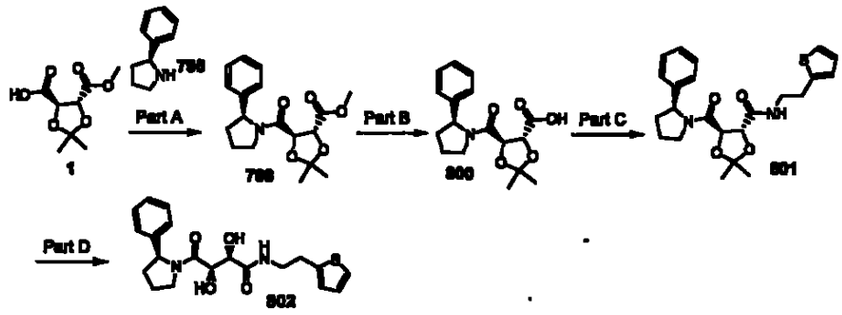
777		526	778		521
779		490	780		501
781		506	782		476
783		526	784		520

785		535	786		555
787		506	788		490
789		504	790		510
791		552	792		528

793		544	794		490
795		494	796		526

Example 18

Example 18A:



Part A:

Following the procedure described in Example 1 Part A, 1 (163 mg, 0.8 mmol), 2S-phenyl-pyrrolidine (798) (Burgess, L.E.; Meyers, A.I.; *J. Org. Chem.* 1991, *56*, 2294) (147 mg, 0.8 mmol), DIEA (560 µL, 3.2 mmol) and HATU (304 mg, 0.8 mmol) were mixed together in DMF (2 mL). Purification by column chromatography (SiO_2, 5%-20% EtOAc/DCM) afforded 799 as an

oil (115 mg, 43%). HPLC-MS t_R = 1.82 min ($UV_{254\ nm}$); Mass calculated for formula $C_{18}H_{23}NO_5$ 333.2, observed LCMS m/z 334.1 (M+H).

Part B:

Following the procedure in Example 1 Part B the material from Part A was saponified. **800**: HPLC-MS t_R = 1.54 min ($UV_{254\ nm}$); Mass calculated for formula $C_{17}H_{21}NO_5$ 319.1, observed LCMS m/z 320.2 (M+H).

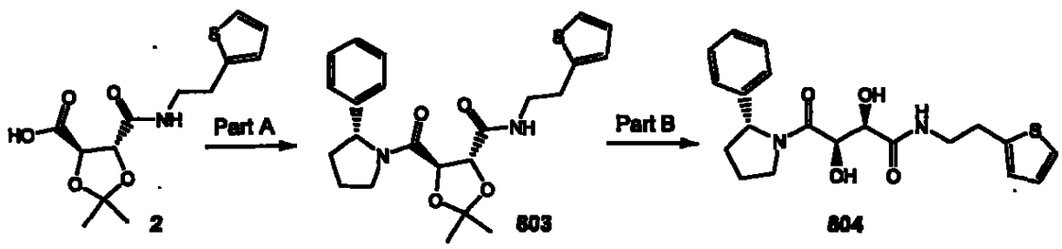
Part C:

Compound **800**, 2-thiopheneethylamine (6 µL, 0.05 mmol), DIEA (18 µL, 0.103 mmol) and HATU (19 mg, 0.05 mmol) were mixed together following the procedure described in Example 1 Part A. **801**: HPLC-MS t_R = 2.01 min ($UV_{254\ nm}$); Mass calculated for formula $C_{23}H_{28}N_2O_4S$ 428.2, observed LCMS m/z 429.2 (M+H).

Part D:

Compound **801** was dissolved in 90:10 TFA:water (2 mL) and stirred for 4 hours. The reaction mixture was quenched with 1:1 acetonitrile:water (4 mL) and concentrated. Purification by reverse phase prep-LC afforded **802** as a white powder (9 mg, 50%, 2 steps). HPLC-MS t_R = 1.54 min ($UV_{254\ nm}$); Mass calculated for formula $C_{20}H_{24}N_2O_4S$ 388.2, observed LCMS m/z 389.2 (M+H).

Example 18B:



2 803 804

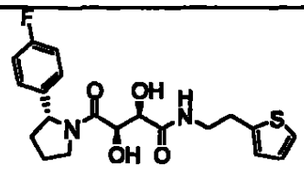
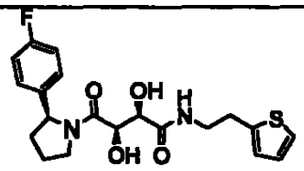
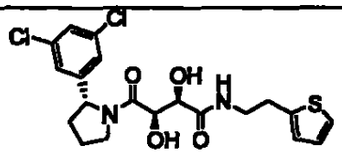
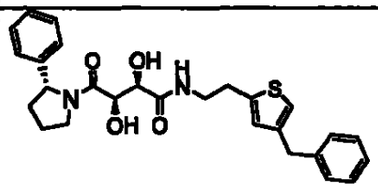
Part A:

Compound **2** (42 mg, 0.14 mmol), 2-phenyl pyrrolidine (22 mg, 0.15 mmol), DIEA (63 µL, 0.36 mmol) and HATU (61 mg, 0.16 mmol) were mixed together

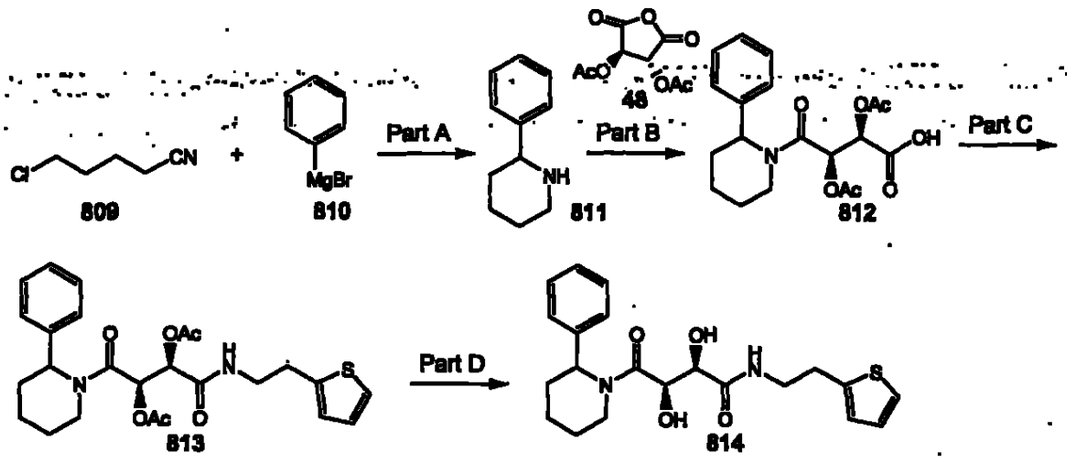
following the procedure described in Example 1 Part A. The desired isomer was separated by reverse phase prep-LC to afford **803** as a white solid. HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); Mass calculated for formula $C_{23}H_{28}N_2O_4S$ 428.2, observed LCMS m/z 429.1 (M+H).

Part B:

Compound **803** was deprotected using the procedure described in Example 1 Part D to afford **804** as a white powder (5 mg, 19% 2 steps). HPLC-MS t_R = 1.50 min ($UV_{254\ nm}$); Mass calculated for formula $C_{20}H_{24}N_2O_4S$ 388.2, observed LCMS m/z 389.2 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
805		406.1	407.2
806		406.1	407.2
807		456.1	457.1
808		478.2	479.2

Example 19:



Part A: 2-Phenyl piperidine

To 5-chlorovaleronitrile (809) (1.23 mL, 11 mmol) and trimethylsilylchloride (4.32 mL, 34 mmol) in toluene (50 mL) under argon at 0 °C was added phenylmagnesium bromide (810) (3M in diethyl ether, 3.67 mL, 11 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 hour. To the reaction mixture was added methanol (50 mL). Sodium borohydride (1.04 g, 27.5 mmol) was added portionwise. After the vigorous bubbling had subsided the reaction mixture was stirred for 1 hour at room temperature. A solution of 50% sodium hydroxide (5 mL) was added to the mixture and it was stirred overnight. The reaction mixture was filtered to remove the precipitate and the solids were washed with ethyl acetate. The filtrate was concentrated in vacuo. The crude reaction mixture was dissolved in ethyl acetate and water. The aqueous layer had a pH of 9. The layers were separated and the organic layer was washed with brine solution, dried over sodium sulfate and concentrated in vacuo to afford an orange oil. The product was purified by column chromatography (SiO_2, 20% ethyl acetate/hexane to 20% ethyl acetate hexane + 2% triethylamine) to afford 811 as a polar yellow oil (927 mg, 52%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.4 – 7.3 (m, 4H), 7.24 (m, 1H), 3.60 (dd, 1H, J = 2.4, 10.4 Hz), 3.21 (m, 1H), 2.81 (dt, 1H, J = 3.2, 10.8 Hz), 1.90 (m, 1H), 1.81 (m, 1H), 1.68 (m, 1H), 1.56 (m, 3H); HPLC-MS t_R = 0.73 min (MS); mass calculated for formula $C_{11}H_{15}N$ 161.1, observed LCMS m/z 162.1 (M+H).

Part B:

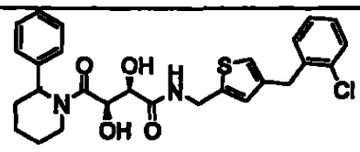
To **48** (108 mg, 0.5 mmol) in DCM (3 mL) was added **811** (80 mg, 0.5 mmol). The reaction mixture was stirred overnight before being poured into 1.0 N HCl and extracted with DCM. The combined organic layers were dried over sodium sulfate, concentrated and freeze-dried to afford **812** as a white solid (119 mg, 63%). Mass calculated for formula $C_{19}H_{23}NO_7$ 377.2, observed LCMS m/z 378.1 (M+H).

Part C:

Prepared as described in Example 1 Part A using **812** (19 mg, 0.05 mmol) to afford a foam **813** (24 mg, 100%). Mass calculated for formula $C_{19}H_{23}NO_7$ 486.2, observed LCMS m/z 487.1 (M+H).

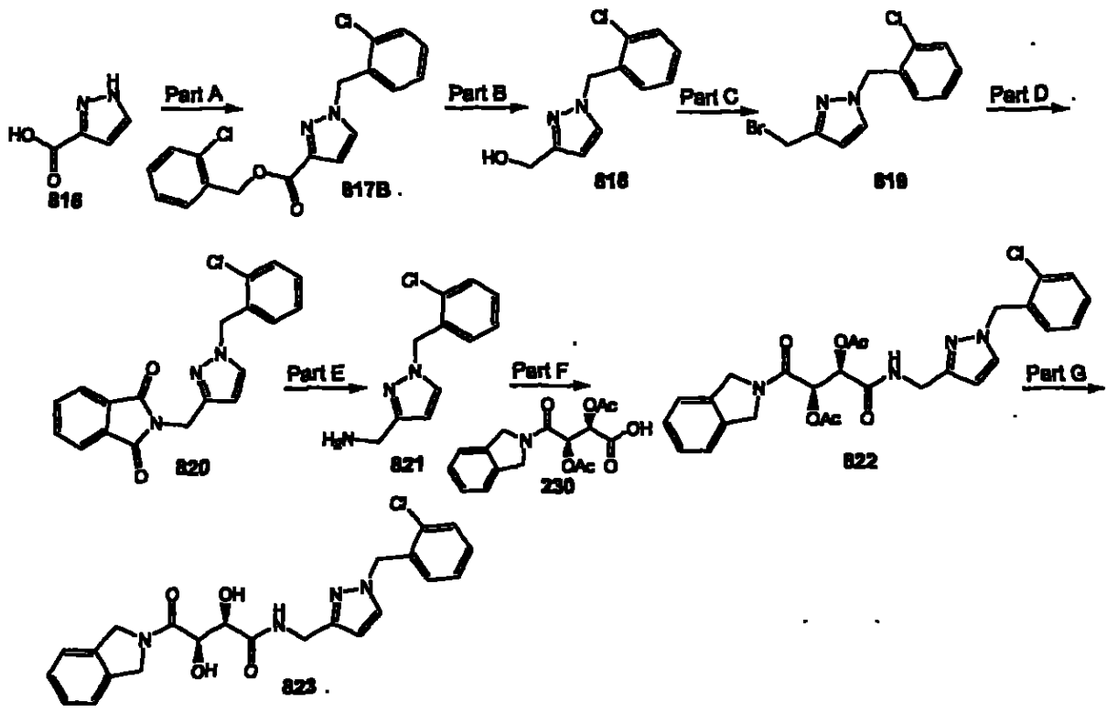
Part D:

Compound **813** (24 mg, 0.05 mmol) was deprotected using the procedure described in Example 2A Part B. Purification by reverse-phase prep-LC afforded **814** as a white powder (9 mg, 45%). HPLC-MS t_R = 4.38 and 4.42 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{21}H_{28}N_2O_4S$ 402.2, observed LCMS m/z 403.1 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
815		512.2	513.1

Example 20:

Example 20A:



Part A:

To 1H-Pyrazole-3-carboxylic acid (**816**) (274 mg, 2.44 mmol) in DMF (10 mL) was added 2-chlorobenzyl bromide (698 µL, 5.38 mmol) and cesium carbonate (1.67 g, 5.12 mmol). The reaction mixture was stirred overnight at room temperature. The solids were removed by filtration and the filtrate was concentrated. Purification by column chromatography (SiO_2, 20% to 30% EtOAc/Hex) separated the regioisomers to afford the **817A** as an oil (136 mg, 15%) and **817B** as a white solid (685 mg, 78%).

1-(2-Chloro-benzyl)-1H-pyrazole-5-carboxylic acid 2-chloro-benzyl ester (**817A**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 1H, J = 2.0 Hz), 7.37 (m, 3H), 7.31 - 7.11 (m, 4H), 7.02 (d, 1H, J = 2.0 Hz), 6.53 (dd. 1H, J = 2.0, 7.6 Hz), 5.91 (s, 2H), 5.39 (s,.2H). HPLC-MS t_R = 2.40 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{14}Cl_2N_2O_2$ 360.0, observed LCMS m/z 361.0 (M+H).

1-(2-Chloro-benzyl)-1H-pyrazole-3-carboxylic acid 2-chloro-benzyl ester (817B): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 1H), 7.44 (d, 1H, J = 2.4 Hz), 7.40 (m, 2H), 7.27 (m, 4H), 7.08 (dd, 1H, J = 1.6, 7.6 Hz), 6.87 (d, 1H, J = 2.4 Hz), 5.54 (s, 2H), 5.51 (s, 2H); HPLC-MS t_R = 2.22 min (UV_{254} nM); mass calculated for formula $C_{18}H_{14}Cl_2N_2O_2$ 360.0, observed LCMS m/z 361.0 (M+H).

Part B:

To **817B** (685 mg, 1.90 mmol) in THF (10 mL) was added 1.0 M $LiAlH_4$ (1.14 mL, 1.14 mmol) with ice cooling. The reaction mixture was stirred for 1 hour. The reaction was quenched with water (1 mL), 3 M NaOH (1 mL) and water (3 mL). The organic layer was decanted and the precipitate was washed with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 1:1 DCM:EtOAc) yielded **818** as an oil (350 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, 1H, J = 2.4 Hz), 7.39 (dd, 1H, J = 2.4, 8.0 Hz), 7.25 (m, 2H), 7.02 (dd, 1H, J = 1.6, 7.2 Hz), 6.30 (d, 1H, J = 2.4 Hz), 5.43 (s, 2H), 4.73 (s, 2H), 2.5 (bs, 1H, OH); HPLC-MS t_R = 1.29 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{11}ClN_2O$ 222.1, observed LCMS m/z 223.1 (M+H).

Part C:

To **818** (350 mg, 1.57 mmol) in toluene (5 mL) was added phosphorous tribromide (163 µL, 1.73 mmol). The reaction mixture was heated to reflux in a pre-heated oil bath for 15 minutes. The mixture was cooled, poured over ice and extracted with EtOAc. The combined organic layer was washed with bicarbonate solution and brine, dried over sodium sulfate and concentrated to yield **819** as a white solid (414 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.25 (m, 2H), 7.00 (dd, 1H, J = 2.0, 7.2 Hz), 6.36 (d, 1H, J = 2.4 Hz), 5.41 (s, 2H), 4.53 (s, 2H); HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{10}BrClN_2$ 284.0, observed LCMS m/z 285.1 (M+H).

Part D:

To **819** (412 mg, 1.44 mmol) in DMF (5 mL) was added phthalimide (255 mg, 1.73 mmol) and cesium carbonate (515 mg, 1.58 mmol). The reaction mixture was stirred overnight at room temperature. The solids were removed by filtration and the filtrate was concentrated. The residue was dissolved in EtOAc and water. The layers were separated. The organic layer was washed with brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 5% EtOAc/DCM) yielded **820** as a solid (418 mg, 82%). HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{14}ClN_3O_2$ 351.1, observed LCMS m/z 352.2 (M+H).

Part E:

To **820** (418 mg, 1.19 mmol) in ethanol (20 mL) was added hydrazine monohydrate (231 µL, 4.75 mmol) and the reaction was heated to reflux for 3 hours. The mixture was cooled and diluted with 50% EtOAc/hexanes (40 mL). The solids were removed by filtration and were thoroughly washed with 50% EtOAc/hexanes (30 mL). The filtrate was concentrated. The residue was dissolved in EtOAc and washed with water and brine, dried over sodium sulfate and concentrated to afford **821** as a semi-solid (205 mg, 78%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 1H), 7.38 (d, 1H, J = 2.0 Hz), 7.23 (m, 2H), 6.92 (dd, 1H, J = 2.0, 7.2 Hz), 6.22 (d, 1H, J = 2.0 Hz), 5.39 (s, 2H), 3.91 (s, 2H); HPLC-MS t_R = 0.91 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{12}ClN_3$ 221.07, observed LCMS m/z 222.1 (M+H).

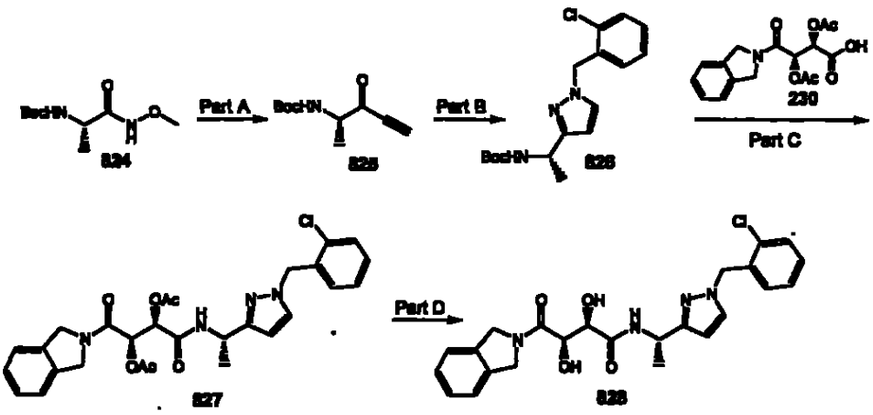
Part F:

To **821** (49 mg, 0.22 mmol) in DMF (2 ml) was added **230** (67 mg, 0.2 mmol), DIEA (77 µL, 0.44 mmol) and HATU (84 mg, 0.22 mmol). The reaction mixture was stirred overnight. The DMF was removed in vacuo and the residue was dissolved in EtOAc. The organic layer was washed with bicarbonate solution, 0.1 N HCl, and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 80% EtOAc/Hex) yielded **822** as a solid (70 mg, 65%). HPLC-MS t_R = 1.80 min ($UV_{254\ nm}$); mass calculated for formula $C_{27}H_{27}ClN_4O_6$ 538.2, observed LCMS m/z 539.2 (M+H).

Part G:

A mixture of **822** (70 mg, 0.13 mmol) and potassium carbonate (90 mg, 0.65 mmol) in MeOH (2 mL) was stirred 1 hour. The reaction was diluted with EtOAc and poured into brine solution. Additional salt was added and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layer was dried over sodium sulfate and concentrated to yield **823** as a white solid (45 mg, 76%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (t, 1H, J = 6.0 Hz), 7.70 (d, 1H, J = 2.0 Hz), 7.46 (dd, 1H, J = 2.0, 8.0 Hz), 7.36 – 7.27 (m, 6H), 6.94 (dd, 1H, J = 2.0, 7.6 Hz), 6.20 (d, 1H, J = 2.0 Hz), 5.68 (d, 1H, J = 6.8 Hz), 5.35 (s, 2H), 5.06 (d, 1H, J = 14.4 Hz), 5.03 (d, 1H, J = 7.6 Hz), 4.91 (d, 1H, J = 14.4 Hz), 4.76 (d, 1H, J = 15.6 Hz), 4.62 (dd, 1H, J = 2.8, 7.6 Hz), 4.61 (d, 1H, J = 14.8 Hz), 4.26 (m, 3H); HPLC-MS t_R = 1.55 min ($UV_{254\ nm}$); mass calculated for formula $C_{23}H_{23}ClN_4O_4$ 454.1, observed LCMS m/z 455.2 (M+H).

Example 20B: Pyrazole Spacer



Part A:

To the Weinreb amide **824** (prepared using the method of De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534) (200 mg, 0.85 mmol) in THF (15 mL) was added lithium (trimethylsilyl)acetylide (4.3 mL, 2.14 mmol) dropwise at 0 °C. The reaction mixture was stirred for 1 hour then diluted with EtOAc (50 mL). The mixture was washed with 0.1 N HCl (50 mL),

dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% EtOAc/Hex) afforded **825** (91 mg, 54%).

Part B:

A mixture of **825** (71 mg, 0.33 mmol), (2-chloro-phenyl)-hydrazine dihydrochloride (89 mg, 0.39 mmol) and potassium carbonate (200 mg, 1.64 mmol) in methanol (5 mL) were stirred at reflux for 12 hours. The reaction mixture was cooled and diluted with EtOAc (50 mL) and water (50 mL). The organic layer was separated, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% EtOAc/Hex) afforded **826** (50 mg, 15%). HPLC-MS t_R = 2.10 min (ELSD); mass calculated for formula $C_{17}H_{22}ClN_3O_2$ 335.1, observed LCMS m/z 336.2 (M+H).

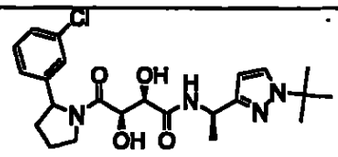
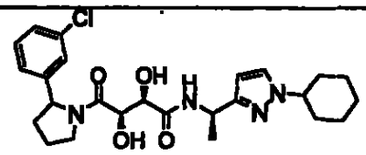
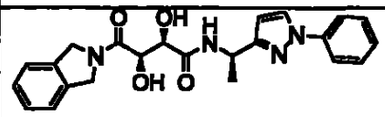
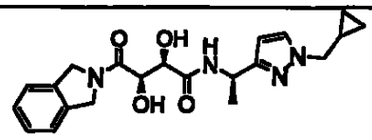
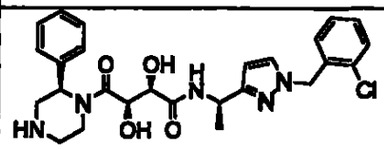
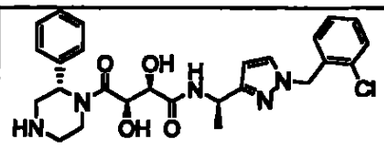
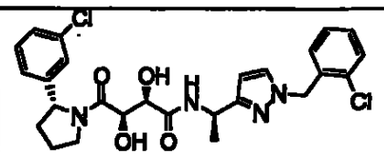
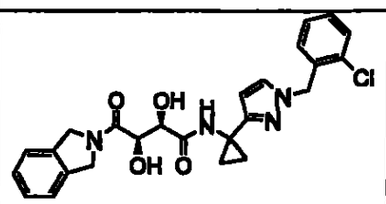
Part C:

Compound **826** (45 mg, 0.13 mmol) was dissolved in 25% TFA/DCM (4 mL) and stirred for 30 minutes. The solvents were removed in vacuo and the material was used without further purification. The residue was dissolved in DMF (5 mL) and **230** (25 mg, 0.07 mmol), DIEA (300 µL, 1.68 mmol) and HATU (32 mg, 0.09 mmol) were added. The reaction mixture was stirred overnight. The DMF was removed in vacuo and the residue was dissolved in EtOAc and water. The organic layer was separated and washed with 0.1 N NaOH, 0.1 N HCl and brine, dried over sodium sulfate and concentrated. Compound **827** was used without further purification.

Part D:

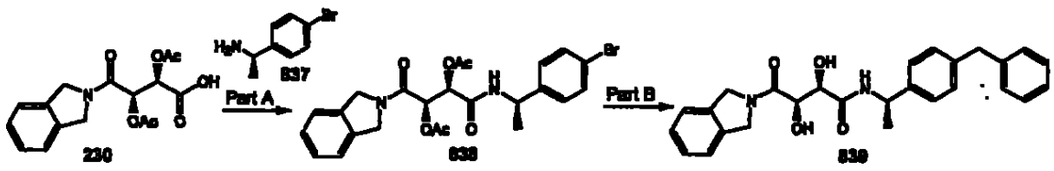
Compound **827** (~25 mg, 0.05 mmol) was dissolved in methanol (5 mL) and a solution on potassium carbonate (50 mg) in water (1 mL) was added. The reaction was stirred for 30 minutes. The reaction mixture was diluted with ethyl acetate and brine. The organic layer was separated, dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded **828** as a white powder (15 mg, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, 1H, J = 8.0 Hz), 7.70 (d, 1H, J = 1.6 Hz), 7.47 (dd, 1H, J = 1.6, 7.6 Hz), 7.35 – 7.26 (m, 6H), 6.89 (dd, 1H, J = 1.6, 7.2 Hz), 6.29 (d, 1H, J = 2.0 Hz), 5.38 (s,

2H), 5.04 (d, 1H, J = 15.2 Hz), 4.97 (m, 2H), 4.90 (d, 1H, J = 14.0 Hz), 4.76 (d, 1H, J = 16.4 Hz), 4.61 (m, 2H), 4.27 (d, 1H, J = 2.4 Hz), 1.39 (d, 3H, J = 6.8 Hz); HPLC-MS t_R = 4.25 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{24}H_{25}ClN_4O_4$ 468.2, observed LCMS m/z 469.1 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
829		462.2	463.1
830		488.2	489.2
831		420.2	421.1
832		398.2	399.1
833		511.2	512.2
834		511.2	512.2
835		530.2	531.1
836		480.2	481.1

Example 21: α-Methyl benzyl amines

Example 21A:



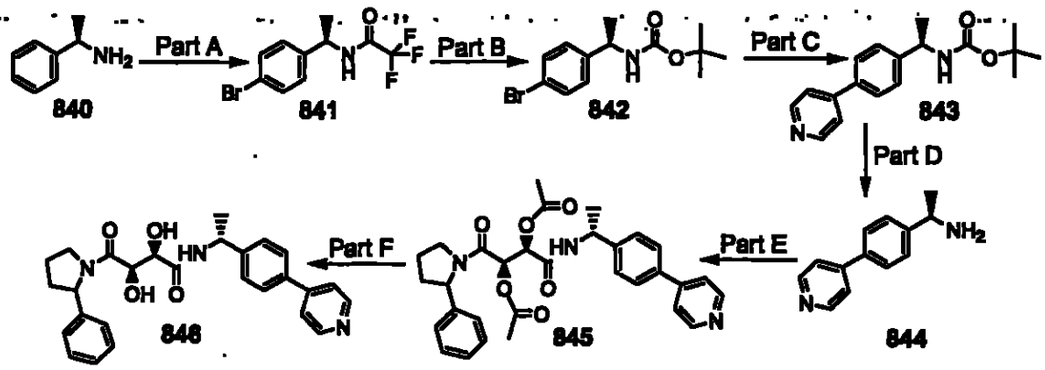
Part A:

A mixture of 1R-(4-bromo-phenyl)-ethylamine (837) (0.18 mL, 1.25 mmol), **230** (349 mg, 1.0 mmol), DIEA (357 µL, 2.0 mmol) and HATU (456 mg, 1.2 mmol) in NMP (10 mL) was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with bicarbonate solution, 0.1 N HCl, and brine, dried over sodium sulfate and concentrated. **838**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (d, 1H, J = 7.6 Hz), 7.49 (dd, 2H, J = 2.0, 6.8 Hz), 7.37 – 7.25 (m, 6H), 5.56 (ABq, 2H, J = 6.8 Hz), 4.99 (d, 1H. J = 13.2 Hz), 4.89 (m, 2H), 4.70 (d, 1H, J = 16.0 Hz), 4.51 (d, 1H, J = 16.4 Hz), 2.09 (s, 3H), 2.03 (s, 3H), 1.32 (d, 3H, J = 7.2 Hz).

Part B:

To **838** (135 mg, 0.26 mmol), $PdCl_2$(dppf) (22 mg, 0.03 mmol), potassium phosphate (166 mg, 0.78 mmol) in dioxane (5 mL) under argon atmosphere was added benzyl-9-BBN (0.5 M in THF, 1.3 mL, 0.65 mmol). The reaction mixture was heated to 60 °C overnight. The reaction mixture was filtered through a celite pad and the pad was rinsed with ethyl acetate. The filtrate was concentrated. The crude product was dissolved in methanol (5 mL) and potassium carbonate (4 mg) was added. The reaction mixture was stirred for 1 hour, filtered and concentrated to afford **839** as a solid (50 mg, 42%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, 1H, J = 7.6 Hz), 7.34 – 7.10 (m, 13H), 5.03 (d, 1H. J = 14.4 Hz), 4.90 (m, 2H), 4.72 (d, 1H, J = 16.8 Hz), 4.58 (m, 2H), 4.20 (d, 1H, J = 3.2 Hz), 3.87 (s, 2H), 1.37 (d, 3H, J = 7.2 Hz); HPLC-MS t_R = 1.89 min (UV_{254nm}); mass calculated for formula $C_{27}H_{28}N_2O_4$ 444.2, observed LCMS m/z 445.1 (M+H).

Example 21B:



Part A:

CH_2Cl_2 (300 mL) and trifluoroacetic anhydride (100 g, 0.476 mol) were added to a 2 liter 3-necked flask. The flask was equipped with a drying tube and cooled in an ice-water bath. A solution of (R)-α-methylbenzylamine (840) (53.72 g, 0.443 mol) dissolved in 100 mL of CH_2Cl_2 was added over 40 min. The ice bath was removed and the reaction mixture was stirred at rt for 3 h. The reaction mixture was cooled with an ice-water bath and methanesulfonic acid (110 mL, 1.69 mol) was added. Dibromodimethylhydantoin (65 g, 0.227 mol) was added in portions over 1 hr 15 min. The reaction mixture was left stirring overnight then poured into a solution prepared from 60 mL of 1 M $NaHSO_3$ and 500 mL of ice and water. The layers were separated and the aqueous layer was extracted with 100 mL of CH_2Cl_2. The combined organic layer was washed with water and brine, then dried with $MgSO_4$. The solvent was evaporated to give a white solid. This material was recrystallized from Et_2O/Hexanes to give compound 841. MS (EI) m/z M+H Obsd 297.16

Part B:

Compound 841 (8.09 g, 27.3 mmol) was dissolved in 40 mL of dioxane, 10 mL of methanol, and 40 mL of 1 M aqueous LiOH. The reaction mixture was stirred at rt for 2.5 h under N_2. Boc anhydride (7.45 g, 34.1 mmol) and EtOAc (25 mL) were added and the reaction mixture was stirred at rt under N_2 for 1.5 h. The reaction mixture was diluted with EtOAc and brine. The layers were separated and the aqueous layer was extracted with EtOAc. The combined

organic layer was washed with citric acid, water, and brine, then dried with $MgSO_4$. The solvents were evaporated and the crude product was purified via flash sgc using a 5%-10% EtOAc/Hexanes gradient as the mobile phase. White solid **842** (7.95 g) was obtained as product. MS (EI) m/z M+Na Obsd 324.01

Part C:

Compound **842** (1.11 g, 3.69) and 4-pyridine boronic acid (0.55 g, 4.48 mmol) were suspended in 1-propanol (8 mL) and stirred for 25 min at 40 °C. Palladium (II) acetate (55 mg, 0.24 mmol) and water (4 mL), were added, followed by sodium carbonate (0.47 g, 4.43 mmol) and triphenyl phosphine (197 mg 0.75 mmol). The reaction mixture was stirred under N_2 at 80 °C for 21 h. The reaction mixture was allowed to cool to rt and diluted with EtOAc and 0.5 M $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated to give an orange solid. The crude product was purified via sgc using 30% EtOAc/Hexanes, followed by 30% EtOAc/Hexanes with 2% added diisopropylethylamine added, followed by 40% EtOAc/Hexanes as the mobile phase. White solid **843** was obtained as product (0.71 g). MS (EI) m/z M+H Obsd 299.10.

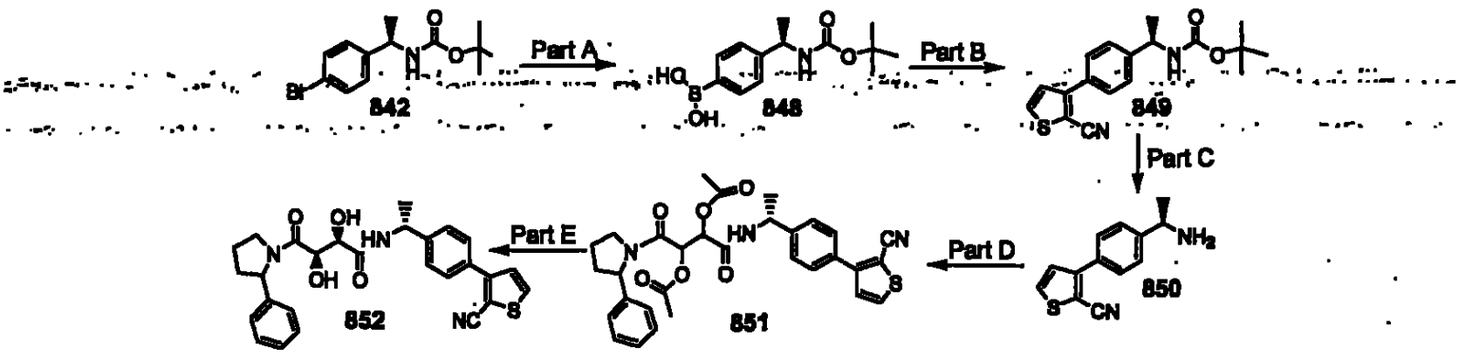
Part D:

Compound **843** (0.70, 2.3 mmol) was suspended in 22 mL of 4 M HCl in dioxane and 8 mL of CH_2Cl_2. The reaction mixture was stirred under N_2 at rt for 6 h, then concentrated to give white solid **844** (0.70 g). MS (EI) m/z M+H Obsd 199.09.

Parts E & F:

Compound **846** was prepared using procedures similar to those described in Example 14, Steps E&F. MS (EI) m/z M+H Obsd 460.1

Example 21C:



Part A:

A 500 mL Schlenck Flask equipped with a stir bar was flame dried under N_2 flow, capped with a septum, and allowed to cool to rt. A solution of n-butyl lithium in hexanes (55 mL, 2.5 Molar, 137.4 mmol) was added via syringe. The flask was cooled in a dry ice/2-propanol bath. Tetramethylethylene diamine (TMEDA-19.0 g, 167 mmol) was added. Compound **842** (20 g, 66.8 mmol) was dissolved in anhydrous THF (200 mL) and added to the reaction mixture over 30 min via addition funnel. The reaction mixture was stirred at -78 C for 15 min. Triethyl borate was added (21.4 mL, 176 mmol) as a solution in 40 mL of anhydrous THF. The reaction mixture was stirred for 30 min. The reaction mixture was quenched at -78 °C with 1.0 M aq HCl to a pH of 2, then allowed to warm to rt. The reaction mixture was extracted with EtOAc. The organic layer was dried with $MgSO_4$ and concentrated to dryness. The crude product was purified via sgc using 5:95 MeOH:CH_2Cl_2 as the mobile phase. White solid **848** was obtained as product (3.8 grams). Data for **848**: ^{1}HNMR (400 MHz, CD_3OD) δ 7.56 (d, J = 8Hz, 2H), 7.29 (d, J = 8Hz, 2H), 4.58-4.64 (m, 1H), 1.41-1.36 (m, 12H).

Part B:

Compound **848** (300 mg, 1.13 mmol), 3-bromo-2-cyanothiophene (192 mg, 1.02 mmol), acetonitrile (4 mL), Dichloro[1, 1'-bis(diphenylphosphino) ferrocene] palladium(II) dichloride (Strem, 171 mg, 0.23 mmol), and 1.25 mL of 1 M aq K_2CO_3 were added to a microwave tube equipped with a stir bar. N_2 was bubbled through the soln. and the tube was capped. The reaction mixture was irradiated at 150 °C for 5 min in a Personal Chemistry

"Companion" microwave oven. The resulting material was filtered through Celite which was washed with EtOAc. The filtrate was partitioned between EtOAc and water. The organic layer was washed with water and treated with Na_2SO_4 and Darco activated carbon. The mixture was filtered and concentrated to dryness. The crude product was purified via sgc using 60:40 Hexanes: EtOAc as the mobile phase. Compound **849** was obtained as a yellow oil (224 mg) which crystallized on standing. m/z Obsd. M+Na 350.93

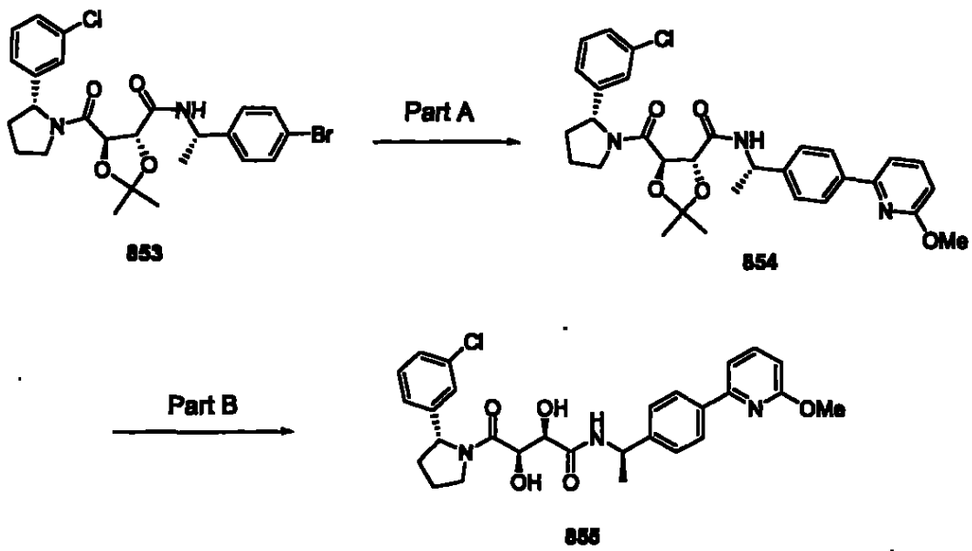
Part C:

Compound **849** (224 mg, 0.682 mmol) was dissolved in 2.8 mL of CH_2Cl_2 and 1.2 mL of trifluoroacetic acid. The reaction mixture was stirred at rt for 2 hours, then concentrated to dryness. The crude product was purified via sgc using 9:1 CH_2Cl_2 :MeOH (NH_3) as the mobile phase to give 110 mg of **850** as an oil. m/z Obsd. M+H 229.10

Parts D and E:

Compounds **851** and **852** were prepared via procedures similar to those described in Example 14, Parts D and E. Data for **851**: m/z Obsd. M+H 574.05. Data for **852**: m/z Obsd. M+Na 511.91.

Example 21D:



Compound **853** was synthesized using the procedures described in Example 1.

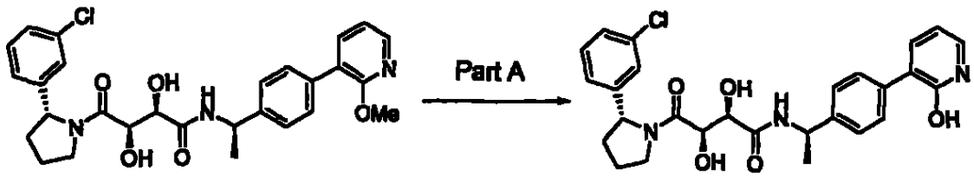
Part A:

Compound **853** (25 mg, 0.050 mmol) was dissolved in THF (1mL) and $PdP(t\text{-}Bu_3)_2$ (5 mg, 0.0097 mmol) was added under an argon atmosphere. 6-Methoxy-2-pyridylzinc bromide (0.5 M in THF, 0.2 mL) was added and the reaction was stirred at 50 °C overnight. The reaction mixture was filtered over a bed of celite and then evaporated under reduced pressure. Purification by reverse phase prep-LC afforded an off-white solid **854** (10 mg, 38%) after lyophilization. HPLC-MS t_R = 6.138 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{31}H_{34}ClN_3O_5$ 563.2, observed LCMS m/z 564.1 (M+H).

Part B:

Compound **854** (10 mg, 0.0188 mmol) was dissolved in MeOH (0.3 mL) and TFA (4 mL) and stirred for 2 hours at room temperature. The solvent was removed to provide the pure product **855** (9.36 mg, 95%). HPLC-MS t_R = 5.098 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{28}H_{30}ClN_3O_5$ 523.1, observed LCMS m/z 524.1 (M+H).

Example: 21E:



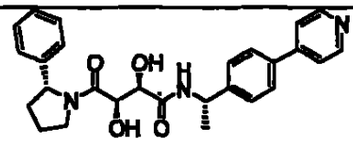
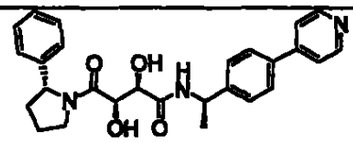
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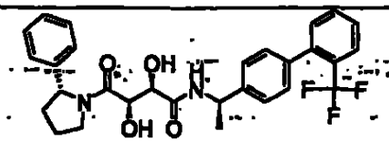
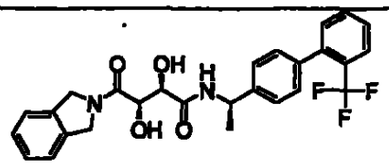
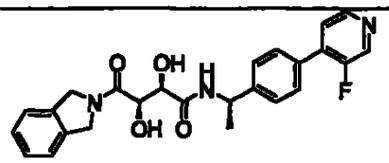
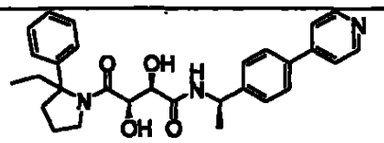
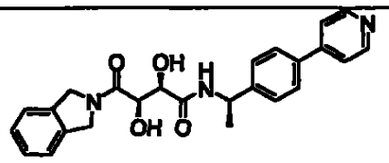
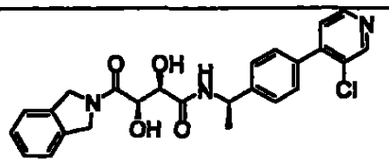
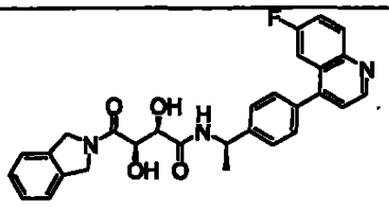
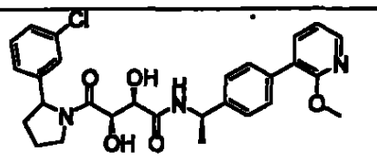
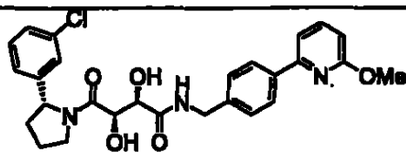
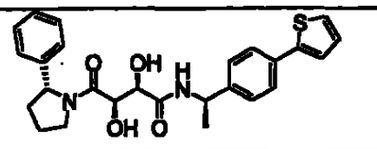
Compound 856 was synthesized using the Suzuki procedures desribed in Example 12.

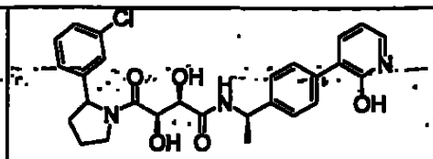
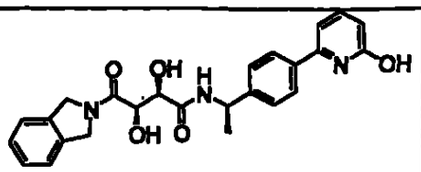
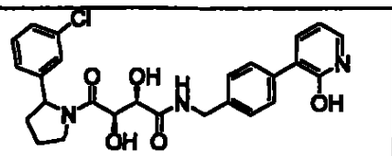
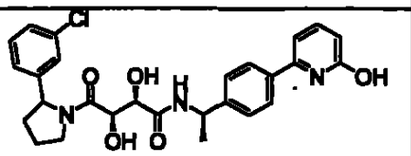
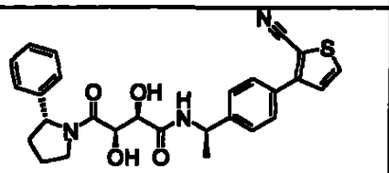
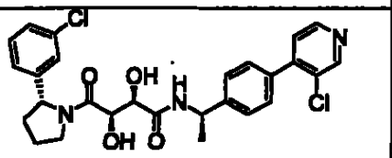
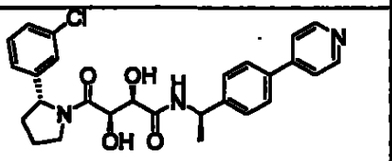
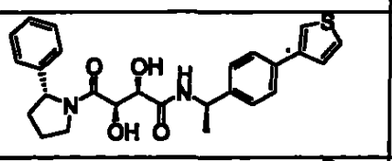
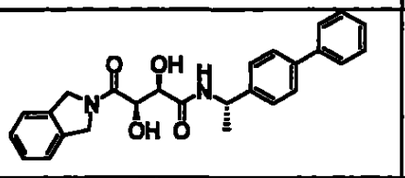
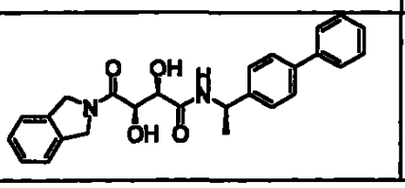
Part A:

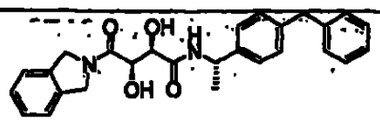
Compound 856 (160 mg, 0.30 mmol) was dissolved in acetonitrile (5 mL) and sodium iodide (140 mg, 1.0 mmol) was added followed by trimethylsilylchloride (105 mg, 1.0 mmol). Water (0.1 mL) was added and the reaction mixture was stirred at reflux for 4 hours. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded an off-white solid 857 (86 mg, 56%) after lyophilization. HPLC-MS t_R = 3.72 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{27}H_{28}ClN_3O_5$ 509.1, observed LCMS m/z 510.1 (M+H).

The following table contains compounds made using the procedures described in Example 21 A – E.

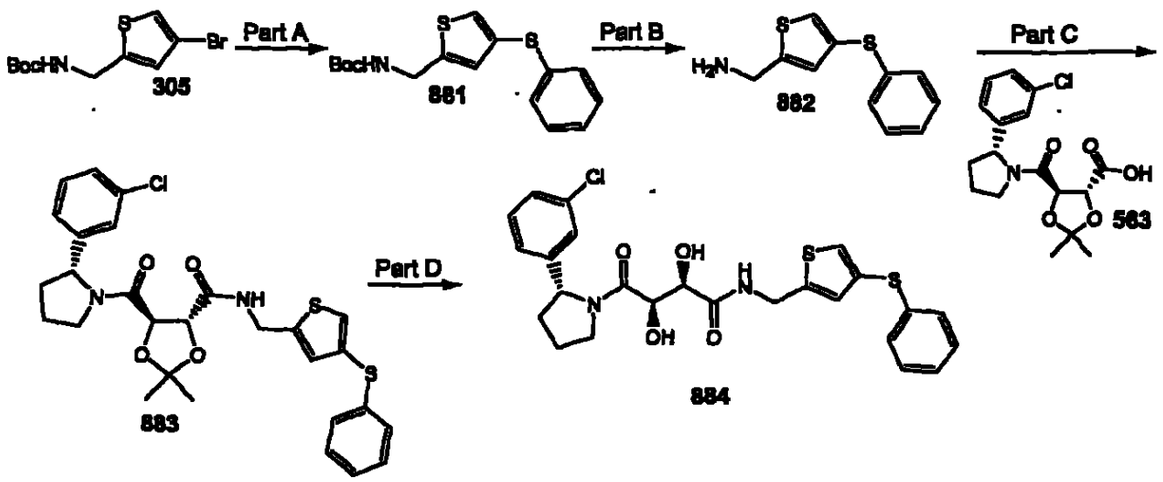
Compound #	Structure	Exact mass	MS m/e (M+H)
858		459.2	460.1
859		459.2	460.1

860		526.2	527.7
861		498.2	499.0
862		449.2	450.0
863		487.3	488.1
864		431.2	432.1
865		465.2	466.1
866		499.2	500.0
867		523.2	524.2
868		509.2	510.1
869		464.2	464.9

870		509.2	510.2
871		447.2	448.2
872		495.2	496.2
873		509.2	510.2
874		489.2	511.9 (M+Na)
875		527.1	528.1
876		493.1	494.1
877		464.2	464.9
878		430.2	431.2
879		430.2	431.2

880		444.2	445.2

Example 22



Part A:

To **305** (100 mg, 0.34 mmol) in THF (2 mL) at –90 °C under argon was added n-butyl lithium (1.6 M, 0.140 mL, 0.22 mmol) dropwise. The reaction mixture was stirred for 30 minutes at –90 °C. Then diphenyl disulfide (90 mg, 0.4 mmol) in THF (1 mL) was added slowly. The reaction mixture was stirred for 30 minutes at –90 °C. The reaction mixture was quenched with saturated ammonium chloride solution and warmed to room temperature. The mixture was diluted with ethyl acetate (10 mL) and the layers were separated. The organic layer was washed with water and brine. Dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 5% EtOAc/hexane) afforded **881** (19 mg, 59%). HPLC-MS t_R = 2.28 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{19}NO_2S_2$ 321.09, observed LCMS m/z 322.2 (M+H).

Part B:

To **881** (66 mg, 0.2 mmol) was added 4N HCl in dioxane (1 mL). The reaction mixture was stirred for 1 hour. The solvents were removed in vacuo and the crude product was used without further purification. HPLC-MS t_R = 1.12 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{11}NS_2$ 221.0, observed LCMS m/z 222.1 (M+H).

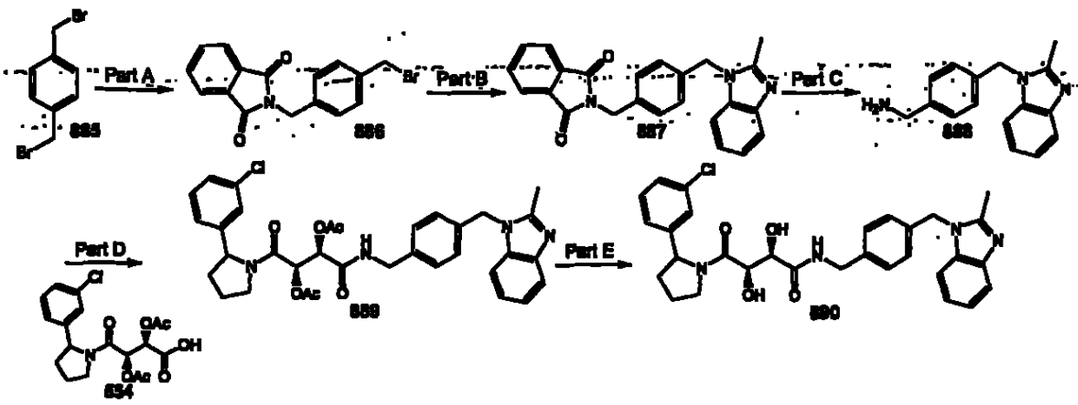
Part C:

To **563** (56 mg, 0.16 mmol) in DMF (2 mL) was added **882** (66 mg, 0.26 mmol), DIEA (82 µL, 0.46 mmol) and HATU (78 mg, 0.24 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Compound **883** (43 mg, 48%) was used without further purification. HPLC-MS t_R = 2.40 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{29}ClN_2O_4S_2$ 556.1, observed LCMS m/z 557.0 (M+H).

Part D:

Compound **883** (25 mg, 0.04 mmol) was dissolved in 80:20 TFA:water (1 mL) and stirred for 1.5 hours. The reaction was quenched with 1:1 water:acetonitrile (1 mL) and the solvents were removed in vacuo. Purification by reverse phase prep-LC afforded **884** as a white solid (5 mg, 22%). HPLC-MS t_R = 2.04 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{25}ClN_2O_4S_2$ 516.1, observed LCMS m/z 517.1 (M+H).

Example 23:



Part A:

A mixture of □□'-dibromo-p-xylene (885) (528 mg, 2.0 mmol), phthalimide (294 mg, 2.0 mmol) and cesium carbonate (717 mg, 2.2 mmol) in DMF (5 mL) was stirred for 4 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in DCM and washed with bicarbonate solution and brine. The organic layer was dried over sodium sulfate and concentrated. Recrystallization from 75% EtOAc/hexanes removed the dialkylated product. The mother liquor was concentrated and the monoalkylated product **886** was isolated by column chromatography (SiO_2, 50% DCM/Hex) as a white solid (110 mg, 16%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 2H, J = 2.4 Hz), 7.72 (d, 2H, J = 2.4 Hz), 7.41 (d, 2H, J = 7.2 Hz), 7.34 (d, 2H, J = 7.2 Hz), 4.84 (s, 2H), 4.46 (s, 2H).

Part B:

A mixture of **886** (110 mg, 0.33 mmol), 2-methyl benzimidazole (44 mg, 0.33 mmol) and cesium carbonate (114 mg, 0.35 mmol) in DMF (5 mL) was stirred overnight at room temperature. The reaction mixture was filtered and concentrated. The residue was partitioned between bicarbonate solution and ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated to afford **887** as an off-white solid (120 mg, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 2H), 7.70 (m, 2H), 7.37 (d, 2H, J = 8.0 Hz), 7.25 – 7.18 (m, 4H), 7.00 (d, 2H, J = 8.7 Hz), 5.30 (s, 2H), 4.82 (s, 2H), 2.57 (s, 3H).

Part C:

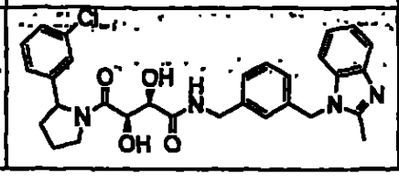
A mixture of **887** (120 mg, 0.31 mmol) and hydrazine hydrate (61 µL, 1.26 mmol) in ethanol (10 mL) was heated to reflux for 3 hours. The reaction mixture was concentrated. The residue was dissolved in ethyl acetate and washed with bicarbonate solution. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated to afford **888** as a yellow oil (31 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, 1H, J = 1.2, 8.4 Hz), 7.51 (dd, 1H, J = 3.2, 6.4 Hz), 7.26 – 7.17 (m, 4H), 7.01 (d, 2H, J = 8 Hz), 5.30 (s, 2H), 3.85 (s, 2H), 2.60 (s, 2H), 2.57 (s, 3H).

Part D:

A mixture of **888** (31 mg, 0.12 mmol), **554** (40 mg, 0.1 mmol), DIEA (38 µL, 0.22 mmol) and HATU (46 mg, 0.12 mmol) in DMF (2 mL) was stirred overnight. The DMF was removed in vacuo. The residue was dissolved in ethyl acetate, washed with bicarbonate solution and brine, dried over sodium sulfate and concentrated to afford **889** as a film (61 mg, 96%). HPLC-MS t_R = 1.38 min ($UV_{254\ nm}$); mass calculated for formula C34H35ClN4O6 630.2, observed LCMS m/z 631.2 (M+H).

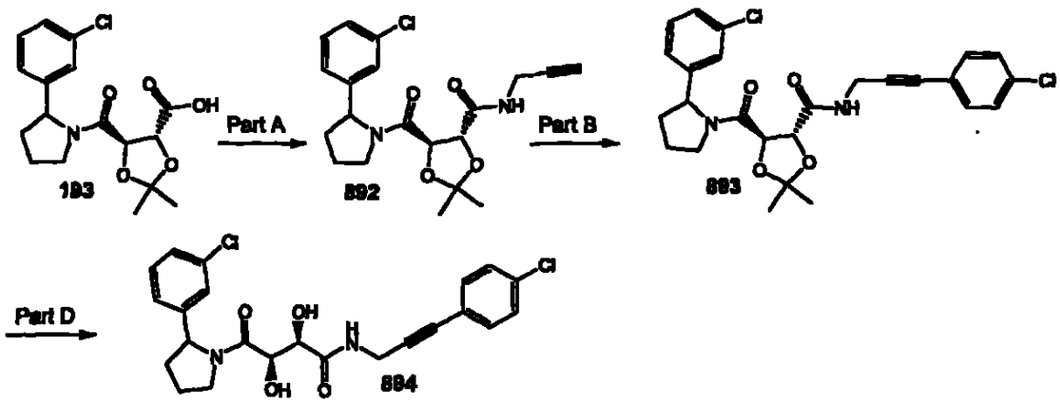
Part E:

To **889** (61 mg, 0.097 mmol) in methanol (2 mL) was added anhydrous hydrazine (5 µL, 0.16 mmol). The reaction mixture was stirred overnight, concentrated, purified by reverse phase prep-LC and treated with HCl to afford **890** as an HCl salt (19 mg, 33%). HPLC-MS t_R = 3.42 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{30}H_{31}ClN_4O_4$ 546.2, observed LCMS m/z 547.2 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
891		546.2	547.2

Example 24: Alkyne linkages

Example 24A:



Part A:

To **193** (200 mg, 0.57 mmol) in DCM (5 mL) was added propargyl amine (62 mg, 1.13 mmol), DIEA (396 µL, 1.71 mmol), DMAP (7 mg, 0.06 mmol) and EDC (140 mg, 0.74 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 60% ethyl acetate/hexanes) afforded **892** as an oil (136 mg, 62%). HPLC-MS t_R = 1.76 and 1.83 min ($UV_{254\ nm}$); Mass calculated for formula $C_{20}H_{23}ClN_2O_4$ 390.1, observed LCMS m/z 391.1 (M+H).

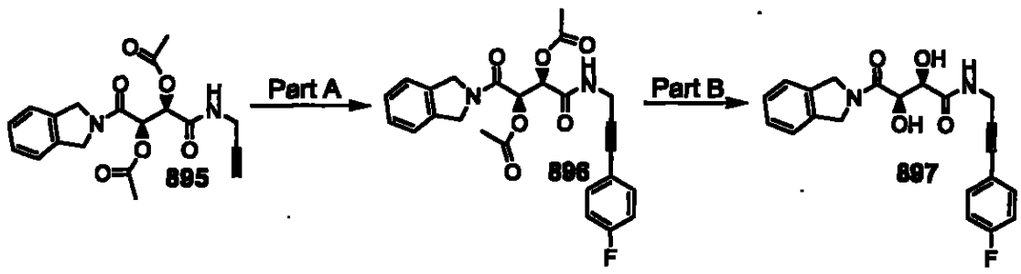
Part B:

To **892** (20 mg, 0.05 mmol) in DMF(1 mL) was added 4-chloro-iodobenzene (24 mg, 0.10 mmol), copper(I) iodide (1 mg, 0.005 mmol), $PdCl_2(Ph_3P)_2$ (1.8 mg, 0.003 mmol) and triethylamine (1 mL). The reaction mixture was stirred overnight at 50 °C under argon atmosphere. The reaction mixture was diluted with ethyl acetate, washed with 0.1 N HCl, dried over sodium sulfate and concentrated. The material was used without further purification. **893**: HPLC-MS t_R = 2.28 and 2.32 min ($UV_{254\ nm}$); Mass calculated for formula $C_{28}H_{28}Cl_2N_2O_4$ 500.1, observed LCMS m/z 501.1 (M+H).

Part C:

Compound **893** was dissolved in 4:1 TFA:water (2 mL) and stirred at room temperature for 1.5 hours. The reaction was quenched with 1:1 water:acetonitrile (2 mL) and concentrated. Purification by reverse phase prep-LC afforded **894** as a solid (2 mg). HPLC-MS t_R = 5.02 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{23}H_{22}Cl_2N_2O_4$ 460.1, observed LCMS m/z 461.2 (M+H).

Example 24 B:



Compound **895** was obtained via procedures described in Example 2A Part A using isoindoline to open the (+)-diacetyl-L-tartaric anhydride and propargyl amine in the coupling procedure.

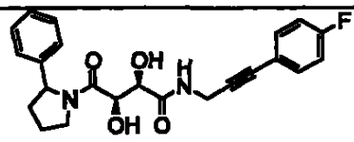
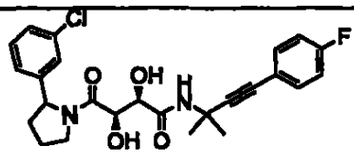
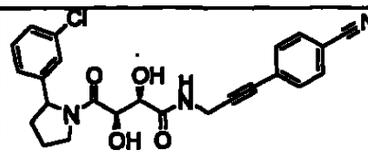
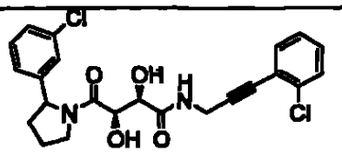
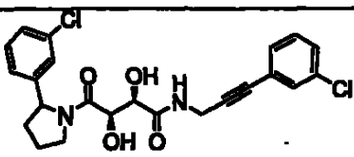
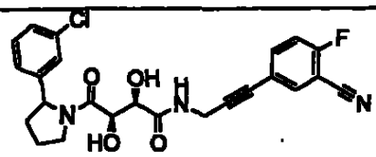
Part A:

Compound **895** (138 mg, 0.371 mmol), p-bromofluorobenzene (244 mg, 1.39 mmol), and dichlorobis(triphenylphosphine) palladium (II) (26 mg, 0.037 mmol) were dissolved in 1.5 mL CH_3CN and 1.5 mL Et_3N. The reaction mixture was heated in a sealed tube under N_2 at 80 °C for 2 h. The reaction mixture was allowed to cool to rt. EOAc and 1.0 M pH 7.0 sodium phosphate

buffer were added. The layers were separated. The organic layer was washed with water and dried with $MgSO_4$. The solvent was evaporated and the crude product was purified via sgc using 3:1 EtOAc:hexanes as the mobile phase to give 20 mg of compound **896**. MS (EI) m/z Obsd M+H 467.19

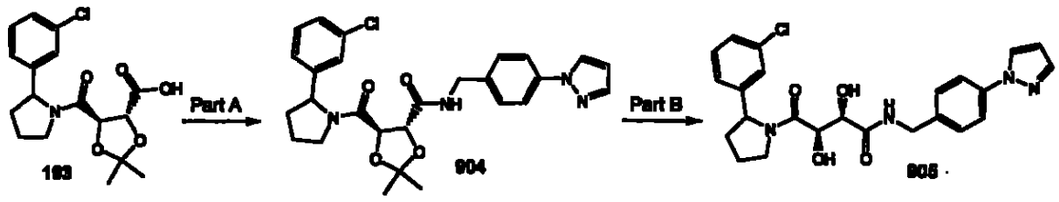
Part B:

Compound **896** (20 mg, 0.043 mmol) was dissolved in 3 mL of 2 M methanolic ammonia. The reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated to dryness. The crude product was purified via prep TLC on silica plates using 97:3 CH_2Cl_2:MeOH as the mobile phase to give 12 mg of **897**. MS (EI) m/z Obsd M+H 383.2.

Compound #	Structure	Exact mass	MS m/z (M+H)
898		410.2	411.1
899		472.2	473.2
900		451.1	452.1
901		460.1	461.2
902		460.1	461.2
903		469.1	470.2

Example 25: N-Linked biaryls

Example 25A:



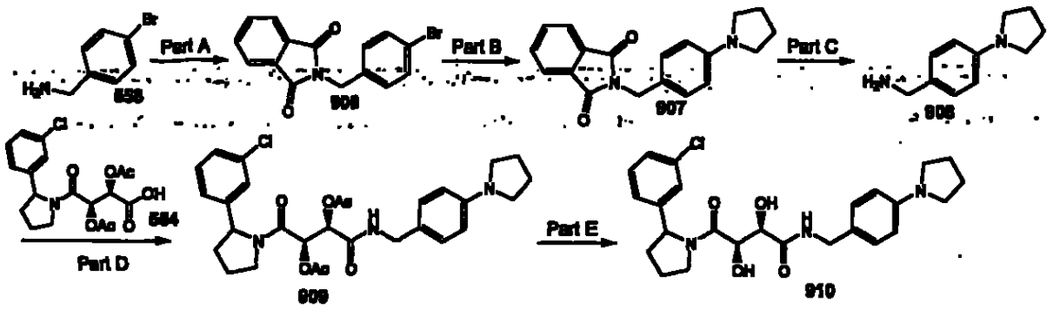
Part A:

To **193** (42 mg, 0.12 mmol) in DMF (2 mL) was added 4-pyrazol-1-yl-benzylamine (25 mg, 0.14 mmol), DIEA (50 µL, 0.29 mmol) and HATU (53 mg, 0.13 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with 0.1 N NaOH and brine, dried over sodium sulfate and concentrated. The crude material was used without further purification. **904**: HPLC-MS t_R = 1.97 and 2.03 min ($UV_{254\ nm}$); Mass calculated for formula $C_{27}H_{29}ClN_4O_4$ 508.2, observed LCMS m/z 509.2 (M+H).

Part B:

Compound **904** was dissolved in 4:1 TFA:water (2 mL) and stirred at room temperature for 2 hours. The reaction was quenched by the addition of 1:1 acetonitrile:water (4 mL) and the solvents were removed in vacuo. Purification by reverse phase prep-LC afforded **905** as a white solid (33 mg). HPLC-MS t_R = 4.16 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{24}H_{25}ClN_4O_4$ 468.2, observed LCMS m/z 469.2 (M+H).

Example 25B:



Part A:

A mixture of 4-bromobenzyl amine hydrochloride (**558**) (2.0 g, 9.0 mmol), monomethyl phthalate (1.94 g, 10.8 mmol), EDC (2.07 g, 10.8 mmol), HOBt (1.82 g, 13.5 mmol) and triethylamine (3.8 mL, 27.0 mmol) in DCM (50 mL) was stirred overnight. The reaction mixture was diluted DCM and washed with 1.0 N HCl, water, bicarbonate solution and brine, dried over sodium sulfate and concentrated. Recrystallization of the mixture from ethyl acetate afforded **906** as a solid (1.72 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.70 (m, 2H), 7.42 (d, 2H, J = 8.2 Hz), 7.29 (d, 2H, J = 8.2 Hz), 4.79 (s, 2H). HPLC-MS t_R = 2.05 min ($UV_{254\ nm}$); Mass calculated for formula $C_{15}H_{10}BrNO_2$ 315.0, observed LCMS m/z 316.0 (M+H).

Part B:

A mixture of **906** (100 mg, 0.32 mmol), pyrrolidine (34 mg, 0.48 mmol), potassium phosphate (171 mg, 0.80 mmol), $Pd_2(dba)_3$ (8 mg, 0.008 mmol) and 2-(dicyclohexylphosphino)biphenyl (11 mg, 0.032 mmol) in dioxane (3 mL) were stirred under argon atmosphere at 90 °C overnight. The reaction mixture was filtered through celite and concentrated. The yellow residue was purified by column chromatography (SiO_2, 5% EtOAc/DCM) to afford **907** (82 mg, 84%). HPLC-MS t_R = 2.13 min (UV_{254nm}); Mass calculated for formula $C_{19}H_{18}N_2O_2$ 306.1, observed LCMS m/z 307.2 (M+H).

Part C:

To **907** (82 mg, 0.268 mmol) in 1:1 ethanol:DCM (4 mL) was added hydrazine monohydrate (52 µL, 1.07 mmol). The reaction mixture was heated to reflux overnight. The precipitate was removed by filtration and the filtrate was concentrated. The residue was dissolved in ethyl acetate, washed with water

and brine, dried over sodium sulfate and concentrated to afford **908** as a white solid (23 mg, 49%). HPLC-MS t_R = 0.86 min (UV_{254nm}); Mass calculated for formula $C_{11}H_{16}N_2$ 176.1, observed LCMS m/z 177.1 (M+H).

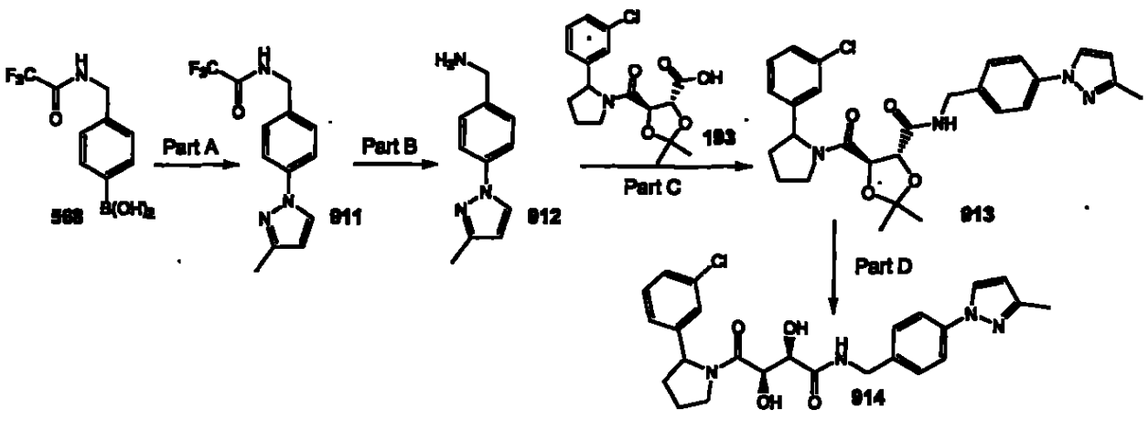
Part D:

A mixture of **554** (30 mg, 0.076 mmol), **908** (17.3 mg, 0.098 mmol), DIEA (40 µL, 0.226 mmol), DMAP (1 mg) and HATU (37 mg, 0.098 mmol) in DMF (1 mL) was stirred overnight. The reaction mixture was poured in water and extracted with ethyl acetate. The combined organic layers were washed with 0.1 N NaOH, water and brine, dried over sodium sulfate and concentrated. Compound **909** was used without further purification.

Part E:

To **909** in 3:1 methanol:water (2 mL) was added potassium carbonate (20 mg). The reaction mixture was stirred for 30 minutes. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded **910** as a solid (2 mg). HPLC-MS t_R = 3.57 min ($UV_{254\ nm}$ 10 min); Mass calculated for formula $C_{25}H_{30}ClN_3O_4$ 471.2, observed LCMS m/z 472.2 (M+H).

Example 25C:



Compound 568 was prepared according to the procedure of Maku, S. et. al. (*J. Comb. Chem.* 2003, 5, 379)

Part A:

A mixture of compound 568 (740 mg, 3 mmol), 3-methylpyrazole (123 mg, 1.5 mmol), copper (II) acetate (409 mg, 2.25 mmol), pyridine (0.25 ml), 3 mmol) in tetrahydrofuran (10 mL) was stirred at room temperature open to the air for 60 hours. The reaction mixture was diluted with ethyl acetate, filtered through celite and concentrated. Purification by column chromatography (SiO_2, 30% ethyl acetate/hexanes to 50% ethyl acetate/ hexane) afforded the product as an impure white solid (450 mg). Further purification by column chromatography (SiO_2, dichloromethane to 5% ethyl acetate / dichloromethane) afforded 911 as a solid (295 mg, 70% purity). ^1H NMR (400 MHz, acetone-d_6) δ 8.97 (bs, 1H, NH), 8.16 (d, 1H, J = 2.4 Hz), 7.76 (d, 2H, J = 8.4 Hz), 7.42 (d, 2H, J = 8.8 Hz), 6.27 (d, 1H, J = 2.4 Hz), 4.55 (d, 2H, J = 5.6 Hz), 2.28 (s, 3H); HPLC-MS t_R = 1.62 min ($UV_{254\ nm}$); Mass calculated for formula $C_{13}H_{12}F_3N_3O$ 283.1, observed LCMS m/z 284.2 (M+H).

Part B:

To 911 (165 mg, 0.43 mmol) in 1:1 methanol: water (2 mL) was added 10% potassium carbonate in 2:1 methanol:water (7mL). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated and the residue was dissolved in ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over sodium sulfate and concentrated to afford 912 as a white solid (69 mg, 86%). HPLC-MS t_R = 0.75 min ($UV_{254\ nm}$); Mass calculated for formula $C_{11}H_{13}N_3$ 187.1, observed LCMS m/z 188.1 (M+H).

Part C:

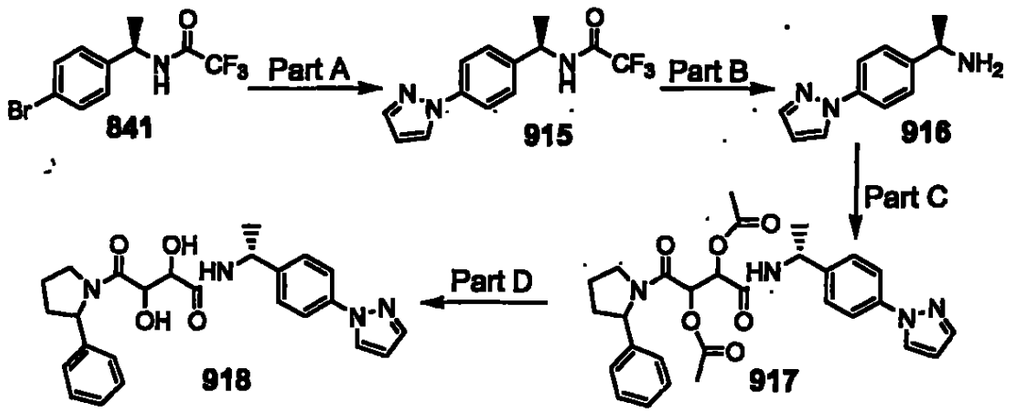
To 193 (65 mg, 0.18 mmol) in DMF (2 mL) was added 912 (38 mg, 0.2 mmol), DIEA (70 μL, 0.4 mmol) and HATU (76 mg, 0.21 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers

were washed with 0.1 N NaOH and brine, dried over sodium sulfate and concentrated. Compound **913** was used without further purification. HPLC-MS t_R = 2.05 and 2.09 min ($UV_{254\ nm}$); Mass calculated for formula $C_{28}H_{31}ClN_4O_4$ 522.2, observed LCMS m/z 523.2 (M+H).

Part D:

Compound **913** was dissolved in 4:1 TFA:water (2 mL) and stirred at room temperature for 2 hours. The reaction was quenched by the addition of 1:1 acetonitrile:water (4 mL) and the solvents were removed in vacuo. Purification by reverse phase prep-LC afforded **914** as a white solid (35 mg). HPLC-MS t_R = 4.31 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{25}H_{27}ClN_4O_4$ 482.1, observed LCMS m/z 483.1 (M+H).

Example 25D:



Part A:

Compound **841** (0.5 g, 1.69 mmol), pyrazole (0.14 g, 2.05 mmol), CuI (0.064 g, 0.336 mmol), 1,10-phenanthroline (0.12 g, 0.66 mmol), and Cs_2CO_3 (1.1 g, 3.37 mmol) were dissolved in dimethylacetamide and stirred for 20 h at 140 °C under N_2. The reaction mixture was allowed to cool to rt and diluted with EtOAc. The resulting mixture was washed with water and concentrated to dryness. The resulting material was purified via flash sgc using CH_2Cl_2:MeOH:conc NH_4OH- (200:10:1) as the mobile phase to give 0.30 g of **915**. Data for **915**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.80-7.74 (m, 3H), 7.48 (d, 2H), 6.55 (s, 1H), 5.23 (m, 1H), 1.68 (d, J=4 Hz, 2H). MS (EI) of m/z Obsd. M+H 283.97

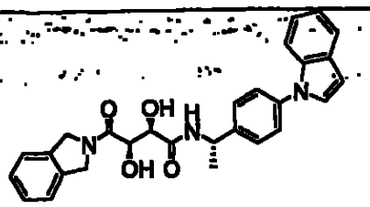
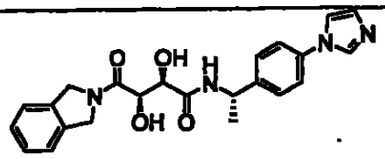
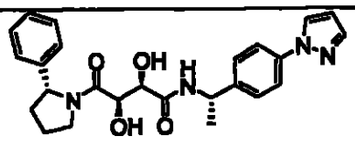
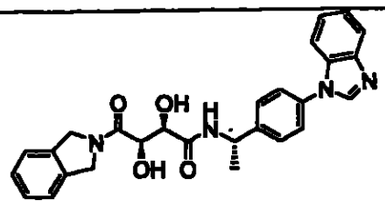
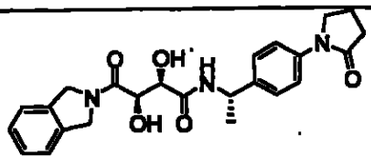
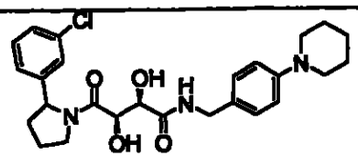
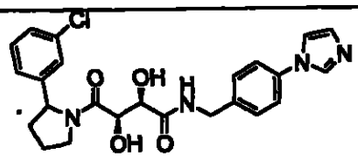
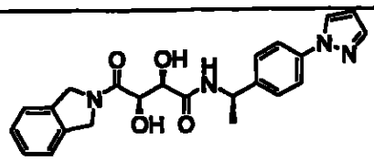
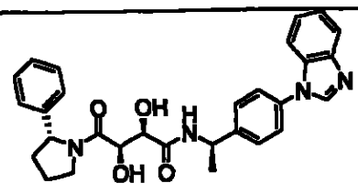
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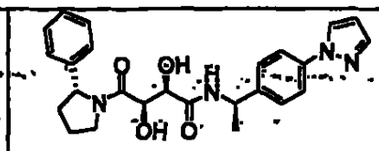
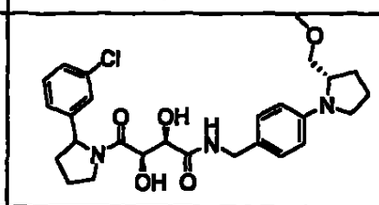
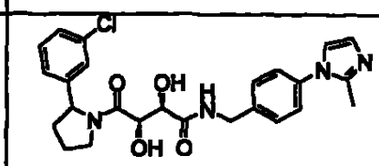
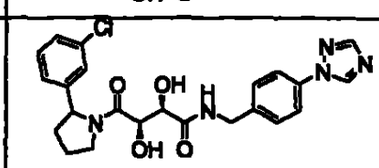
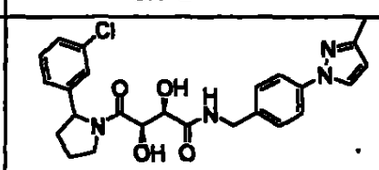
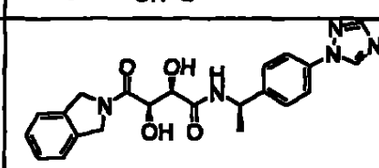
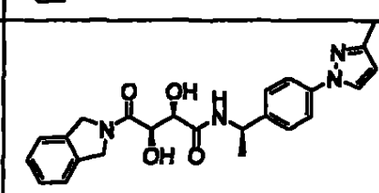
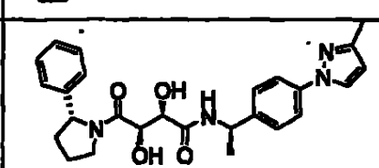
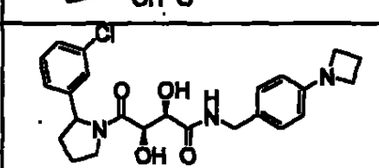
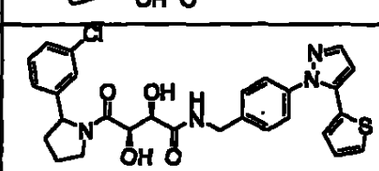
Compound **915** (0.20 g, 0.67 mmol) was dissolved in 10 mL of MeOH. Aqueous LiOH (10 mL/ 1.0 M) was added. The reaction mixture was stirred at rt for 4 h. The solution was partially concentrated in vacuo to remove the MeOH. The resulting material was extracted with EtOAc. The organic layer was washed with water, dried with Na_2SO_4, filtered, and concentrated to give 0.14 g of **916**. Data for **916**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.75 (s, 1H), 7.68 (d, J= 9 Hz, 2H), 7.47 (d, J= 9 Hz, 2H), 4.26-4.13 (m, 1H), 1.44 (d, J= 7 Hz, 3H).

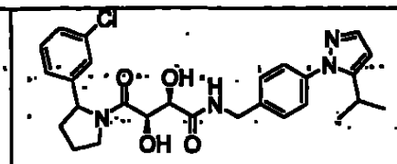
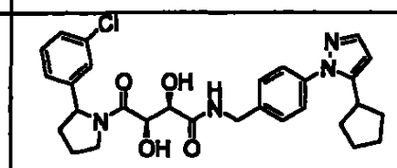
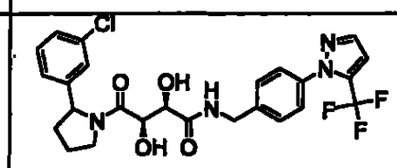
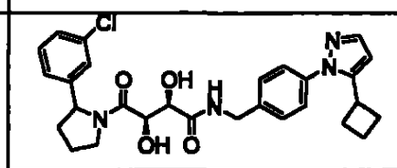
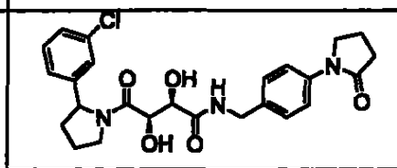
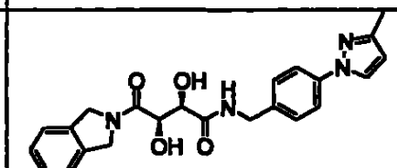
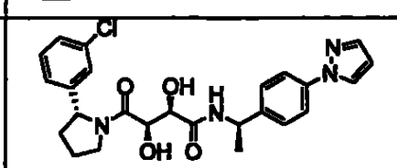
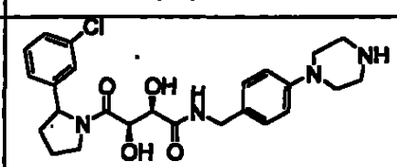
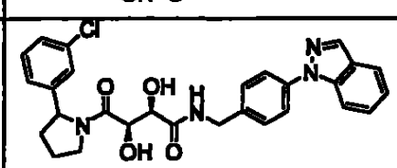
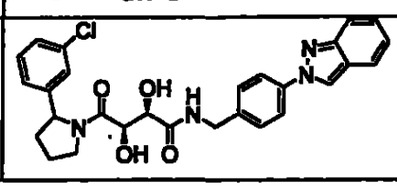
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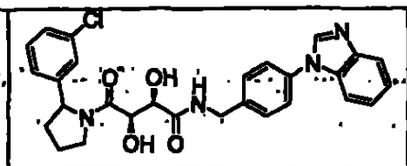
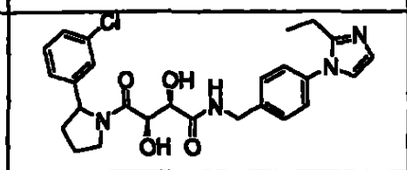
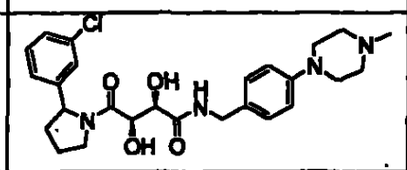
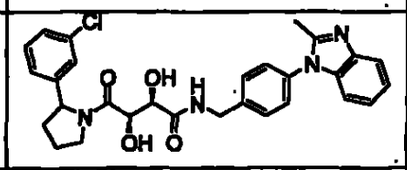
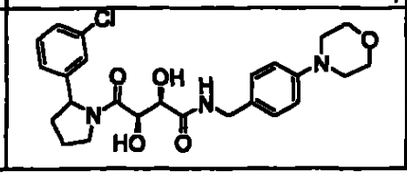
Compounds **917** and **918** were prepared via procedures similar to those described in Example 14 -Parts D and E. Data for **917**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.98-7.62 (m, 4H), 7.46-7.13 (m, 8H), 6.68-6.47 (m, 2H), 5.86-5.41 (m, 2H), 5.24-5.10 (m, 2H), 4.05-3.48 (m, 2H), 2.22-1.79 (m, 10H), 1.58-1.55 (m, 2H). Data for **918**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.80 (s, 1H), 7.75-7.59 (m, 2H), 7.48-6.95 (m, 8H), 6.52 (s, 1H), 5.32-5.13 (m, 2H), 4.97-4.05 (m, 2H), 3.99-3.68 (m, 3H), 2.46-1.80 (m, 4H), 1.62-1.51 (m, 3H); MS (EI) m/z Obsd. M+H 449.1.

Compound #	Structure	Exact mass	MS m/e

			(M+H)
919		469.2	470.1
920		420.2	421.1
921		448.2	449.1
922		470.2	471.1
923		437.2	438.2
924		485.2	486.2
925		468.2	469.1
926		420.2	421.1
927		498.2	499.1

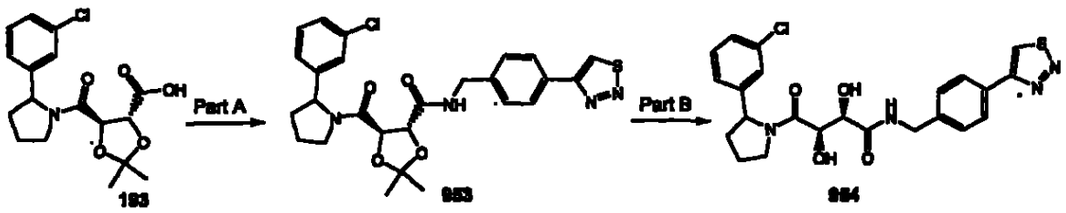
928		448.2	449.1
929		515.2	516.3
930		482.2	483.1
931		469.2	470.0
932		482.2	483.1
933		421.2	422.1
934		434.2	435.1
935		462.2	463.1
936		457.2	458.2
937		550.1	551.0

938		510.2	511.1
939		536.2	537.1
940		536.1	537.1
941		522.2	523.2
942		485.2	486.1
943		420.2	421.1
944		482.1	483.1
945		486.2	487.3
946		518.2	519.2
947		518.2	519.2

948		518.2	519.2
949		496.2	497.2
950		500.2	501.2
951		532.2	533.2
952		487.2	488.2

Example 26: Aryl-heteroaryl biaryl compounds

Example 26A:



Part A:

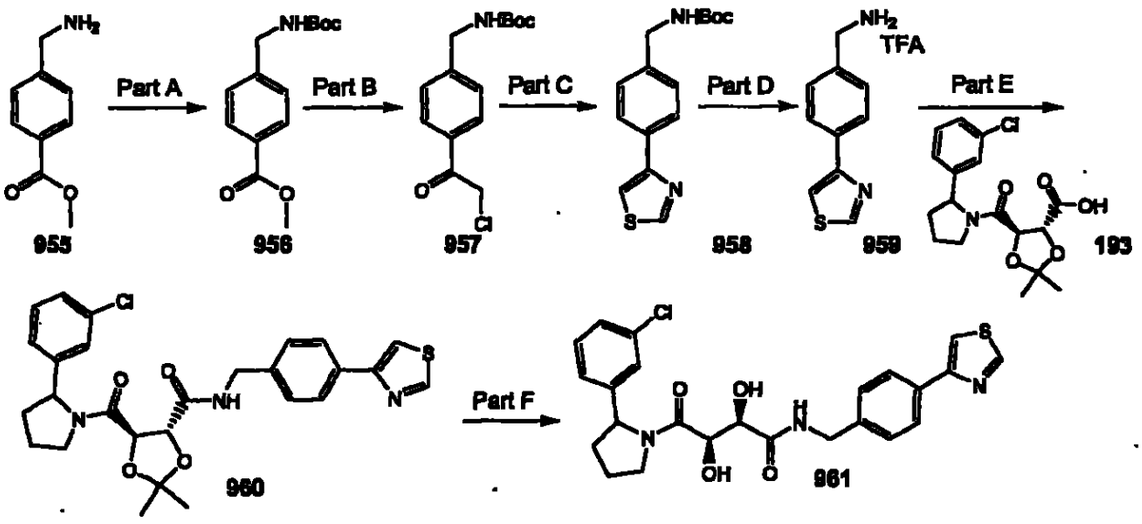
To **193** (42 mg, 0.12 mmol) in DMF (2 mL) was added 4-[1,2,3]thiadiazol-4-yl-benzylamine (25 mg, 0.13 mmol), DIEA (45 µL, 0.26 mmol) and HATU (50 mg, 0.13 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with 0.1 N NaOH and brine, dried over sodium sulfate and concentrated. The crude material

was used without further purification. 953: Mass calculated for formula C26H27ClN4O4S 526.1, observed LCMS m/z 527.1 (M+H).

Part B:

Compound 953 was dissolved in 4:1 TFA:water (2 mL) and stirred at room temperature for 2 hours. The reaction was quenched by the addition of 1:1 acetonitrile:water (4 mL) and the solvents were removed in vacuo. Purification by reverse phase prep-LC afforded 954 as a white solid (21 mg). HPLC-MS t_R = 4.21 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{23}H_{23}ClN_4O_4S$ 486.1, observed LCMS m/z 487.1 (M+H).

Example 26B: Biaryl C-C linkage



Part A:

To 4-aminomethyl-benzoic acid methyl ester (955) (2 g, 9.92 mmol) in dichloromethane (25 mL) was added Boc anhydride (2.27 g, 10.4 mmol) and triethylamine (2.76 mL, 19.84 mmol). The reaction mixture was stirred overnight. The reaction mixture was diluted with dichloromethane, washed with water and brine, dried over sodium sulfate and concentrated to afford 956 as a white solid (2.40 g, 91%). HPLC-MS t_R = 1.76 min (UV_{254nm}); Mass calculated for formula $C_{14}H_{19}NO_4$ 265.1, observed LCMS m/z 288.2 (M+Na).

Part B:
Compound **957** (257 mg, 80%) was synthesized following the procedure described in Example 10B Part A. HPLC-MS t_R = 1.77 min (UV_{254nm}); Mass calculated for formula $C_{14}H_{18}ClNO_3$ 283.1, observed LCMS m/z 306.1 (M+Na).

Part C:
To **957** (49 mg, 0.17 mmol) in DMF (2 mL) was added thioformamide (21 mg, 0.35 mmol) and pyridine (50 µL). The reaction mixture was stirred for 72 hours. The mixture diluted with ethyl acetate, washed with 0.1 N sodium hydroxide, water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded **958** (25 mg, 50%). HPLC-MS t_R = 1.80 min (UV_{254nm}); Mass calculated for formula $C_{15}H_{18}N_2O_2S$ 290.1, observed LCMS m/z 291.1 (M+H).

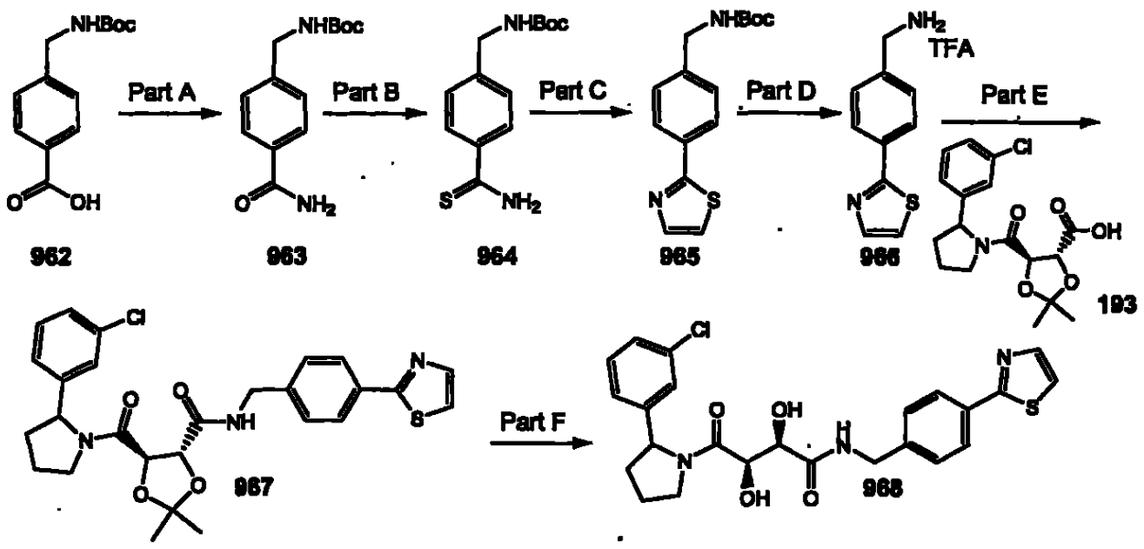
Part D:
Compound **958** (25 mg, 0.084 mmol) was stirred in dichloromethane (2 mL) and TFA (1 mL) at room temperature for 1 hour. The solvents were removed in vacuo to afford **959** as an oil (26 mg). ^1H NMR (400 MHz, CD_3OD) δ 9.07 (d, 1H, J = 2.0 Hz), 8.03 (d, 2H, J = 8.4 Hz), 7.96 (d, 1H, J = 1.6 Hz), 7.52 (d, 2H, J = 8.0 Hz), 4.16 (s, 2H).

Part E:
To **193** (23 mg, 0.065 mmol) in DMF (2 mL) was added **959** (26 mg, 0.084 mmol), DIEA (34 µL, 0.20 mmol) and HATU (32 mg, 0.084 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with 0.1 N NaOH and brine, dried over sodium sulfate and concentrated. The crude material was used without further purification. **960**: HPLC-MS t_R = 2.00 and 2.05 min ($UV_{254\ nm}$); Mass calculated for formula $C_{27}H_{28}ClN_3O_4S$ 525.2, observed LCMS m/z 526.1 (M+H).

Part F:

Compound **960** was dissolved in 4:1 TFA:water (2 ml) and stirred at room temperature for 2 hours. The reaction was quenched by the addition of 1:1 acetonitrile:water (4 mL) and the solvents were removed in vacuo. Purification by reverse phase prep-LC afforded **961** as a white solid (14 mg). HPLC-MS t_R = 4.17 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{24}H_{24}ClN_3O_4S$ 485.1, observed LCMS m/z 486.1 (M+H).

Example 26C: Biaryl C-C linkage



Part A:

To 4-(tert-butoxycarbonylamino-methyl)-benzoic acid (**962**) (500 mg, 1.99 mmol) in tetrahydrofuran (5 mL) in an ice bath was added DIEA (347 µL, 1.99 mmol). The reaction mixture was stirred for 15 minutes and ethyl chloroformate (190 µL, 1.99 mmol) was added. The reaction mixture was stirred for an additional 15 minutes and ammonia in dioxane (0.5 M, 4.18 mL, 2.09 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 2 hours. The solvent was removed in vacuo and the residue was partitioned between ethyl acetate and water. The layers

were separated and the aqueous layer was saturated with sodium chloride and extracted with ethyl acetate. The combined organic layers were washed brine, dried over sodium sulfate and concentrated to afford **963** as a white solid (540 mg), which contained some mixed anhydride as an impurity. ^{1}H NMR (400 MHz, CD_3OD) δ7.81 (d, 2H, J = 8.0 Hz), 7.35 (d, 2H, J = 8.4 Hz), 7.21 (bs, 1H, NH), 4.28 (s, 2H), 1.47 (s, 9H).

Part B:

To **963** (500 mg, 2.0 mmol) in tetrahydrofuran (20 mL) was added Lawesson's reagent (485 mg, 1.2 mmol). The reaction mixture was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate. The mixture was washed with 0.1 N sodium hydroxide, water and brine, dried over sodium sulfate and concentrated to a yellow residue. Purification by column chromatography (SiO_2, 40% ethyl acetate/hexanes) afforded **964** as a pale yellow solid (432 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 2H, J = 8.4 Hz), 7.32 (d, 2H, J = 8.4 Hz), 4.36 (d, 2H, J = 5.6 Hz), 1.48 (s, 9H).

Part C:

To **964** (70 mg, 0.263 mmol) in DMF (2 mL) was added chloroacetaldehyde (50% in water, 41 mg, 0.526 mmol). The reaction was stirred overnight at room temperature. An additional 2 equivalents of chloroacetaldehyde was added and the reaction was stirred for 24 hours. The reaction was still not complete so the mixture was heated to 50 °C for 2 days. The mixture diluted with ethyl acetate, washed with 0.1 N sodium hydroxide, water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded **965** (31 mg). HPLC-MS t_R = 1.84 min ($UV_{254\ nm}$); Mass calculated for formula $C_{15}H_{18}N_2O_2S$ 290.1, observed LCMS m/z 291.1 (M+H).

Part D:

Compound **965** (31 mg, 0.106 mmol) was stirred in dichloromethane (2 mL) and TFA (1 mL) at room temperature for 1 hour. The solvents were removed

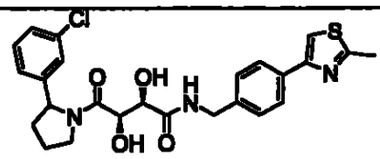
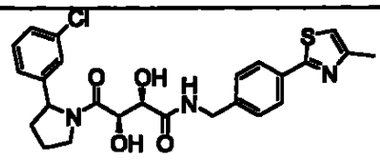
In vacuo to afford **966** as an oil (60 mg). ^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (d, 2H, J = 8.8 Hz), 7.90 (d, 1H, J = 3.2 Hz), 7.85 (d, 1H, J = 3.6 Hz), 7.56 (d, 2H, J = 8.8 Hz), 4.18 (s, 2H).

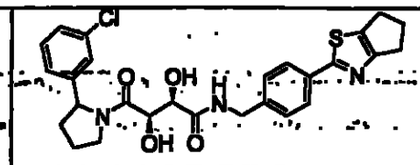
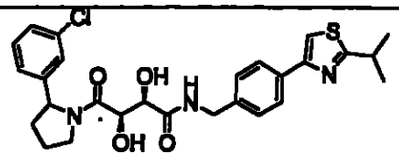
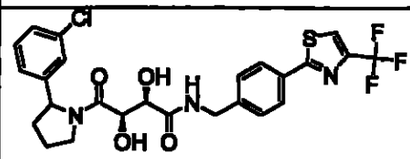
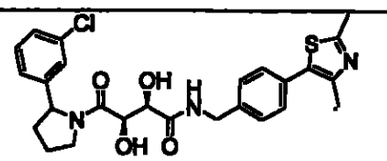
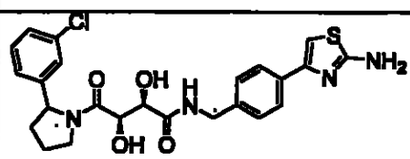
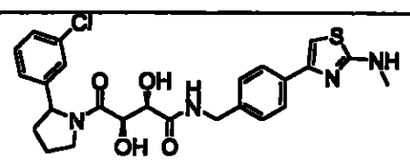
Part E:

To **193** (29 mg, 0.082 mmol) in DMF (2 mL) was added **966** (32 mg, 0.106 mmol), DIEA (43 µL, 0.25 mmol) and HATU (40 mg, 0.106 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with 0.1 N NaOH and brine, dried over sodium sulfate and concentrated. The crude material was used without further purification. **967**: HPLC-MS t_R = 2.03 and 2.08 min ($UV_{254\ nm}$); Mass calculated for formula $C_{27}H_{28}ClN_3O_4S$ 525.2, observed LCMS m/z 526.1 (M+H).

Part F:

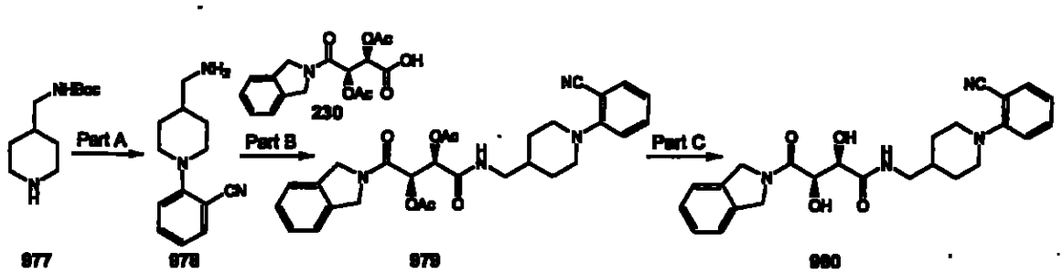
Compound **967** was dissolved in 4:1 TFA:water (2 mL) and stirred at room temperature for 2 hours. The reaction was quenched by the addition of 1:1 acetonitrile:water (4 mL) and the solvents were removed in vacuo. Purification by reverse phase prep-LC afforded **968** as a white solid (15 mg). HPLC-MS t_R = 4.21 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{24}H_{24}ClN_3O_4S$ 485.1, observed LCMS m/z 486.1 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
969		499.1	500.1
970		499.1	500.1

971		525.2	526.2
972		527.2	528.1
973		553.1	554.0
974		513.2	514.2
975		500.1	501.1
976		514.1	515.1

Example 27: Piperidine-aryl compounds

Example 27A: Piperidine-aryl



Part A:

Step 1: A mixture of piperidin-4-ylmethyl-carbamic acid tert-butyl ester (977) (2.5 g, 11.66 mmol), 2-fluoro-3-cyanobenzene (1.55 g, 12.8 mmol) and DIEA (3 mL, 17.5 mmol) in NMP (5 mL) under argon atmosphere was stirred overnight at 120 °C. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded a white solid (3.1 g).

Step 2: To the material from Step 1 (2 g) in dichloromethane (5 mL) at 0 °C was added TFA (5 mL). The mixture was stirred at room temperature for 1 hour. The mixture was quenched with acetonitrile and concentrated. The residue was dissolved in ethyl acetate, washed with sodium carbonate solution and brine, dried over sodium sulfate and concentrated to yield **978** as an oil which solidified to a waxy solid (920 mg). HPLC-MS t_R = 0.63 min ($UV_{254\ nm}$); Mass calculated for formula $C_{13}H_{17}N_3$ 215.1, observed LCMS m/z 216.2 (M+H).

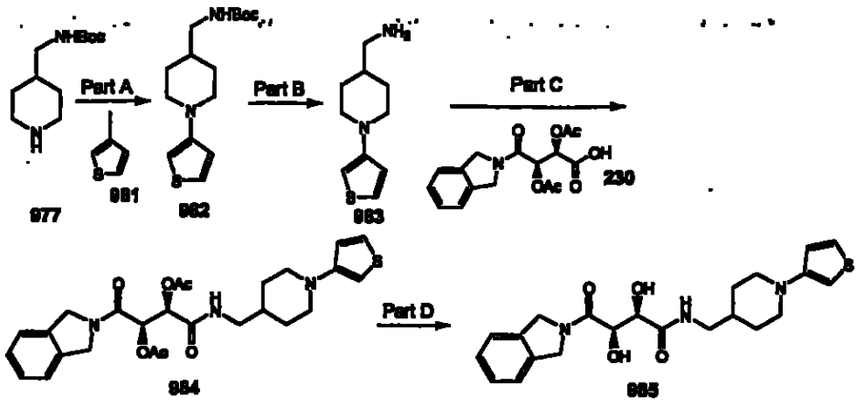
Part B:

To **978** (120 mg, 0.55 mmol) in DMF (2 mL) was added **230** (167 mg, 0.5 mmol), DIEA (0.21 mL, 1.2 mmol) and HATU (211 mg, 0.55 mmol). The mixture was stirred for 3 hours at room temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated. The material was used without further purification.

Part C:

To **979** in methanol (4 mL) was added 7.0 N ammonia in methanol (2 mL) was added. The mixture was stirred for 2 hours at room temperature and concentrated. Purification by reverse phase prep-LC afforded **980** as a white powder (80 mg) upon lypholization. HPLC-MS t_R = 4.03 min ($UV_{254\ nm}$); Mass calculated for formula $C_{25}H_{28}N_4O_4$ 448.2, observed LCMS m/z 449.2 (M+H).

Example 27B: Piperidine-aryl



Part A:

A mixture of **977** (200 mg, 0.93 mmol), 3-iodothiophene (981) (294 mg, 1.4 mmol), copper(I)iodide (36 mg, 0.19 mmol), proline (43 mg, 0.37 mmol) and potassium carbonate (258 mg, 1.87 mmol) in DMSO (1.5 mL) was stirred overnight at 80 °C in a 4 mL vial. The reaction mixture was diluted with ethyl acetate and washed with water (3X) and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate / hexanes) afforded **982** (94 mg, 34%).

Part B:

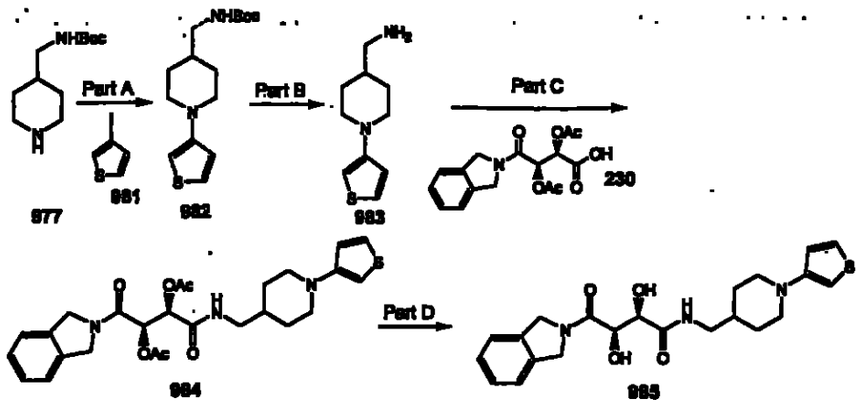
Compound **982** (42 mg, 0.14 mmol) was dissolved in DCM (2 mL) and TFA (1 mL). The mixture was stirred for 1 hour and concentrated to afford **983** in quantitative yield. HPLC-MS t_R = 0.35 min ($UV_{254\ nm}$); Mass calculated for formula $C_{10}H_{16}N_2S$ 196.1, observed LCMS m/z 197.2 (M+H).

Part C:

Compound **984** was prepared according to the procedure described in Example 27A Part B. HPLC-MS t_R = 1.36 min (UV_{254nm}); Mass calculated for formula $C_{28}H_{31}N_3O_6S$ 513.2, observed LCMS m/z 514.2 (M+H).

Part D:

Example 27B: Piperidine-aryl



Part A:

A mixture of **977** (200 mg, 0.93 mmol), 3-Iodothiophene (981) (294 mg, 1.4 mmol), copper(I)iodide (36 mg, 0.19 mmol), proline (43 mg, 0.37 mmol) and potassium carbonate (258 mg, 1.87 mmol) in DMSO (1.5 mL) was stirred overnight at 80 °C in a 4 mL vial. The reaction mixture was diluted with ethyl acetate and washed with water (3X) and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate / hexanes) afforded **982** (94 mg, 34%).

Part B:

Compound **982** (42 mg, 0.14 mmol) was dissolved in DCM (2 mL) and TFA (1 mL). The mixture was stirred for 1 hour and concentrated to afford **983** in quantitative yield. HPLC-MS t_R = 0.35 min ($UV_{254\ nm}$); Mass calculated for formula $C_{10}H_{16}N_2S$ 196.1, observed LCMS m/z 197.2 (M+H).

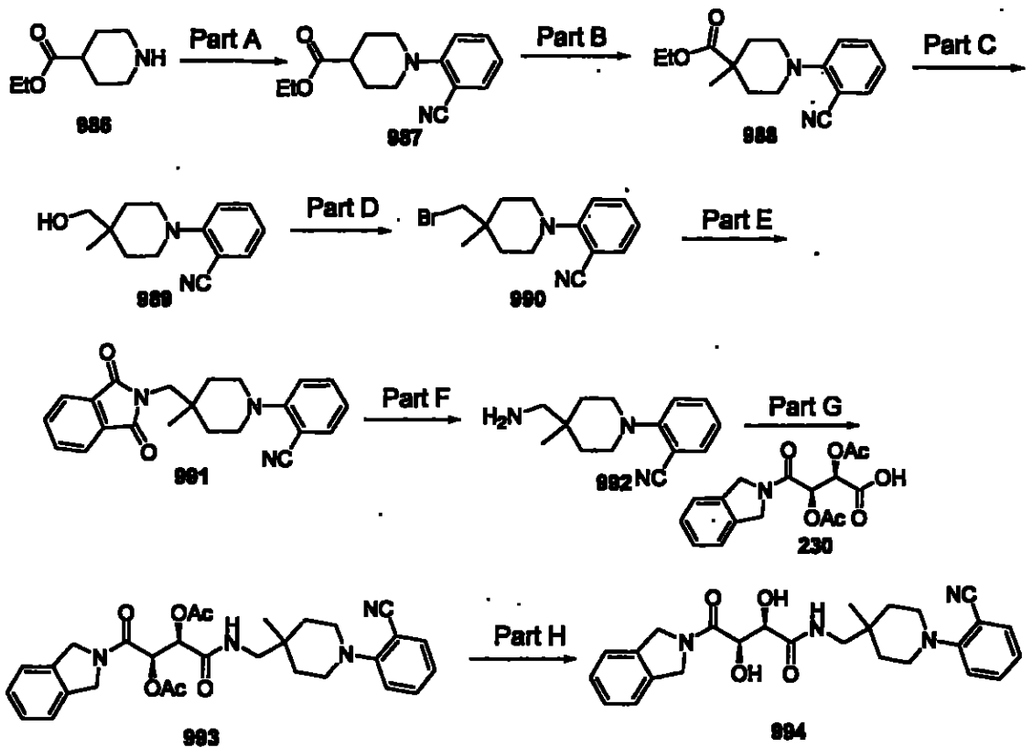
Part C:

Compound **984** was prepared according to the procedure described in Example 27A Part B. HPLC-MS t_R = 1.36 min (UV_{254nm}); Mass calculated for formula $C_{28}H_{31}N_3O_6S$ 513.2, observed LCMS m/z 514.2 (M+H).

Part D:

Compound 985 was prepared according to the method described in Example 25 Part E. HPLC-MS t_R = 2.85 min (UV_{254nm}, 10 min.); Mass calculated for formula $C_{22}H_{27}N_3O_4S$ 429.2, observed LCMS m/z 430.1 (M+H).

Example 27C:



Part A:

Compound 986 (1.13 g, 7.23 mmol) was dissolved in N-methylpyrrolidinone (4 mL) and 2-fluorobenzonitrile (0.90 g, 7.5 mmol) was added followed by DIEA (2.5 mL, 14.4 mmol). The reaction was stirred at 120 °C overnight. The cooled reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded a white solid 987 (1.5 g, 81%). HPLC-MS t_R = 1.95 (UV_{254nm}); mass calculated for formula $C_{15}H_{18}N_2O_2$ 258.14, observed LCMS m/z 259.1 (M+H).

Part B:

Diisopropylamine (0.330 mL, 2.32 mmol) was dissolved in THF (20 mL) and cooled in an ice bath. A solution of n-BuLi (2.5M in hexanes, 1 mL) was added dropwise and stirred for 15 minutes. The reaction mixture was then cooled to –78 °C and a solution of compound **987** (400 mg, 1.6 mmol) in THF (10 mL) was added dropwise. Stirring was continued at this temperature for 30 minutes before a solution of iodomethane (450 mg, 3.2 mmol) in THF (10 mL) was added dropwise. The reaction was stirred for 30 minutes at this temperature and then 1 hour at room temperature. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated to provide the product **988** that was used without purification. HPLC-MS t_R = 2.10 (UV_{254nm}); mass calculated for formula $C_{18}H_{20}N_2O_2$ 272.15, observed LCMS m/z 273.2 (M+H).

Part C:

Compound **988** was dissolved in THF (20 mL) and lithium borohydride (60 mg, 2.6 mmol) was added. The reaction mixture was refluxed for 5 hours. The cooled reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded a white solid **989** (300 mg). HPLC-MS t_R = 1.57 ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{18}N_2O$ 230.1, observed LCMS m/z 231.3 (M+H).

Part D:

Compound **989** (300 mg, 1.3 mmol) was dissolved in toluene (5 mL) and phosphorus tribromide (0.06 mL, 0.52 mmol) was added. The reaction was stirred at reflux for 3 hours. The cooled reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated to provide the product **990** that was used without purification.

Part E:

Compound **990** was dissolved in DMF (10 mL) and cesium carbonate (850 mg, 2.6 mmol) and phthalimide (190 mg, 1.3 mmol) were added and stirred overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded a white solid **991** (90 mg). HPLC-MS t_R = 2.14 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{21}N_3O_2$ 359.1, observed LCMS m/z 360.1.

Part F:

Compound **991** (90 mg, 0.25 mmol) was dissolved in ethanol (3 mL) and hydrazine hydrate (0.5 mL) was added. The reaction was stirred for 3 hours and the solids were filtered. The solvent was evaporated to provide the desired product **992** that was used without purification.

Part G:

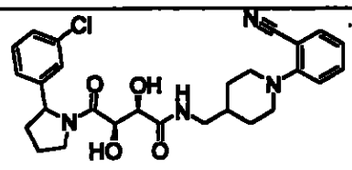
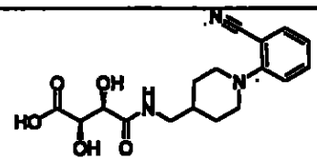
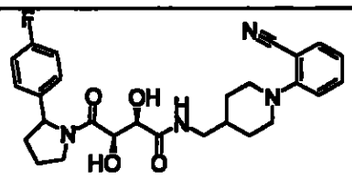
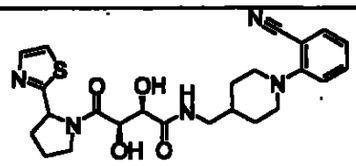
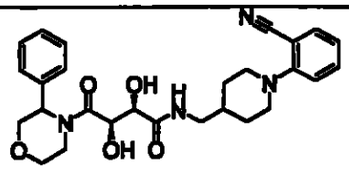
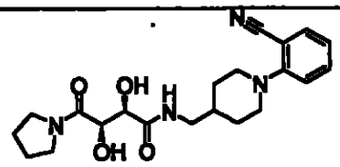
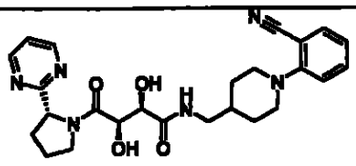
Compound **992** was dissolved in DMF (5 mL) and compound **230** (84 mg, 0.25 mmol) and HATU (114 mg, 0.30 mmol) were added and stirred overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, ethyl acetate) afforded a white foam **993** (100 mg). HPLC-MS t_R = 1.99 min ($UV_{254\ nm}$); mass calculated for formula $C_{30}H_{34}N_4O_6$ 546.2, observed LCMS m/z 547.2.

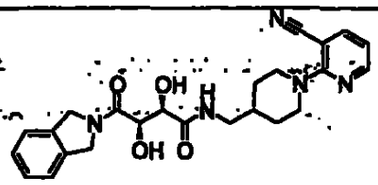
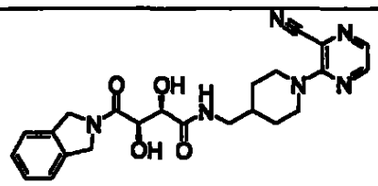
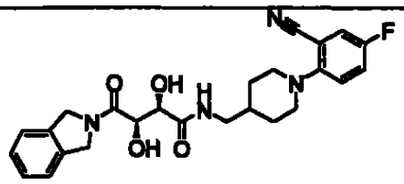
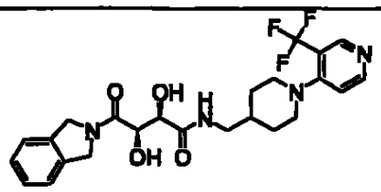
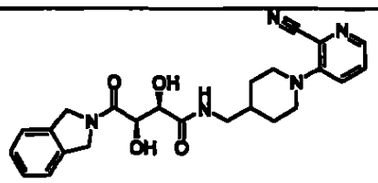
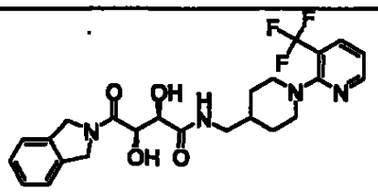
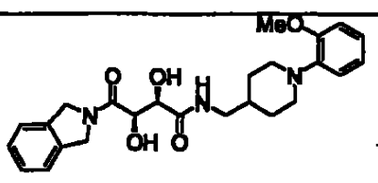
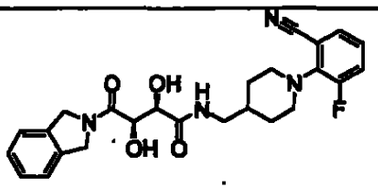
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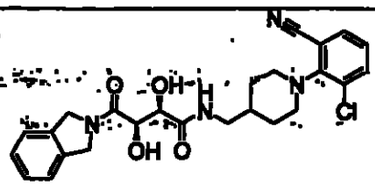
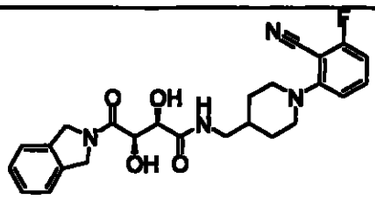
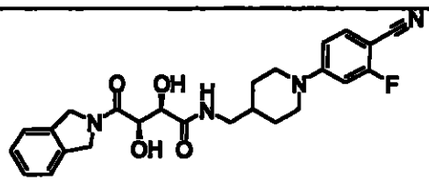
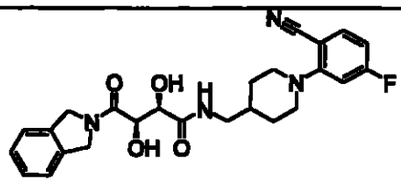
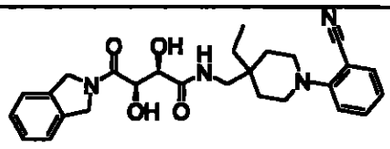
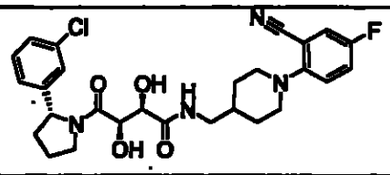
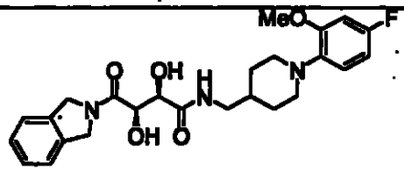
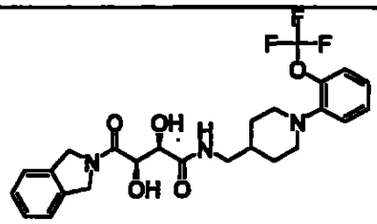
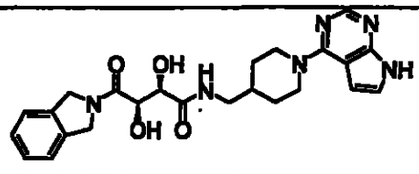
Compound **993** (100 mg, 0.182 mmol) was dissolved in methanol (5 mL) and potassium carbonate (100 mg) was added and stirred for 30 minutes. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded a white solid **994** (7 mg, 8%) after lyophilization. HPLC-MS

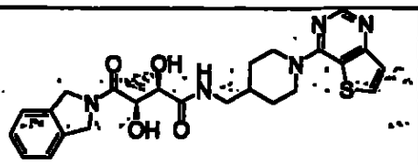
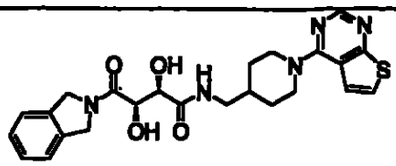
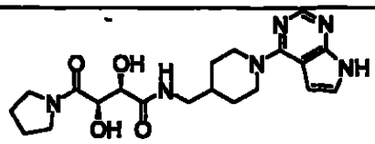
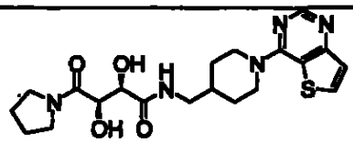
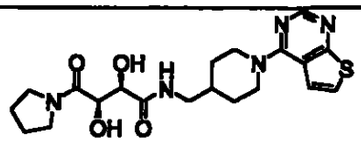
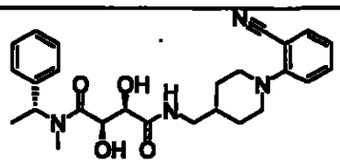
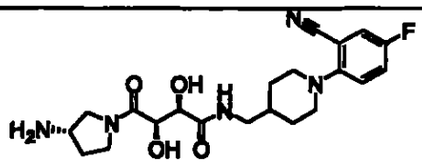
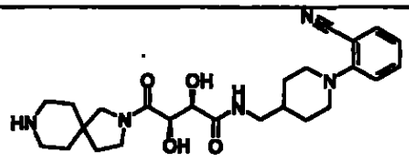
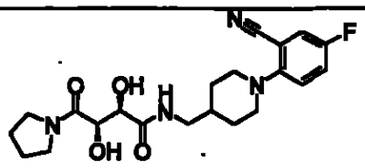
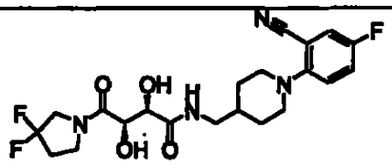
t_R = 4.32 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{28}H_{30}N_4O_4$ 462.23, observed LCMS m/z 463.1 (M+H).

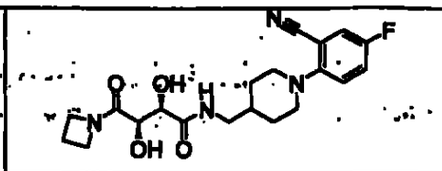
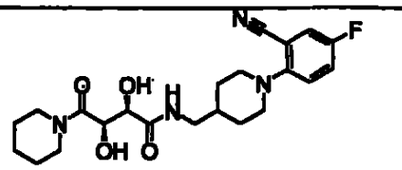
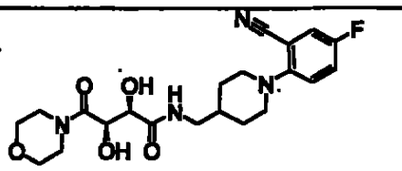
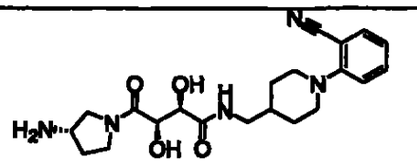
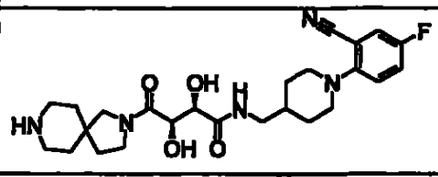
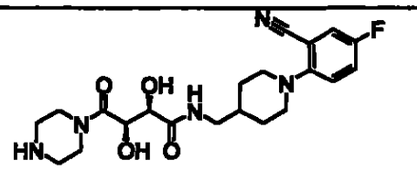
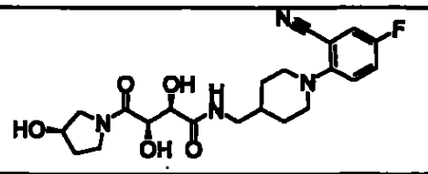
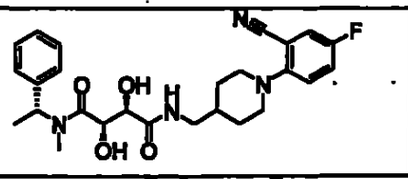
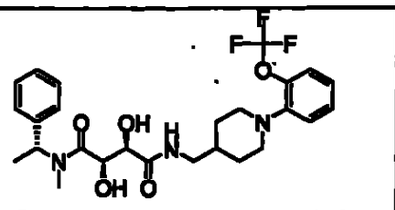
The following table contains compounds that were prepared using the procedures described in Example 27 A – C. Compounds such as 1002 were made from the chloropyridyl precursor using the procedures described in Example 27A Part A.

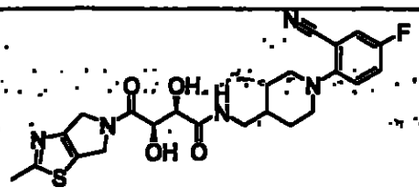
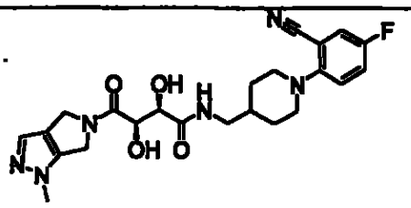
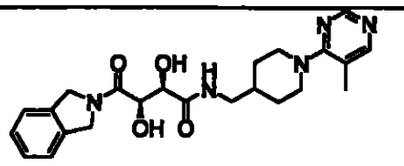
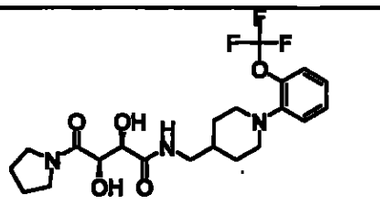
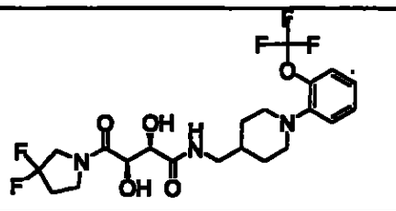
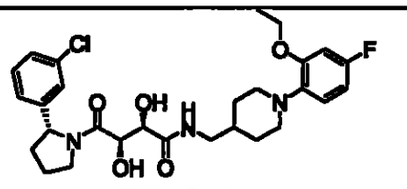
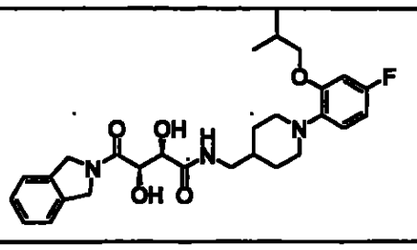
Compound #	Structure	Exact mass	MS m/z (M+H)
995		510.2	511.1
996		347.1	348.3
997		494.2	495.2
998		483.2	484.1
999		492.2	493.1
1000		400.2	401.2
1001		478.2	479.2

1002		449.2	450.2
1003		450.2	451.1
1004		466.2	467.2
1005		492.2	493.1
1006		449.2	450.1
1007		492.2	493.1
1008		453.2	454.2
1009		466.2	467.2

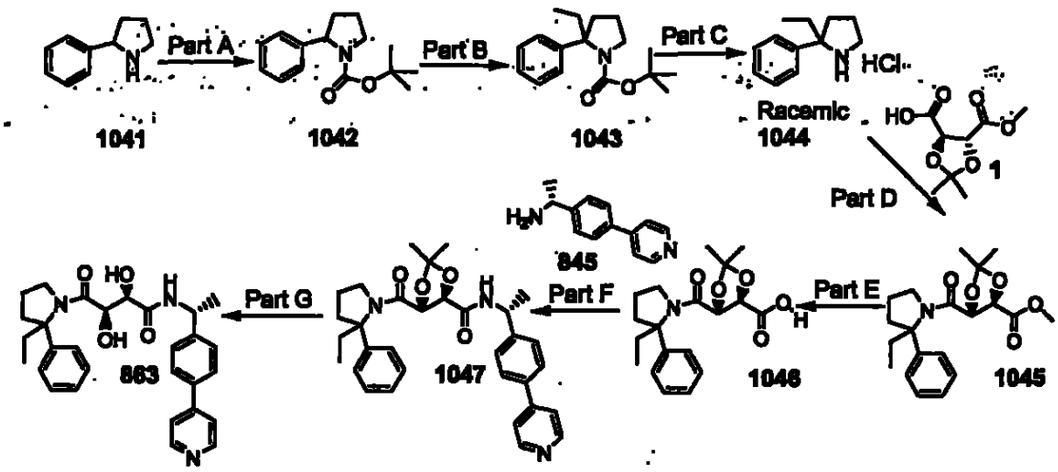
1010		482.2	483.1
1011		466.2	467.2
1012		466.2	467.2
1013		466.2	467.2
1014		476.2	477.1
1015		528.2	529.2
1016		471.2	472.1
1017		507.2	508.2
1018		464.2	465.2

1019		481.2	482.2
1020		481.2	482.2
1021		416.2	417.3
1022		433.2	434.2
1023		433.2	434.2
1024		464.2	465.2
1025		433.2	434.2
1026		469.3	470.2
1027A		418.2	419.2
1027B		454.2	455.2

1027C		404.2	405.2
1028		432.2	433.2
1029		434.2	435.2
1030		415.2	416.2
1031		487.3	488.2
1032		433.2	434.2
1033		434.2	435.2
1034A		482.2	483.3
1034B		523.2	524.2

1035		487.2	488.2
1036		470.2	471.2
1037		439.2	440.2
1038A		459.2	460.1
1038B		495.2	496.2
1039		547.2	548.2
1040		513.3	514.3

Example 28: Alkylated phenyl pyrrolidines



Part A:

2-Phenyl pyrrolidine (1041) (3.14 g, 21.4 mmol) was dissolved in THF (40 mL). Aqueous NaOH (12 mL, 25%) was added, followed by Boc anhydride. The reaction mixture was stirred at rt for 70 h. The layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with 1.0 M pH=7.0 sodium phosphate buffer and brine, then dried with $MgSO_4$. Evaporation of the solvents gave a yellow oil which was purified by column chromatography (SiO_2, 9:1 Hexanes:EtOAc) to give a 5.1 g of a clear oil as product **1042**. MS (EI) m/z M+Na Obsd 270.08

Part B:

A 100 mL Schlenck flask was equipped with a stir bar, flame dried under N_2 flow, capped with a septum, and allowed to cool to rt. Compound **1042** (0.50 g, 2.02 mmol) was added and the flask was recapped. Anhydrous THF (8.5 mL) was added via syringe and the flask was cooled in a dry ice/2-propanol bath. Sec butyl lithium (1.6 mL, 2.34 mmol) was added via syringe. The reaction mixture was left stirring at -78 °C for 30 m. Iodoethane (180 µL, 2.25 mmol) was added and the reaction mixture was stirred for 2 hr. Additional iodoethane was added (80 µL, 1.0 mmol) was added and the reaction mixture was stirred for 45 minutes. The reaction mixture was quenched with 1.0 M pH 7.0 sodium phosphate buffer and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with water and brine, then dried with $MgSO_4$ and

concentrated to a clear oil. The crude product was purified by column chromatography (SiO_2, 0%-20% EtOAc/Hexanes) to give 0.12 g of compound **1043**. MS (EI) m/z M+Na Obsd 298.15.

Part C:

Compound **1043** (0.12 g, 0.43 mmol) was dissolved in 10 mL of 4 M HCl in dioxane. The reaction mixture was stirred at rt for 2.25 h. The reaction mixture was concentrated to dryness giving white solid **1044** (112 mg). MS (EI) m/z Obsd M+H 176.12.

Part D:

Compound **1044** (104 mg, 0.49 mmol) and **1** (0.120 g, 0.588 mmol) were dissolved in CH_2Cl_2 (2 mL). Diisopropyl ethylamine (200 µL, 1.12 mmol) was added, followed by PyBrop (249 mg, 0.78 mmol). The reaction mixture was left stirring overnight at rt under N_2. The reaction mixture was diluted with CH_2Cl_2 then washed with 1.0 m pH 7.0 sodium phosphate buffer, aq $NaHCO_3$, and brine. The organic layer was dried with $MgSO_4$ and concentrated to a clear oil. The crude product was purified purified by column chromatography (SiO_2, 0%-40% EtOAc/Hexanes) to give 0.16 g of compound **1045**. MS (EI) m/z Obsd M+H 362.08

Part E:

Compound **1045** (0.15 g, 0.42 mmol) was dissolved in dioxane (1.6 mL) and water (0.4 mL). Lithium hydroxide was added (19 mg, 0.45 mmol). The reaction mixture was stirred at rt for 2 h 15 m. The solution was concentrated to give **1046** as a clear oil. MS (EI) m/z Obsd M+H 348.09

Part F:

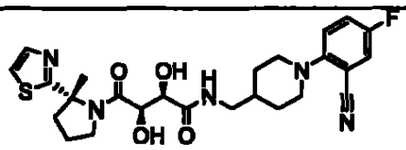
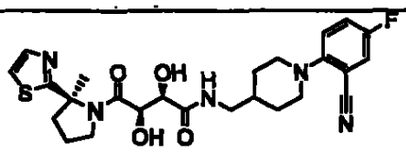
Compound **1046** (69 mg, 0.19 mmol) and **845** (51 mg, 0.22 mmol) were dissolved in DMF (1 mL) and diisopropylamine (100 µL, 0.58 mmol). PyBrop was added (108 mg, 0.338 mmol) and the reaction was stirred overnight at rt. The reaction mixture was diluted with EtOAc and washed with 1.0 M pH 8.0 sodium phosphate buffer and brine. The organic layer was dried with $MgSO_4$ and concentrated to a yellow oil. The crude product was purified via prep TLC

on silica plates using 95:5 CH_2Cl_2:MeOH as the mobile phase. Compound **1047** was obtained as a clear oil (74 mg). MS (EI) m/z Obsd M+H 528.20.

Part G:

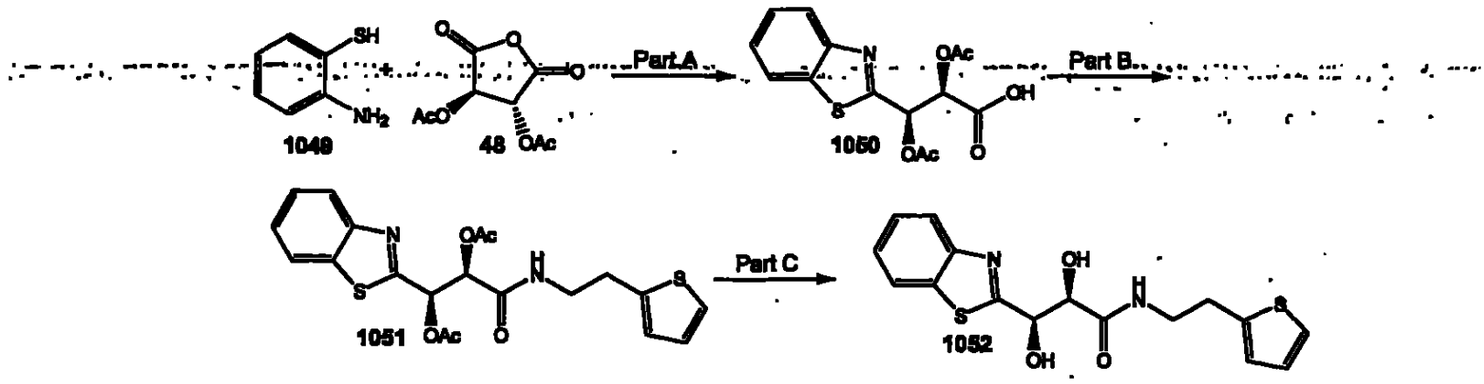
Compound **1047** (74 mg, 0.14 mmol) was dissolved in 5 mL of 9:1 trifluoroacetic acid:water solution. The reaction mixture was stirred at rt for 3 h 10 m, then concentrated to dryness. The crude product was purified purified by column chromatography (SiO_2, 0%-7% MeOH/ CH_2Cl_2) to give 26 mg of compound **863**. MS (EI) m/z Obsd M+H 488.1.

Compound **1048A,B** was prepared from Boc-proline OMe using the above alkylation procedures and the thiazole ring was constructed as described in Example 10A.

Compound #	Structure	Exact mass	MS m/e (M+H)
1048A		515.2	516.2
1048B		515.2	516.2

Example 29:

Example 29A:



Part A:

A mixture of 2-amino-benzenethiol (**1049**) (247 uL, 2.31 mmol) and **48** (500 mg, 2.31 mmol) in benzene was heated at reflux overnight with a dean-stark trap. The reaction mixture was cooled and concentrated. The mixture was recrystallized from 30% ethyl acetate/hexanes to afford **1050** (267 mg) as a brown powder. HPLC-MS t_R = 1.35 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{13}NO_6S$ 323.1, observed LCMS m/z 324.1 (M+H).

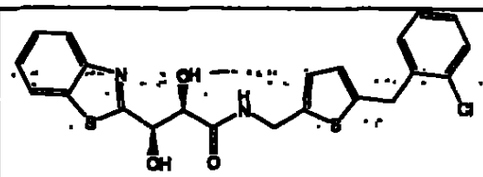
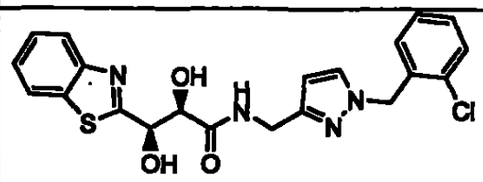
Part B:

Compound **1051** was prepared from compound **1050** (32 mg, 0.1 mmol) using the standard HATU coupling strategy described in Example 2 Part A. Purification by column chromatography (SiO_2, 10% ethyl acetate/dichloromethane) afforded the product as an orange solid (27 mg). HPLC-MS t_R = 1.78 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{20}N_2O_5S_2$ 432.1, observed LCMS m/z 433.0 (M+H).

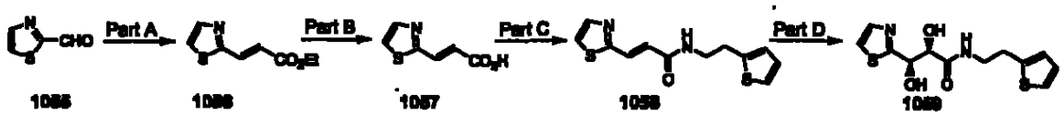
Part C:

Compound **1052** was prepared following the procedure described in Example 2 Part B. HPLC-MS t_R = 1.39 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{16}N_2O_3S_2$ 348.1, observed LCMS m/z 349.0 (M+H).

Compound #	Structure	Exact mass	MS m/z (M+H)

1053		458.1	459.0
1054		442.1	443.0

Example 29B:



Part A:

To sodium hydride (95%, 115 mg, 4.55 mmol) in DME (10 mL) under argon was added triethylphophonacetate dropwise. Within a few minutes the reaction mixture was clear. After 1 hour the aldehyde **1055** (400 uL, 4.55 mmol) was added. After 15 minutes water and diethyl ether were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated to afford **1056** as an orange oil (666 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, 1H, J = 3.2 Hz), 7.79 (d, 1H, J = 16.0 Hz), 7.43 (d, 1H, J = 3.2 Hz), 6.71 (d, 1H, J = 16.0 Hz), 4.29 (q, 2H, J = 7.5 Hz), 1.36 (t, 3H, J = 7.5 Hz).

Part B:

To ester **1056** (84 mg, 0.46 mmol) in THF (2 mL) was added 1.0 M lithium hydroxide solution (0.5 mL, 0.5 mmol). The reaction mixture was stirred overnight. The reaction mixture was made acidic with 1.0 N HCl solution and extracted with ethyl acetate. Sodium chloride was added to the aqueous layer during the extractions. The combined organic layer was dried over sodium sulfate and concentrated to afford **1057** as a film (65 mg, 92%). ^{1}H NMR (400

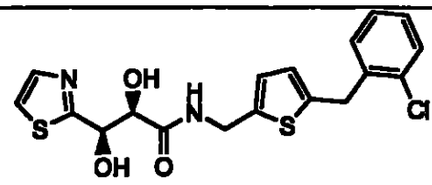
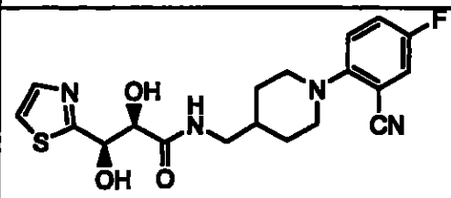
MHz, $CDCl_3$) δ 7.97 (d, 1H, J = 3.0 Hz), 7.89 (d, 1H, J = 15.7 Hz), 7.49 (d, 1H, J = 3.0 Hz), 6.75 (d, 1H, J = 15.7 Hz).

Part C:

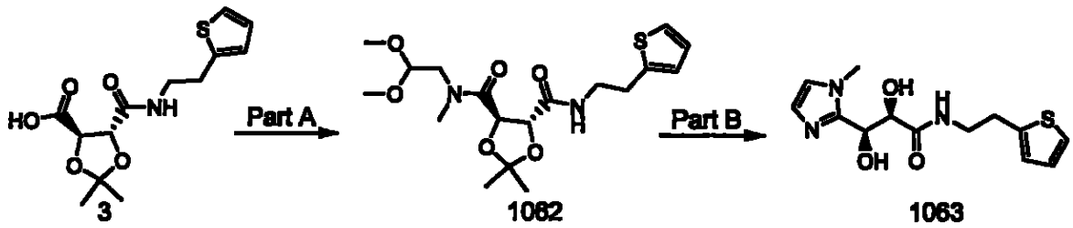
Compound **1058** was prepared from Compound **1057** (32 mg, 0.21 mmol) using the standard HATU coupling strategy described in Example 2 Part A. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexane) afforded the product as a film (35 mg, 63%). HPLC-MS t_R = 1.35 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{12}N_2OS_2$ 264.0, observed LCMS m/z 265.1 (M+H).

Part D:

Compound **1059** was prepared using a modified Sharpless dihydroxylation procedure (*Chem. Rev.* **1994**, *94*, 2483). A flask was charged with $(DHQ)_2PHAL$ (10 mg, 10 mol %), $K_3Fe(CN)_6$ (128 mg, 0.39 mmol), postassium carbonate (54 mg, 0.39 mmol), methane sulfonamide (24 mg, 0.26 mmol) and potassium osmium tetraoxide dihydrate (1 mg, 2 mol%). To the solids was added alkene 4 (35 mg, 0.13 mmol) in tert-butanol:water (1:1, 2.5 mL). The reaction mixture was stirred overnight at room temperature. The reaction mixture was cooled in an ice bath and sodium metabisulfite (38 mg, 0.2 mmol) was added. The mixture was stirred for 30 minutes. The reaction mixture was diluted with ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with 2.0 N potassium hydroxide solution and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 80% ethyl acetate/hexane) afforded the product as a white solid after lypholization (5 mg, 13%). HPLC-MS t_R = 1.00 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{14}N_2O_3S_2$ 298.0, observed LCMS m/z 299.0 (M+H).

Compound #	Structure	Exact mass	MS m/z (M+H)
1060		408.0	409.0
1061		404.1	405.1

Example 29C:



Part A:

Compound **1062** was prepared following the procedures described in Example 1.

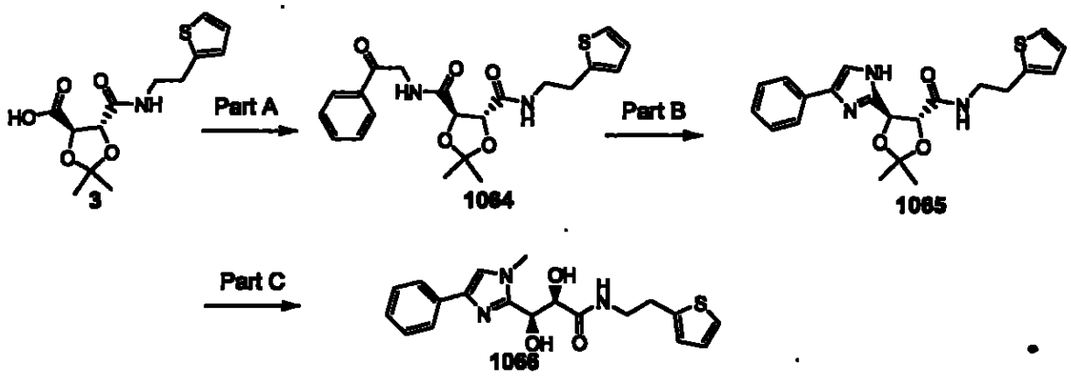
HPLC-MS t_R = 1.69 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{28}N_2O_6S$ 400.2, observed LCMS m/z 401.2 (M+H).

Part B:

Compound **1062** (198 mg, 0.69 mmol) and ammonium acetate (1.9 g, 24.7 mmol) in acetic acid (6 ml) were heated overnight at 110 °C. The reaction mixture was concentrated. The residue was suspended in DCM and the solids removed by filtration. The filtrate was concentrated to afford a mixture of acetonid protected product and **1063**. The residue was treated with 80% TFA:water (2 mL) and stirred overnight. The solvents were removed. Purification by prep-HPLC afforded **1063** (11 mg, 4%) as a TFA salt. HPLC-

MS t_R = 0.79 min ($UV_{254\ nm}$); mass calculated for formula C13H17N3O3S 295.1, observed LCMS m/z 296.1 (M+H).

Example 29D:



Part A:

Compound **1064** was prepared following the procedures described in Example 1.

HPLC-MS t_R = 1.77 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{24}N_2O_5S$ 416.14, observed LCMS m/z 417.1 (M+H).

Part B:

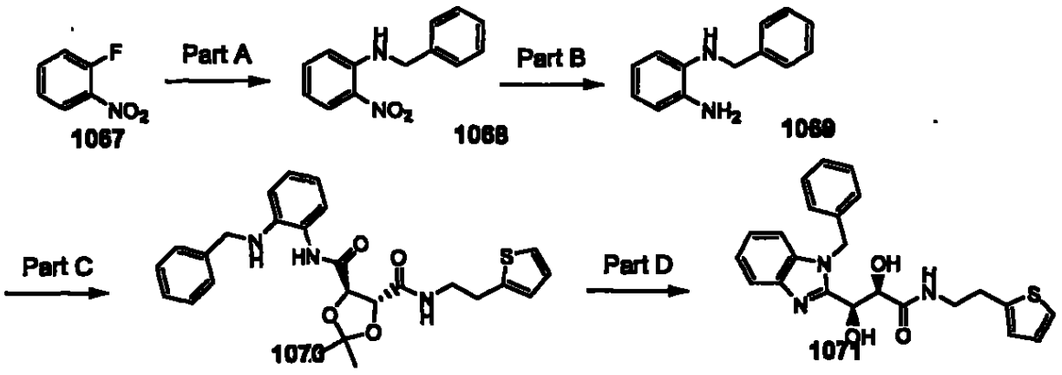
Compound **1064** (216 mg, 0.52 mmol) and ammonium acetate (2 g, 25.9 mmol) in acetic acid (6 ml) were heated overnight at 110 °C. The reaction mixture was concentrated. The residue was suspended in DCM and the solids removed by filtration. The filtrate was concentrated and purified by reverse phase chromatography (Gilson) to afford **1065** (80 mg, 30%) as a TFA salt (80% purity). HPLC-MS t_R = 1.38 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{23}N_3O_3S$ 397.1, observed LCMS m/z 398.2 (M+H).

Part C:

A mixture of compound **1065** (63 mg, 0.127 mmol), iodomethane (10 μL, 0.16 mmol) and cesium carbonate (206 mg, 0.634 mmol) in DMF (6 ml) was stirred overnight at room temperature. The reaction mixture was concentrated. The residue was suspended in ethyl acetate and the solids removed by filtration.

The filtrate was concentrated to afford the crude acetonide protected product. The residue was treated with 90% TFA:water (3 mL) and stirred for 3 h at 50 °C. The solvents were removed. Purification by prep-HPLC afforded 1066 (12 mg, 19%) as a TFA salt. HPLC-MS t_R = 2.87 min (10 min; $UV_{254\ nm}$); mass calculated for formula $C_{19}H_{21}N_3O_3S$ 371.1, observed LCMS m/z 372.1 (M+H).

Example 29E:



Part A:

According to a modification of a procedure by Goker, H. et. al. *(Il Farmaco* **1998**, 53, 415-420) a mixture of 1-fluoro-2-nitro-benzene (**1067**) (1.1 mL, 10.4 mmol) and benzylamine (2.35 mL, 21.5 mmol) in DMF (5 mL) was heated overnight at 80 °C. The reaction mixture was concentrated to give an orange solid which was filtered, washed with water and dried to afford benzyl-(2-nitro-phenyl)-amine (**1068**) (2.5 g, 100%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.44 (b, 1H, NH), 8.22-8.19 (dd, 1H), 7.41-7.27 (m, 6H), 6.84-6.81 (dd, 1H), 6.70-6.66 (m, 1H), 4.58-4.57 (d, 2H).

Part B:

To a solution of benzyl-(2-nitro-phenyl)-amine (**1068**) (2.5 g, 10.43 mmol) in ethanol (150 mL) and water (10 mL) was added iron (8.7 g, 155.7 mmol) followed by 30 drops of concentrated HCl, and the resulting mixture was heated overnight at reflux. The reaction mixture was quenched with water, diluted with DCM and the layers were separated. The organic layer was washed with saturated sodium bicarbonate solution, brine, dried over sodium

sulfate and concentrated to give a brown oily residue. Further purification by column chromatography (SiO_2, 20% ethyl acetate/hexanes) afforded N-benzyl-benzene-1,2-diamine (**1069**) as a dark yellow oil (1.18 g, 57%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.24 (m, 5H), 6.82-6.67 (m, 4H), 4.32 (s, 2H), 3.56 (b, 3H, NH).

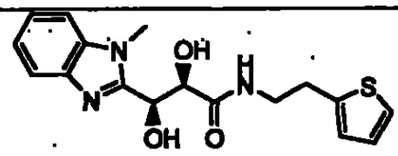
Part C:

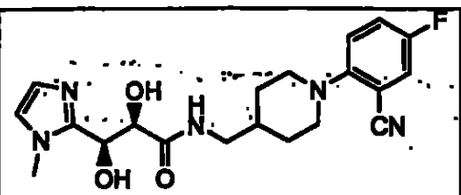
Compound **1070** was prepared following the procedures described in Example 29C Part A. HPLC-MS t_R = 2.13 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{29}N_3O_4S$ 479.2, observed LCMS m/z 480.1 (M+H).

Part D:

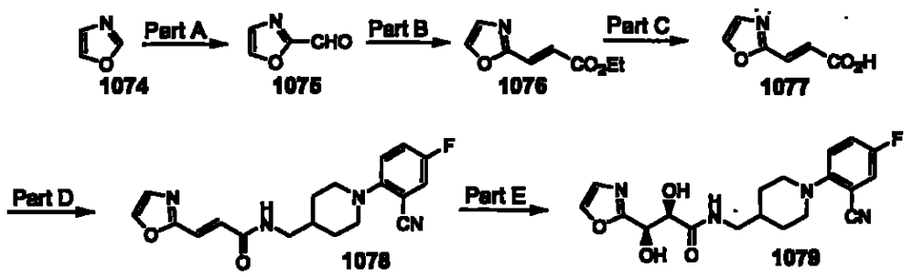
A mixture of compound **1070** (75 mg, 0.156 mmol) and p-toluenesulfonic acid monohydrate (30 mg, 0.156 mmol) in toluene (3 ml) was heated overnight at reflux. The reaction mixture was concentrated to a residue identified as the acetonide deprotected product by LC-MS. Further purification by reverse phase chromatography afforded **1071** (40 mg, 48%) as a TFA salt (95% purity). HPLC-MS t_R = 3.52 min (10 min; $UV_{254\ nm}$); mass calculated for formula $C_{23}H_{23}N_3O_3S$ 421.1, observed LCMS m/z 422.2 (M+H).

The following compounds were synthesized by procedures described in Example 29C-E.

Compound #	Structure	Exact mass	MS m/z (M+H)
1072		345.1	346.1

1073		401.2	402.2

Example 29F:



Part A:

According to a procedure Hodges, J. C. et al (*J. Org. Chem.* 1991, *56*, 449-452) to a cold (–78 °C) solution of oxazole (1074) (1g, 14.4 mmol) in 45 mL of THF was added dropwise nBuLi (9 mL, 14.4 mmol, 1.6 M soln in hexane), and the resulting solution was stirred at –78 °C for 25 min. Then DMF (1.12 mL, 14.4 mmol) was added dropwise, followed by THF (5 mL) and the resulting mixture was allowed to warm up slowly to room temperature, and was stirred overnight. The reaction mixture was quenched by the addition of silica gel (3 g), concentrated, and the resulting slurry was diluted with DCM and loaded on a silica gel column. Flash chromatography (3% ethyl acetate/DCM) afforded oxazole-2-carbaldehyde (1075) (165 mg, 12%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.9 (s, 1H), 7.46 (s, 1H).

Part B:

Compound 1076 was prepared from compound 1075 (165 mg, 1.7 mmol) using the procedure described in Example 29B Part A. Purification by column chromatography (SiO_2, 20% ethyl acetate/hexane) afforded the product as a yellow solid (107 mg, 34%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.45 (d, 1H, J = 16.0 Hz), 7.27 (s, 1H), 6.74 (d, 1H, J = 16.0 Hz), 4.29 (q, 2H, J = 7.3 Hz), 1.36 (t, 3H, J = 7.3 Hz).

Part C:

Compound **1077** was prepared from compound **1076** (107 mg, 0.58 mmol) using the procedure described in Example 29B Part B. Work-up afforded the product as a pale yellow solid (77 mg, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.9 (s, 1H), 8.25 (s, 1H), 7.44 (s, 1H), 7.27 (d, 1H, J = 16.0 Hz), 6.62 (d, 1H, J = 16.0 Hz).

Part D:

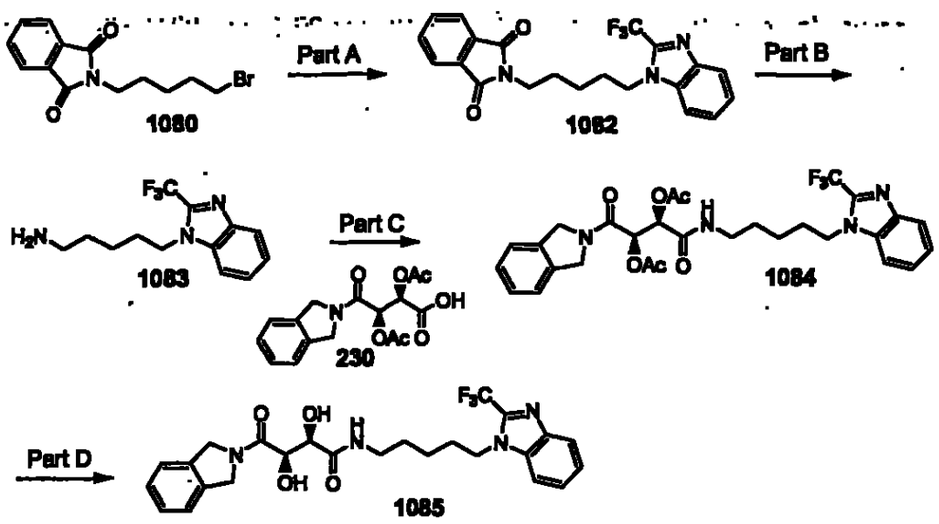
Compound **1078** was prepared from compound **1077** (165 mg, 1.7 mmol) using the procedure described in Example 29B Part C. After standard HATU coupling work-up the solid residue was triturated with 1:1 DCM/hexane, filtered and washed with 1:1 DCM/hexane to give **1078** (123 mg, 70%) as a pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (t, 1H), 8.20 (s, 1H), 7.69-7.66 (dd, 1H), 7.49-7.44 (m, 1H), 7.38 (s, 1H), 7.20-7.16 (dd, 1H), 7.14 (d, 1H, J = 16.0 Hz), 6.94 (d, 1H, J = 16.0 Hz), 3.41-3.38 (d, 2H), 3.16 (t, 2H), 2.72 (t, 2H), 1.81-1.78 (d, 2H), 1.64-1.58 (m, 1H), 1.40-1.30 (m, 2H). HPLC-MS t_R = 1.63 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{18}FN_4O_2$ 354.15, observed LCMS m/z 355.1 (M+H).

Part E:

Compound **1079** was prepared from compound **1078** (118 mg, 0.33 mmol) using the procedure described in Example 29B Part D. Purification by column chromatography (SiO_2, 5% MeOH/DCM) afforded the product as a white solid (28 mg, 22%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.88 (t, 1H), 7.69-7.66 (dd, 1H), 7.48-7.43 (m, 1H), 7.20-7.16 (dd, H), 7.14 (s, 1H), 5.83-5.81 (d, 1H), 5.72-5.70 (d, 1H), 4.93-4.90 (dd, 1H), 4.23-4.21 (d of d, 1H), 3.38-3.36 (d, 2H), 3.04 (t, 2H), 2.69 (t, 2H), 1.77-1.72 (d, 2H), 1.62-1.56 (m, 1H), 1.32-1.23 (m, 2H). ^{19}F NMR (400 MHz, DMSO-d_6) δ -120.6 ppm. HPLC-MS t_R = 3.32 min (10 min; $UV_{254\ nm}$); mass calculated for formula $C_{19}H_{21}FN_4O_4$ 388.15, observed LCMS m/z 389.2 (M+H).

Example 30:

Example 30A:



Part A:

A mixture of 2-(5-bromo-pentyl)-isoindole-1,3-dione (1080) (2.0 g, 6.77 mmol), 2-trifluoromethyl-1H-benzoimidazole (1.2 g, 6.45 mmol) and potassium carbonate (1.78 g, 12.9 mmol) in NMP (5 ml) was stirred overnight at room temperature. The reaction mixture was partitioned between ethyl acetate and water, and the resulting organic layer was washed with water, brine, dried over sodium sulfate and concentrated to give an oil. Further purification by column chromatography (SiO_2, 25 % ethyl acetate/hexanes) afforded compound 1082 as a colorless oil (1.88 g, 73%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.88-7.86 (d, 1H), 7.85-7.83 (m, 2H), 7.73-7.71 (m, 2H), 7.49-7.34 (m, 3H), 4.31 (t, 2H), 3.72 (t, 2H), 1.99-1.92 (m, 2H), 1.80-1.73 (m, 2H), 1.53-1.45 (m, 2H).

Part B:

To a solution of compound 1082 (1.88 g, 4.68 mmol) in EtOH (50 mL) was added hydrazine monohydrate (0.45 mL, 9.36 mmol) and the resulting mixture was heated for 3 h at 60 °C, during which time a white precipitate formed. The reaction mixture was filtered, washed with EtOH and the filtrate was concentrated. The residue was suspended in ether, stirred for 10 min at room temperature, filtered and washed with ether, and the resulting filtrate was concentrated to afford compound 1083 as an oil (1.10 g, 87%). ^1H NMR (400

MHz, $CDCl_3$) δ 7.90-7.88 (d, 1H), 7.46-7.37 (m, 3H), 4.33 (t, 2H), 2.76 (t, 2H), 2.02-1.40 (m, 6H).

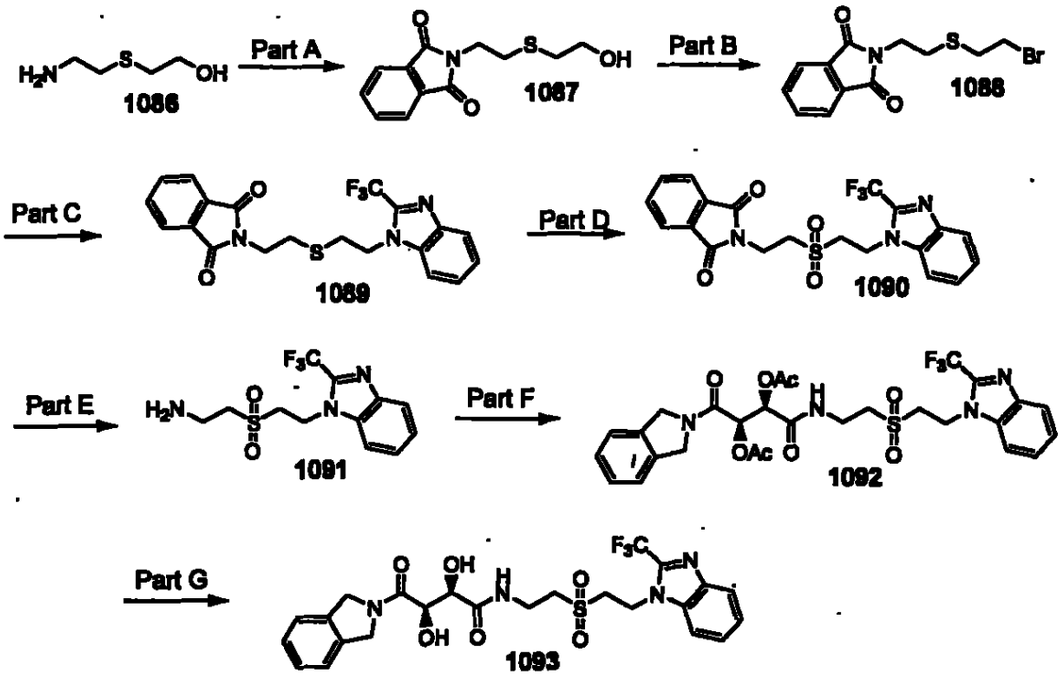
Part C:

Compound **1084** was prepared from **1083** and **230** following the procedures described in Example 2.

Part D:

Compound **1085** was prepared following the procedures described in Example 2. HPLC-MS t_R = 4.14 min (10 min; $UV_{254\ nm}$); mass calculated for formula $C_{25}H_{27}F_3N_4O_4$ 504.2, observed LCMS m/z 505.1 (M+H).

Example 30B:



Part A:

According to a modification of a procedure by Lown, J. W. et. al. (*J. Org. Chem.* **1982**, *47*, 2027-2033) a mixture of 2-(2-amino-ethylsulfanyl)-ethanol (**1086**) (1.82, 15 mmol) and phthalimide (2.22 g, 15 mmol) in toluene (35 ml) was heated overnight at reflux. The reaction mixture was concentrated to a

residue, which was purified by column chromatography (SiO_2, 25 % ethyl acetate/DCM to 50% ethyl acetate/DCM) to afford compound **1087** as an off-white solid (2.98 g, 79%). ^1H NMR (400 MHz, $CDCl_3$) δ7.87-7.85 (m, 2H), 7.75-7.72 (m, 2H), 3.94 (t, 2H), 3.80 (t, 2H), 2.89-2.82 (m, 4H).

Part B:

According to a modification of a procedure by Nair, S. A. et. al. (*Synthesis* **1995**, 810-814) to an ice-cold solution of compound **1087** (628 mg, 2.5 mmol) and carbon tetrabromide (1.04 g, 3.12 mmol) in DCM (25 mL) was added triphenylphosphine (920 mg, 3.5 mmol) in two portions over 10 min. The reaction mixture was allowed to warm up to room temperature and stirred overnight at room temperature. The mixture was concentrated and the resulting residue was purified by column chromatography (SiO_2, 30 % ethyl acetate/hexanes) to afford compound **1088** as a white solid (733 mg, 93%). ^1H NMR (400 MHz, $CDCl_3$) δ7.88-7.86 (m, 2H), 7.75-7.73 (m, 2H), 3.92 (t, 2H), 3.53 (t, 2H), 3.04 (t, 2H), 2.90 (t, 2H).

Part C:

Compound **1089** was prepared following the procedures described in Example 30A, Part A. ^1H NMR (400 MHz, $CDCl_3$) δ7.89-7.87 (d, 1H), 7.86-7.84 (m, 2H), 7.74-7.72 (m, 2H), 7.58-7.56 (d, 1H), 7.46 (t, 1H), 7.38 (t, 1H), 4.52 (t, 2H), 3.92 (t, 2H), 3.02 (t, 2H), 2.89 (t, 2H); ^{19}F NMR (400 MHz, $CDCl_3$) δ–64.7 ppm.

Part D:

To a solution of compound **1089** (250 mg, 0.6 mmol) in DCM (5 mL) was added m-chloroperoxybenzoic acid (336 mg, 1.5 mmol) and the resulting mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM, washed with saturated sodium bicarbonate solution, brine, dried over sodium sulfate and concentrated to give compound **1090** (284 mg) as a white solid which was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ7.92-7.90 (d, 1H), 7.90-7.88 (m, 2H), 7.78-7.76 (m, 2H), 7.66-

7.62 (d of t, 1H), 7.54-7.51 (t of d, 1H), 7.46-7.44 (t of d, 1H), 4.89 (t, 2H), 4.20 (t, 2H), 3.65 (t, 2H), 3.46 (t, 2H); ^{19}F NMR (400 MHz, $CDCl_3$) δ –62.5 ppm.

Part E:

Compound **1091** was prepared following the procedures described in Example 30A, Part B. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.91-7.89 (d, 1H), 7.63-7.61 (d, 1H), 7.51-7.48 (t of d, 1H), 7.44-7.40 (t of d, 1H), 4.90 (t, 2H), 3.71 (t, 2H), 3.31 (t, 2H), 3.12 (t, 2H); ^{19}F NMR (400 MHz, $CDCl_3$) δ–62.5 ppm.

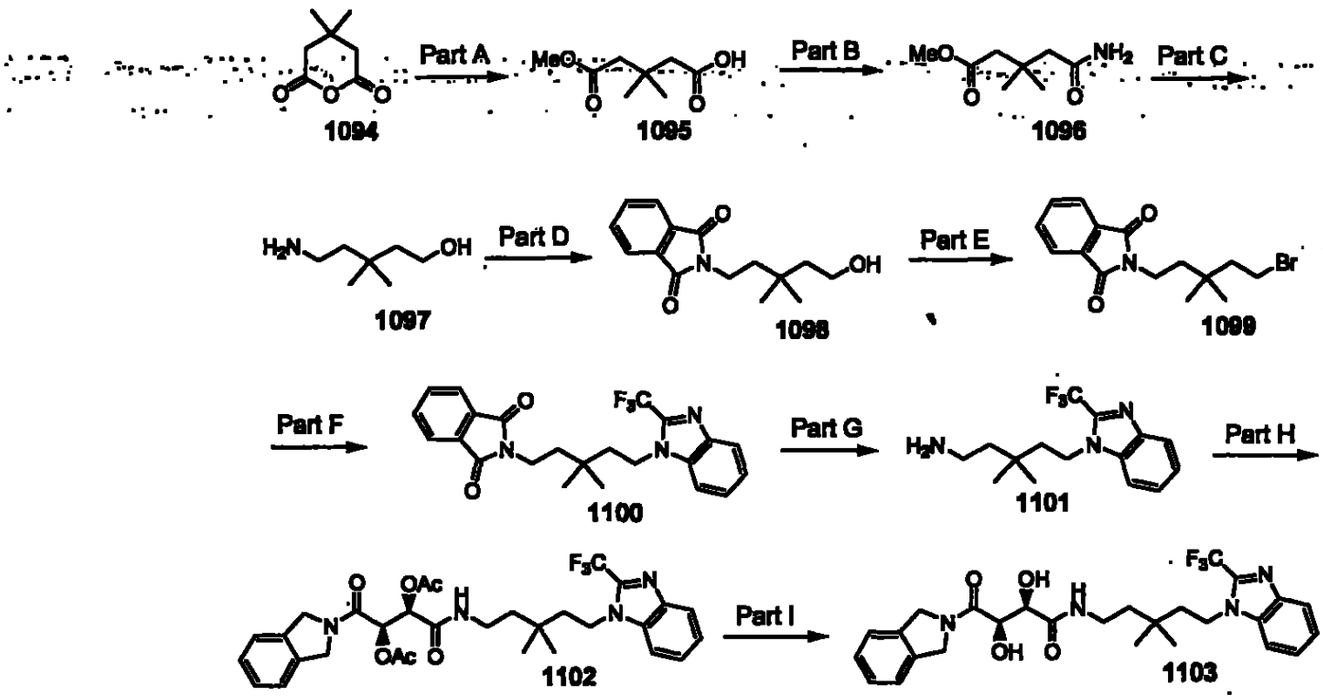
Part F:

Compound **1092** was prepared following the procedures described in Example 27A, Part B, and used without further purification. HPLC-MS t_R = 1.65 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{29}F_3N_4O_8S$ 638.17, observed LCMS m/z 639.1 (M+H).

Part G:

Compound **1093** was prepared following the procedures described in Example 27A, Part C. HPLC-MS t_R = 3.57 min (10 min; $UV_{254\ nm}$); mass calculated for formula $C_{24}H_{25}F_3N_4O_8S$ 554.14, observed LCMS m/z 555.1 (M+H).

Example 30 C:



Part A:

According to a modification of a procedure by Brown, R. F. et. al. (*J. Am. Chem.* Soc. 1955, 77, 1083-1089) a mixture of 3,3-dimethyl glutaric anhydride (1094) (7.1 g, 50 mmol) and methanol (40 mL) was heated overnight at reflux. The reaction mixture was concentrated to give compound 1095 as a colorless oil (8.46 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 2.50 (s, 2H), 2.48 (s, 2H), 1.16 (s, 6H).

Part B:

To an ice-cold solution of compound 1095 (8.46 g, 48.5 mmol) in DCM (30 mL) was added dropwise oxalyl chloride (7 mL, 80 mmol), followed by DMF (2 drops) and the resulting mixture was heated for 3.5 h at reflux. The reaction mixture was concentrated to give the corresponding acid chloride (4-chlorocarbonyl-3,3-dimethyl-butyric acid methyl ester) as a brown oil (7.89 g, 84%) which was used without further purification in the next step.

To an ice-cold solution of ammonia in 1,4-dioxane (30 mL of a solution containing 2.2 g ammonia dissolved in 100 mL of 1,4-dioxane, 38.8 mmol - approx) was added dropwise a solution of 4-chlorocarbonyl-3,3-dimethyl-butyric acid methyl ester (3 g, 15.5 mmol) in 1,4-dioxane (3 mL) and after the

addition was complete the resulting white slurry was stirred 45 min at room temperature. The reaction mixture was diluted with ethyl-acetate, filtered and concentrated to give compound **1096** as a viscous yellow oil (2.62 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 2.43 (s, 2H), 2.31 (s, 2H), 1.14 (s, 6H).

Part C:

To an ice-cold solution of LAH (42 mL, 1 M sol in THF, 42 mmol) was added dropwise a solution of compound **1096** (2.02 g, 11.6 mmol) in THF and the resulting mixture was heated overnight at reflux. The reaction mixture was cooled to 0 °C and quenched by dropwise addition of brine, when a paste-like solid formed. This solid was triturated and sonicated several times with ethyl acetate, and the combined organic extracts were concentrated to give compound **1097** as an oil (1.17 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (t, 2H), 2.71 (t, 2H), 1.53 (t, 2H), 1.41 (t, 2H), 0.92 (s, 6H).

Part D:

Compound **1098** was prepared following the procedures described in Example 30B, Part A. HPLC-MS t_R = 1.88 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{19}NO_3$ 261.14, observed LCMS m/z 262.0 (M+H).

Part E:

Compound **1099** was prepared following the procedures described in Example 30B, Part B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.82 (m, 2H), 7.71-7.69 (m, 2H), 3.70-3.66 (m, 2H), 3.47-3.42 (m, 2H), 1.97-1.92 (m, 2H), 1.61-1.57 (m, 2H), 1.03 (s, 6H).

Part F:

Compound **1100** was prepared following the procedures described in Example 30B, Part C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.87 (d, 1H), 7.86-7.84 (m, 2H), 7.73-7.71 (m, 2H), 7.5-7.57 (d, 1H), 7.47-7.43 (t of d, 1H), 7.39-7.35 (t of d, 1H), 4.46-4.41 (m, 2H), 3.79-3.75 (m, 2H), 1.89-1.85 (m, 2H), 1.74-1.69 (m, 2H), 1.18 (s, 6H); ^{19}F NMR (400 MHz, $CDCl_3$) δ–62.7 ppm.

Part G:

Compound 1101 was prepared following the procedures described in Example 30B, Part E. HPLC-MS t_R = 1.13 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{20}F_3N_3$ 299.16, observed LCMS m/z 300.1 (M+H).

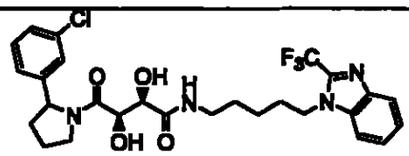
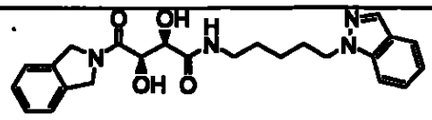
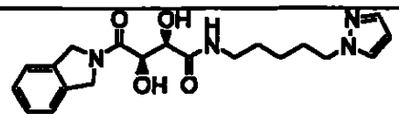
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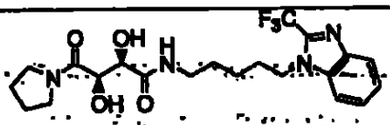
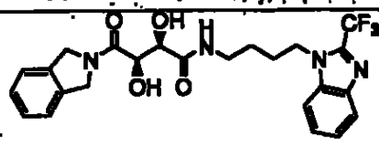
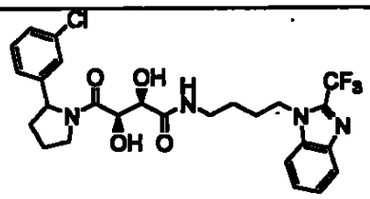
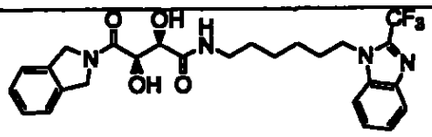
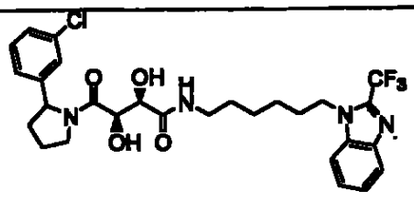
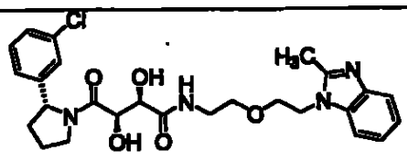
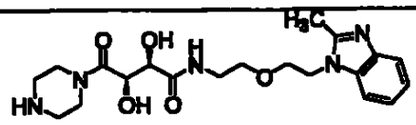
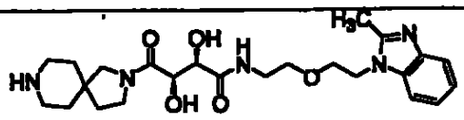
Compound 1102 was prepared following the procedures described in Example 27A, Part B, and used without further purification. HPLC-MS t_R = 2.0 min ($UV_{254\ nm}$); mass calculated for formula C31H35F3N4O6 616.25, observed LCMS m/z 617.2 (M+H).

Part I:

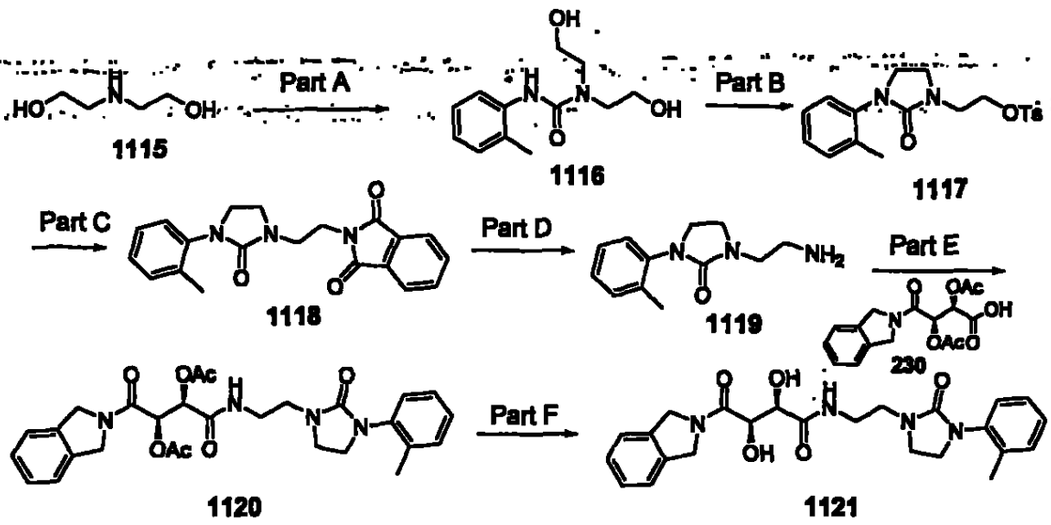
Compound 1103 was prepared following the procedures described in Example 27A, Part C. HPLC-MS t_R = 4.52 min (10 min, $UV_{254\ nm}$); mass calculated for formula $C_{27}H_{31}F_3N_4O_4$ 532.23, observed LCMS m/z 533.2 (M+H).

The following compounds were synthesized using procedures described in Example 30 A-C.

Compound #	Structure	Exact mass	MS m/e (M+H)
1104		566.2	567.2
1105		436.21	437.2
1106		386.2	387.2

1107		456.2	457.1
1108		490.18	491.1
1109		552.18	553.2
1110		518.2	519.1
1111		580.21	581.2
1112		514.2	515.2
1113		419.2	420.2
1114		473.3	474.3

Example 31:



Part A:

Compound **1115** (790 mg, 7.5 mmol) was dissolved in THF (10 mL) and cooled in an ice bath. 2-Methylphenylisocyanate (500 mg, 3.75 mmol) was added in portions and the resulting solution was stirred at room temperature for 2 hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 1 N HCl solution, bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded a white solid **1116** (1.02 g, 56%). HPLC-MS t_R = 0.95 (UV_{254nm}); mass calculated for formula $C_{12}H_{18}N_2O_3$ 238.1, observed LCMS m/z 239.2 (M+H).

Part B:

Compound **1116** (1.02 g, 4.2 mmol) was dissolved in THF (25 mL) and cooled in an ice bath. Potassium *t*-butoxide (1.5 g, 13.2 mmol) was added in portions and the reaction mixture was stirred for 10 minutes. A solution of *p*-toluenesulfonyl chloride (1.91 g, 10.8 mmol) in THF (5 mL) was added dropwise and the reaction was stirred 30 minutes at 0°C and 30 minutes at room temperature. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 1 N HCl solution, bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl

acetate/hexanes) afforded a white solid **1117** (0.750 g, 48%). HPLC-MS t_R = 1.87 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{22}N_2O_4S$ 374.1, observed LCMS m/z 375.1 (M+H).

Part C:

Compound **1117** (750 mg, 2.0 mmol) was dissolved in DMF (10 mL) and phthalimide (441 mg, 3.0 mmol) and cesium carbonate (1.95 g, 6.0 mmol) were added and stirred overnight. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 1 N HCl solution, bicarbonate solution and brine; dried over sodium sulfate and concentrated. The solid residue was recrystallized from ethyl acetate/hexanes to provide **1118** (500 mg, 72%) as a white solid. HPLC-MS t_R = 1.63 ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{19}N_3O_3$ 349.1, observed LCMS m/z 350.2 (M+H).

Part D:

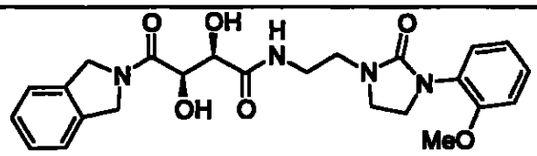
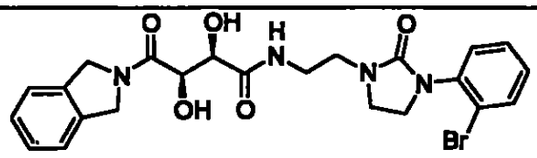
Compound **1118** (110 mg, 0.29 mmol) was dissolved in ethanol (3 mL) and hydrazine hydrate (0.10 mL) was added. The reaction was stirred for 3 hours at room temperature. The solids were removed by filtration and the solution was evaporated under reduced pressure. The residue was dissolved in 1 N NaOH solution and extracted with ethyl acetate. The combined organic layers were washed with brine; dried over sodium sulfate and concentrated to provide compound **1119** that was used without purification.

Part E:

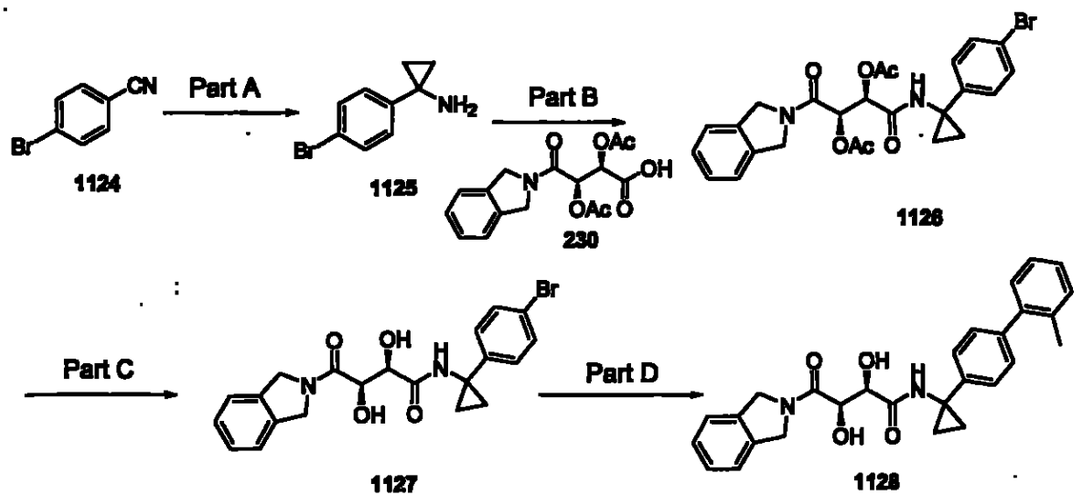
Compound **1119, 230** (97 mg, 0.29 mmol), DIEA (0.125 mL, 0.7 mmol) and HATU (133 mg, 0.348 mmol) were combined in DMF (3 ml) and stirred overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 1 N HCl solution, bicarbonate solution and brine; dried over sodium sulfate and concentrated to provide compound **1120** that was used in the next step without purification. HPLC-MS t_R = 1.68 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{32}N_4O_7$ 536.2, observed LCMS m/z 537.3(M+H).

Part F:

Compound 1120 was dissolved in methanol (5 mL) and potassium carbonate (150 mg) was added and stirred for 30 minutes. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 1 N HCl solution, bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded 1121 as a white solid (16 mg) after lyophilization. HPLC-MS t_R = 3.48 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{24}H_{28}N_4O_5$ 452.2, observed LCMS m/z 453.1(M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
1122		468.20	469.1
1123		516.10	517.0

Example 32:



Part A:

Compound **1124** (360 mg, 2.00 mmol) was dissolved in diethylether (10 mL) and cooled to -70 °C. Titanium isopropoxide (624 mg, 2.2 mmol) was added and stirred for 10 minutes. Ethylmagnesium chloride (1M in THF, 4 mL, 4 mmol) was added dropwise and the reaction was stirred another 10 minutes at this temperature before warming to room temperature and stirring for an additional 30 minutes. Boron trifluoroetherate (864 mg, 4 mmol) was added and the solution was stirred for 2 hours. The reaction was quenched with 1 N HCl and washed with diethylether. The aqueous layer was made basic by addition of 1N NaOH solution and then extracted with ethyl acetate. The combined organic layers were washed with brine; dried over sodium sulfate and concentrated to provide compound **1125** that was used without purification.

Part B:

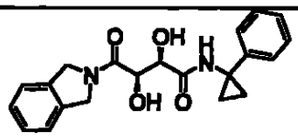
Compound **1125** was dissolved in DMF (5 mL) and compound **230** (50 mg, 0.140 mmol) and HATU (69 mg, 0.182 mmol) were added and stirred overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 1N HCl, bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded a white solid **1126** (60 mg, 81%). HPLC-MS t_R = 1.928 ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{25}BrN_2O_6$ 528.0, observed LCMS m/z 529.1 (M+H).

Part C:

Compound **1126** (60 mg, 0.1427 mmol) was dissolved in MeOH (5 mL) and potassium carbonate (100 mg) was added followed by stirring for 30 minutes. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded a white solid **1127** (10 mg, 15.8%) after lyophilization. HPLC-MS t_R = 4.192 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{21}H_{21}BrN_2O_4$ 444.0, observed LCMS m/z 445.1 (M+H).

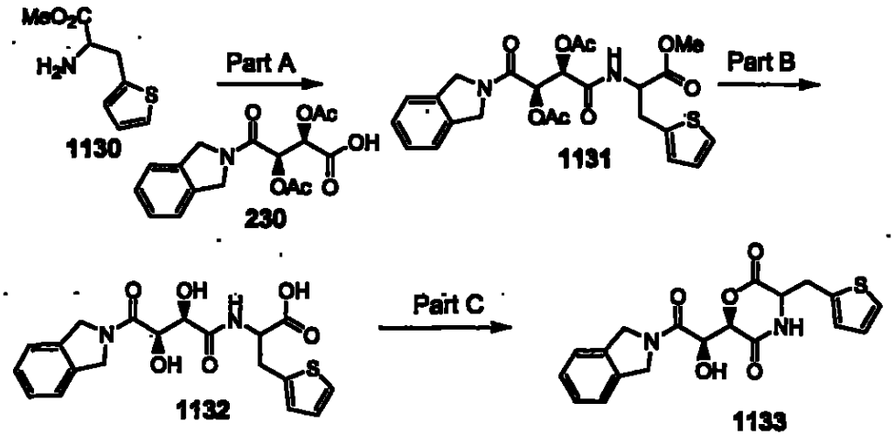
Part D:

Compound **1127** (7.6 mg, 0.017 mmol) was dissolved in dioxane (2 mL) and $Pd(dba)_3$ (3 mg), triphenylphosphine (4.4 mg, 0.017 mmol), potassium phosphate (8 mg, 0.0377 mmol), and 2-methylphenylboronic acid (4.3 mg, 0.034 mmol) were added under a nitrogen atmosphere. The reaction mixture was heated to 90 °C overnight and then filtered over a bed of celite and concentrated. Purification by reverse phase prep-LC afforded a white solid **1128** (5 mg, 65%) after lyophilization. HPLC-MS t_R = 4.095 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{28}H_{28}N_2O_4$ 456.2, observed LCMS m/z 457.3 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
1129		366.16	367.1

Example 33: Constrained Analogs

Example 33A:



Part A:

To 2-amino-3-thiophen-2-yl-propionic acid methyl ester hydrochloride (**1130**) (120 mg, 0.54 mmol) in DMF (2 mL) was added **230** (150 mg, 0.45 mmol),

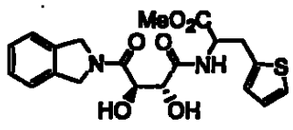
DIEA (160 □M, 0.9 mmol) and HATU (205 mg, 0.54 mmol). The reaction mixture was stirred overnight at room temperature, and diluted with ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in compound **1131**.

Part B:

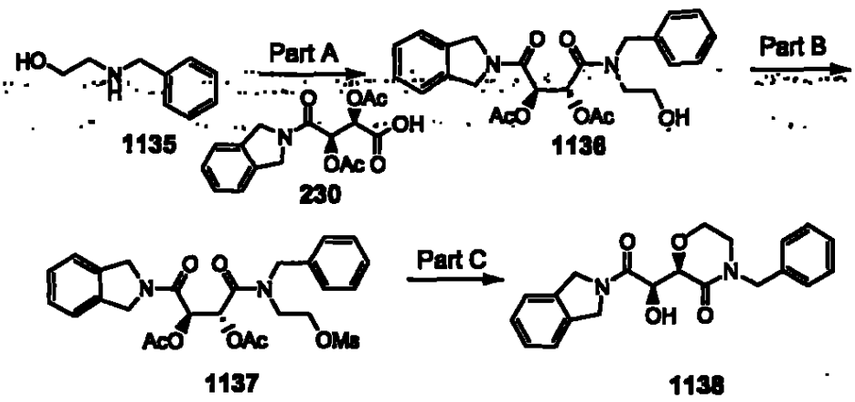
Compound **1131** was dissolved in 5 mL of MeOH, 10 mL of 10% K_2CO_3 aqueous solution was added. After stirring at room temperature for 1 h, the reaction mixture was concentrated in *vacuo*, and then acified with 1N HCL to PH 2. The solution was then extracted with EtOAc, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated, affording compound **1132** as a white solid. Mass calculated for formula $C_{19}H_{20}N_2O_6S$ 404.1, observed LCMS m/z 405.0.0 (M+H).

Part C:

Compound **1132** (40 mg, 0.1 mmol) in 1 mL of DMF was added with PS carbodiimide resin (117 mg, 1.28 mmol/g loading, 0.15 mmol) and dimethylaminopyridine (3 mg, 0.024 mmol). After stirring overnight at 50 °C, the solid was filtered off, and the solution was concentrated in *vacuo*. Purification by reverse phase prep-LC afforded compound **1133** as a white solid. HPLC-MS t_R = 3.59 min ($UV_{254\ nm}$, 10 min), Mass calculated for formula $C_{25}H_{28}ClN_3O_4S$ 386.1, observed LCMS m/z 387.0 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
1134		418.1	419.0

Example 33B:



Part A:

2-Benzylamino-ethanol (1135) (0.676 g, 4.5 mmol) in DMF (10 mL) was added **230** (1.0 g, 3 mmol), and HATU (1.71 g, 4.5 mmol). The reaction mixture was stirred overnight at room temperature, and diluted with ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in compound **1136** (1.1 g, 80%). Mass calculated for formula $C_{25}H_{28}N_2O_7$ 468.2, observed LCMS m/z 469.1 (M+H).

Part B:

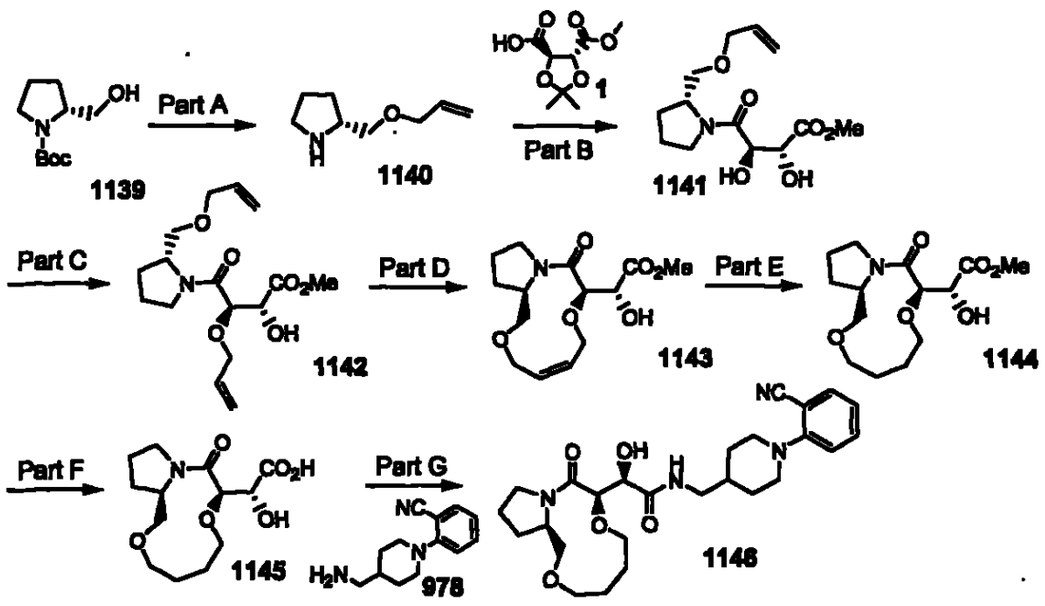
Compound **1136** (468 mg, 1 mmol) and DIEA (261 mL, 1.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise with mesyl chloride (116 mL, 1.5 mmol) at 0 °C. After stirring at 0 °C for 10 min, the reaction mixture was allowed to stir at room temperature for 1.5 h, then concentrated to dryness. The residue was extracted with ethyl acetate, washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in **1137** (511 mg, 93%).

Part C:

Compound **1137** (389 mg, 0.71 mmol) in MeOH (20 mL) was added with solid K_2CO_3 (323 mg, 2.34 mmol). After stirring at room temperature for 2 h, it was concentrated to remove the solvent, then dissolved in EtOAc and water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, brine, and concentrated. Purification by reverse phase prep-LC afforded **1138** as a

white solid. HPLC-MS t_R = 3.89 min ($UV_{254\ nm}$, 10 min), Mass calculated for formula $C_{21}H_{22}N_2O_4$ 366.16; observed LCMS m/z 367.4 (M+H).

Example 33C:



Part A:

Step 1: (R)- Boc-prolinol (1139) (2.0 g, 9.94 mmol) in THF (5 mL) was added into NaH (0.437 g, 60% in mineral oil, 10.93 mmol) in 10 mL of THF at 0 °C. After stirring at 0 °C for 10 min, allyl bromide (1.32 g, 10.93 mmol) was added. Te reaction mixture was allowed to stir overnight at room temperature. After filtration, the solution was concentrated to dryness, the residue was taken up with EtOAc, washed with 1N citric acid, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated, resulting in a colorless oil (2.30 g, 96%).

Step 2: The above material in CH_2Cl_2 (10 mL) was added dropwise with 3 mL of TFA at 0 °C. After stirring at room temperature for 1 h, the solution was concentrated. The residue was dissolved in EtOAc, washed with concentrated Na_2CO_3, brine, dried over over Na_2SO_4, and concentrated, resulting in compound 1140 as a colorless oil (1.06 g, 75% for two steps).

Part B:

Step 1: To compound **1140** (500 mg, 3.54 mmol) in DMF (10 mL) was added 1 (867 mg, 4.25 mmol) DIEA (1.48 mL, 8.5 mmol) and HATU (1.615 g, 4.25 mmol) at 0 °C. After stirring at room temperature for 5 h, the reaction mixture was diluted with ethyl acetate and water. The organic phase was washed with 1 N citric acid, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated. Column purification (SiO_2, EtOAc/Hexane 40:60) afforded a colorless oil (650 mg, 57%).
Step 2: The above material was treated with 5 mL of TFA/H_2O (80:20) at 0 °C. After stirring at room temperature for 2 h, it was concentrated to dryness. Column purification (SiO_2, EtOAc/Hexane 70:30) afforded compound **1141** (500 mg, 88%) as a colorless oil.

Part C:
Step 1: To compound **1141** (250 mg, 0.87 mmol) in toluene (20 mL) was added dibutyltin oxide (217 mg, 0.87 mmol). The reaction mixture was refluxed for 1 h, using Dean-stark apparatus for azotropic removal of water. After cooling to room temperature, the solvent was stripped to dryness under reduced pressure. The resulting oil was dried in *vacuo* for 2 h.
Step 2: To the above oil was added CsF (198 mg, 1.30 mmol). The mixture was then placed in vacuo for 2 h. Allyl bromide (220 mg, 1.83 mmol) in DMF (10 mL) was added at 0 °C. After stirring at room temperature under argone for 30 h, the reaction mixture was concentrated, and then taken up with EtOAc. The solution was washed with saturated KF solution, and brine, dried over Na_2SO4, and concentrated. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, brine, and concentrated. Column chromatography (SiO_2, EtOAc/Hexane 60:40) afforded compound **1142** as a colorless oil (130 mg, 45%). Mass calculated for formula $C_{16}H_{25}NO_6$ 327.17, observed LCMS m/z 328.1 (M+H).

Part D:
Compound **1142** (110 mg, 0.33 mmol) in dichloromethane (200 mL) was added with Grubbs' second-generation catalyst (Scholl, M.; Ding, S.; Lee, C.W.; Grubbs, R.H., *Org. Lett*, **1999**, *1*, 953-956.). After stirring at room temperature under argone for 3.5 h, the solution was concentrated under

reduced pressure. Column chromatography (SiO_2, EtOAc) afforded **1143** as a white solid (60 mg, 60%), Mass calculated for formula $C_{14}H_{21}NO_6$ 299.14, observed LCMS m/z 300.1 (M+H).

Part E:

To **1143** (60 mg, 0.2 mmol) in EtOAc (10 mL) was added 10% Pd/C (10 mg). The reaction mixture was allowed to stir at room temperature under H_2 for 2 h, then concentrated. Column chromatography (SiO_2, EtOAc) afforded **1144** as a white solid (50 mg, 83%), Mass calculated for formula $C_{14}H_{23}NO_6$ 301.15, observed LCMS m/z 302.1 (M+H).

Part F:

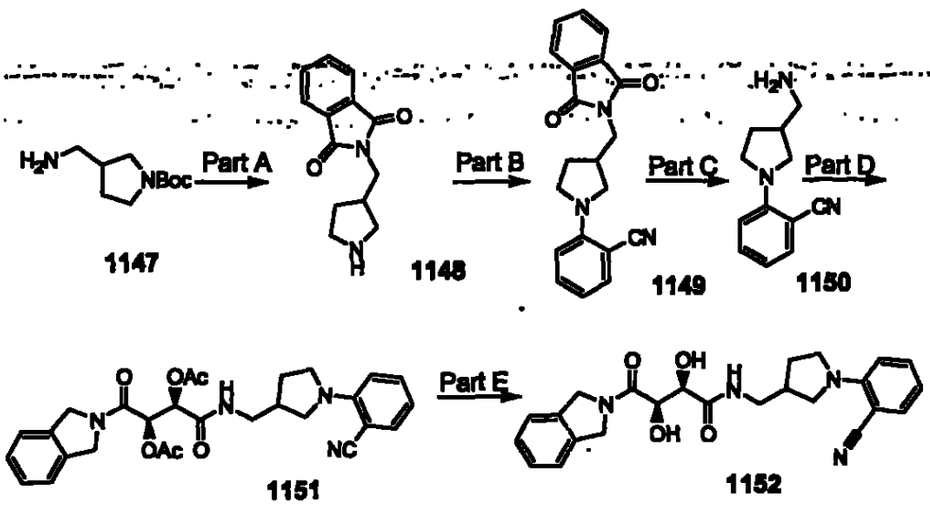
Compound **1144** (20 mg, 0.067 mmol) in MeOH (2 mL) was mixed with solid K_2CO_3 (20 mg, 0.14 mmol). After stirring at room temperature for 5 h, the reaction mixture was concentrated, and then taken up with EtOAc and water. It was acidified with 1N HCl. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated to afford **1145** as a white solid (12 mg, 63%), Mass calculated for formula $C_{13}H_{21}NO_6$ 287.1, observed LCMS m/z 288.1 (M+H).

Part G:

A mixture of **1145** (12 mg, 0.042 mmol), **978** (13.5 mg, 0.063 mmol), DIEA (0.018 mL, 0.1 mmol) and HATU (24 mg, 0.063 mmol) in DMF (1 mL) was stirred overnight at room temperature, and then diluted with ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated. Purification by reverse phase prep-LC afforded **1146** as a white solid. HPLC-MS t_R = 4.22 min (UV_{254} nm, 10 min), mass calculated for formula $C_{21}H_{22}N_2O_4$ 484.3, observed LCMS m/z 485.2 (M+H).

Example 34

Example 34A:



Part A

Step 1: A mixture of 3-(aminomethyl)-1-N-(*tert*-butoxycarbonyl)-pyrrolidine (**1147**) (200 mg, 1.0 mmol), monomethyl phthalate (216 mg, 1.2 mmol), EDC (229 mg, 1.2 mmol), HOBt (162 mg, 1.2 mmol) and triethylamine (0.79 mL, 2.0 mmol) in DCM (4 mL) was stirred overnight. The reaction mixture was diluted with DCM and washed with 0.1 N HCl, water, saturated sodium bicarbonate solution, water, and brine, dried over sodium sulfate and concentrated. The residue was purified by column chromatography (SiO_2, 33% EtOAc/hexane) to afford a white solid (110 mg, 33%). HPLC-MS t_R = 1.89 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{22}N_2O_4$ 330.2, observed LCMS m/z 353.2 (M+Na).

Step 2: Compound **1148** was prepared from the material from step 1 following the procedure as described in Example 27 Part A step 2.

Part B

Compound **1149** was prepared following the procedure as described in Example 27 Part A step 1. HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{17}N_3O_2$ 331.1, observed LCMS m/z 332.2 (M+H).

Part C

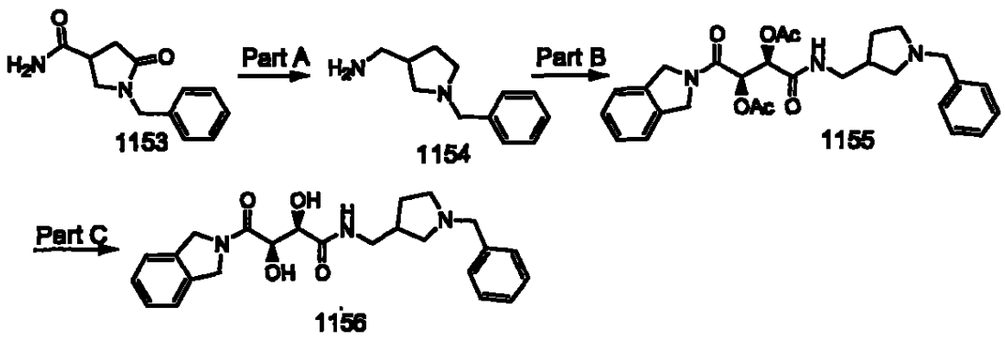
Compound **1149** (0.33 mmol) and hydrazine hydrate (65 μL, 1.34 mmol) in ethanol (3 mL) were refluxed for 2 hours. The reaction mixture was cooled

and filtered. The filtrate was concentrated and **1150** was used without further purification.

Part D and E

Compounds **1151** and **1152** were prepared following the procedures described in Example 5 Part D and E. Data for **1151**: HPLC-MS t_R = 1.78 min ($UV_{254\ nm}$); mass calculated for formula C28H30N4O6 518.2, observed LCMS m/z 519.2 (M+H). Data for **1152**: HPLC-MS t_R = 1.52 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{28}N_4O_4$ 434.2, observed LCMS m/z 435.2 (M+H).

Example 34B:



Part A

To a solution of 1-benzyl-5-oxo-3-pyrrolidinecarboxamide (**1153**) (50 mg, 0.23 mmol) in THF (1 mL) was added 1M solution of lithium aluminum hydride in THF (0.69 mL, 0.69 mmol). The reaction mixture was stirred at 50 °C for 3 hours, cooled, quenched with aqueous ammonium chloride solution. After addition of 1N sodium hydroxide solution, the mixture was diluted with ethyl acetate, stirred for 20 minutes, and filtered through a pad of Celite. The filtrate was washed with 1N sodium hydroxide solution and brine, dried over sodium sulfate and concentrated to give **1154** as an oil (14 mg, 32%). HPLC-MS t_R =

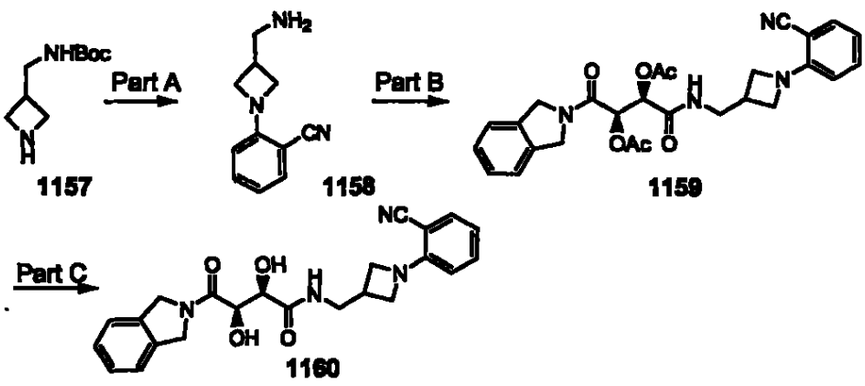
0.22 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{18}N_2$ 190.2, observed LCMS m/z 191.2 (M+H).

Part B and C .

Compounds **1155** and **1156** were prepared following the procedures described in Example 5 Part D and E. Data for **1156**: HPLC-MS t_R = 0.91 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{29}N_3O_4$ 423.2, observed LCMS m/z 424.1 (M+H).

Example 35

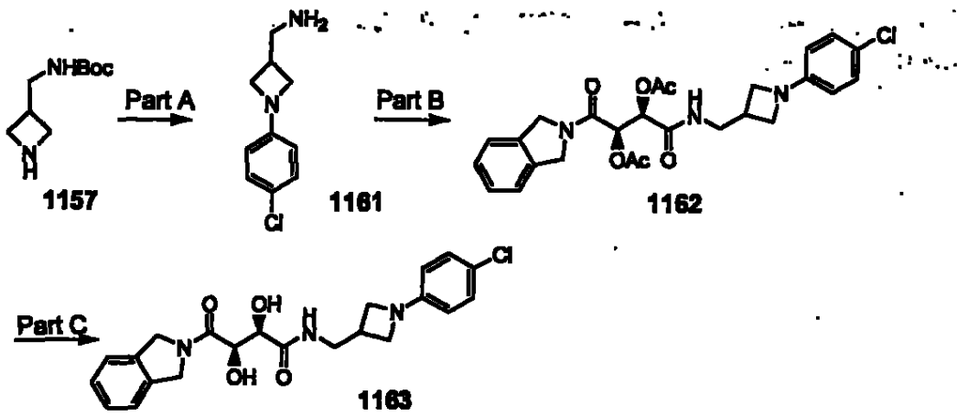
Example 35A:



Part A and B and C:

Compounds **1158, 1159** and **1160** were prepared following the procedures described in Example 27 Part A, B and C. Data for **1158**: HPLC-MS t_R = 0.76 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{13}N_3$ 187.1, observed LCMS m/z 188.1 (M+H). Data for **1159**: HPLC-MS t_R = 1.72 min ($UV_{254\ nm}$); mass calculated for formula $C_{27}H_{28}N_4O_6$ 504.2, observed LCMS m/z 505.1 (M+H). Data for **1160**: HPLC-MS t_R = 1.43 min ($UV_{254\ nm}$); mass calculated for formula $C_{23}H_{24}N_4O_4$ 420.2, observed LCMS m/z 421.1 (M+H).

Example 35B:



Part A

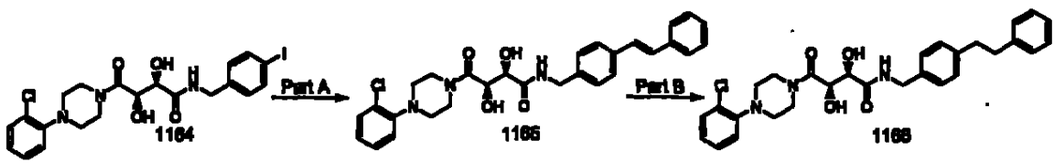
Step 1: A mixture of azetidin-3-ylmethyl-carbamic acid tert-butyl ester (**1157**) (20 mg, 0.107 mmol), 4-chloro-1-iodobenzene (38.4 mg, 0.161 mmol), copper iodide (4.0 mg, 0.021 mmol), L-proline (4.8 mg, 0.042 mmol) and potassium carbonate (29.6 mg, 0.214 mmol) in DMSO (2 mL) under Argon atmosphere was stirred at 80 °C overnight. The reaction mixture was diluted with EtOAc, washed with water and brine, dried over sodium sulfate and concentrated. HPLC-MS t_R = 2.13 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{21}ClN_2O_3$ 296.1, observed LCMS m/z 297.2 (M+H).

Step 2: Compound **1161** was prepared from the material from step 1 following the procedure as described in Example 27 Part A step 2.

Part B and C

Compounds **1162** and **1163** were prepared following the procedures described in Example 5 Part D and E. Data for **1162**: HPLC-MS t_R = 1.93 min ($UV_{254\ nm}$); mass calculated for formula C26H28ClN3O6 513.2, observed LCMS m/z 514.2 (M+H). Data for **1163**: HPLC-MS t_R = 1.63 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{24}ClN_3O_4$ 429.2, observed LCMS m/z 430.1 (M+H).

Example 36:



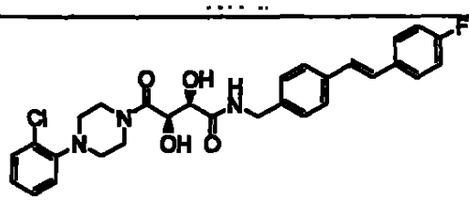
Compound **1164** was prepared using procedures described in Example 2. HPLC-MS t_R = 1.88 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{23}ClIN_3O_4$ 543.0, observed LCMS m/z 544.0 (M+H).

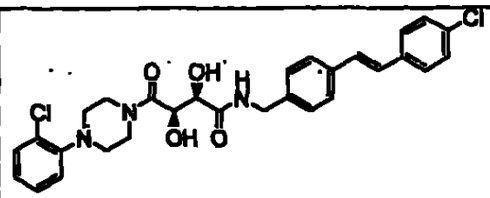
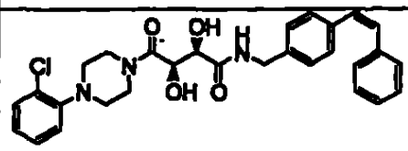
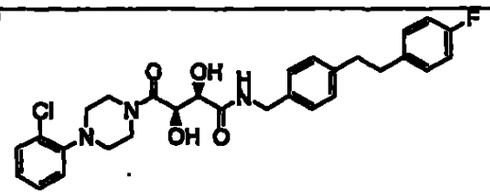
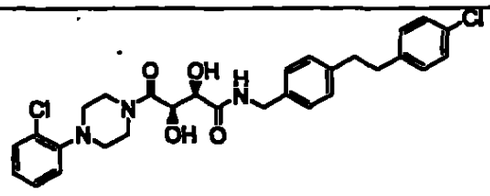
Part A:

Compound **1165** was prepared from **1164** and styrenyl boronic acid using the coupling conditions described in Example 3 Part F. HPLC-MS t_R = 2.11 min ($UV_{254\ nm}$); mass calculated for formula $C_{29}H_{30}ClN_3O_4$ 519.2, observed LCMS m/z 520.0 (M+H).

Part B:

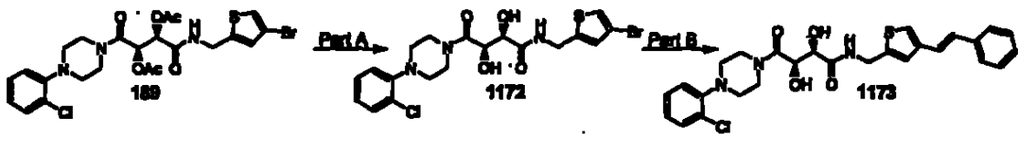
A mixture of **1165** (10 mg, 0.02 mmol) and palladium on carbon (10 wt%, 2 mg) in THF (2 mL) under hydrogen (atmospheric pressure) was stirred overnight. The reaction mixture was filtered through celite and concentrated. Purification by prep-LC afforded **1166** as an off-white solid (5 mg). HPLC-MS t_R = 5.42 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{29}H_{32}ClN_3O_4$ 521.2, observed LCMS m/z 522.2 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
1167		537.2	538.1

1168		553.2	554.0
1169		519.2	520.2
1170		539.2	540.2
1171		555.2	556.0

Example 37: Alkyl Suzuki

Example 37A:



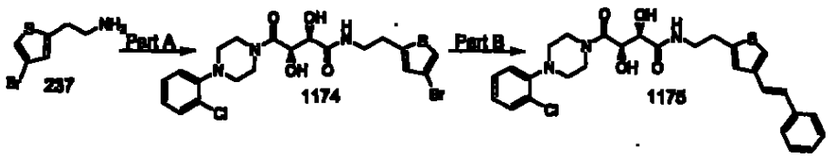
Part A:

Compound **1172** was prepared from **189** using the procedures described in Example 2A Part B. HPLC-MS t_R = 4.83 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{19}H_{21}BrClN_3O_4S$ 501.0, observed LCMS m/z 502.0 (M+H).

Part B:

Compound **1173** was prepared using the procedures described in Example 36 Part A. HPLC-MS t_R = 5.37 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{27}H_{28}ClN_3O_4S$ 525.2, observed LCMS m/z 526.2 (M+H).

Example 37B:



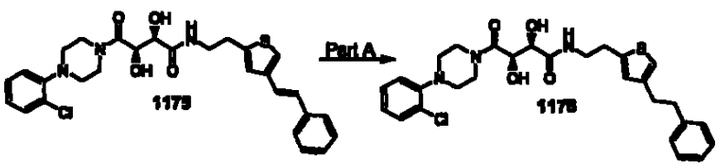
Part A:

Compound **1174** was prepared from **237** using the procedures described in Example 2. HPLC-MS t_R = 4.76 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{20}H_{23}BrClN_3O_4S$ 515.0, observed LCMS m/z 516.0 (M+H).

Part B:

Compound **1175** was prepared using the procedures described in Example 36 Part A. HPLC-MS t_R = 2.29 min ($UV_{254\ nm}$,); mass calculated for formula $C_{28}H_{30}ClN_3O_4S$ 539.2, observed LCMS m/z 540.2 (M+H).

Example 37C:



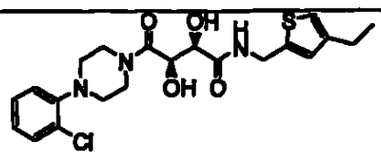
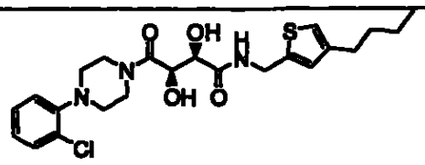
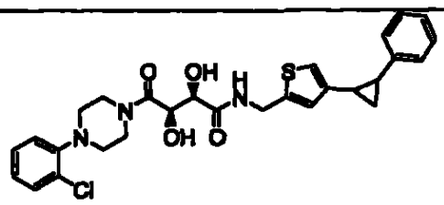
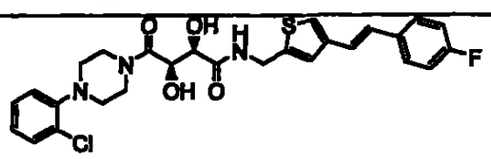
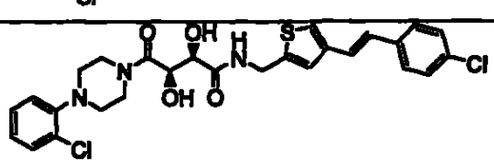
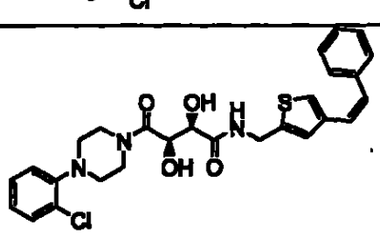
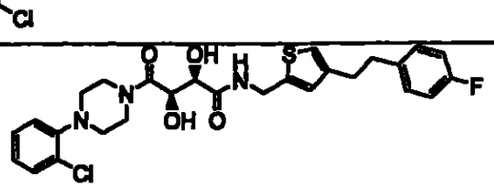
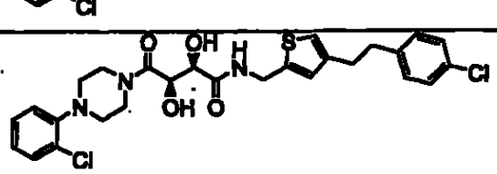
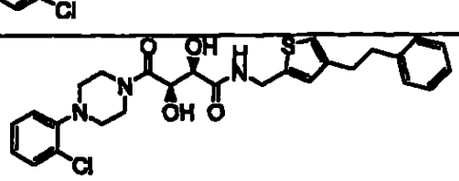
Part A:

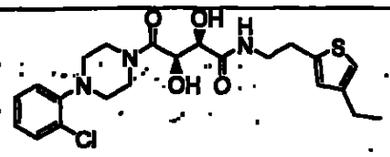
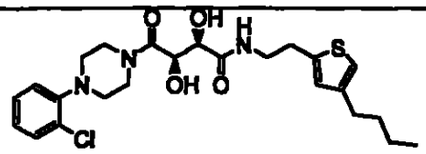
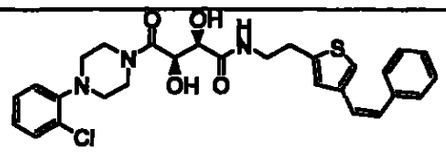
Compound **1176** was prepared using procedures described in Example 36 Part B.

HPLC-MS t_R = 5.50 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{28}H_{32}ClN_3O_4S$ 541.2, observed LCMS m/z 542.2 (M+H).

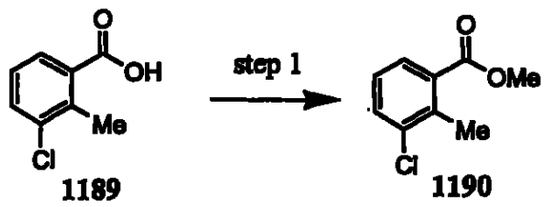
583

572

Compound #	Structure	Exact mass	MS m/e (M+H)
1177		451.1	452.2
1178		479.2	480.2
1179		539.2	540.1
1180		543.1	544.0
1181		559.1	560.0
1182		525.2	526.2
1183		545.2	546.1
1184		561.1	562.0
1185		527.2	528.1

1186		465.2	466.1
1187		493.2	494.1
1188		539.2	540.1

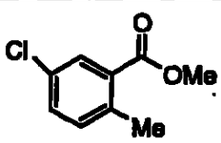
Example 38: Isoindoline analogs

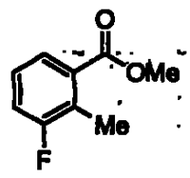


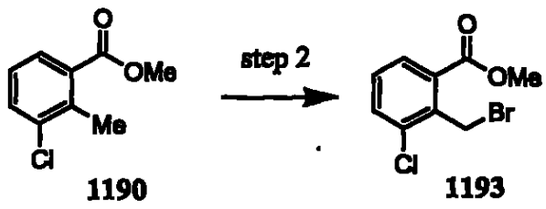
1189 1190

Step 1

To 3-chloro-2-methylbenzoic acid **1189** (4.95 g, 0.0290 mol) dissolved in DMF (70 mL) was added cesium carbonate (14.18 g, 0.0435 mol) and methyl iodide (5.35 g, 2.3 mL, 0.0377 mol). The reaction mixture was stirred at room temperature for 20 h. The reaction mixture was concentrated, and EtOAc (200 mL) was added. The organic solution was washed with water (2 x 100 mL), dried ($MgSO_4$), filtered, and concentrated to give 4.43 g (83%) of the product **1190** as a yellow oil. MS for M-Cl:149

Compound #	Structure	MS
1191		M-Cl: 149

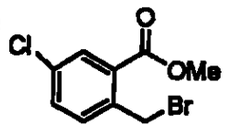
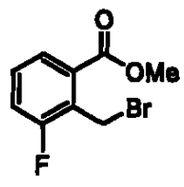
1192		M+1: 169

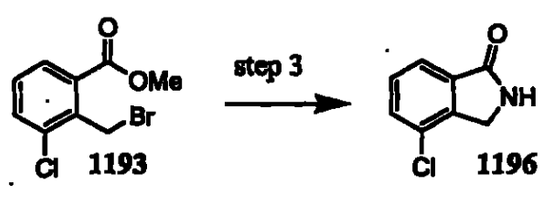


1190 1193

Step 2

To compound 1190 (4.42 g, 0.0239 mol) dissolved in CCl_4 (100 mL) was added n-bromosuccinimide (5.11 g, 0.287 mol) and benzoyl peroxide (0.58 g, 0.00239 mol). The reaction mixture was heated at reflux for 16 h then cooled to room temperature. The solid was removed by filtration and washed with CH_2Cl_2. The filtrate was concentrated to give 7.80 g of the product 1193 with succinimide as a yellow oil and solid mixture.

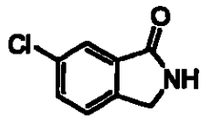
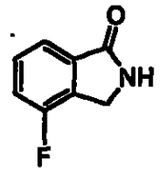
Compound #	Structure
1194	
1195	

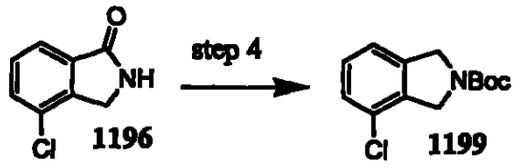


1193 1196

Step 3

Compound **1193** (6.31 g, 0.0239 mol) was dissolved in 7 N NH_3 in MeOH (50 mL) and stirred at room temperature for 3 h then heated at reflux for 4 h. The reaction mixture was cooled to room temperature and concentrated. The residue was suspended in CH_2Cl_2 (150 mL), and the solid was removed by filtration and washed with CH_2Cl_2. The filtrate was concentrated, and the crude product was purified by silica gel flash chromatography (eluant: 5% MeOH-CH_2Cl_2 to 10% MeOH-CH_2Cl_2) to give 3.68 g (92%) of the product **1196** as a white solid. MS for M+1: 168.

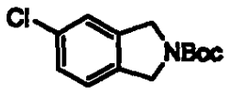
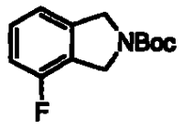
Compound #	Structure	MS (M+1)
1197		168
1198		152



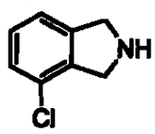
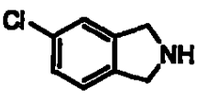
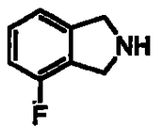
Step 4

To compound **1196** (1.00 g, 5.97 mmol) suspended in dry THF (15 mL) was added borane (1 M in THF, 14.9 mL, 14.0 mmol). The reaction mixture was heated at reflux for 5 h then cooled to 0 °C. EtOH (15 mL) and potassium carbonate (2 g) were carefully added portionwise. The reaction mixture was heated at reflux for 16 h then cooled to 0 °C, and $(tBOC)_2O$ (1.95 g, 8.95 mmol) was added. The reaction mixture was stirred at room temperature for 3

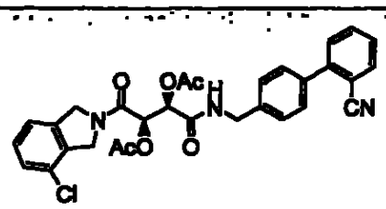
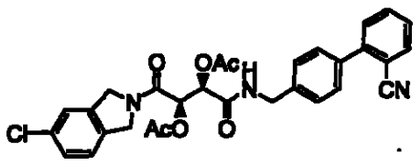
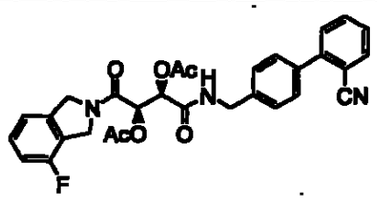
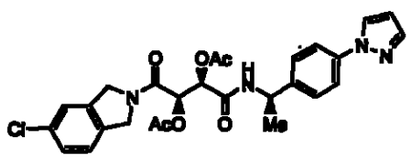
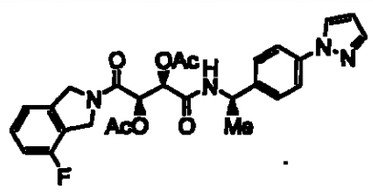
h then concentrated. Water (30 mL) was added, and the aqueous solution was extracted with 3 x 30 mL of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by silica gel flash chromatography (eluant: 5% EtOAc- CH_2Cl_2) to give 0.56 g (37%) of the product **1199** as a yellow oil. MS for M+1-tBu: 198.

Compound #	Structure	MS
1200		M+2-tBu = 198
1201		M+2-tBu: 182

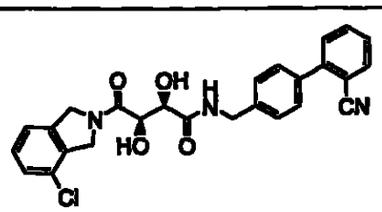
The following intermediates were prepared according to the procedure of Example 11B Part F.

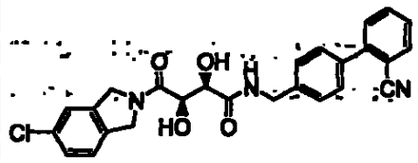
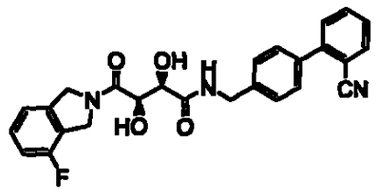
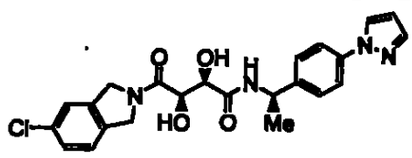
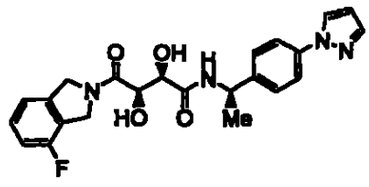
Compound #	Structure	MS (M+1)
1202		154
1203		154
1204		138

The following intermediates were prepared according to the procedure of Example 2

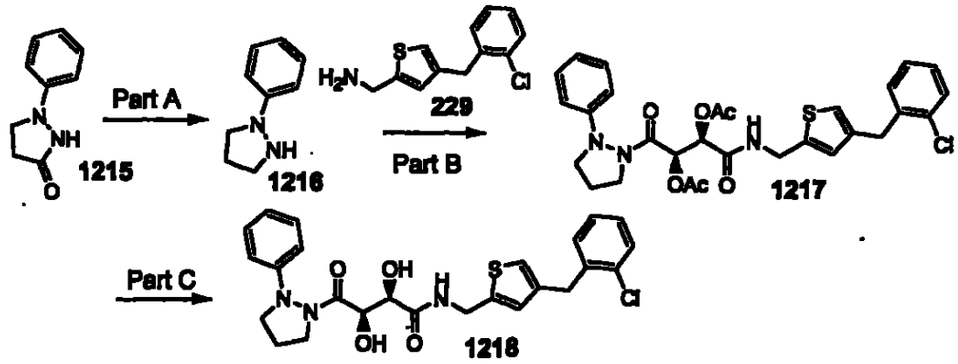
Compound #	Structure	MS (M+1)
1205		560
1206		560
1207		544
1208		539
1209		523

The following compounds were prepared according to the procedure of Example 2

Compound #	Structure	MS (M+1)
1210		476

1211		476
1212		460
1213		455
1214		439

Example 39: Hydrazinoamides



Part A:

1-Phenyl-pyrazolidin-3-one (1215)(1.0 g, 6.16 mmol) in 15 mL of THF was added dropwise to the mixture of $AlCl_3$ (0.82 g, 6.16 mmol) and 12 mL of 1 M $LiAlH_4$ (12 mmol) in THF at 0°C under argone. The reaction mixture was then

allowed to stir at room temperature for 4 h. It was quenched with 10 mL of 1N NH_4Cl solution; diluted with EtOAc and 15% NaOH aqueous solution. After filtration, the organic layer was separated, dried over Na_2SO_4, and concentrated. Column chromatography (SiO_2, EtOAc/Hexane, 20:80) afforded **1216** as colorless oil.

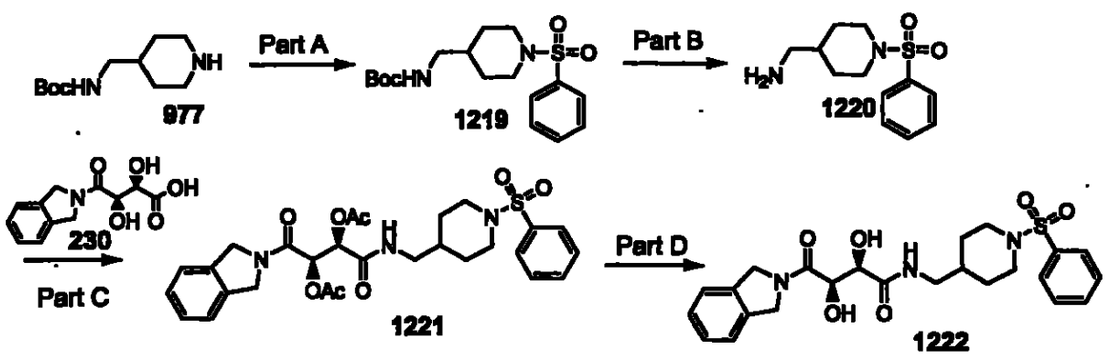
Part B:

Compound **1217** was prepared according to the procedure described in Example 2A Part A from **1216** (15 mg, 0.1 mmol).

Part C:

Compound **1217** was dissolved in 1 mL of MeOH, 0.5 mL of 7N NH_3 in MeOH was added. After stirring at room temperature for 1 h, the reaction mixture was concentrated in *vacuo*. Purification by reverse phase prep-LC afforded compound **1218** as a white solid. HPLC-MS t_R = 5.09 min ($UV_{254\ nm}$, 10 min), Mass calculated for formula $C_{25}H_{28}ClN_3O_4S$ 499.1, observed LCMS m/z 500.0 (M+H).

Example 40: Piperidine sulfonamides



Part A:

Phenylsulfonyl chloride (212 mg, 1.2 mmol) was slowly added to a solution of 4-(Boc-aminomethyl)piperidine (**977**) (214 mg, 1 mmol) in 1.0 mL of pyridine at 0 °C. The reaction mixture was allowed to stir at room temperature overnight, and diluted with ethyl acetate and water. The organic layer was

washed with 1 N citric acid, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in **1219** (320 mg; 90%). Mass calculated for formula $C_{17}H_{28}N_2O_4S$ 354.2, observed LCMS m/z 355.2 (M+H), 299.2 (M-55)

Part B:

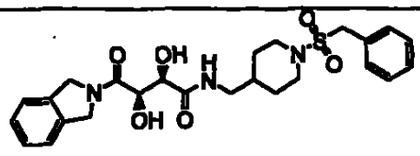
To the solution of **1219** (200 mg, 0.54 mmol) in THF (5 mL) was added 2 mL of 4 N HCl in dioxane. The reaction mixture was stirred at room temperature for 1 h, and concentrated to afford **1220** (105 mg, 66 %).

Part C:

To **1220** (105 mg, 0.36 mmol) in DMF (2 mL) was added **230** (100 mg, 0.3 mmol), DIEA (750 μL, 0.6 mmol) and HATU (137 mg, 0.36 mmol). The reaction mixture was stirred overnight at room temperature, and diluted with ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in **1221**.

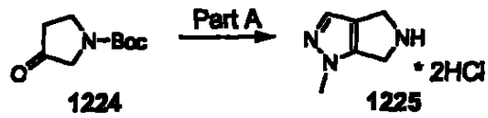
Part D:

Compound **1221** was dissolved in 4 mL of MeOH, 2 mL of 7N NH_3 in MeOH was added. After stirring at room temperature for 1 h, the reaction mixture was concentrated in vacuo. Purification by reverse phase prep-LC afforded **1222** as a white solid. HPLC-MS t_R =3.59 min ($UV_{254\ nm}$, 10 min), Mass calculated for formula $C_{24}H_{29}N_3O_6S$ 488.2, observed LCMS m/z 488.1 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
1223		501.2	502.1

Example 41: Heterocyclic isoindoline analogs

Example 41A:

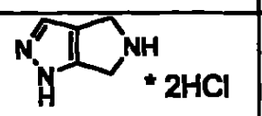
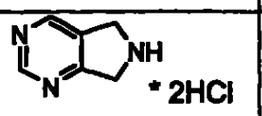
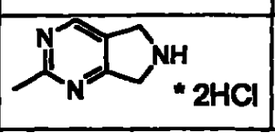


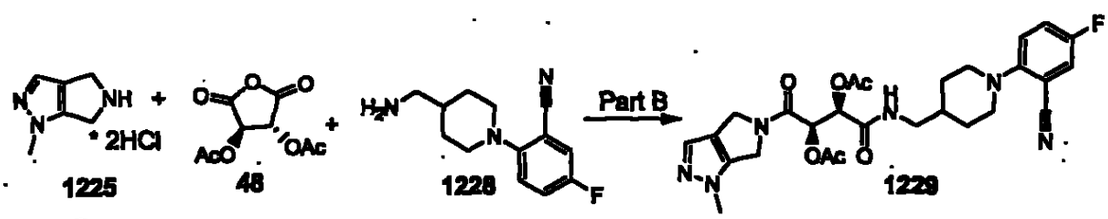
1224 1225

Part A:

Compound **1225** (70% overall yield) was prepared from **1** according to the procedures of Fukui, H. *et. al.* (*Heterocycles* **2002**, *56*, 257)

The following analogs were prepared according to this reference:

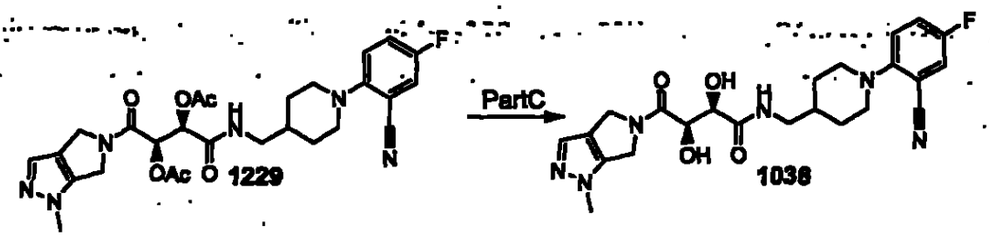
Compound #	Structure	Overall yield
1225		73%
1226		47%
1227		66%



1225 48 1228 1229

Part B:

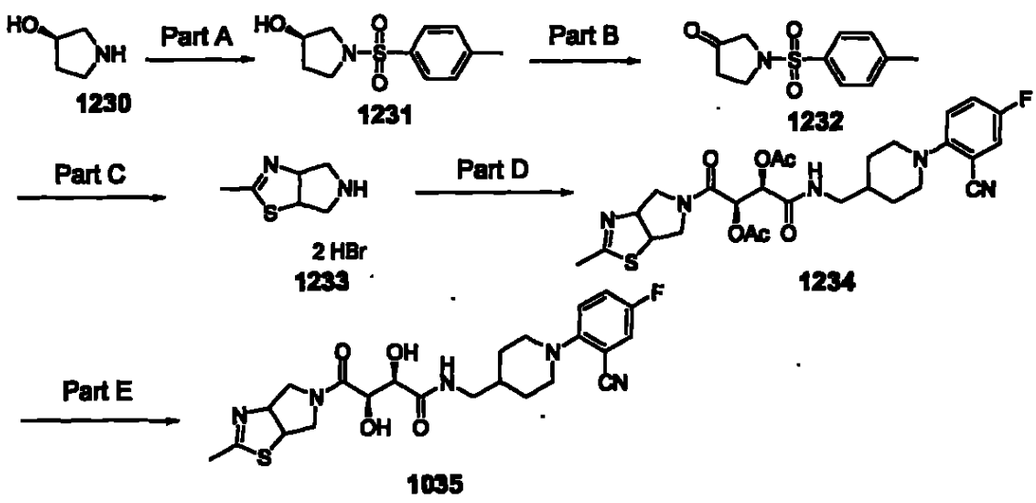
Compound **1228** was prepared according to procedures described in Example 27A. HPLC-MS t_R = 0.95 min (UV_{254nm}); mass calculated for formula C13H16FN3 233.1, observed LCMS m/z 234.2 (M+H). Compound **1229** was prepared according to the procedures described in Example 2A Part A. HPLC-MS t_R = 1.57 min ($UV_{254\ nM}$); mass calculated for formula $C_{27}H_{31}FN_6O_6$ 554.23, observed LCMS m/z 555.2 (M+H).



Part C:

Comppound 1036 was synthesized using the procedure found in Example 2A, Part B. Purification by reverse phase prep-LC afforded a white solid after lyophilization. HPLC-MS t_R = 3.39 min ($UV_{254\ nM}$, 10 min); mass calculated for formula $C_{23}H_{27}FN_8O_4$ 470.21, observed LCMS m/z 471.2 (M+H).

Example 41B:



Part A:

Compound 1230 (2.18 g, 17.7 mmol) was dissolved in methylene chloride (35 mL) and cooled in an ice bath. Triethylamine (5 mL, 35.4 mmol) was added followed by p-toluenesulfonyl chloride (3.35 g, 17.7 mmol) in portions. The reaction mixture was stirred for 3 hours at room temperature and then quenched with water and extracted with methylene chloride. The combined organic layers were washed with 1 N HCl solution, bicarbonate solution and

brine; dried over sodium sulfate and concentrated to provide the desired product **1231** (3.85 g), that was used without purification: HPLC-MS t_R = 1.26 min (UV_{254nm}); mass calculated for formula $C_{11}H_{15}NO_3S$ 241.08, observed LCMS m/z 242.2 (M+H).

Part B:

Compound **1231** (3.82 g, 15.78 mmol) was dissolved in methylene chloride (100 mL) and pyridinium chlorochromate (6.7 g, 31 mmol) was added followed by crushed molecular sieves (3.5 g). The reaction was stirred overnight and then diethylether (150 mL) was added and stirring was continued for an additional hour. The solids were filtered and the solvent was evaporated under reduced pressure. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded a white solid **1232** (3.20 g, 84%). HPLC-MS t_R = 1.43 min ($UV_{254\ nM}$); mass calculated for formula $C_{11}H_{13}NO_3S$ 239.06, observed LCMS m/z 240.1 (M+H).

Part C:

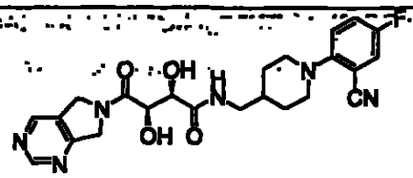
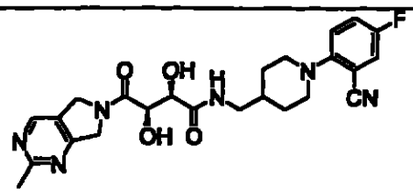
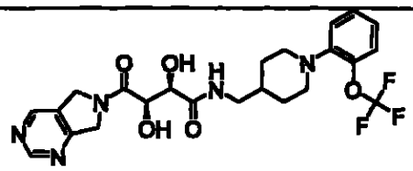
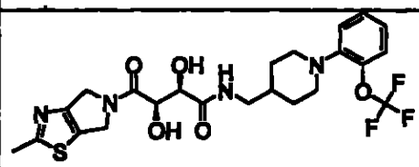
Reactions were performed using procedures from Heterocycles, Vol. 41, No. 7, 1995.

Part D:

Reaction was performed using the procedure found in Example 2A, Part A. **1234**: HPLC-MS t_R = 1.702 min ($UV_{254\ nM}$); mass calculated for formula $C_{27}H_{30}FN_5O_6S$ 571.19, observed LCMS m/z 572.2 (M+H).

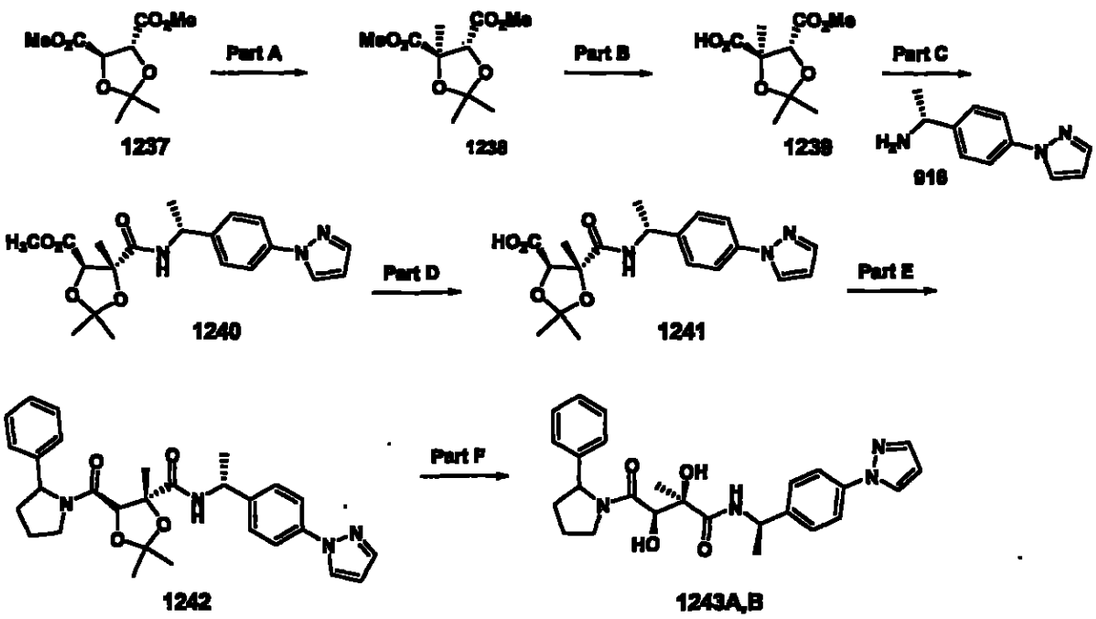
Part E:

Reaction was performed using the procedure found in Example 2A, Part B. Purification by reverse phase prep-LC afforded a white solid after lyophilization. **1035**: HPLC-MS t_R = 3.66 min ($UV_{254\ nM}$, 10 min); mass calculated for formula $C_{23}H_{28}FN_5O_4S$ 487.2, observed LCMS m/z 488.2 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
1235A		468.2	469.2
1235B		482.2	483.2
1236A		509.2	510.2
1236B		528.2	529.2

Example 42:

Example 42A:



Part A:

To a solution of dimethyl 2,3-O-isopropylidene-L-tartrate **1237** (10.9 g, 50 mmol) in dry THF (150 mL) and DMPU (25 mL) was added methyl iodide (4.7 mL, 75.5 mmol). The reaction mixture was cooled to -78 °C and a 1M solution in THF of $LiN(TMS)_2$ (55mL, 55 mmol) was added via dropping funnel in 45 minutes period to the reaction mixture. THF reaction mixture was stirred at -78 °C for 2 hours then warmed to -20 °C and quenched carefully with water (20 mL). The reaction mixture was poured into EtOAc (150 mL) and the organic layer was separated and washed with water (1 x 50 mL) followed by brine (1 x 50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 10% Et_2O/hexane followed by 15% Et_2O/hexane) afforded the desired compound **1238** as clear oil (9.7 g, 83%). LCMS m/z: 233.1 (M+H).

Part B:

A pH 8 buffer solution was prepared by titrating a solution of 0.1 M sodium phosphate (300 mL) with 1M HCl to final pH of 8. To a mixture of compound **1238** in pH 8 buffer solution was added esterase (41 units/mg,15 mg, 615 units). Added aq. 1N NaOH (6.5 mL) slowly via syringe during a period of 3.5 hours to the reaction mixture to maintain the pH of the reaction mixture in the range of 7.9-8.2. The reaction mixture was extracted with Et_2O (2 x 50 mL). The aqueous layer was acidified to pH 3 using 12N HCl then extracted with EtOAc (4 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to afford the desired compound **1239** (1.36 g, 72%). LCMS m/z: 219.1 (M+H).

Part C:

To a solution of compound **916** (0.1 g, 0.535 mmol) in DMF (1.5 mL) was added compound **1239** (0.092 g, 0.5 mmol), triethyl amine (0.2 mL, 1.4 mmol) and HATU (0.365 g, 0.96 mmol). The reaction mixture was stirred for 18 hours and then diluted with CH_2Cl_2 (5 mL) and washed with aq. 0.5N NaOH solution (3 mL). The organic layer was dried over $MgSO_4$ and concentrated. Purification by column chromatography (SiO_2, 30% EtOAc/hexane followed by

40% EtOAc/hexane) afforded the compound **1240** as a white foam (0.162 g, 67%). LCMS m/z 388.1 (M+H).

Part D:

To a solution of compound **1240** (0.175 g, 0.452 mmol) in THF (2 mL) and MeOH (2 mL) at 0 °C was added aq. 1.0 M LiOH (0.91 mL, 0.91 mmol). The reaction mixture was warmed to room temperature and stirred for 1 hour. The reaction mixture was acidified with aq. 1N HCl (0.95 mL) and diluted with brine (1.5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to afford compound **1241** as a white foam (0.182 g, 100%). LCMS m/z: 374.1 (M+H).

Part E:

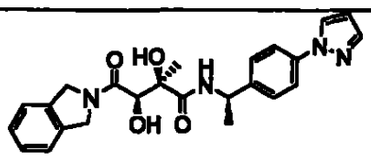
To a solution of compound **1241** (0.179 g, 0.48 mmol) in DMF (3 mL) was added 2-phenylpyrrolidine hydrogen chloride salt (0.092 g, 0.5 mmol), triethyl amine (0.2 mL, 1.4 mmol) and HATU (0.365 g, 0.96 mmol). The reaction mixture was stirred for 4.5 hours and then diluted with EtOAc (10 mL) and washed with water (1.5 mL) followed by brine (1.5 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by prep. plate chromatography (SiO_2, 66%EtOAc/hexane). Two diastereomeric compounds **1242** were isolated. Diastereomer compound **1242A** (0.067 g, 28%), LCMS m/z 503.1 (M+H) and diastereomer compound **1242B** (0.095 g, 28%), LCMS m/z 503.1 (M+H).

Part F:

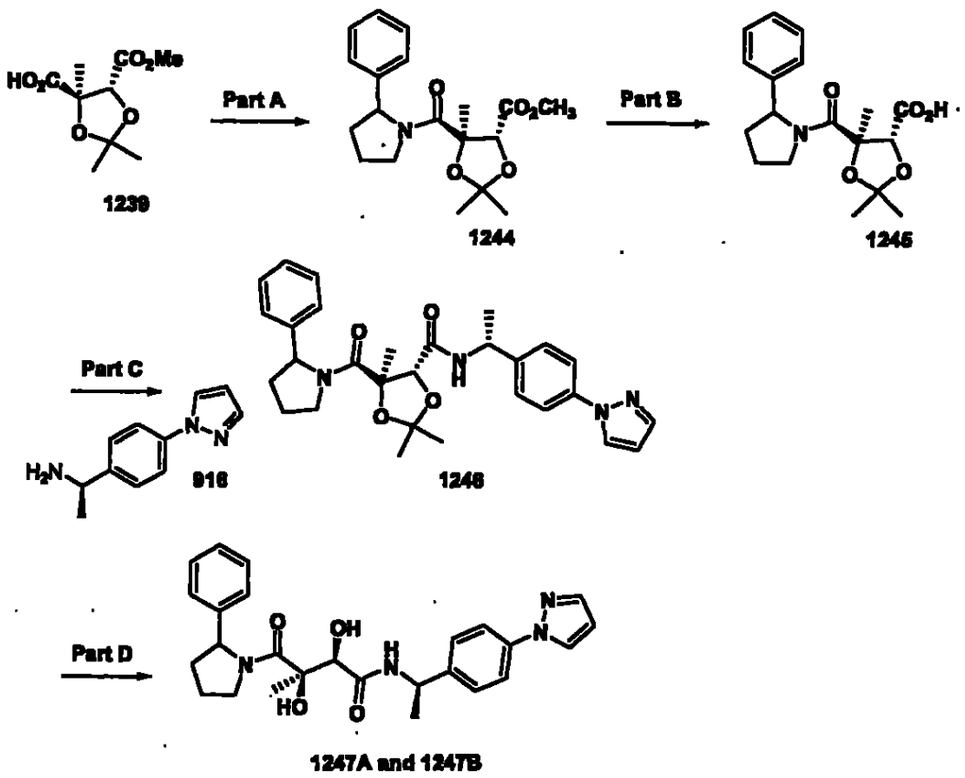
To a solution of compound **1242A** (0.06 g, 0.119 mmol) in CH_2Cl_2 (1 mL) was added TFA (4 mL) followed by water (0.5 mL). The reaction mixture was stirred at 80 °C temperature for 3 hours and then concentrated. The residue was purified by column chromatography (SiO_2, 5% MeOH/CH_2Cl_2) to afford **1243A** (0.012 g, 22%), LCMS m/z 463.1 (M+H).

To a solution of compound **1242B** (0.088 g, 0.18 mmol) in CH_2Cl_2 (1 mL) was added TFA (4 mL) followed by water (0.5 mL). The reaction mixture was stirred at 23 °C temperature for 18 hours and then concentrated. The residue was purified by column chromatography (SiO_2, 5% MeOH/CH_2Cl_2) to

afford 1243B (0.05 g, 66%), LCMS m/z 463.1 (M+H).

Compound #	Structure	Exact mass	MS m/z (M+H)
1243C		434.2	435.1

Example 42B:



Part A:

To a solution of compound 1239 (200 mg, 0.917 mmol) and 2-phenylpyrrolidine (177 mg, 0.96 mmol) in CH_2Cl_2 (5 mL) at 23 °C was added DIEA (0.35 mL, 2.01 mmol) followed by PyBOP (0.367 g, 1.146 mmol) and

the reaction mixture was stirred for 18 hours. The reaction mixture was concentrated and the residue was purified by column chromatography (SiO_2, 20% EtOAc/hexane followed by 30% EtOAc/hexane) to afford the desired compound **1244** as an oil (0.16 g, 50%). LCMS m/z: 348.1 (M+H).

Part B:

Compound **1244** was converted to compound **1245** using the procedure as described in Example 42A Part D. LCMS m/z: 374.1 (M+H).

Part C:

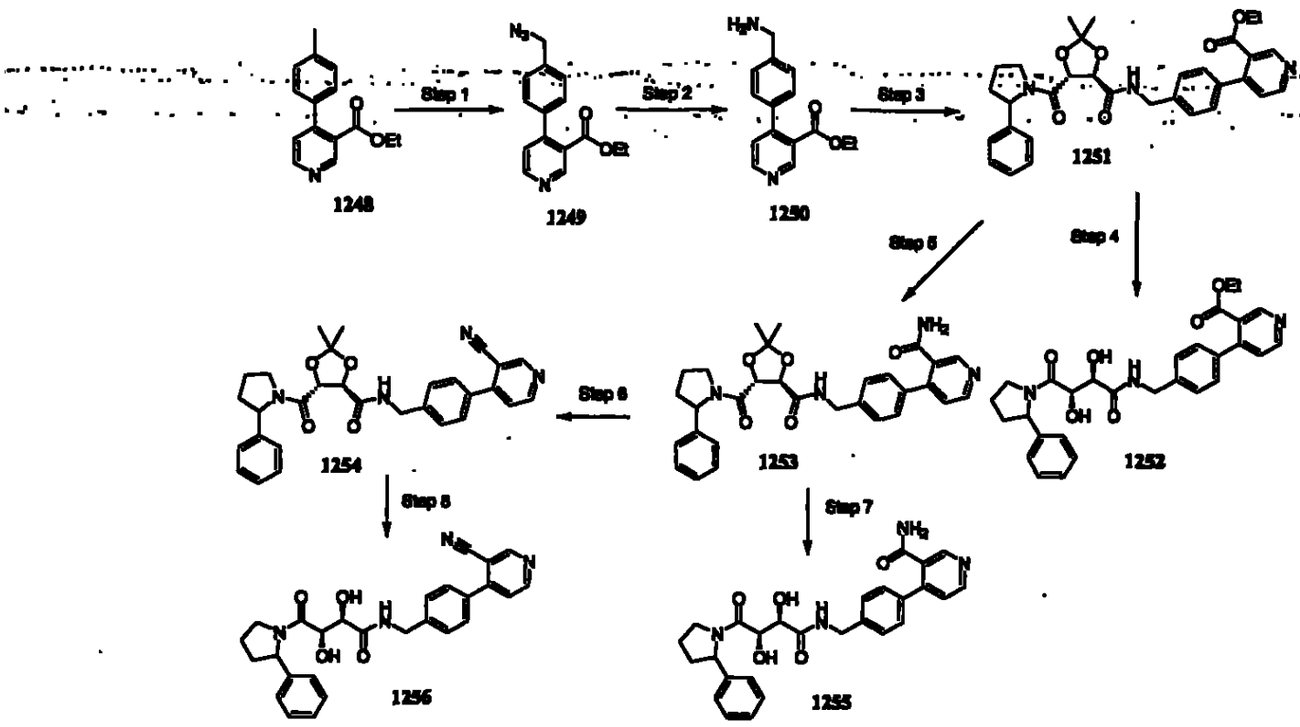
Compound **1245** was converted to compound **1246** using the procedure as described in Example 42A Part E. LCMS m/z: 503.1 (M+H).

Part D:

Compound **1246** was converted to **1247A** and **1247B** using the procedure as described in Example 42A Part F. Two diastereomeric compounds **1247** were isolated. Diastereomer **1247A** (16% yield), LCMS m/z: 463.1 (M+H) and diastereomer **1247B** (16% yield), LCMS m/z: 463.1 (M+H).

Example 43:

Example 43A:



Step 1:

Compound **1248** was prepared according to the literature procedure: Shiao, M.-J.; Liu, K.-H.; Lin, P.-Y *Heterocycles* **1993**, *36*, 3, 507.

A solution of **1248** (2.20 g, 9.10 mmol), NBS (1.81 g, 10.20 mmol), 1,1'-azobis(cyclohexanecarbonitrile) (0.113 g, 0.46 mmol) in CCl_4 (40 mL) was stirred at 75 °C for 24 hours. The reaction was cooled to room temperature, and the mixture was diluted with CH_2Cl_2 and sat. Na_2CO_3. The organic layer was removed, and the aqueous phase was extracted with CH_2Cl_2 (4x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The crude product mixture was used without further purification.

A solution of the crude product mixture prepared above and sodium azide (0.75 g, 11.5 mmol) in a MeOH (15 mL)/DMF(15 mL)/DMSO (15 mL) solvent mixture was stirred at room temperature for 24 hours. The reaction was diluted with H_2O and EtOAc. The organic layer was removed, and the aqueous phase was extracted with EtOAc (1x). The combined organics were washed with H_2O (3x), brine (1x), dried (Na_2SO_4), filtered, and concentrated.

The resulting brown oil was purified by silica gel chromatography to furnish **1249** (1.2 g, 4.25 mmol, 47% yield over 2 steps). MS m/e: 283.1 (M+H).

Step 2:

To a solution of **1249** (1.2 g, 4.2 mmol) in THF (20 mL) at room temperature was added PPh_3 (1.1g, 4.2 mmol). The reaction was stirred at room temperature for 1 hour at which time H_2O (2 mL) was added. The resulting mixture was stirred for 24 hours. After concentration, the mixture was taken up in Et_2O and 0.25 N HCl. The organic phase was removed, and the aqueous phase was basicified with sat. Na_2CO_3 and extracted with EtOAc (4x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The compound was purified by silica gel chromatography to furnish **1250** (0.51 g, 47% yield). MS m/e: 257.1 (M+H).

Step 3:

Compound **1251** was prepared with **1250** in a similar manner as previously stated in Example 12B.

Step 4:

Compound **1252** was prepared in a similar fashion from **1251** as previously stated in Example 12B. MS m/e: 518.1 (M+H).

Step 5:

To a solution of **1251** (0.20 g, 0.36 mmol) in THF (2 mL)/MeOH (2 mL)/ H_2O (2 mL) was added LiOH (0.050 g, 1.2 mmol). The reaction was stirred at room temperature for 20 hours. The reaction was acidified to pH ~ 4 with 1 N HCl and diluted with EtOAc. The organic layer was removed and the aqueous phase was extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The compound was used without further purification.

To the crude product mixture prepared above in CH_2Cl_2 (2 mL) was added NMM (0.200 mL, 1.82 mmol), EDCI (0.100 g, 0.52 mmol), and HOBt (0.059 g, 0.38 mmol). This mixture was stirred for 10 minutes at which time NH_4Cl (0.100 g, 1.86 mmol) was added. After 72 hours of stirring, the reaction was quenched with H_2O and diluted with EtOAc. The organic layer

was removed, and the aqueous phase was extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography to yield **1253** (0.062 g, 61 % yield over 2 steps). MS m/e: 529.1 (M+H).

Step 6:

To a solution of **1253** (0.050 g, 0.095 mmol) in CH_2Cl_2 (2 mL) cooled to 0 °C was added DIEA (0.050 mL, 0.28 mmol) followed by TFAA (0.030 mL, 0.22 mmol). The reaction was stirred at 0 °C for 3 hours and then quenched with 1 N NaOH. The organic layer was removed, and the aqueous phase was acidified with 1 N HCl to pH ~ 4. The aqueous phase was then extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography to furnish **1254** (0.042 g, 0.082 mmol, 88% yield). MS m/e: 511.1 (M+H).

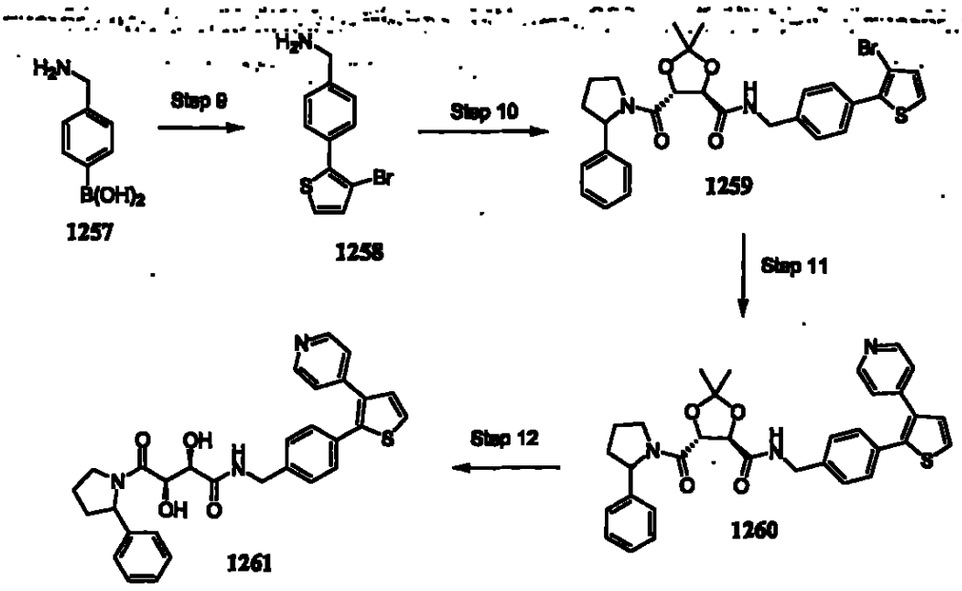
Step 7:

Compound **1255** was prepared in a similar fashion from **1253** as previously stated in Example 12B. MS m/e: 489.1 (M+H).

Step 8:

Compound **1256** was prepared in a similar fashion from **1254** as previously stated in Example12A. MS m/e: 471.1 (M+H).

Example 43B:



Step 9:

A solution of aminomethylphenyl boronic acid hydrochloride (1257) (2.0 g, 10.7 mmol), 2,3-dibromothiophene (2.7 g, 11.0 mmol), and $Pd(dppf)Cl_2$ (0.51 g, 0.69 mmol) in CH_3CN (40 mL)/1 M K_2CO_3 (40 mL) was stirred at 80 °C for 3 hours. The reaction was cooled to room temperature and diluted with EtOAc. The organic layer was removed, and the aqueous phase was extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The brown oil was purified by silica gel chromatography to furnish 1258 (1.4 g, 5.3 mmol, 50% yield) as a brown oil. MS m/e: 268.1 (M+H).

Step 10:

Compound 1259 was prepared in a similar fashion from 1258 as previously stated in Example 12B. MS m/e: 569.1 (M+H).

Step 11:

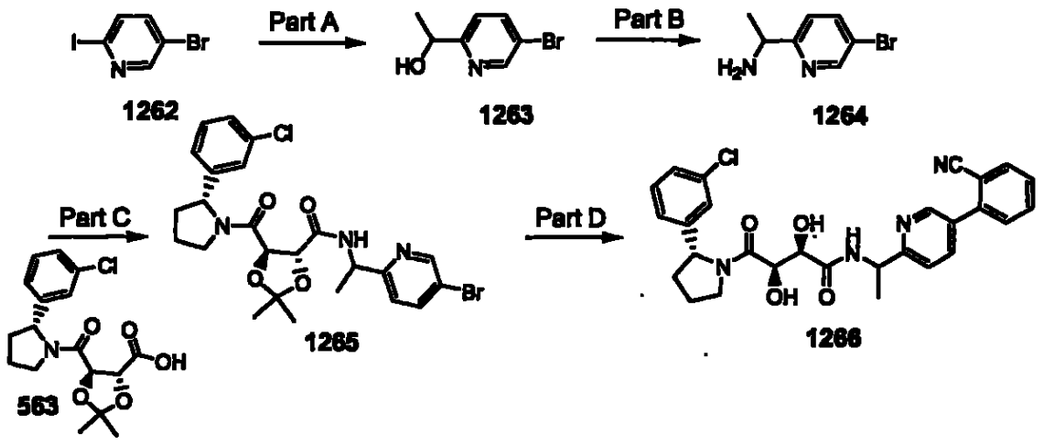
A solution of 1259 (0.059 g, 0.10 mmol), pyridine-4-yl boronic acid (0.017 g, 0.14 mmol), and $Pd(dppf)Cl_2$ (0.010 g, 0.014 mmol) in CH_3CN (1 mL)/1 M K_2CO_3 (1 mL) was heated in SmithCreator microwave (2-5 mL vessel, 150 °C

for 5 minutes). The liquid was concentrated, and the residue was purified by silica gel chromatography to furnish **1260** (0.057 g, 0.10 mmol; 99% yield). MS m/e: 568.1 (M+H).

Step 12:

Compound **1261** was prepared in a similar fashion from **1260** as previously stated in Example 12A MS m/e: 528.1 (M+H).

Example 44:



Part A:

Isopropylmagnesium chloride (2.0 M solution in THF, 5 mL, 10 mmol) was added dropwise to the solution of 2-Iodo-5-bromopyridine (1262) in THF (20 mL) at –40°C in an acetonitrile/dry ice bath. After stirring for 1 h at this temperature for 1 h, acetaldehyde (0.615 mL, 1 mmol) in 5 mL of THF was slowly added. The reaction mixture was allowed to stir at –40 °C for 0.5 h, then quenched with 1 N NH_4Cl (5 mL) solution, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and water. Organic layer was separated, washed with 1N NH_4Cl, brine, dried over Na_2SO_4, and concentrated, affording **1263** as a colorless oil (1.95 g, 97%). ^1H NMR ($CDCl_3$, 300 MHz), δ 8.58 (d, *J* = 2.4 Hz, 1H), 7.80 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.21 (d, *J* = 8.6Hz, 1H), 4.87 (br q, *J* = 6.2 Hz, 1H), 3.79 (br s, 1H), 1.50 (d, *J* = 6.2 Hz, 3H). Mass calculated for formula C_7H_8BrNO 200.98, observed LCMS m/z 202.0 (M+H).

Part B:

Diisopropyl azodicaboxylate (1.2 g, 6 mmol) in THF (5 mL) was added into a solution of **1263** (1.0 g, 5 mmol), phththalimide (0.88 g, 6 mmol) and triphenylphosphine (1.57 g, 6 mmol) in 20 mL of THF. After stirring overnight at room temperature, the reaction mixture was concentrated to dryness. It was then dissolved in 30 mL of ethanol, added with hydrazine monohydrate (5 mL), heated to reflux for 3 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved with ethyl acetate and 1 N HCl. The aqueous phase was backed extracted with ethyl acetate. The organic extract was discarded. The aqueous phase was added with 1N NaOH to pH 12. It was extracted with EtOAc (30 mL x 3). The ester extract was combined, washed with brine, dried over Na_2SO_4, and concentrated, resulting in **1264** (0.61 g, 61%). ^1H NMR ($CDCl_3$, 300 MHz), δ 8.58 (s, 1H), 7.75 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 4.15 (q, *J* = 6.5 Hz, 1H), 1.43 (d, *J* = 6.5 Hz, 3H). Mass calculated for formula $C_7H_8BrN_2$ 199.99, observed LCMS m/z 201.0 (M+H).

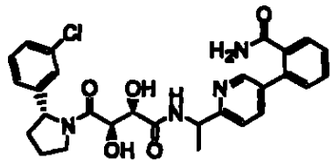
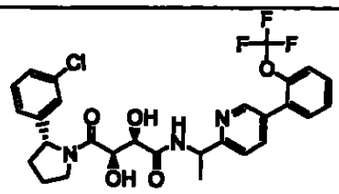
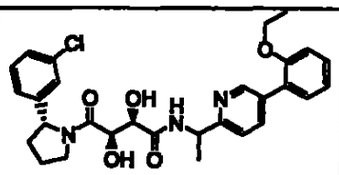
Part C:

To **1264** (400 mg, 2 mmol) in DMF (5 mL) was added **563** (707 mg, 2 mmol), and HATU (912 mg, 2.4 mmol). The reaction mixture was stirred overnight at room temperature, and diluted with ethyl acetate and water. The organic layer was washed with saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in **1265** (600 mg, 56%). Mass calculated for formula $C_{24}H_{27}BrClN_3O_4$ 535.09, observed LCMS m/z 534.1 (M+H).

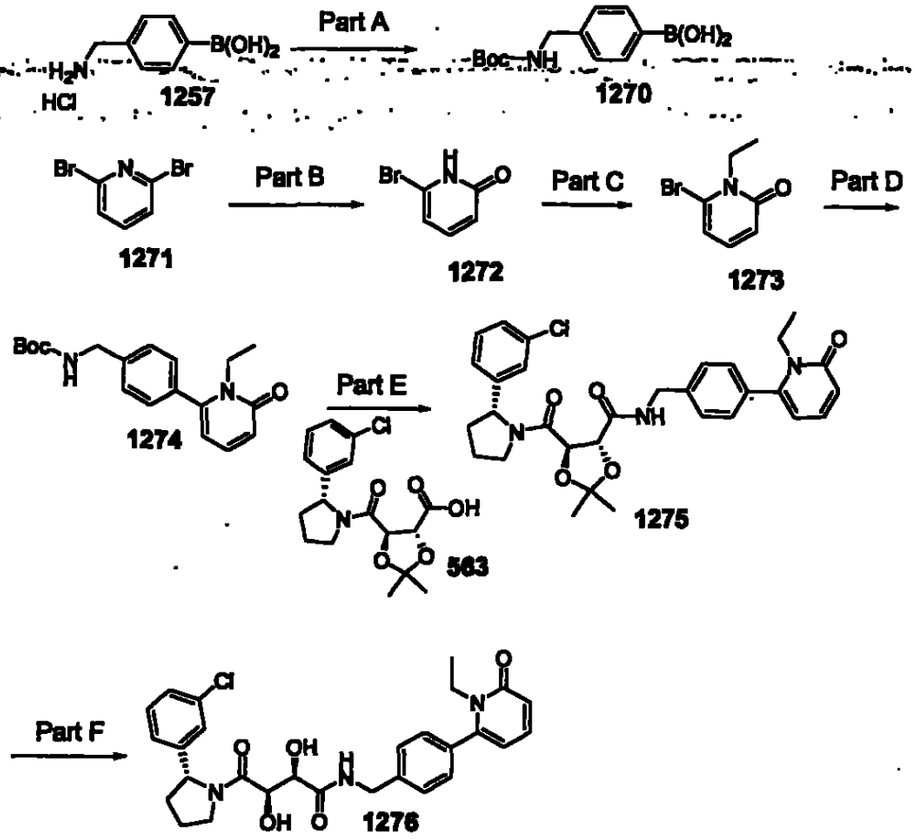
Part D:

Step 1: To **1265** (120 mg, 0.22 mmol) in 1 mL of dioxane, was added with 2-cyanophenylboronic acid (49 mg, 0.33 mmol), potassium phosphate (142 mg, 0.66 mmol) and $PdCl_2$(dppf) (7.2 mg, 0.0088 mmol, 4 mol%). The reaction mixture was stirred overnight at 80 °C under argon, then diluted with EtOAc and water, washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated.

Step 2: The above residue was dissolved in 0.5 mL of TFA/H_2O (80:20) and stirred at room temperature for 2 h. The reaction mixture was quenched with ACN/H_2O (50:50) and concentrated in *vacuo*. Purification by reverse phase prep-LC afforded **1266** as a white solid. HPLC-MS t_R = 4.04 min ($UV_{254\ nm}$, 10 min), Mass calculated for formula $C_{28}H_{27}ClN_4O_4$ 518.17, observed LCMS m/z 519.1 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
1267		536.2	537.1
1268		577.2	578.0
1269		537.20	538.2

Example 45:



Part A:

Compound **1257** (1.00 g, 5.34 mmol) was dissolved in THF (15 mL) and saturated sodium bicarbonate solution (20 mL). Di-*t*-butyldicarbonate (1.28 g, 5.88 mmol) was added and the solution was stirred overnight at room temperature. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated to provide a white solid **1270** (560 mg, 42%). HPLC-MS t_R = 1.34 (UV_{254nm}); mass calculated for formula $C_{12}H_{18}BNO_4$ 251.13, observed LCMS m/z 274.1 (M+Na).

Part B:

Compound **1271** (2.0 g, 8.5 mmol) was dissolved in *t*-butanol (25 mL) and potassium *t*-butoxide (10g) was added and stirred at reflux for 24 hours. The solvents were removed under reduced pressure and the reaction was quenched with water and extracted with chloroform. The aqueous layer was

acidified and extracted with chloroform. The combined organic layers were dried over sodium sulfate and concentrated to provide a yellow solid **1272** (1.10 g, 74%). HPLC-MS t_R = 0.76 min ($UV_{254\ nm}$); mass calculated for formula C_6H_4BrNO 172.95, observed LCMS m/z 174.0 (M+H).

Part C:

Compound **1273** was prepared according to the procedure of Lui, H. et. al. (Tet. Lett. **1995**, 36, 8917). Data for **1273**: HPLC-MS t_R = 1.12 ($UV_{254\ nm}$); mass calculated for formula C_7H_8BrNO 200.98, observed LCMS m/z 202.0 (M+H).

Part D:

Compound **1273** (50 mg, 0.247 mmol) was dissolved in dioxane (5 mL) and compound **1270** (93 mg, 0.370 mmol), potassium phosphate (108 mg, 0.51 mmol), triphenylphosphine (10 mg), and $Pd(dba)_3$ (5 mg) were added and stirred at 90 °C overnight. The reaction was filtered through celite and purified by column chromatography (EtOAc) to provide the desired product **1274** as a white solid (60 mg, 75%). HPLC-MS t_R = 1.64 ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{24}N_2O_3$ 328.18, observed LCMS m/z 329.2 (M+H).

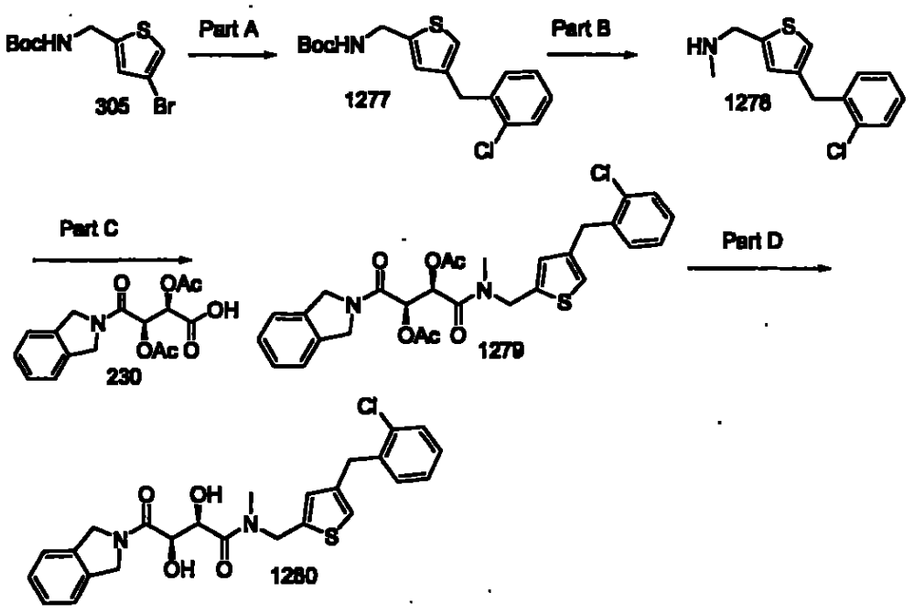
Part E:

Compound **1274** (60 mg, 0.183 mmol) was dissolved in methylene chloride (4 mL) and TFA (1 mL) was added. The reaction mixture was stirred for 1 hour and then the solvent was removed under reduced pressure. The residue was dissolved in DMF (5 mL) and compound **583** (63.5 mg, 0.183 mmol), HATU (90.5 mg, .0.2379 mmol), and DIEA (0.5 mL) were added and stirred overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 1 N HCl solution, bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification of the residue by column chromatography (EtOAc) provided compound **1275** as a white solid (87 mg, 85%). HPLC-MS t_R = 1.81 min ($UV_{254\ nm}$); mass calculated for formula $C_{31}H_{34}ClN_3O_5$ 563.22, observed LCMS m/z 564.1(M+H).

Part F:

Compound **1276** was synthesized using procedures similar to Example 1, Part D. HPLC-MS t_R = 1.48 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{30}ClN_3O_5$ 523.19, observed LCMS m/z 524.2(M+H).

Example 46:



Part A:

Compound **1277** was prepared from **305** according to the procedures described in Example 4A Part A.

Part B:

To **1277** (150 mg, 0.44 mmol) in THF (5 mL) was added lithium hexamethyldisilazide (1.0 M, 0.66 mL, 0.66 mmol) at 0 °C. The reaction mixture was stirred for 10 minutes. To the reaction mixture was added methyl iodide (0.034 mL, 0.53 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and washed with 1.0 N citric acid, satureated sodium bicarbonate solution and

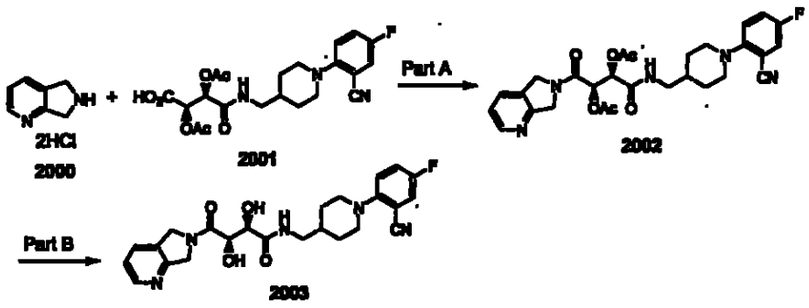
brine, dried over sodium sulfate and concentrated. The residue was dissolved in DCM (5 ml) and treated with 4N HCl in dioxane (2 mL). The reaction was stirred at room temperature and concentrated. Compound **1278** was used without further purification.

Part C and D:

Compound **1280** was obtained from **1278** and **230** using the procedures described in Example 4A Part D and E. Data for **1280**: HPLC-MS t_R = 5.05 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{25}H_{25}ClN_2O_4S$ 484.1, observed LCMS m/z 485.0 (M+H).

Example 47: Heterocyclic Isoindolines

Example 47A:



Compound **2000** was prepared according to the procedures in US Patent 5,371,090.

Compound **2001** was prepared using procedures described in Example 2 and 27. HPLC-MS t_R = min ($UV_{254\ nm}$); mass calculated for formula C21H24FN3O7 449.2, observed LCMS m/z 450.1 (M+H).

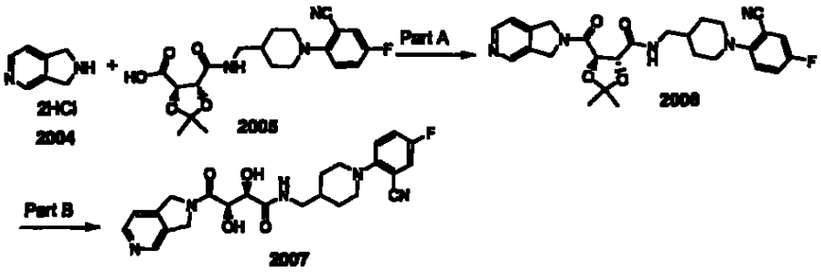
Part A:

Compound **2002** was prepared using the coupling conditions described in Example 2. HPLC-MS t_R = 1.60 min ($UV_{254\ nm}$); mass calculated for formula C28H30FN5O6 551.2, observed LCMS m/z 552.1 (M+H).

Part B:

Compound 2002 (50 mg) was dissolved in methanol (2 mL). To this solution was added 7.0 M ammonia in methanol (2 mL). The reaction mixture was stirred for 1 hour at room temperature and concentrated. Purification by prep-LC and conversion to a hydrochloric salt afforded 2003 as an off-white solid (32 mg). HPLC-MS t_R = 1.35 min ($UV_{254\ nm}$); mass calculated for formula C24H26FN5O4 467.2, observed LCMS m/z 468.1 (M+H).

Example 47B:



Compound 2004 was prepared according to the procedures in US Patent 5,371,090.

Compound 2005 was prepared using procedures described in Example 1 and 27.

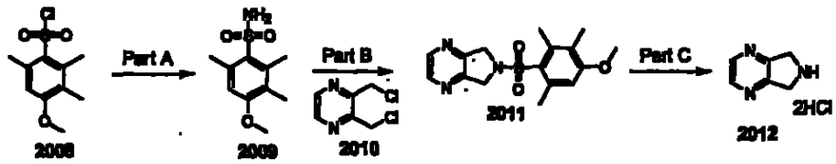
Part A:

Compound 2006 was prepared using the coupling conditions described in Example 1. HPLC-MS t_R = 1.40 min ($UV_{254\ nm}$); mass calculated for formula C27H30FN5O4 507.2, observed LCMS m/z 508.1 (M+H).

Part B:

Compound 2006 (50 mg) was deprotected using procedures described in Example 1. Purification by prep-LC and conversion to a hydrochloric salt afforded 2007 as an off-white solid (32 mg). HPLC-MS t_R = 1.09 min ($UV_{254\ nm}$); mass calculated for formula C24H26FN5O4 467.2, observed LCMS m/z 468.1 (M+H).

Example 47C:



2008 2009 2010 2011 2012

Part A:

Sulfonyl chloride **2008** (2.44 g, 9.8 mmol) was dissolved in dioxane (40 mL) and cooled in an ice bath. Ammonia gas was bubbled into the reaction mixture for 10 minutes. The reaction mixture was warmed to room temperature and filtered. The filtrate was concentrated. The crude product was recrystallized from ethyl acetate/hexanes to afford **2009** as an off-white solid (1.74 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 (s, 2H), 6.74 (s, 1H), 3.80 (s, 3H), 2.57 (s, 3H), 2.48 (s, 3H), 2.08 (s, 3H); HPLC-MS t_R = 1.43 min ($UV_{254\ nm}$); mass calculated for formula C10H15NO3S 229.1, observed LCMS m/z 230.1 (M+H).

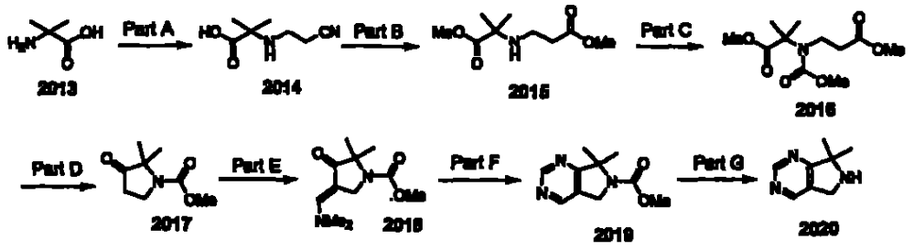
Part B:

To sodium hydride (95%, 131 mg, 5.19 mmol) in DMF (10 mL) was added sulfonamide **2009** (596 mg, 2.6 mmol). The reaction mixture was heated to 70 °C and stirred for 45 minutes. To this mixture was added 2,3-bis(chloromethyl)pyrazine (**2010**) (Yoshiizumi, K. et. al. *Bioorg. Med. Chem.* **2003**, *11*, 433) (448 mg, 2.53 mmol) in DMF (3 mL). The reaction mixture was heated at 70 °C overnight. The reaction mixture was cooled and poured into water. The aqueous layer was salted and extracted with chloroform. The combined organics were washed with water, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 30% ethyl acetate/hexanes) afforded recovered sulfonamide **2009** (218 mg) and **2011** (245 mg). HPLC-MS t_R = 1.82 min ($UV_{254\ nm}$); mass calculated for formula C16H19N3O3S 333.1, observed LCMS m/z 334.1 (M+H).

Part C:

A mixture of sulfonamide **2011** (245 mg, 0.73 mmol), anhydrous methanesulfonic acid (3 mL) and 1:9 thioanisole:trifluoroacetic acid (3 mL) was stirred for 3 hours at room temperature. The reaction mixture was poured over ice and treated with 50% sodium hydroxide (10 mL). The aqueous layer was salted and extracted with chloroform. The combined organics were dried over sodium sulfate and concentrated. The residue was dissolved in 1.0 M HCl (5 mL) and extracted with ether. The aqueous layer was lyophilized to afford **2012** (105 mg) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, NH), 8.58 (s, 2H), 4.59 (m, 4H).

Example 47D:



Part A:

Compound **2014** was prepared according to the procedure in *Helv. Chim. Acta.* **1986**, 905-907.

Part B:

Acetyl chloride (20 mL) was added dropwise to methanol (130 mL) cooled in an ice bath. This solution was then added to compound **2014** (5.00 g, 31.8 mmol) and stirred overnight at reflux. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and 1N NaOH. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to provide **2015** (5.0 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.69 (s, 3H), 2.77 (t, 2H), 2.5 (t, 2H), 1.32 (s, 6H).

Part C:

Compound **2015** (5.00 g, 24 mmol) was dissolved in THF (60 mL) and saturated sodium bicarbonate (60 mL) and cooled in an ice bath. Methyl chloroformate (2.93 g, 31.2 mmol) was added dropwise and the reaction was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% ethyl acetate/hexanes) afforded **2016** (5.5 g). ^1H NMR (400 MHz, $CDCl_3$) δ 3.72-3.68 (m, 9H), 3.65-3.6 (t, 2H), 2.66 (t, 2H), 1.5 (s, 6H).

Part D:

Compound **2016** (1.66 g, 6.36 mmol) was dissolved in THF (20 mL) and cooled on an ice bath. Potassium hydride (35% in oil, 1.12 g, 9.54 mmol) was added in portions and stirring was continued for 2 hours at room temperature. The reaction was slowly quenched with water, acidified to pH 3, and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated (1.5 g). A portion of the residue (350 mg) was dissolved in MeOH (5 mL) and 6N HCl (5 mL) and stirred at reflux for 3 hours and room temperature overnight. The solvent was evaporated under reduced pressure and partitioned between ethyl acetate and water. The organic layer was washed with water, dried over sodium sulfate, and concentrated to yield **2017** (150 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 3.72-3.55 (m, 5H), 2.5 (t, 2H), 1.4-1.25 (m, 6H).

Part E:

According to a modification of a procedure by Fukui, H. et al. (*Heterocycles* **2002**, *56*, 257-264) a mixture of ketone **2017** (200 mg, 1.17 mmol) and N,N-dimethylformamide dimethyl acetal (3 mL) was heated at 100 °C for 2h, and then concentrated to give enamino-ketone **2018** (244 mg, 92%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.31 (m, 1H), 4.54-4.51 (d, 2H), 3.78-3.22 (d, 3H), 3.12 (s, 6H), 1.48 (s, 3H), 1.40 (s, 3H).

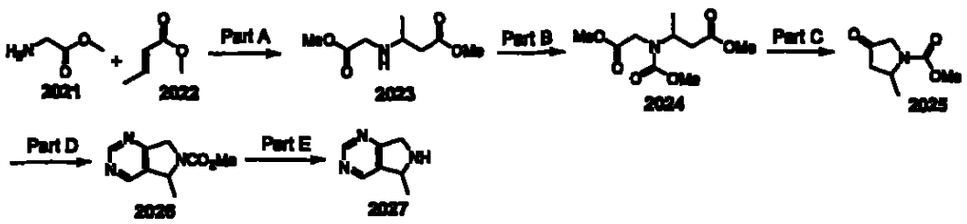
Part F:

According to a modification of a procedure by Fukui, H. et al. (*Heterocycles* 2002, 56, 257-264) a mixture of enamino-ketone 2018 (690 mg, 3.05 mmol) and formamidine acetate (3.17 g, 30.5 mmol) in ethanol (15 mL) was heated at reflux for 3 days, and then concentrated. The residue was partitioned between dichloromethane and water, and extracted with dichloromethane. The combined organic extracts were concentrated to give an oil which was chromatographed (SiO_2, 50%-80% ethyl acetate/hexane) to give pyrimidine 2019 (334 mg, 53%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.67 (s, 1H, broad), 4.76-4.71 (d, 2H), 3.84-3.77 (d, 3H), 1.75 (s, 3H), 1.67 (s, 3H).

Part G:

A mixture of compound 2019 (235 mg, 1.13 mmol), powder potassium hydroxide (900 mg, 16 mmol) and hydrazine monohydrate (1.36 mL, 28 mmol) in ethylene glycol (5 mL) was heated at 100 °C overnight. The reaction mixture was cooled to rt, poured into brine and extracted several times with dichloromethane. The combined organic extracts were washed with brine and concentrated to give compound 2020 (121 mg, 72 %). ^1H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.58 (s, 1H), 4.24 (s, 2H), 1.47 (s, 6H). HPLC-MS t_R = 0.2 min ($UV_{254\ nm}$); mass calculated for formula C8H11N3 149.1, observed LCMS m/z 150.1 (M+H).

Example 47E:



Part A:

To a mixture of methyl crotonate (2022) (2.0 g, 20 mmol) and methyl glycine hydrochloride (2021) (5.5 g, 44 mmol) in methanol (27 mL) was added triethylamine (6.4 mL, 46 mmol). The mixture was stirred at room temperature for 2 days and filtered to remove the white precipitate. The filtrate was

concentrated and the residue was dissolved in ethyl acetate, washed with sodium bicarbonate solution, water and brine, dried over sodium sulfate and concentrated to afford **2023** as a light yellow oil (2.4 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.69 (s, 3H), 3.46 (d, J = 3.2 Hz, 2H), 3.14 (m, 1H), 2.45 (m, 2H), 1.15 (d, J = 7.2 Hz, 3H).

Part B:

Compound **2023** (2.42 g, 13 mmol) was dissolved in THF (20 mL) and saturated sodium bicarbonate (20 mL) and cooled in an ice bath. Methyl chloroformate (1.2 mL, 15 mmol) was added dropwise and the reaction was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated to afford **2024** (2.9 g).

Part C:

Compound **2024** (1.30 g, 5.26 mmol) was dissolved in THF (20 mL) and cooled on an ice bath. Potassium hydride (35% in oil, 1.12 g, 9.54 mmol) was added in portions and the mixture was stirred at room temperature overnight. The reaction was slowly quenched with water, acidified to pH 3, and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexane) afforded an oil (1.27 g). This oil (1.27 g) was dissolved in MeOH (5 mL) and 6N HCl (5 mL) and stirred at reflux overnight. The mixture was extracted with ethyl acetate and the combined organic layers were washed with sodium bicarbonate solution, water and brine, dried over sodium sulfate and concentrated to afford **2025** (663 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.5 (bs, 1H), 3.95 (m, 1H), 3.78 (s, 3H), 3.70 (m, 1H), 2.73 (m, 1H), 2.25 (m, 1H), 1.28 (m, 3H).

Part D:

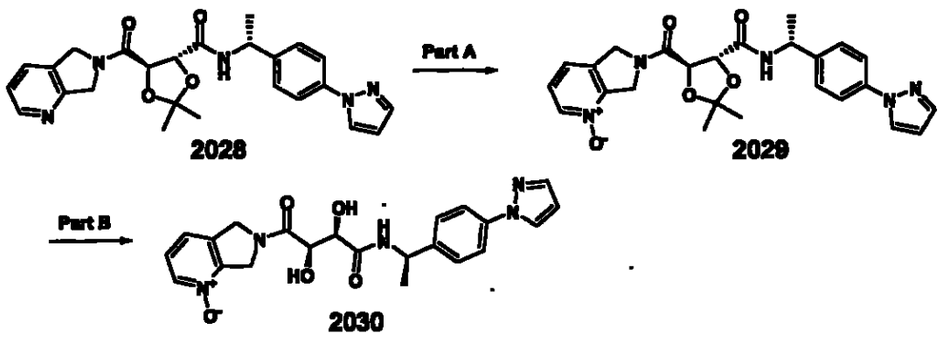
Compound **2026** was prepared from the material from part C according to procedures described in Example 47D Part E and Part F. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 9.13 (s, 1H), 8.61 (m, 1H), 5.24 (m, 1H), 4.88 – 4.64 (m, 2H), 3.82 (m, 3H), 1.59 (m, 3H).

Part E:

A mixture of compound **2026** (300 mg, 1.45 mmol), powder potassium hydroxide (600 mg, 10.7 mmol) and hydrazine monohydrate (1.0 mL, 21 mmol) in ethylene glycol (5 mL) was heated at 100 °C overnight. The reaction mixture was cooled to rt, poured into brine and extracted several times with dichloromethane. The combined organic extracts were washed with brine and concentrated to give compound **2027** (105 mg, 54 %).

Example 47F:



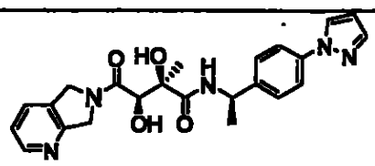
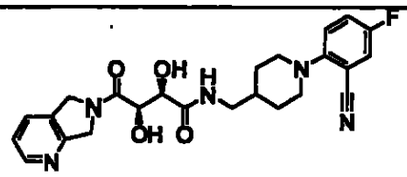
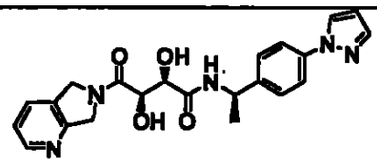
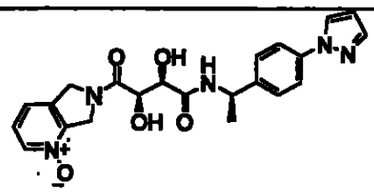
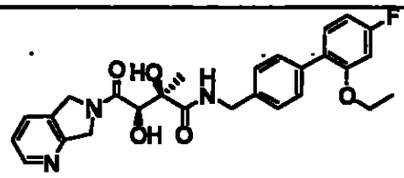
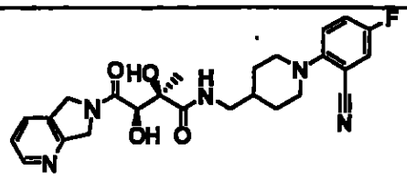
Part A:

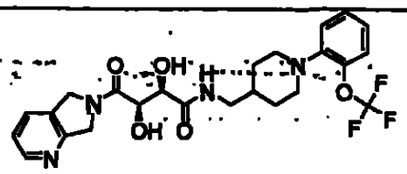
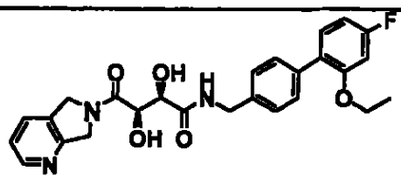
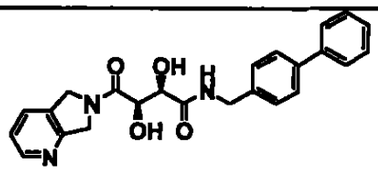
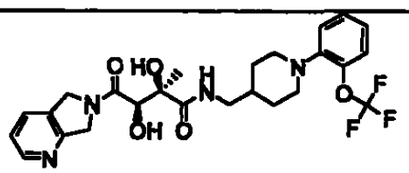
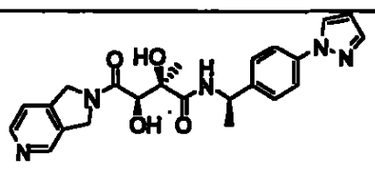
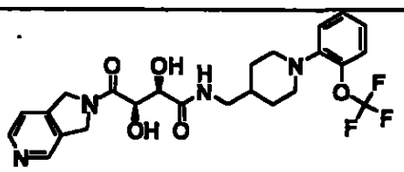
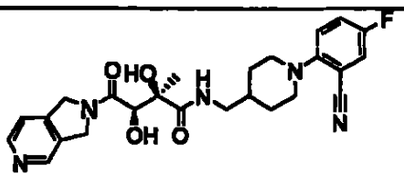
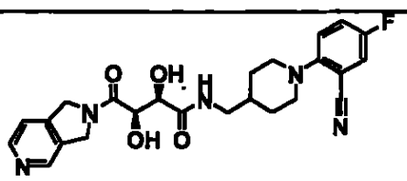
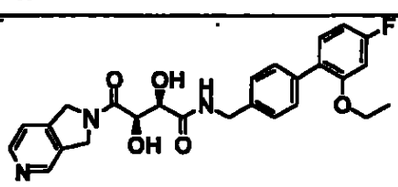
To a solution of compound **2028** (0.29 g, 0.63 mmol) in CH_2Cl_2 at 0 °C was added 70% m-CPBA (0.31 g, 1.26 mmol) and the reaction mixture was warmed to room temperature and stirred for 1 hour. Diluted with CH_2Cl_2 (5 mL) and washed with a solution of water (6 mL) and concentrated NH_4OH (0.5 mL). Aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and 5% MeOH/CH_2Cl_2 (2 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 5% MeOH/CH_2Cl_2) afforded the desired product with some impurity. Dissolved the impure product in EtOAc (15 mL) and washed with 10% NH_4OH (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers (EtOAc and CH_2Cl_2) were dried over $MgSO_4$, filtered and concentrated to give the desired compound **2029** (0.25 g, 92%).

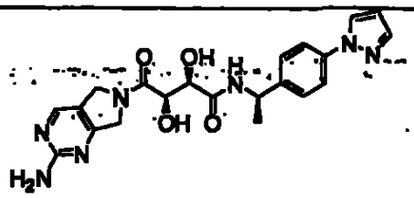
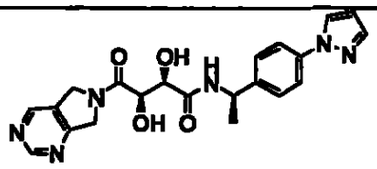
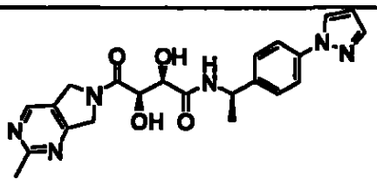
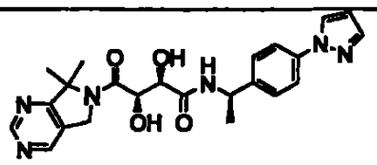
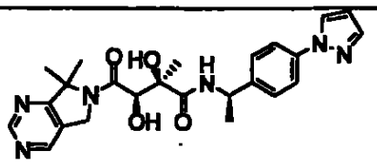
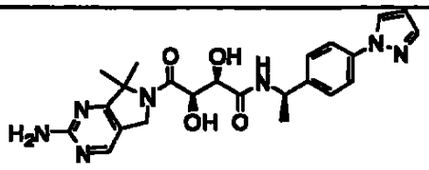
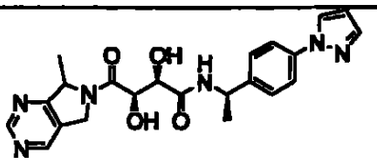
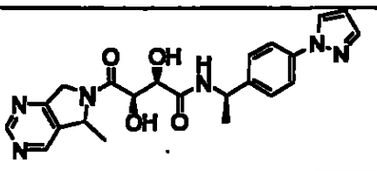
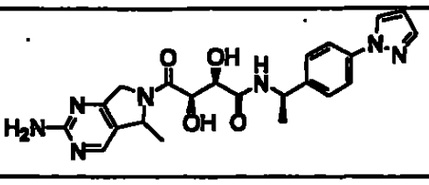
Part B:

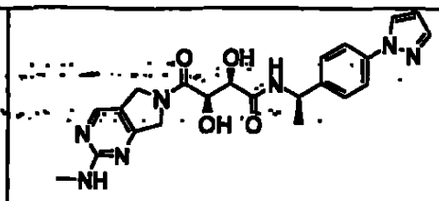
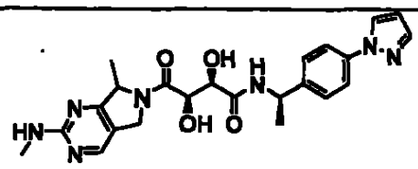
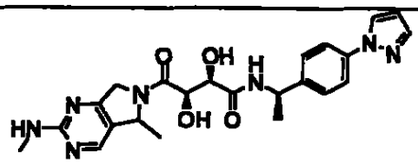
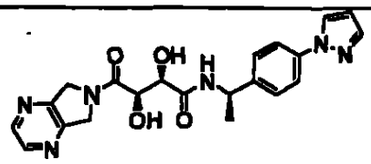
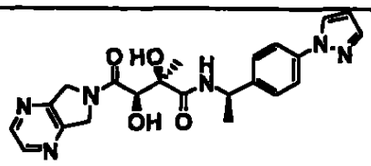
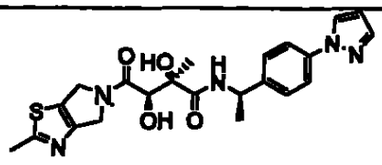
Compound 2030 was obtained from compound 2029 using the TFA deprotection procedure as described in Example 1.

The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2031		435.2	436.2
2003		467.2	468.1
2032		421.2	422.1
2030		437.2	438.1
2033		493.2	494.1
2034		481.2	482.1

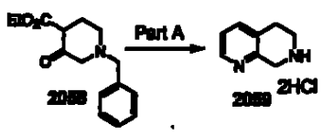
2035		508.2	509.1
2036		479.2	480.1
2037		417.2	418.2
2038		522.2	523.2
2039		435.2	436.1
2040		508.2	509.1
2041		481.2	482.2
2007		467.2	468.1
2042		479.2	480.1

2043		437.2	438.1
2044		422.2	423.1
2045		436.2	437.2
2046		450.2	451.1
2047		464.2	465.1
2048		465.2	466.1
2049		436.2	437.0
2050		436.2	437.2
2051		451.2	452.2

2052		451.2	452.0
2053		465.2	466.1
2054		465.2	466.1
2055		422.2	423.1
2056		436.2	437.1
2057		455.2	456.1

Example 48: Heterocyclic tetrahydroisoquinoline analogs

Example 48A:

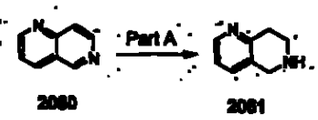


Part A:

Compound 2059 was synthesized according to the literature procedures.

(Dow, R.L.; Schneider, S.R. *J. Heterocyclic Chem.* 2001, *38*, 535).

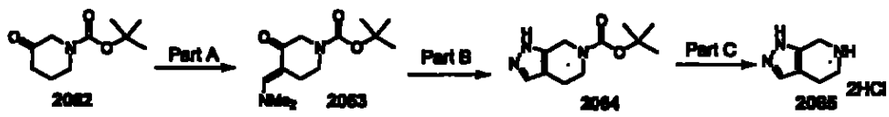
Example 48B:



Part A:

Compound **2061** was synthesized according to the procedures of US patent 5,037,834.

Example 48C:



Part A:

According to a modification of a procedure by Fukui, H. et al. (*Heterocycles* **2002**, *56*, 257-264) a mixture of ketone **2062** (2.5 g, 12.5 mmol) and N,N-dimethylformamide dimethyl acetal (21 mL) was heated at 100 °C for 2h. The mixture was concentrated to a residue which was passed through a short silica gel column (9:1:90 methanol:triethylamine:dichloromethane) to give enamino-ketone **2063** (3.1, 97%) as a viscous brown oil. HPLC-MS t_R = 1.34 min ($UV_{254\ nm}$); mass calculated for formula C13H22N2O3 254.1, observed LCMS m/z 255.1 (M+H).

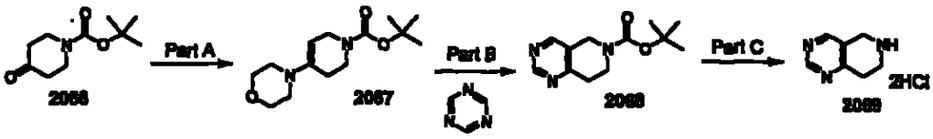
Part B:

According to a modification of a procedure by Fukui, H. et al. (*Heterocycles* **2002**, *56*, 257-264) a mixture of enamino-ketone **2063** (732 mg, 2.88 mmol) and hydrazine monohydrate (0.28 mL, 5.76 mmol) in ethanol (8 mL) was heated at reflux overnight, and then concentrated. The residue was partitioned between dichloromethane and water, and extracted with dichloromethane. The combined organic extracts were concentrated to give an oil which was chromatographed (SiO_2, 80% ethyl acetate/hexane) to give compound **2064** as an oil (major isomer, 300 mg, 46%). HPLC-MS t_R = 1.39 min ($UV_{254\ nm}$); mass calculated for formula C11H17N3O2 223.1, observed LCMS m/z 224.2 (M+H).

Part C:

Compound **2064** (300 mg, 1.34 mmol) was deprotected according to a procedure described by Fukui, H. et al. (*Heterocycles* **2002**, *56*, 257-264) to give compound **2065** (57 mg, 22 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.9 (s, 1H, broad), 9.4 (s, 1H, broad), 7.57 (s, 1H), 4.19 (t, 2H), 3.30-3.26 (m, 2H), 2.78 (t, 2H). HPLC-MS t_R = 0.2 min ($UV_{254\ nm}$); mass calculated for formula C6H9N3 123.1, observed LCMS m/z 124.2 (M+H).

Example 48D:



Part A:

A mixture of ketone **2066** (4.0 g, 20 mmol), morpholine (7.5 mL, 85 mmol) and p-toluenesulfonic acid monohydrate (160 mg, 0.84 mmol) in benzene (30 mL) was heated at reflux for 3 days using a Dean-Stark trap. The mixture was then washed with saturated sodium bicarbonate solution and concentrated to give **2067** as a yellow oil (4.36 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (s, 1H, broad), 3.96-3.95 (m, 2H), 3.77-3.73 (m, 4H), 3.55 (t, 2H), 2.83-2.80 (m, 4H), 2.18 (t, 2H), 1.49 (s, 9H).

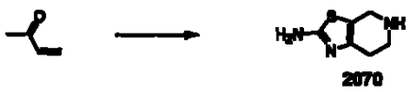
Part B:

According to a modification of a procedure by Gündisch, D. et. al. (*Bioorg. Med. Chem.* **2002**, *10*, 1-9) a mixture of enamine **2067** (2.27 g, 8.48 mmol) and 1,3,5-triazine (688 mg, 8.48 mmol) in 1,4-dioxane (10 mL) was heated at 100 °C in a sealed tube overnight. The reaction mixture was concentrated and chromatographed (SiO_2, 50-65% ethyl acetate/hexane) to give pyrimidine **2068** as a yellow oil (665 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.49 (s, 1H), 4.64 (s, 2H), 3.80 (t, 2H), 3.00 (t, 2H), 1.54 (s, 9H). HPLC-MS t_R = 1.32 min ($UV_{254\ nm}$); mass calculated for formula C12H17N3O2 235.1, observed LCMS m/z 236.1 (M+H).

Part C:

Compound **2068** (100 mg) was deprotected using procedures described in Example 48C to give amine **2069** as a yellow solid (68 mg; 78%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.67 (s, 2H, broad), 9.01 (s, 1H), 8.67 (s, 1H), 4.33 (t, 2H), 3.50-3.45 (m, 2H), 3.09 (t, 2H). HPLC-MS t_R = 0.18 min ($UV_{254\ nm}$); mass calculated for formula C7H9N3 135.1, observed LCMS m/z 136.2 (M+H).

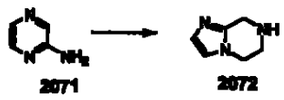
Example 48E:



2070

Compound **2070** was prepared from methyl vinyl ketone in 6 steps following procedures described in US Patent 5,037,834/1991.

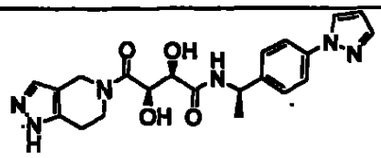
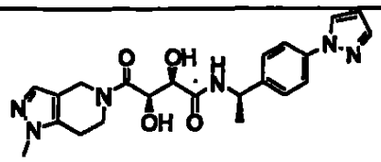
Example 48F:

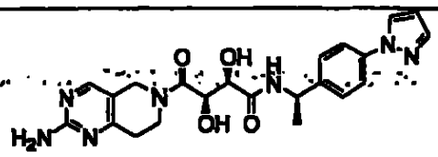
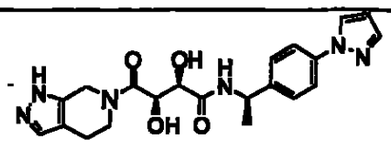
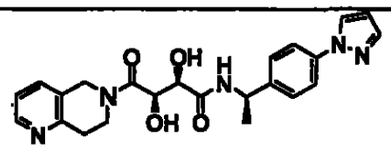
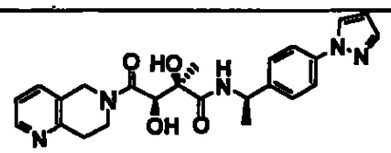
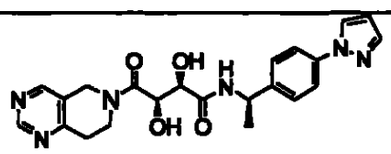
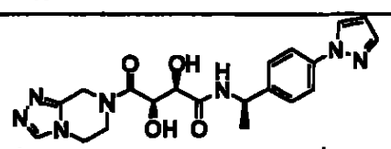
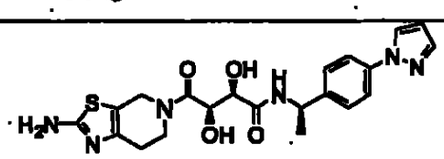
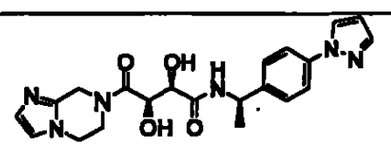
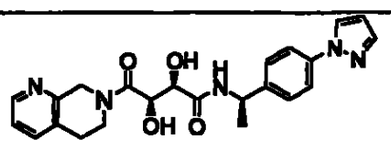
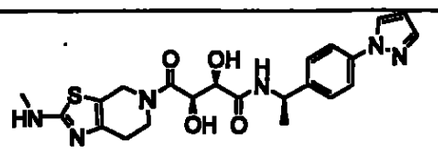


2071 2072

Compound **2072** was prepared from 2-aminopyrazine (**2071**) in 2 steps following procedures described by Sablayrolles, C. et. al. (*J. Med. Chem.* **1984**, *27*, 206-212) and Bonnet, P. A. et. al. (*J. Chem. Res. Miniprint FR* **1984**, *2*, 0468-0480).

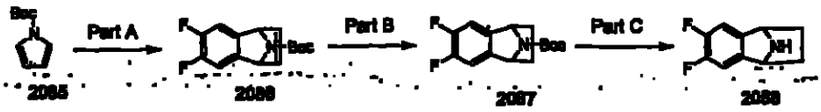
The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2073		424.2	425.0
2074		438.2	439.1

2075		451.2	452.0
2076		424.2	425.1
2077		435.2	436.1
2078		449.2	450.1
2079		436.2	437.1
2080		425.2	426.1
2081		456.2	457.1
2082		424.2	425.1
2083		435.2	436.1
2084		470.2	471.1

Example 49:

Example 49A:



Part A:

Compound **2086** was prepared according to the procedure in *Org. Lett.* **2002**, *4*, 24, 4353-4356.

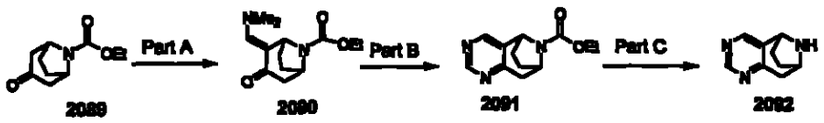
Part B:

Compound **2087** was prepared according to the procedure in *Org. Lett.* **2002**, *4*, 24, 4353-4356. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (t, 2H), 5.1 (bs, 2H), 2.15 (m, 2H), 1.4 (s, 9H), 1.3 (m, 2H).

Part C:

Compound **2087** (80 mg, 0.30 mmol) was dissolved in 4 M HCl in dioxane (2 mL) and stirred at room temperature for 1 hr. The reaction was diluted with diethyl ether (5 mL) and the resulting solid was filtered to provide **2088** as an HCl salt (45 mg).

Example 49B:



Part A:

Compound **2090** was prepared according to the procedure in *Bioorg. Med. Chem.* **2002**, *10*, 5, 1197-1206.

Part B:

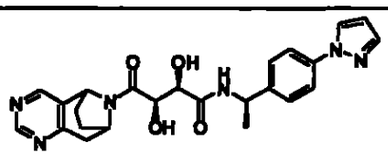
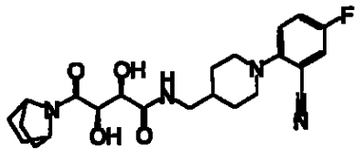
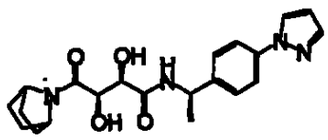
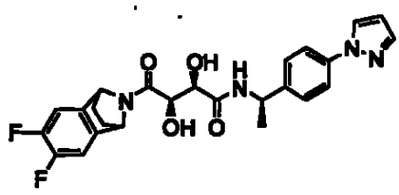
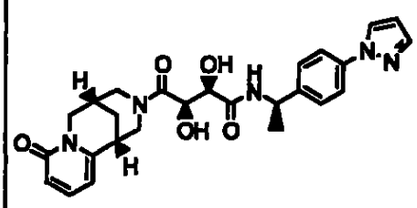
Compound **2091** was prepared according to the procedure in *Bioorg. Med. Chem.* **2002**, *10*, 5, 1197-1206. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.40 (s, 1H), 5.10 (bs, 1H), 4.70 (bs, 1H), 4.10 (m, 2H), 3.40 (bs, 1H), 2.50 (s, 1H), 2.40-2.30 (m, 2H), 1.80 (m, 2H), 1.75 (m, 2H), 1.25 (m, 3H).

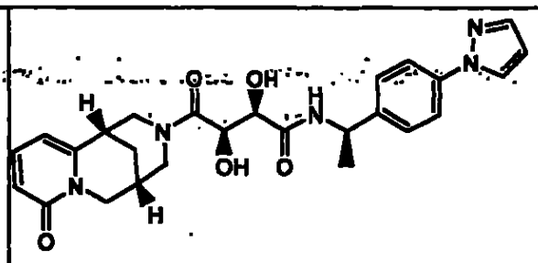
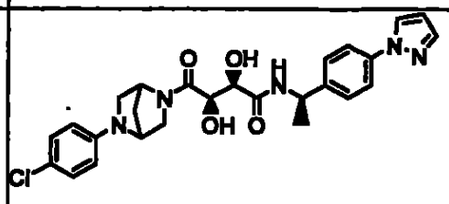
Part C:

Compound **2091** (350 mg, 1.5 mmol) was dissolved in ethylene glycol (4 mL) and KOH (0.5 g) and hydrazine monohydrate (1 mL) were added and stirred

at 100 °C for 12 hours. The reaction mixture was poured into brine and extracted with methylene chloride. The combined organic layers were washed with water, dried over sodium sulfate and concentrated to afford 2092 (150 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.40 (s, 1H), 4.30 (d, 1H), 4.00 (t, 1H), 3.20 (m, 1H), 2.80 (m, 1H), 2.20-2.10 (m, 2H), 2.00-1.90 (m, 2H), 1.80-1.60 (m, 2H).

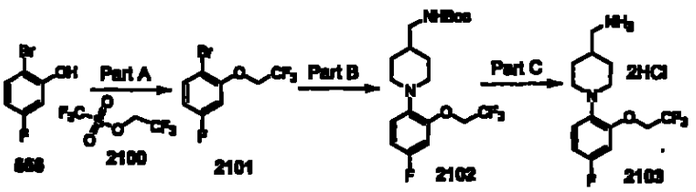
The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2093		462.2	463.1
2094		444.2	445.1
2095		398.2	399.3
2096		482.2	483.1
2097		491.2	492.1

2098		491.2	492.1
2099		509.2	510.1

Example 50: Piperidine-aryl compounds

Example 50A:



Part A:

A mixture of 2-bromo-5-fluorophenol (**556**) (0.111 mL, 1 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (**2100**) (279 mg, 1.2 mmol) and cesium carbonate (358 mg, 1.1 mmol) in NMP (5 mL) was stirred at room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water (2x) and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, hexanes to 2% ethyl acetate/hexanes) afforded **2101** (232 mg) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 1H), 6.70 (m, 2H), 4.40 (q, 2H, J = 8.0 Hz).

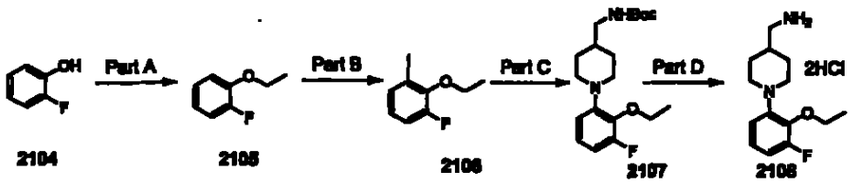
Part B:

Compound **2102** was prepared according to the procedures in Example 27B Part A. HPLC-MS t_R = 2.10 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{26}F_4N_2O_3$ 406.2, observed LCMS m/z 407.2 (M+H).

Part C:

Compound **2102** (8 mg, 0.02 mmol) was dissolved in 3:1 DCM:TFA (4 mL) and stirred for 1 hour at room temperature. The solvent was removed in vacuo. The residue was dissolved in ether and treated with 1.0 M HCl in ether (1 mL). The solvents were concentrated to afford **2103** as a white solid (8 mg).

Example 50B:



Part A:

A mixture of 2-fluorophenol (**2104**) (1.0 mL, 10.7 mmol), ethyl iodide (1.05 mL, 13 mmol) and potassium carbonate (1.66 g, 12 mmol) in acetone (20 mL) was stirred at room temperature overnight. Additional ethyl iodide (0.24 mL, 3 mmol) was added to the reaction and the mixture was stirred for 24 hours. The mixture was filtered and concentrated. The residue was partitioned between water and ethyl acetate. The layers were separated. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated to afford **2105** (1.23 g) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (m, 2H), 6.96 (m, 1H), 6.87 (m, 1H), 4.12 (q, 2H, J = 7.1 Hz), 1.48 (t, 3H, J = 7.1 Hz).

Part B:

To arene **2105** (1.23 g, 8.8 mmol) and TMEDA (1.32 mL, 8.8 mmol) in THF (20 mL) at –78 °C under argon was added s-BuLi (1.4 M, 6.3 mL, 8.8 mmol). The reaction mixture was stirred for 2 hours at –78 °C. To the reaction mixture was added iodine (2.23 g, 8.8 mmol) in THF (10 mL) at –78 °C. The reaction was stirred for 10 minutes then warmed to 0 °C. The reaction mixture

was poured into water and extracted with diethyl ether. The combined organics were washed with water (2x), 5% sodium hydrogensulfite and brine, dried over sodium sulfate and concentrated. The crude product **2106** (1.70 g) was a mixture of 75:25 product:starting material by ^{1}H NMR. It was used without further prurification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 1H), 6.94 (m, 1H), 6.81 (m, 1H), 4.11 (q, 2H, J = 7.1 Hz), 1.47 (t, 3H, J = 7.1 Hz).

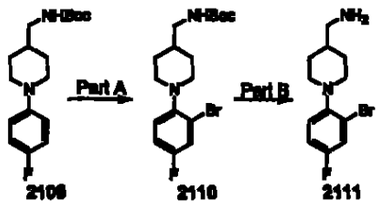
Part C:

Compound **2107** was prepared according to the procedures in Example 27B Part A. HPLC-MS t_R = 2.15 min ($UV_{254\ nm}$); mass calculated for formula C19H29FN2O3 352.2, observed LCMS m/z 353.2 (M+H).

Part D:

Compound **2107** (276 mg, 0.78 mmol) was dissolved in 3:1 DCM:TFA (4 mL) and stirred for 1 hour at room temperature. The solvent was removed in vacuo. The residue was dissolved in ether and treated with 1.0 M HCl in ether (1 mL). The solvents were concentrated to afford **2108** as a white solid (241 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (bs, NH), 6.97 (m, 1H), 6.75 (m, 1H), 6.63 (m, 1H), 4.04 (q, 2H, J = 6.9 Hz), 3.33 (m, 2H), 2.76 (m, 2H), 2.62 (m, 2H), 1.80 (m, 2H), 1.70 (m, 1H), 1.38 (m, 2H), 1.32 (t, 3H, J = 7.1 Hz).

Example 50C:



Compound **2109** was prepared using procedures described in Example 27. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 – 6.80 (m, 4H), 4.64 (m, 1H), 3.55 (m, 2H), 3.09 (m, 2H), 2.65 (m, 2H), 1.82 (m, 2H), 1.60-1.50 (m, 2H), 1.49 (s, 9H), 1.42 (m, 1H).

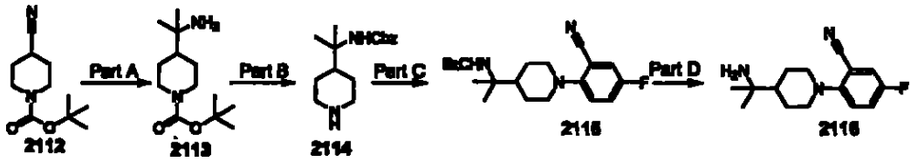
Part A:

To compound **2109** (100 mg, 0.32 mmol) and pyridine (0.026 mL, 0.32 mmol) in DMF (2 mL) was added NBS (115 mg, 0.64 mmol). The mixture was stirred at room temperature for 2 hours and diluted with ethyl acetate. The mixture was washed with sodium carbonate solution, water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 5% ethyl acetate/hexane) afforded **2110** as a white solid (88 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.3 (m, 1H), 7.0 (m, 2H), 4.65 (bs, 1H), 3.28 (m, 2H), 3.10 (m, 2H), 2.61 (m, 2H), 1.8 (m, 2H), 1.65 – 1.4 (m, 12 H).

Part B:

To **2110** (21 mg, 0.055 mmol) in dichloromethane (2 mL) at 0 °C was added TFA (1 mL). The mixture was stirred at room temperature for 1 hour. The mixture was quenched with acetonitrile and concentrated. Compound **2111** was used without further purification.

Example 50D:



Part A:

Compound **2113** was prepared from 1-N-(*t*-butoxycarbonyl)-4-cyano-piperidine (**2112**) according to a procedure described in *J. Org. Chem.* **1992**, *57*, 4521-4527.

Part B:

Step 1: To **2113** (100 mg, 0.41 mmol) in THF (2 mL) were added benzyl chloroformate (0.089 mL, 0.619 mmol) and potassium carbonate (114 mg, 0.82 mmol). The mixture was stirred at room temperature overnight, diluted with ethyl acetate, washed with water, brine, dried over sodium sulfate and concentrated. The product was purified by column chromatography (SiO_2,

10% ethyl acetate/hexane to 25% ethyl acetate/hexane) to give a pale yellow oil (80 mg). HPLC-MS t_R = 2.14 min ($UV_{254\ nm}$); Mass calculated for C21H32N2O4 376.5, observed LSMS m/z 399.2 (M+Na).

Step 2: The material from step 1 (80 mg) was stirred in 4 N HCl in 1,4-dioxane (2mL) for 1 hour. The solvent was removed in vacuum and **2114** was used without further purification.

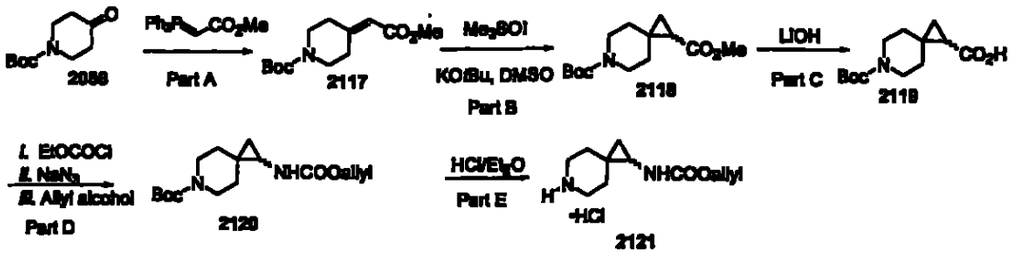
Part C:

A mixture of **2114**, 2,5-difluorobenzonitrile (32.5 mg, 0.234 mmol) and DIEA (0.113 mL, 0.637 mmol) in NMP (2 mL) under argon atmosphere was stirred overnight at 100 °C. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexane) afforded **2115** as a yellow oil (26 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.3 – 7.2 (m, 6H), 7.2 (m, 1H), 7.0 (m, 1H), 5.05 (s, 2H), 4.7 (m, 1H), 3.52 (m, 2H), 2.77 (m, 2H), 2.15 (m, 1H), 1.8 (m, 2H), 1.63 (m, 2H), 1.32 (s, 6H).

Part D:

A mixture of **2115** (26 mg) and 10% palladium on carbon (5 mg) in ethanol (4 mL) under hydrogen atmosphere was stirred for 3 hours. The mixture was filtered through a pad of celite and the filtrate was concentrated to give **2116** as a yellow residue (20 mg), which was used without further purification.

Example 50E:



Part A:

Methyl (triphenylphosphoranylidene)acetate (104.5 g, 0.31 mmol) was added to a solution of *N*-Boc-piperidinone (**2066**) (49.79 g, 0.25 mol) in toluene (625

mL). The resulting reaction mixture was heated to reflux and stirred for 17 h. The reaction mixture was then cooled to room temperature and concentrated under vacuum. The resulting residue was then pre-adsorbed on silica gel and purified by eluting it through a plug of silica gel with 50% ethyl acetate/hexanes, to yield unsaturated ester **2117** (62.16 g, 0.243 mol) as a white solid.

Part B:

Potassium *tert*-butoxide (450 g, 0.41 mol) was added to a solution of trimethylsulfoxonium iodide (90.0 g, 0.41 mol) in DMSO (700 mL), in one portion. The mixture was stirred at room temperature for 3 h. The unsaturated ester **2117** (59.64 g, 0.23 mol) was dissolved in DMSO (0.26 L) and added to the reaction mixture. The reaction mixture was stirred for 20 h at room temperature and then added to brine (1 L). Saturated aqueous NH_4Cl was then added to the reaction mixture in order to adjust the pH to approximately 7. The reaction mixture was then extracted several times with ether, the ether extracts combined, washed with water and brine, dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum to yield ester **2118** (53.5 g, 0.20 mol) as an oil.

Part C:

An aqueous LiOH solution (2N, 200 mL) was added to a solution of the ester **2118** (53.5 g, 0.20 mol) in THF (200 mL). The mixture was then stirred at room temperature for 17 h, diluted with water (750 mL) and washed with ether. The ether phase was discarded, and the aqueous phase acidified to a pH of 3-4 with 6N HCl. The acidified aqueous phase was then extracted with ether several times. The ether washes were combined, washed with water and brine, dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum to provide carboxylic acid **2119** (49.25 g, 0.19 mol) as a white solid.

Part D:

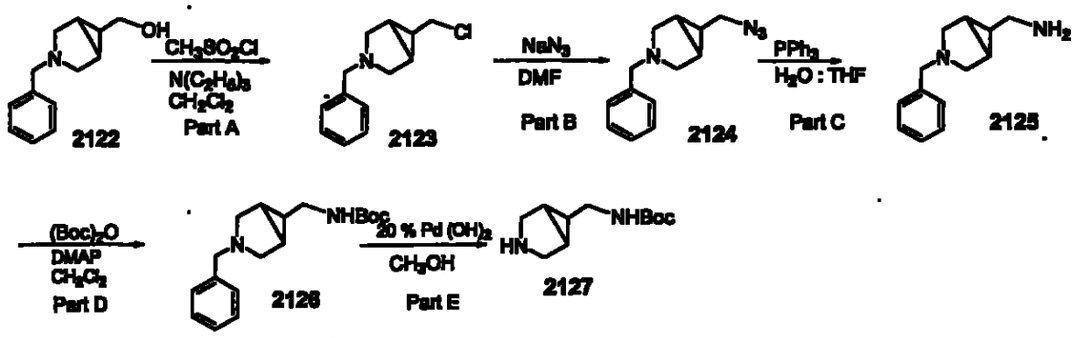
Triethylamine (8.7 g, 0.086 mol) followed by ethyl chloroformate (9.4 g, 0.086 mol) was added to a solution of carboxylic acid **2119** (20.0 g, 0.078 mol) in acetone (78 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 40

minutes. Sodium azide (10.2 g, 0.15 mol) in water (50 mL) was then added to the mixture. The mixture was then allowed to warm to room temperature and stirred for 4 h. Water was then added, and then the mixture was extracted several times with CH_2Cl_2. The organic extracts were combined and washed with water and brine, dried over magnesium sulfate and concentrated under vacuum to provide an oil. The oil was taken up into toluene (200 mL), allyl alcohol (5.5 g, 0.094 mol) was added, and the mixture was heated to reflux and stirred at reflux for 17 h. The reaction mixture was then cooled to room temperature and EtOAc (250 mL) was added. Then, the mixture was washed with water and brine, dried over magnesium sulfate and concentrated under vacuum. The resulting residue was purified by silica gel chromatography (35% ethyl acetate/hexanes) to provide the carbamate **2120** (24.4 g, 0.061 mol).

Part E:

A solution of HCl/Et_2O (2 N, 50 mL) was added to a solution of the carbamate **2120** (24.4 g, 0.061 mol) in CH_2Cl_2 (100 mL). The reaction mixture was stirred overnight and then concentrated under vacuum to yield **2121** as a hygroscopic foam (17.4 g, 0.052 mol).

Example 50F:



Starting alcohol (**2122**) (1*α*, 5*α*, 6*α*)-3-benzyl-6-hydroxymethyl-3-azabicyclo[3.1.0]hexane was prepared by known methods (i.e., Brighty, K. E; Castaldi, M. J *Synlett*, **1996**, 1097).

Part A:

Alcohol **2122** (11 g, 54 mmol) and triethylamine (38 mL, 27 mmol) were dissolved in CH_2Cl_2 (200 mL) and cooled to 0 °C. The cooled solution was stirred, and CH_3SO_2Cl (as a CH_2Cl_2 solution; 6 mL, 78 mmol, 25 mL CH_2Cl_2) was added dropwise, and the stirring was continued for 3-4 h. The reaction mixture was then washed two times with 100 mL of water and two times with 100 ml of brine. The organic and aqueous phases were separated, and the organic phase was dried, and concentrated to provide a crude product. The crude product was purified by silica gel chromatography (eluted with 1:6 ethyl acetate:hexane). The appropriate fractions were collected from the chromatography column and concentrated to provide pure chloro compound **2123** as an oil (7 g, 59%).

Part B:

The chloro compound **2123** was dissolved in DMF (100 mL) and treated with NaN_3 (10.3 g, 157 mmol), and the mixture was stirred vigorously for 36-48 h. The reaction mixture was then diluted with 100 mL water and extracted with ethyl acetate (2 x 100 mL). The organic extracts were combined, dried, and concentrated to yield pure azide **2124** (6.2 g, 87%).

Part C:

The azide **2124** (6.2 g, 27 mmol) and triphenylphosphine (15 g, 57 mmol) were dissolved in 100 mL of THF, and then water (6 mL, 333 mmol) was added. The resulting mixture was stirred vigorously for 16-24 h. The solvent was removed and the crude amine **2125** was obtained without further purification.

Part D:

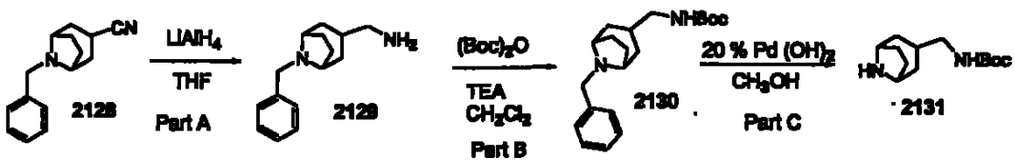
The crude amine **2125** and N, N-dimethylaminopyridine (0.66 g, 5.4 mmol) were dissolved in CH_2Cl_2 (100 mL). To this solution was added di-tert-butyldicarbonate (7 g, 33 mmol), in portions, and the reaction mixture was stirred for 16 h. The reaction mixture was then washed two times (50 mL) with water and once with brine (50 mL). The organic phase was isolated and dried, and the solvent was removed under reduced pressure. The crude product was subjected to silica gel chromatography using 1:3 ethyl acetate:hexane as

the eluting solvent. The eluted fractions were combined and concentrated to yield 6.9 g of pure carbamate **2126** (84%).

Part E:

The carbamate **2126** (1.9 g, 6.3 mmol) was dissolved in methanol (100 mL) and mixed with palladium hydroxide (20%, 0.4 g). The mixture was transferred to a Parr bottle, which was then charged with hydrogen (20 psi). The Parr bottle was shaken for 10 h. The remaining hydrogen was removed from the Parr bottle under vacuum, and the reaction was filtered through Celite. The filtrate was then concentrated to provide pure amine **2127** (1.4 g).

Example 50G:



2128 2129 2130 2131

N-Benzyltropinanecarbonitrile **2128** was prepared using known procedures (see, for example: Montzka, T. A.; Matiskella, J. D.; Partyka, R. A. *Tetrahedron Letters* **1974**, *14*, 1325; Lowe, J. A.; Drozda, S. E.; McLean, S.; Bryce, D. K.; Crawford, R.T.; Snider, R. M.;Tsuchiya, M. *J. Med. Chem.* **1994**, *37*, 2831).

Part A:

$LiAlH_4$ was added to dry THF (40 mL) and the mixture was then cooled to 0 °C. Then carbonitrile **2128** (0.9 g, 3.8 mmol, in a 10 mL THF solution) was added to the mixture dropwise. The reaction mixture was allowed to warm to ambient temperature and stirred for 48 h, then cooled to back to 0 °C and quenched by the sequential addition of 1 mL of water, 2 mL of 0.5 N aq. NaOH, and 1 mL of water. The resulting mixture was stirred vigorously for 2 h and then filtered through Celite. The filtrate was concentrated to yield pure **2129** as an oil (0.9 g, 100%).

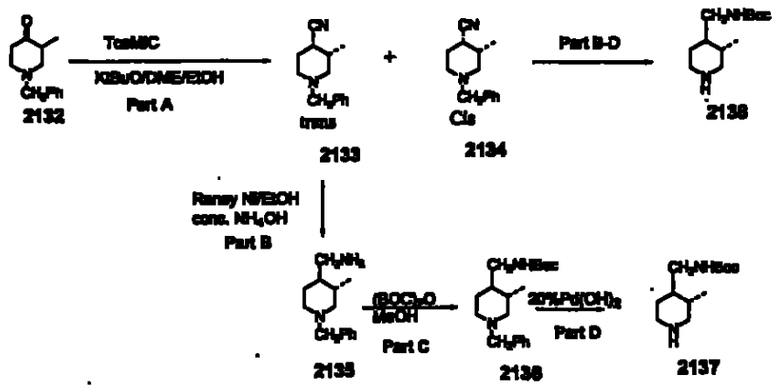
Part B:

The crude product **2129** and triethylamine (TEA) (0.6 mL, 4.3 mmol) were dissolved in CH_2Cl_2 (50 mL). Di-tert-butyldicarbonate (0.85 g, 3.9 mmol) was added to this solution in portions, and the reaction mixture was stirred for 16 h. The reaction mixture was then washed two times with 50 mL of water and once with 50 mL of brine. The organic phase was dried and the solvent was removed under reduced pressure. The crude product was subjected to silica gel chromatography using 2.5% ammonia saturated methanol in CH_2Cl_2 as the eluting solvent. The eluted fractions were combined and concentrated to yield 0.78 g of pure carbamate product **2130** (61%).

Part C:

The carbamate **2130** (0.8 g, 2.3 mmol) was dissolved in methanol (60 mL) and treated with palladium hydroxide (20%, 0.08 g). The mixture was transferred to a Parr bottle, which was then charged with hydrogen (20 psi). The Parr bottle was shaken for 10 h. The hydrogen was removed from the Parr bottle under vacuum, and the reaction mixture was filtered through Celite. The filtrate was then concentrated to provide pure amine **2131** (0.6 g).

Example 50H:



Part A:

Tosylmethyl Isocyanide (TosMIC) (7.2 g, 37 mmol) was added to 3-methyl-N-benzyl piperidone (**2132**) (4.25 g, 20.93 mmol) in DME (150 mL) and cooled to 0 °C. Ethyl alcohol (2.9 mL) and potassium tert-butoxide (7 g, 62.4 mmol) were added to the reaction mixture and stirred at room temperature for 4 hours. The reaction mixture

was poured into ice and extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. The resulting residue was purified by silica gel chromatography (20% ethyl acetate/hexane) to give first **2133** (trans isomer, 1.85 g, 41%), and second **2134** (cis isomer, 1.05 g, 22%).

Part B:

The trans intermediate **2133** (2.0 g, 9.34 mmol) was dissolved in ethyl alcohol (50 mL) and Raney Nickel (wet, 5.0 g) was added under N_2, followed by addition of conc. ammonium hydroxide (1.0 mL). The mixture was subjected to H_2 atmosphere at 50 p.s.i. for 16 hours with vigorous shaking. The reaction was filtered through celite under N_2 and the filtrate was concentrated under vacuum to provide 1.8 g (88%) of intermediate **2135.**

Part C:

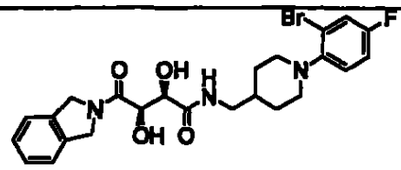
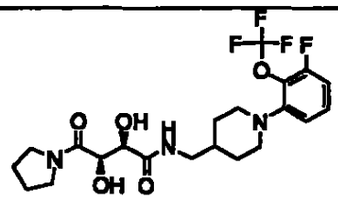
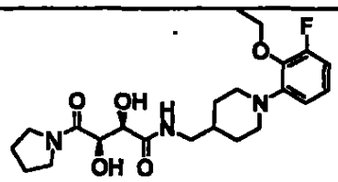
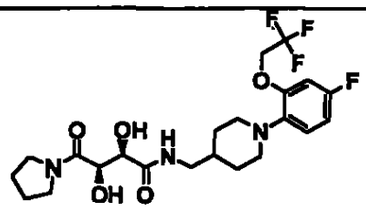
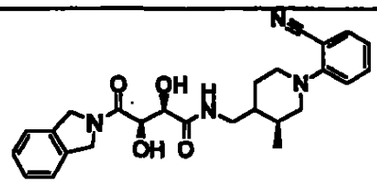
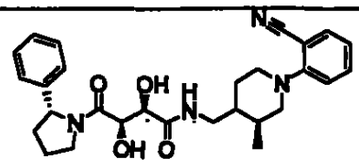
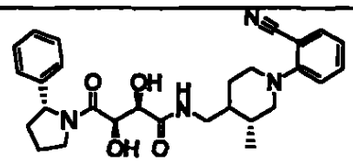
Intermediate **2135** (1.0 g, 4.6 mmol) was dissolved in methyl alcohol (35 mL). A solution of BOC-anhydride (1.2 g, 5.5 mmol) in methyl alcohol (15 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for one hour, then at ambient temperature for an additional hour. The solvent was removed under vacuum to provide a crude product that was purified by silica-gel column chromatography using ethyl acetate as the eluting solvent. The relevant fractions were collected and concentrated under reduced pressure to yield 1.1 g (76%) of intermediate **2136.**

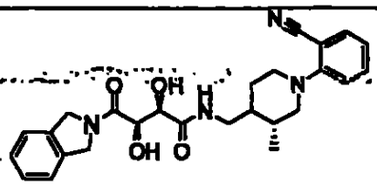
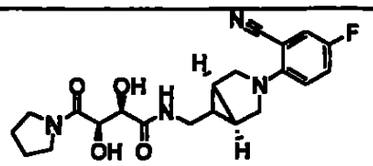
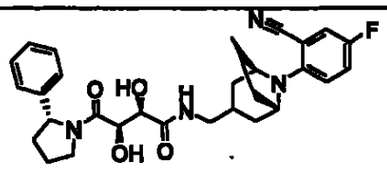
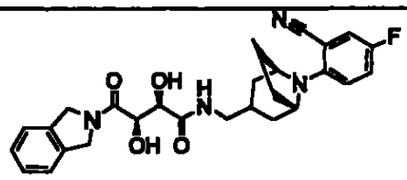
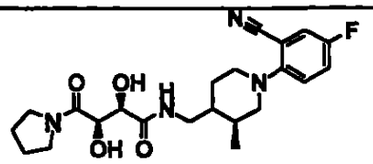
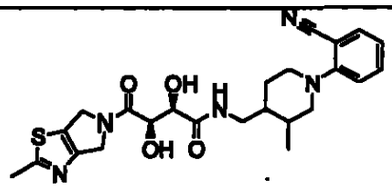
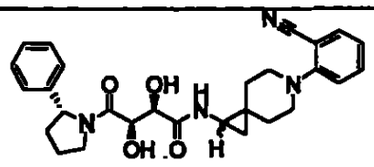
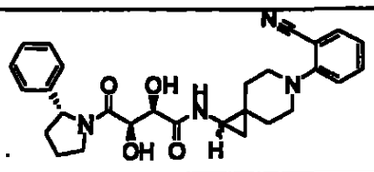
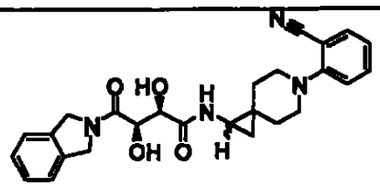
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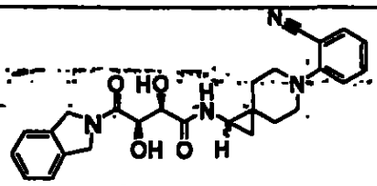
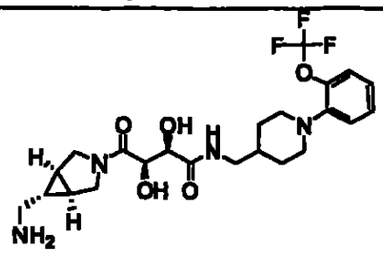
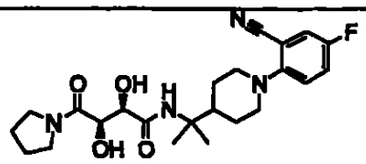
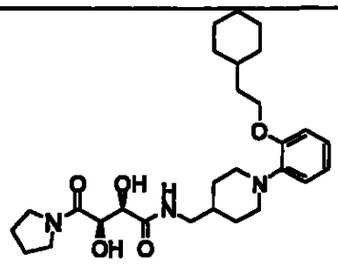
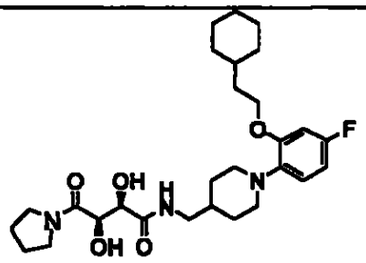
Intermediate **2136** (0.5 g, 1.57 mmol) was dissolved in methyl alcohol (25 mL). Palladium hydroxide (20 wt % Pd, 0.1 g) was added under N_2. The resulting mixture was exposed to H_2 atmosphere at 20 p.s.i. for 16 hours with vigorous shaking. The reaction mixture was filtered through celite and washed with methyl alcohol (1 X 25 mL). The filtrate was concentrated under vacuum to provide intermediate **2137** (0.38 g) as an oil which was used in the next step without further purification.

Intermediate **2138** was prepared using methods similar to those used in Part B-D.

The following compounds were prepared using previously described procedures.

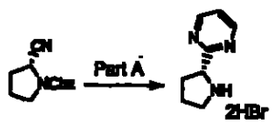
Compound #	Structure	Exact mass	MS m/z (M+H)
2139		519.1	520.1
2140		477.2	478.1
2141		437.2	438.1
2142		491.2	492.1
2143		462.2	463.1
2144		490.3	491.1
2145		490.3	491.3

2146		462.2	463.3
2147		416.2	417.2
2148		520.2	521.1
2149		492.2	493.3
2150		432.2	433.2
2151		483.2	484.1
2152		488.2	489.1
2153		488.2	489.1
2154		460.2	461.1

2155		460.2	461.3
2156		500.2	500.1
2157		446.2	447.3
2158		501.3	502.3
2159		519.3	520.3

Example 51:

Example 51A:

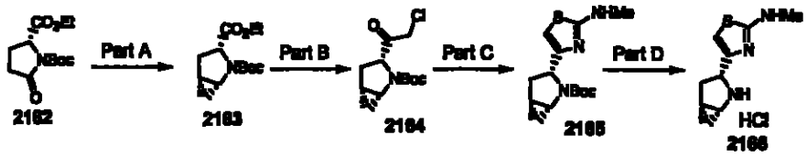


2160 2161

Part A:

Compound **2161** was synthesized according to the procedures of WO02060894A2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.58 (bs, NH), 8.89 (m, 2H), 7.57 (m, 1H), 4.88 (m, 1H), 3.80 (m, 2H), 2.06 (m, 4H).

Example 51B:



Part A:

Compound **2163** was synthesized from Compound **2162** (made according to the procedures of WO2004/052850) according to the procedures of Hanessian et. al.(*Bioorg. Med. Chem Lett.* **1998**, *8*, 2123 and the references therein.) HPLC-MS t_R = 1.90 min ($UV_{254\ nm}$); mass calculated for formula C13H21NO4 255.2, observed LCMS m/z 278.2 (M+Na).

Part B:

Compound **2164** was synthesized according to the procedures of Example 10B Part A. HPLC-MS t_R = 1.79 min ($UV_{254\ nm}$); mass calculated for formula C12H18ClNO3 259.1, observed LCMS m/z 282.1 (M+Na).

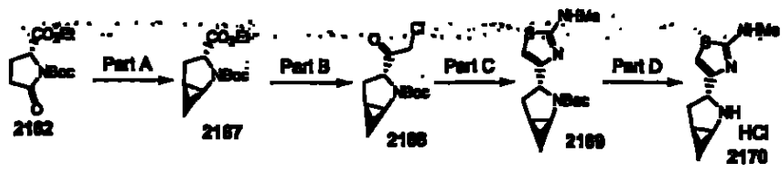
Part C:

Compound **2164** (190 mg) was cyclized with N-methylthiourea in DMF (2 mL) to afford **2165** (81 mg) according to the procedures of Example 10B Part B. HPLC-MS t_R = 1.27 min ($UV_{254\ nm}$); mass calculated for formula C14H21N3O2S 295.1, observed LCMS m/z 296.2 (M+H).

Part D:

To compound **2165** (81 mg) in methanol (2 mL) was added 4.0 M HCl/dioxane (1 mL) with ice bath cooling. The reaction mixture was stirred for 1.5 hours and concentrated. The residue was suspended in DCM (5 mL) and concentrated to afford impure **2166**. The material was used without purification.

Example 51C:



Part A:

Compound **2167** was synthesized from Compound **2162** (made according to the procedures of WO2004/052850) according to the procedures of Hanessian et. al. *Bioorg. Med. Chem Lett.* **1998**, *8*, 2123 and the references therein. HPLC-MS t_R = 1.83 min (MS); mass calculated for formula C13H21NO4 255.2, observed LCMS m/z 278.2 (M+Na).

Part B:

Compound **2168** was synthesized according to the procedures of Example 10B Part A. HPLC-MS t_R = 1.78 min (MS); mass calculated for formula C12H18ClNO3 259.1, observed LCMS m/z 282.1 (M+Na).

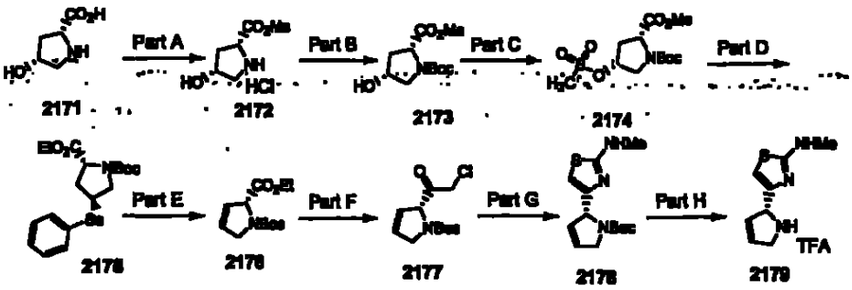
Part C:

Compound **2168** (117 mg) was cyclized with N-methylthiourea in DMF (2 mL) to afford **2169** (35 mg) according to the procedures of Example 10B Part B. HPLC-MS t_R = 1.16 min ($UV_{254\ nm}$); mass calculated for formula C14H21N3O2S 295.1, observed LCMS m/z 296.2 (M+H).

Part D:

To compound **2169** (35 mg) in methanol (2 mL) was added 4.0 M HCl/dioxane (1 mL) with ice bath cooling. The reaction mixture was stirred for 1.5 hours and concentrated. The residue was suspended in DCM (5 mL) and concentrated to afford impure **2170**. The material was used without purification.

Example 51D:



Part A:

To hydroxy proline **2171** (1.52 g, 11.6 mmol) in methanol (25 mL) in an ice bath was added thionyl chloride (0.95 mL, 13 mmol). The ice bath was removed and the reaction mixture was heated to reflux overnight. The reaction mixture was cooled and concentrated. The residue was dissolved in methanol and concentrated. The residue was dissolved in diethyl ether and concentrated to afford **2172** quantitatively. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (bs, 1H), 8.95 (bs, 1H), 4.50 (d, 1H, J = 7.0 Hz), 4.36 (m, 1H), 3.75 (s, 3H), 3.16 (m, 2H), 2.31 (m, 1H), 2.13 (m, 1H).

Part B:

To compound **2172** (2.11 g, 11.6 mmol) in DCM (25 mL) was added DIEA (4.2 mL, 24 mmol) and a solution of BOC-anhydride (3.03 g, 13. 9 mmol) in DCM (25 mL) with ice bath cooling. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction mixture was washed with water, 0.1 N HCl, bicarbonate solution and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, loaded with ethyl acetate and eluted with 30% ethyl acetate/hexane to ethyl acetate) afforded **2173** (2.66 g) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ rotomers 4.40-4.29 (m, 2H), 3.81 and 3.80 (s, 3H), 3.75 –3.64 (m, 1H), 3.57-3.50 (m, 1H), 2.35 (m, 1H), 2.11 (m, 1H), 1.48 and 1.44 (s, 9H).

Part C:

To compound **2173** (2.66 g, 10.8 mmol) in DCM (50 mL) in an ice bath was added triethyl amine (1.66 mL, 11.9 mmol) and methanesulfonyl chloride (1.09 mL, 14.1 mmol) dropwise. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction mixture was quenched

with ice water and the layers were separated. The aqueous layer was extracted with DCM. The combined organic layers were washed with 0.1 N HCl and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded **2174** (3.36 g) as an oil. HPLC-MS t_R = 1.49 min (ELSD); mass calculated for formula C12H21NO7S 323.1, observed LCMS m/z 346.1 (M+Na).

Part D:

To diphenylselenide (1.97 g, 6.3 mmol) in ethanol (20 mL) in an ice bath was added sodium borohydride (472 mg, 12.5 mmol) portion wise. The reaction mixture was stirred for 10 minutes after the bubbling had ceased. The above solution was added to compound **2174** (3.36 g, 10. 4 mmol) in ethanol (10 mL). The reaction mixture was heated to reflux for 2 hours. The reaction was cooled and the solvents removed in vacuo. The residue was partitioned between water (50 mL) and ethyl acetate (50 mL). The layers were separated. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 5% to 20% ethyl acetate/hexanes) afforded **2175** (2.91 g) as an oil. HPLC-MS t_R = 2.32 min ($UV_{254\ nm}$); mass calculated for formula C18H25NO4Se 399.1, observed LCMS m/z 422.0 (M+Na).

Part E:

To **2175** (481 mg, 1.21 mmol) in DCM (5 mL) in an ice bath was added dropwise pyridine (0.162 mL, 2.0 mmol) and 50% hydrogen peroxide (0.161 mL, 2.63 mmol). The ice bath was removed and the reaction mixture was stirred at room temperature for 1.25 hours. The reaction mixture was diluted with ethyl acetate (50 mL), washed with 0.1 N HCl, bicarbonate solution and brine, dried over sodium sulfate and concentrated to afford **2176** (272 mg) as a yellow oil. HPLC-MS t_R = 1.81 min (MS); mass calculated for formula C12H19NO4 241.1, observed LCMS m/z 264.1 (M+Na).

Part F:

Compound **2177** (123 mg) was prepared from **2176** (202 mg, 0.84 mmol) according to the procedure described in Example 10B Part B. HPLC-MS t_R =

1.70 min (MS); mass calculated for formula C11H16ClNO3 245.1, observed LCMS m/z 264.1 (M+Na).

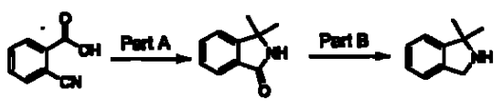
Part G:

Compound **2178** (48 mg) was prepared as described in Example 51B Part C from compound **2177** (123 mg, 0.5 mmol). HPLC-MS t_R = 1.12 min (UV_{254} nm); mass calculated for formula C13H19N3O2S 281.1, observed LCMS m/z 282.1 (M+H).

Part H:

A mixture of compound **2178** (48 mg, 0.17 mmol), TFA (2 mL) and DCM (2 mL) were stirred at room temperature for 1 hour. The solvents were removed and the residue was dissolved in DCM (5 ml) and concentrated to afford **2179** (70 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (bs, NH), 6.75 (s, 1H), 6.26 (d, 1H, J = 6.3 Hz), 5.92 (d, 1H, J = 7.5 Hz), 5.77 (m, 1H), 4.43 (d, 1H, J =17.2 Hz), 4.28 (d, 1H, J =17.2 Hz), 3.11 (s, 3H).

Example 51E:



2180 2181 2182

Part A:

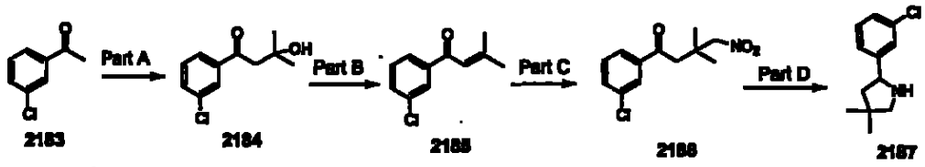
Compound **2180** was prepared using a modification of the procedure in *J. Org. Chem.* **1998**, *63*, 8, 2451-2455. Compound **2180** (0.400 g, 2.72 mmol) was dissolved in THF (60 mL) and cooled in a dry ice/acetone bath. A solution of methyllithium (1.6 M in diethylether, 18 mL) was added dropwise and the solution was warmed to room temperature. The reaction was quenched with brine after 10 minutes. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organics were washed with 1N HCl, saturated sodium bicarbonate and water, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded **2181** (0.200 g). HPLC-MS t_R = 1.126 min

($UV_{254\ nm}$); mass calculated for formula $C_{10}H_{11}NO$ 161.1, observed LCMS m/z 162 (M+H).

Part B:

Compound **2181** (0.200 g, 1.24 mmol) was dissolved in THF (10 mL) and a solution of borane (2.5 M in THF, 3 mL) was added dropwise and the solution was stirred at reflux overnight. The reaction was quenched with a solution of 1 M sodium hydroxide (2 mL) and methanol (2 mL) and reflux was continued for 5 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organics were washed with saturated sodium bicarbonate, water, dried over sodium sulfate and concentrated to afford **2182** (65 mg). HPLC-MS t_R = 0.595 min ($UV_{254\ nm}$); mass calculated for formula $C_{10}H_{11}N$ 147.1, observed LCMS m/z 148 (M+H).

Example 51F:



Part A:

Compound **2184** was prepared using a modification of the procedure in *J. Med.Chem.*. 1994, *37*, 23, 3878-3881. Compound **2183** (2.0 g, 12.9 mmol) was dissolved in methylene chloride and cooled in an ice bath. Triethylamine (3.61 mL, 26 mmol) was added followed by the dropwise addition of TMSOTf (2.81 mL, 15.5 mmol). The reaction was warmed to room temperature and stirred for 30 minutes. Saturated sodium bicarbonate was added slowly to quench the reaction and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate. In a separate flask $TiCl_4$ (1M in toluene, 20 mL) was added to methylene chloride (80 mL) at –78 °C. Acetone (1.2 g, 22 mmol) was added and stirred for 2 minutes. The silyl enol ether from the earlier was added and the reaction was stirred for 4 hours. After warming to room temperature, the reaction was quenched with saturated sodium bicarbonate and extracted with methylene chloride. The combined organic layers were dried over sodium

sulfate and evaporated. Purification by column chromatography (SiO_2, 33% ethyl acetate/hexanes) afforded **2184** (600 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 1H), 7.80 (d, 1H), 7.55 (d, 1H), 7.40 (t, 1H), 3.15 (s, 2H), 1.40 (s, 6H).

Part B:

Compound **2184** (600 mg, 2.84 mmol) was dissolved in methylene chloride (2 mL) and pyridine (2 mL) and cooled in an ice bath. TFAA (0.894 g, 4.26 mmol) was added dropwise and stirred 1 hour at room temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with 1N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. The residue was dissolved in methylene chloride (5 mL) and DBU (0.5 mL) was added and stirred for 1 hour at room temperature. The reaction mixture was partitioned between methylene chloride and water. The organic layers were washed with 1N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 10% ethyl acetate/hexanes) afforded **2185** (460 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 1H), 7.80 (d, 1H), 7.50 (d, 1H), 7.40 (t, 1H), 6.70 (m, 1H), 2.20 (d, 3H), 2.05 (d, 3H).

Part C:

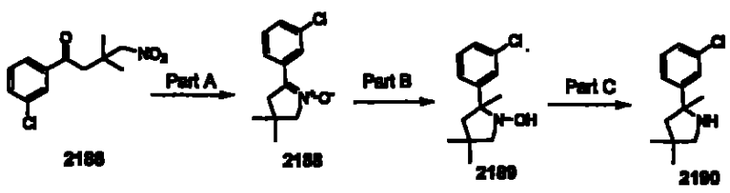
Compound **2185** (460 mg, 2.38 mmol) was dissolved in nitromethane (295 mg, 4.76 mmol) and benzyltrimethylammonium hydroxide (40% weight in MeOH, 200 mg) and stirred for 2 hours at room temperature. The reaction was quenched with acetic acid (1 mL) and partitioned between diethyl ether and water. The organic layer was dried over sodium sulfate and concentrated to afford **2186** (550 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 1H), 7.80 (d, 1H), 7.58 (d, 1H), 7.40 (t, 1H), 4.70 (s, 2H), 3.10 (s, 2H), 1.30 (s, 6H).

Part D:

Compound **2187** was prepared according to the procedure in *Chem. Ber.* **1958**, *91*, 1978-1980. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 1H), 7.22 (m,

2H), 7.18 (m, 1H), 4.30 (m, 1H), 2.90-2.80 (dd, 2H), 2.00 (m, 1H), 1.50 (m, 1H), 1.15 (d, 6H).

Example 51G:



Part A:

Compound **2186** (500 mg, 1.96 mmol) and ammonium chloride (104 mg, 1.96 mmol) were dissolved in THF (5 mL) and water (5 mL) and cooled in an ice bath. Zn dust (637 mg, 9.8 mmol) was added in portions and stirred overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. The residue was dissolved in methylene chloride (10 mL) and m-CPBA (510 mg, 2.94 mmol) was added and stirred for 2 hours. The reaction mixture was partitioned between methylene chloride and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated to yield **2188** (300 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 1H), 7.65 (m, 2H), 7.40-7.30 (m, 2H), 3.80 (t, 2H), 2.80 (t, 2H), 1.20 (s, 6H).

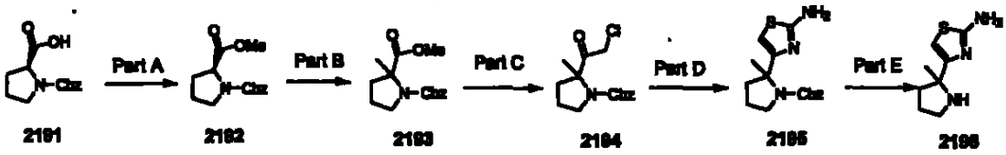
Part B:

Compound **2188** (300 mg, 1.35 mmol) was dissolved in THF (10 mL) and MeMgBr (3M in THF, 5 mL) was added dropwise. After stirring for 30 minutes at room temperature the reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated to afford **2189** (280 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (t, 1H), 7.42 (m, 1H), 7.30-7.20 (m, 2H), 3.20 (m, 2H), 2.00 (m, 2H), 1.55 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H).

Part C:

Compound **2189** (280 mg, 1.26 mmol) was dissolved in 1N HCl (10 mL) and Zn dust (0.5 g) was added. The reaction mixture was stirred at 60 °C for 12 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated to afford **2190** (110 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (bs, 1H), 7.38 (m, 1H), 7.30-7.20 (m, 2H), 2.85 (m, 1H), 2.75 (m, 1H), 2.05 (m, 1H), 1.85 (m, 1H), 1.50 (s, 3H), 1.20 (s, 3H), 0.95 (s, 3H).

Example 51H:



Part A:

Compound **2191** (2.8 g, 11.2 mmol) was dissolved in toluene (10 mL) and MeOH (10 mL) and cooled in an ice bath. A solution of TMS diazomethane in hexanes (2M, 8.4 mL) was added dropwise until yellow color persisted. The reaction was quenched with acetic acid until color became clear and the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with 1N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated to afford **2192** (3.1 g). The product was used without purification.

Part B:

Diisopropylamine (3.9 mL, 28 mmol) was dissolved in THF (20 mL) and cooled to –40 °C. A solution of n-BuLi (2.5M in hexanes, 8.9 mL) was added dropwise and the reaction was stirred for 30 minutes. Compound **2192** (3.1 g, 11.2 mmol) dissolved in THF (10 mL) was added dropwise at –78 °C and stirred for another 30 minutes. Iodomethane (3.1 g, 22.4 mmol) was added dropwise and the reaction was stirred for one additional hour. The reaction was warmed to room temperature and quenched with brine and extracted with ethyl acetate. The combined organic layers were washed with water, brine,

dried over sodium sulfate and concentrated to provide **2193** (2.5 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 5.20-5.00 (m, 2H), 3.70-3.40 (d, 3H), 3.70-3.60 (m, 2H), 2.20 (m, 1H), 1.90 (m, 3H), 1.60 (d, 3H).

Part C:

Diisopropylamine (1.24 mL, 8.85 mmol) was dissolved in THF (10 mL) and cooled to –40 °C. A solution of n-BuLI (2.5M in hexanes, 3.5 mL) was added dropwise and the reaction was stirred for 30 minutes. This solution was added dropwise to a solution of compound **2193** (450 mg, 1.61 mmol) and chloroiodomethane (1.12 g, 6.44 mmol) in THF (10 mL) at –78 °C. The reaction was stirred for 30 minutes and then quenched by the dropwise addition of acetic acid (1 mL) in THF (5 mL). After 10 minutes of stirring the reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded **2194** (330 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 5.20-5.00 (m, 2H), 4.40-4.00 (m, 2H), 3.80-3.60 (m, 2H), 2.20 (m, 1H), 2.00-1.8 (m, 3H), 1.60-1.40 (m, 3H).

Part D:

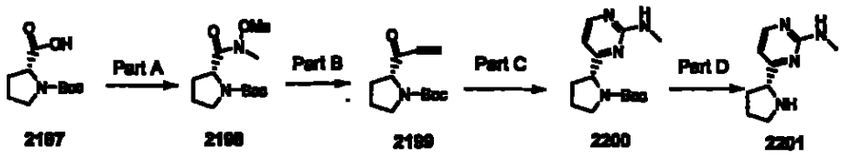
Compound **2194** (175 mg, 0.59 mmol) was dissolved in DMF (5 mL) and thiourea (91 mg, 1.2 mmol) was added and stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded **2195** (115 mg). HPLC-MS t_R = 1.17 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{19}N_3O_2S$ 317.1, observed LCMS m/z 318.1 (M+H).

Part E:

Compound **2195** (115 mg, 0.36 mmol) was dissolved in 30% HBr/AcOH (2 mL) and stirred for 2 hours. The solvent was removed under reduced pressure and the residue was dissolved in water and washed with diethyl

ether. The aqueous layer was lyophilized to provide **2196** as a di-HBr salt (100 mg).

Example 511:



Part A:

Compound **2197** (2.3 g, 10.6 mmol), 4-chloro-2,6-dimethoxytriazine (2.4 g, 13.9 mmol) and NMM (7.3 mL, 53 mmol) were dissolved in THF (50 mL) and stirred for 1 hour. N,O- dimethylhydroxylamine hydrochloride (2.05 g, 21.2 mmol) was added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with 1N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded **2198** (2.0 g). ^1H NMR (400 MHz, $CDCl_3$) δ 4.70-4.60 (m, 1H), 3.75 (m, 3H), 3.60-3.40 (m, 2H), 3.20 (s, 3H), 2.20 (m, 1H), 2.00-1.80 (m, 3H), 1.50-1.40 (m, 9H).

Part B:

Compound **2198** (550 mg, 2.13 mmol) was dissolved in THF (10 mL) and a solution of lithium (trimethylsilyl)acetylide (0.5 M in THF, 12 mL) was added dropwise and stirred overnight. The reaction mixture was partitioned between ethyl acetate and 1N HCl. The organic layer was washed with 1N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% ethyl acetate/hexanes) afforded **2199** (370 mg). HPLC-MS t_R = 1.69 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{17}NO_3$ 223.1, observed LCMS m/z 168.1 (M-(t-butyl)).

Part C:

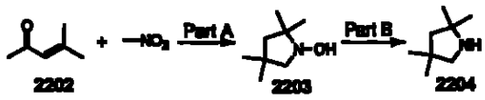
Compound **2199** (350 mg, 1.56 mmol) and diethylamine (228 mg, 3.13 mmol) were dissolved in EtOH (1.5 mL) and water (1.5 mL) and stirred for 3 hours.

The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. The residue was combined with methyl guanidine hydrochloride (756 mg, 7.8 mmol) and sodium carbonate (826 mg, 7.8 mmol) in EtOH (6 mL) and refluxed for 48 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 80% ethyl acetate/hexanes) afforded **2200** (210 mg). HPLC-MS t_R = 1.26 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{22}N_4O_2$ 278.1, observed LCMS m/z 279.1 (M+H).

Part D:

Compound **2200** (105 mg, 0.377 mmol) was dissolved in 4 M HCl in dioxane (2 mL) and methanol (0.5 mL) and stirred at room temperature for 1 hr. The reaction mixture was concentrated and triturated with diethyl ether to afford **2201** (74 mg) as an HCl salt. ^1H NMR (400 MHz, DMSO-d_6) δ 10.00 (bs, 1H), 8.70 (bs, 1H), 8.30 (s, 1H), 6.70 (d, 1H), 4.60 (bs, 1H), 3.40 (m, 2H), 2.75 (s, 3H), 2.40 (m, 1H), 2.00-1.80 (m, 3H).

Example 51J:



2202 2203 2204

Part A:

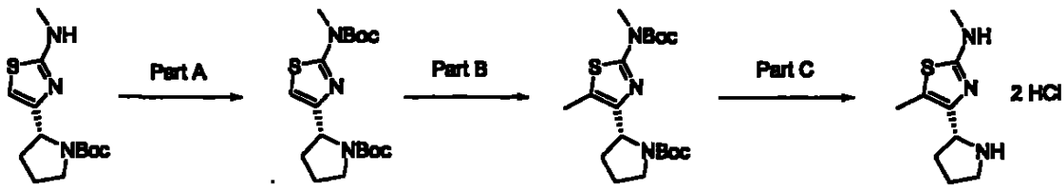
Compound **2203** was prepared according to a procedure described in *J. Org. Chem.* **1991**, *57*, 7034-7038.

Part B:

A mixture of **2203** (200 mg, 1.42 mmol) and zinc dust (278 mg, 4.25 mmol) in concentrated hydrochloric acid (1.4 mL) and water (5.8 mL) was stirred at reflux overnight. The mixture was made basic with potassium hydroxide pellets, decanted and the aqueous solution extracted with ethyl acetate. The

combined organic layers were washed with brine, dried over sodium sulfate and concentrated to give **2204** as a yellow sticky solid (95 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (m, 2H), 1.88 (s, 2H), 1.66 (s, 6H), 1.30 (s, 6H).

Example 51K:



2205 **2206** **2207** **2208**

Compound **2205** was prepared using procedures described in Example 10B.

Part A:

To the solution of 2-methylaminothiazole **2205** (100 mg, 0.35 mmol) and DMAP (135 mg, 1.0 mmol) in THF (5 mL), Boc_2O (218 mg, 1.0 mmol) was added at room temperature. The resulting mixture was stirred overnight and then diluted with ethyl acetate (30 mL). The organics was washed with water, Brine and dried over sodium sulfate and concentrated. The residue which was purified by column chromatography (SiO_2, 20% ethyl acetate/hexanes) afforded the protected product **2206** (130 mg) as semi-oil. HPLC-MS t_R = 2.42 min ($UV_{254\ nm}$); mass calculated for formula C18H29N3O4S 383.2, observed LCMS m/z 384.1 (M+H).

Part B:

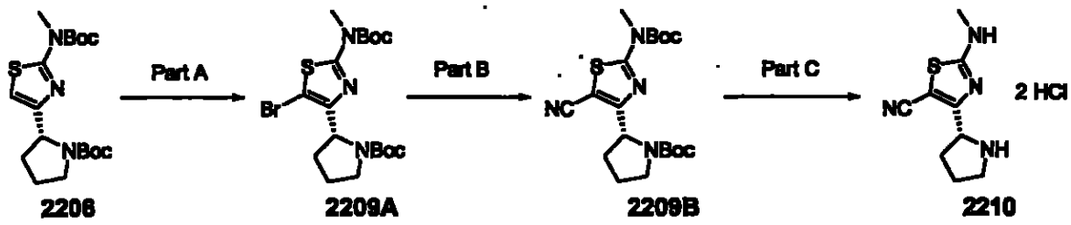
The solution of thiazole **2206** (150 mg, 0.39 mmol) in THF (5 mL) was cooled to –78 °C, and *n*-BuLi (2.5 M in hexane, 0.19 mL, 0.47 mmol) was added slowly. The resulting mixture was stirred at –78 °C for 30 min, and then iodomethane (0.1 mL, 1.55 mmol) was added. The mixture was stirred for another 30 min followed by the addition of saturated NH_4Cl solution (15 mL). The aqueous layer was extracted with ethyl acetate. The combined organics were washed with water, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 10% ethyl acetate/hexanes) afforded recovered thiazole **2206** (36 mg) and **2207** (100 mg). HPLC-MS t_R =

2.51 min ($UV_{254\ nm}$); mass calculated for formula C19H31N3O4S 397.2, observed LCMS m/z 398.2 (M+H).

Part C:

To a solution of 5-methylthiazole **2207** (100 mg, 0.25 mmol) in dioxane (2 mL) was added HCl (4N in dioxane, 4 mL) followed by water (0.5 mL). The mixture was stirred at room temperature for 1 hour and concentrated. The resulting residue **2208** (72 mg) was dried under vacuum and used in the next step without further purification.

Example 51L:



2206 **2209A** **2209B** **2210**

Part A:

To the solution of thiazole **2206** (190 mg, 0.5 mmol) in chloroform (5 mL), NBS (107 mg, 0.6 mmol) was added. The mixture was heated to 50 °C and stirred for 1 hour. After cooling to room temperature, the mixture was concentrated and purified by column chromatography (SiO_2, 10% ethyl acetate/hexanes) to afford 5-bromothiazole **2209A** (221 mg). HPLC-MS t_R = 2.65 min ($UV_{254\ nm}$); mass calculated for formula C18H28BrN3O4S 461.1, observed LCMS m/z 462.1 (M+H).

Part B:

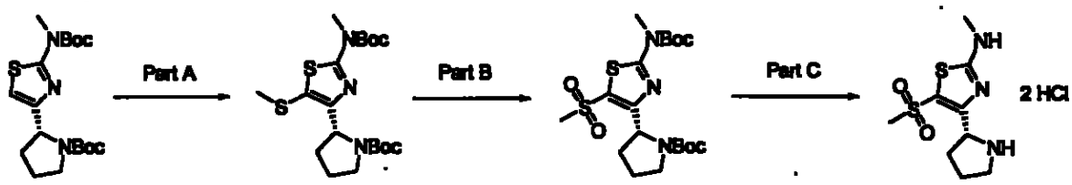
A mixture of 5-bromothiazole **2209A** (221 mg, 0.48 mmol), $Zn(CN)_2$ (117 mg, 1.0 mmol), $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and DPPF (55 mg, 0.1 mmol) in a 25-ml round bottom flask was flushed with argon for 3 min. Under the argon, DMA (3 mL) was added and the flask was sealed under the argon atmosphere. The mixture was heated to 85 °C and stirred overnight. After cooling to room temperature, ethyl acetate (30 mL) was added to dilute the

reaction mixture and the solution was filtered through celite. The filtrate was concentrated and purified by column chromatography (SiO_2, 10% ethyl acetate/hexanes) to afford 5-cyanothiazole **2209B** (167 mg) as oil. HPLC-MS t_R = 2.39 min ($UV_{254\ nm}$); mass calculated for formula C19H28N4O4S 408.2, observed LCMS m/z 409.2 (M+H).

Part C:

Compound **2210** (110 mg) was prepared from **2209B** (167 mg; 0.41 mmol) according to the procedure described in Example 51K Part C. HPLC-MS t_R = 0.62 min ($UV_{254\ nm}$); mass calculated for formula C9H12N4S 208.1, observed LCMS m/z 209.1 (M+H).

Example 51M:



2206 **2211** **2212** **2213**

Part A:

A solution of *n*-BuLi (2.5 M in hexane, 0.24 mL, 0.6 mmol) was added slowly to a solution of thiazole **2206** (190 mg, 0.5 mmol) in THF (5 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 1 hour, and then methyl disulfide (94 mg, 1.0 mmol) was added. The mixture was stirred for another one hour, and then warmed to room temperature slowly. Then saturated NH_4Cl solution was added to quench the reaction. The mixture was extracted with ethyl acetate (30 mL x.3). The combined organics were dried over sodium sulfate, concentrated and purified by column chromatography (SiO_2, 10% ethyl acetate/hexanes) to afford 5-methylsulfidethiazole **2211** (137 mg) and recovered thiazole **2206** (38 mg). HPLC-MS t_R = 2.62 min ($UV_{254\ nm}$); mass calculated for formula C19H31N3O4S2 429.2, observed LCMS m/z 430.1 (M+H).

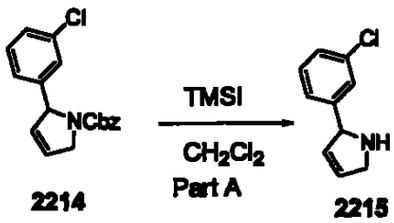
Part B:

A mixture of sulfide **2211** (137 mg, 0.32 mmol) and m-CPBA (~77%; 230 mg, 1.0 mmol) in dichloromethane (10 mL) was stirred at room temperature overnight. Ethyl acetate (80 mL) was added to dilute the mixture and the organics were washed with saturated sodium bicarbonate solution twice followed by brine, dried over sodium sulfate, concentrated. The residue was purified by column chromatography (SiO_2, 20% ethyl acetate/hexanes) afforded 5-methylsulfonethiazole **2212** (141 mg). HPLC-MS t_R = 2.62 min ($UV_{254\ nm}$); mass calculated for formula C19H31N3O6S2 461.2, observed LCMS m/z 406.1 (M+H- t-Bu).

Part C:

Compound **2213** (110 mg) was prepared from **2212** (141 mg, 0.30 mmol) according to the procedure described in Example 51K Part C. HPLC-MS t_R = 0.63 min ($UV_{254\ nm}$); mass calculated for formula C9H15N3O2S2 261.1, observed LCMS m/z 262.0 (M+H).

Example 51N:



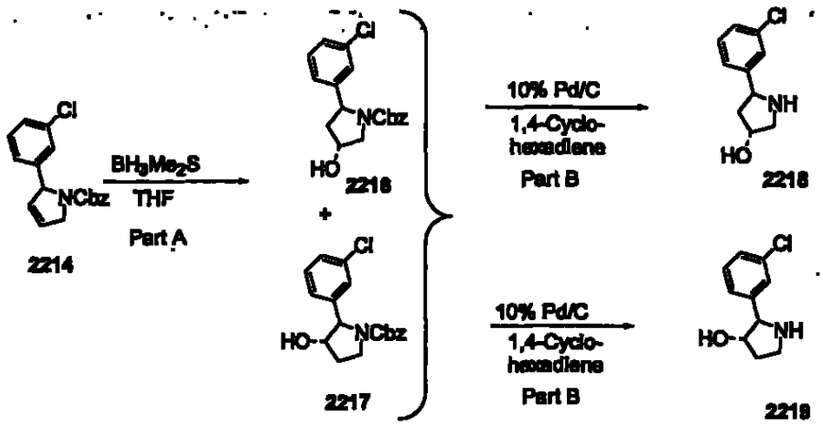
2214 **2215**

Starting pyrroline derivative **2214** was prepared by known methods (Billet, M; Schoenfelder, A; Klotz, P.; Mann, A.. *Tetrahedron Letters*, 2002, 1453).

Part A:

Trimethylsilyl Iodide (0.44 g, 2.24 mmol) was added dropwise to a solution of **2214** (0.47 g, 1.5 mmol; 20 mL CH_2Cl_2) at room temperature and stirred for 3 hours. The mixture was cooled to 0 °C before quenching with methanol (5 mL). The solvent was removed under reduced pressure to provide crude amine **2215**, which was used without further purification.

Example 510:



Part A:

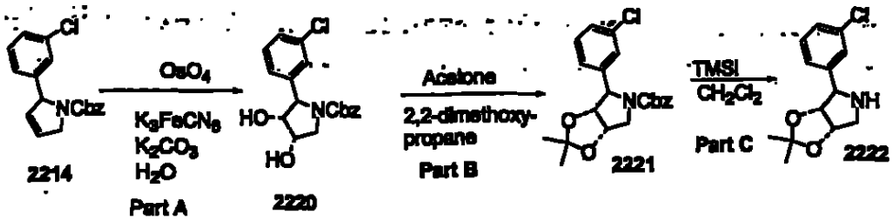
Borane dimethyl sulfide (2.0 M solution in toluene, 1.45 mL, 2.9 mmol) was added dropwise to a solution of intermediate **2214** (0.65 g, 2 mmol) in THF (10 mL) at 0 °C. After addition, the mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with dropwise addition of water (1.0 mL) and 3N NaOH (3.0 mL). The resulting mixture was stirred for 5 minutes and then cooled to 0 °C before adding 30% H_2O_2 (6.0 mL) dropwise. The mixture was stirred at ambient temperature for 2 hours and then treated with 5% $Na_2S_2O_3$ (25 mL) and stirred additional half hour. The reaction mixture was diluted with ethyl acetate (100 mL), and the organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated under vacuum to provide a crude residue which was purified by silica-gel column chromatography (1:3 to 1:2 ethyl acetate / hexane) to give first intermediate **2217** (0.3 g, 44%) followed by intermediate **2216** (0.2 g, 29%).

Part B:

Intermediate **2216** (0.075 g, 0.22 mmol) was dissolved in ethyl alcohol (1.5 mL). Then 1,4-cyclohexadiene (0.21 mL, 2.24 mmol) was added, followed by addition of 10% Pd/C under N_2. The reaction mixture was stirred at r.t. for 2 hours, filtered through celite and concentrated under vacuum to give intermediate **2218** (0.035 g, 80%).

Compound **2219** was prepared by using methods similar to those described in Parts A-B for intermediate **2218**.

Example 51P:



Part A:

Intermediate **2214** (0.1 g, 0.3 mmol) was dissolved in *t*-butanol (3 mL) and water (3 mL). Potassium hexacyanoferrate (0.31 g, 0.94 mmol) and potassium carbonate (0.13 g, 0.94 mmol) were added and stirred for 15 minutes. To this mixture osmium tetraoxide (0.005 g, 0.02 mmol) was added and stirred for 16 h. The reaction was diluted with ethyl acetate (50 mL) and the organics were washed once with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to provide intermediate **2220** (0.1 g, 91%).

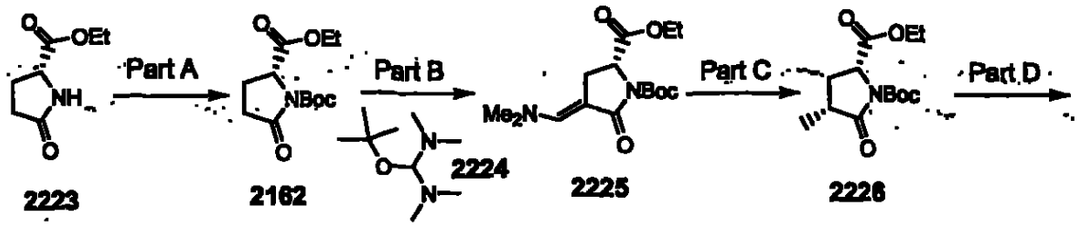
Part B:

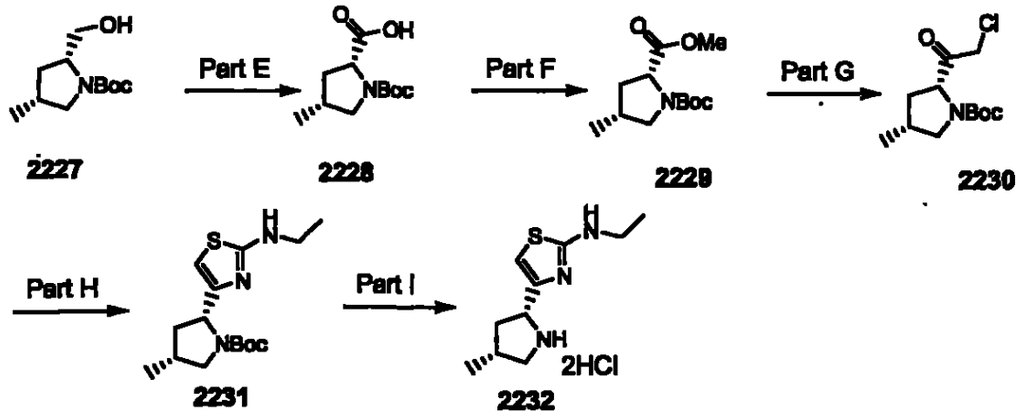
Diol **2220** (0.1 g, 0.28 mmol) was dissolved in acetone (5 mL) and 2,2-dimethoxypropane (0.045 g, 0.43 mmol) was added, followed by addition of catalytic amount of p-toluenesulfonic acid (0.06 g, 0.03 mmol). The reaction mixture was stirred at room temperature for 14 h. The solvent was removed under vacuum to provide a crude product which was purified by silica-gel preparative chromatography using ethyl acetate/hexane (1/3) as the eluting solvent to yield **2221** (0.075 g, 68%).

Part C:

Intermediate **2221** (0.06 g, 0.15 mmol) was dissolved in CH_2Cl_2 (0.5 mL), followed by addition of trimethylsilyl iodide (0.034 mL, 0.24 mmol) at 0 °C. The mixture was stirred at r.t. for 2 hours. The reaction was quenched with methanol (5 mL) and stirred for another 2 hours. The reaction mixture was concentrated to provide the crude amine **2222**, which was used without additional purification.

Example 51Q:





Part A:

Compound **2223** (2.2 g, 13.9 mmol) was dissolved in methylene chloride (25 mL) and triethylamine (3.9 mL, 27.8 mmol), DMAP (100 mg), and di-*t*-butyldicarbonate (3.33 g, 15.3 mmol) were added. The reaction mixture was stirred for 5 hours at room temperature and then diluted with water and methylene chloride. The organic layers were washed with 1N HCl, saturated sodium bicarbonate, water, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 33% ethyl acetate/hexanes) afforded the desired product (3.0 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (m, 1H), 4.20 (q, 2H), 2.70-2.60 (m, 1H), 2.50 (m, 1H), 2.40-2.30 (m, 1H), 2.05 (m, 1H), 1.50 (s, 9H), 1.20 (t, 3H).

Part B:

Compound **2162** (630 mg, 2.44 mmol) was added to *t*-butoxy-bis(dimethylamino)methane (**2224**) (0.705 mL, 3.42 mmol) and stirred at 80 °C overnight. The excess reagent was removed under reduced pressure to provide **2225** that was used without purification (750 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (m, 1H), 4.50 (m, 1H), 4.30-4.20 (m, 2H), 3.30 (m, 1H), 3.00 (s, 6H), 2.80 (m, 1H), 1.50 (s, 9H), 1.30 (m, 3H).

Part C:

Compound **2225** (750 mg, 2.4 mmol) was dissolved in ethyl acetate (12 mL) and 10% Pd-C (200 mg) was added under an argon atmosphere. The reaction mixture was placed under a hydrogen atmosphere and stirred for 96 hours at room temperature. The reaction was filtered and the solvent was evaporated. Purification by column chromatography (SiO_2, 33% ethyl acetate/hexanes) afforded the desired product (350 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 4.50 (m, 1H), 4.25 (q, 2H), 2.60 (m, 2H), 1.65 (m, 1H), 1.50 (s, 9H), 1.32 (t, 3H), 1.28 (d, 3H).

Part D:

Compound **2226** (200 mg, 0.73 mmol) was dissolved in THF (2 mL) and borane dimethyl sulfide (2M in THF, 1.5 mL) was added. The reaction mixture was stirred for 40 hours and then cooled in an ice bath and quenched slowly with methanol. The solvent was evaporated and the residue was purified by column chromatography (SiO_2, 33% ethyl acetate/hexanes) to afford the desired product (80 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 3.95 (m, 1H), 3.75-3.50 (m, 3H), 2.75 (t, 1H), 2.25 (m, 2H), 1.50 (s, 9H), 1.20 (m, 1H), 1.00 (d, 3H).

Part E:

Compound **2227** (70 mg, 0.32 mmol) was dissolved in acetone (3 mL) and Jones Reagent (1 mL) was added dropwise. The reaction mixture was stirred overnight and then quenched with methanol. The mixture was then filtered and concentrated. The residue was dissolved in saturated sodium bicarbonate and washed with diethyl ether. The aqueous layer was acidified to pH 2 and then extracted with ethyl acetate. The ethyl acetate layers were dried over sodium sulfate and concentrated to provide the desired product (55 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 4.30-4.20 (m, 1H), 3.80-3.70 (m, 1H), 2.95 (m, 1H), 2.50-2.30 (m, 1H), 2.25 (m, 1H), 1.80-1.60 (m, 1H), 1.50 (d, 9H), 1.05 (m, 3H).

Part F:

Compound **2228** (370 mg, 1.62 mmol) was dissolved in toluene (2 mL) and methanol (2 mL) and cooled in an ice bath. A solution of trimethylsilyl diazomethane (2M in hexanes, 1.5 mL) was added dropwise. The solution was stirred for 1 hour and then concentrated. The residue was dissolved in ethyl acetate and water. The organic layer was washed with 1N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated to provide the methyl ester **2229** (310 mg).

Part G:

In a separate flask diisopropylamine (1.0 mL) was dissolved in THF (10 mL) and cooled to -78 °C. A solution of *n*-butyl lithium (2.5 M in hexanes, 2.55 mL) was added dropwise and stirred for 30 minutes. This solution was added dropwise to a solution of the methyl ester **2229** (310 mg, 1.27 mmol) and chloroiodomethane (0.9 g, 5.08 mmol) in THF (5 mL) at -78 °C. After thirty minutes the reaction was quenched dropwise with acetic acid (1 mL) in THF (5 mL). The reaction mixture was warmed to room temperature and diluted with water and ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded the desired alpha-chloro ketone **2230** (150 mg).

Part H:

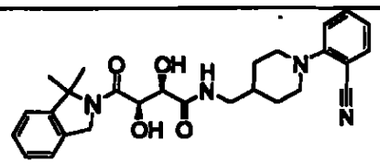
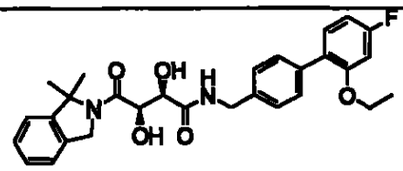
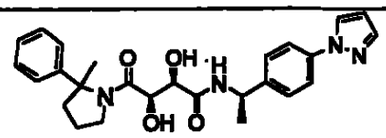
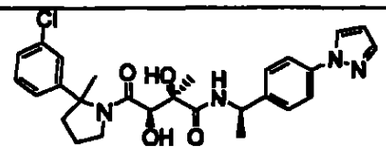
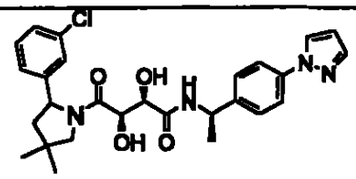
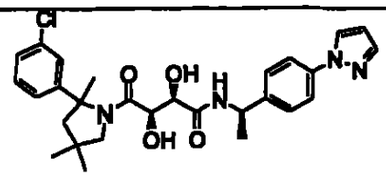
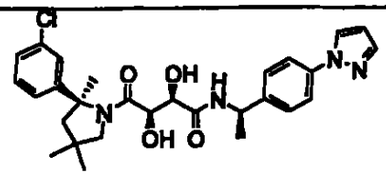
The alpha-chloro ketone **2230** (150 mg, 0.575 mmol) was dissolved in DMF (5 mL) and ethyl thiourea (134 mg, 1.15 mmol) was added and stirred at 80 °C overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, ethyl acetate) afforded the desired product **2231** (85 mg). HPLC-MS t_R = 1.35 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{25}N_3O_2S$ 311.1, observed LCMS m/z 312.1 (M+H).

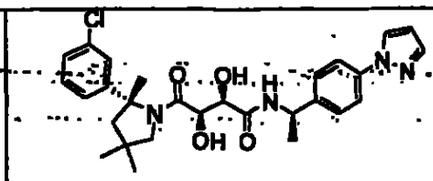
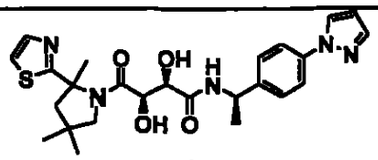
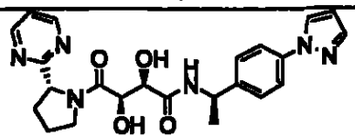
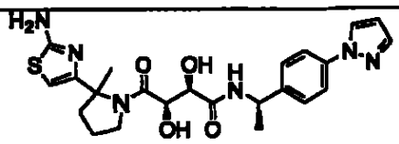
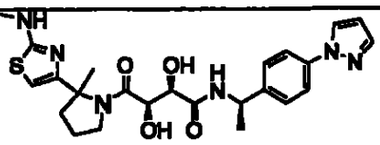
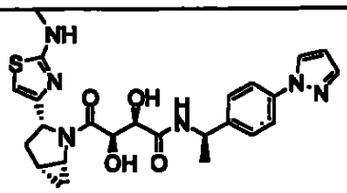
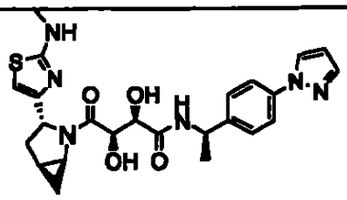
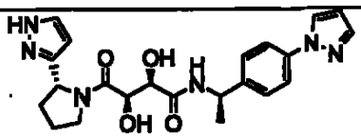
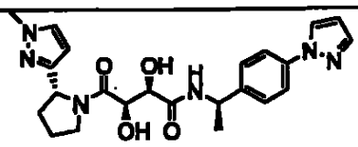
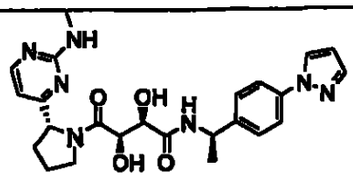
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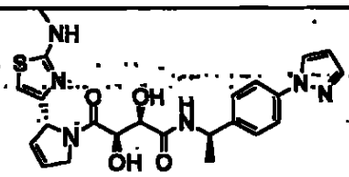
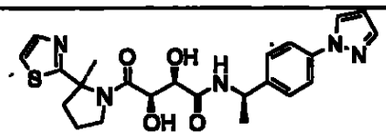
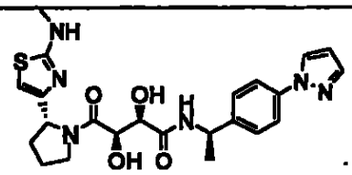
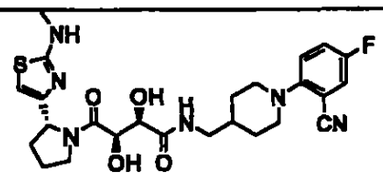
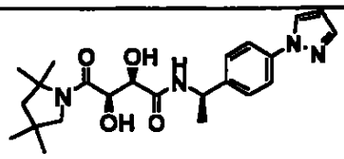
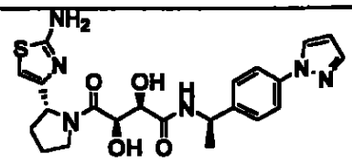
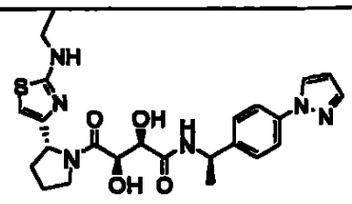
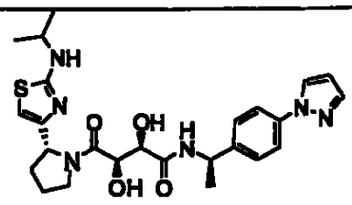
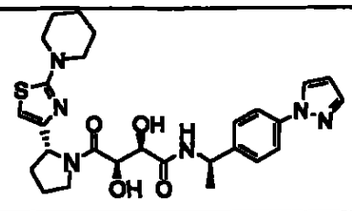
Compound **2231** (85 mg, 0.30 mmol) was dissolved in 4M HCl in dioxane (2mL) and methanol (0.5 mL) and stirred for 30 minutes. The solvents were

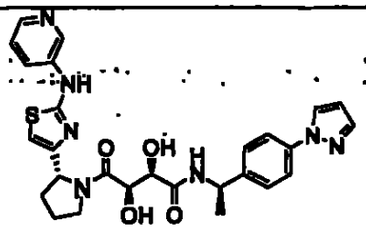
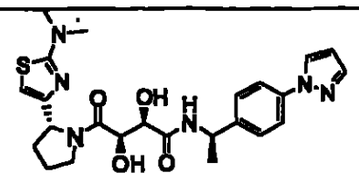
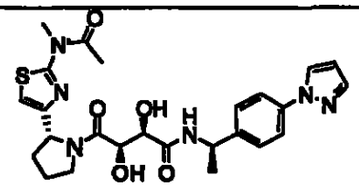
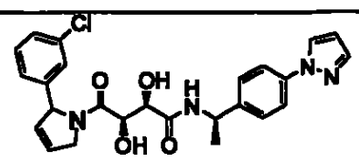
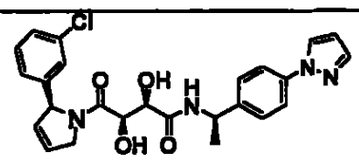
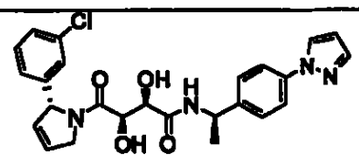
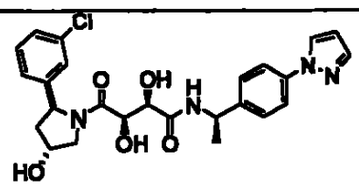
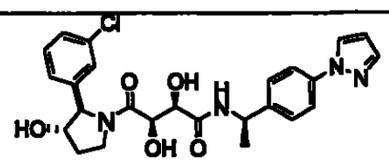
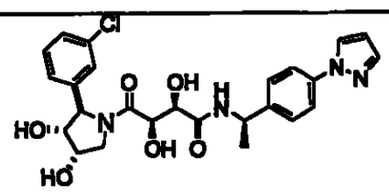
removed to provide 2232 as a di-HCl salt (65 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (bs, 1H), 8.70 (bs, 1H), 7.80 (bs, 1H), 6.70 (s, 1H), 4.50 (m, 1H), 3.30-3.20 (m, 2H), 2.75-2.65 (m, 2H), 2.40 (m, 2H), 1.70 (m, 1H), 1.15 (t, 3H), 1.10 (d, 3H).

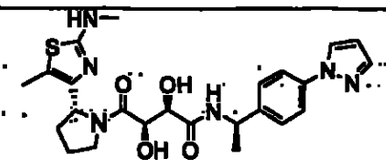
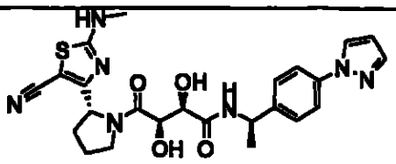
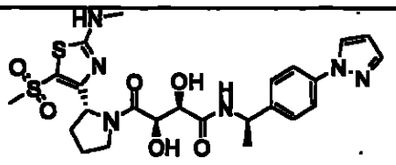
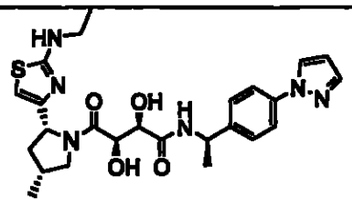
The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2233		494.2	495.2
2234		506.2	507.1
2235		462.2	463.1
2236		510.2	511.1
2237		510.2	511.1
2238		524.2	525.1
2239		524.2	525.1

2240		524.2	525.1
2241		497.2	498.1
2242		450.2	451.1
2243		484.1	485.0
2244		498.2	499.1
2245		496.2	497.1
2246		496.2	497.1
2247		438.2	439.1
2248		452.2	453.1
2249		479.2	480.1

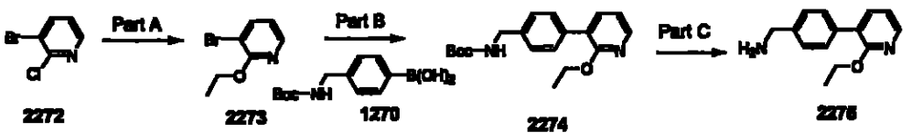
2250		482.2	483.1
2251		469.2	470.0
2252		484.2	485.1
2253		530.2	531.1
2254		428.2	429.2
2255		470.2	471.1
2256		498.2	499.1
2257		512.2	513.1
2258		538.2	539.2

2259		547.2	548.2
2260		498.2	499.1
2261		526.2	527.1
2262		480.2	481.1
2263		480.2	481.1
2264		480.2	481.3
2265		498.2	499.1
2266		498.2	499.1
2267		514.2	515.1

2268		498.2	499.1
2269		509.2	510.1
2270		562.2	563.0
2271		512.2	513.1

Example 52:

Example 52A:



Part A:

Sodium pellets (1.0 g, 43 mmol) were dissolved in ethanol (35 mL). Compound **2272** (1.4 g, 7.2 mmol) was added to the solution and the reaction was refluxed overnight. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated to afford **2273** (1.3 g). The product was used without further purification. HPLC-MS t_R = 1.92 min ($UV_{254\ nm}$); mass calculated for formula C_7H_8NOBr 201.0, observed LCMS m/z 202.1 (M+H).

Part B:

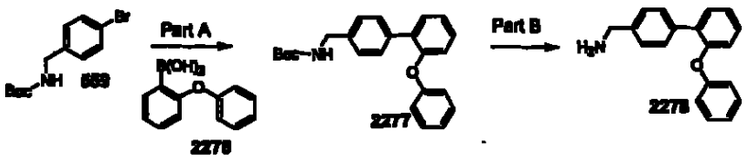
Compound **2273** (171 mg, 0.8592 mmol) was dissolved in toluene (10 mL). The boronic acid **1270** (409 mg, 1.69 mmol), $Pd_2(dba)_3$ (38 mg, 0.0423 mmol),

S-PHOS (34 mg, 0.084 mmol), potassium phosphate (358 mg, 1.69 mmol) were added to the solution and stirred at reflux overnight. The reaction mixture was cooled to room temperature and filtered, and the toluene was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The combined organic layers were dried over sodium sulfate and concentrated to afford **2274** (190 mg). The material was used without further purification. HPLC-MS t_R = 2.21 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{24}N_2O_3$ 328.2, observed LCMS m/z 329.2 (M+H).

Part C:

Compound **2274** (190 mg, 0.584 mmol) was dissolved in methylene chloride (4 mL) and TFA (1 mL) and stirred for 30 minutes. The solvents were removed to provide **2275** as the TFA salt (190 mg).

Example 52B:



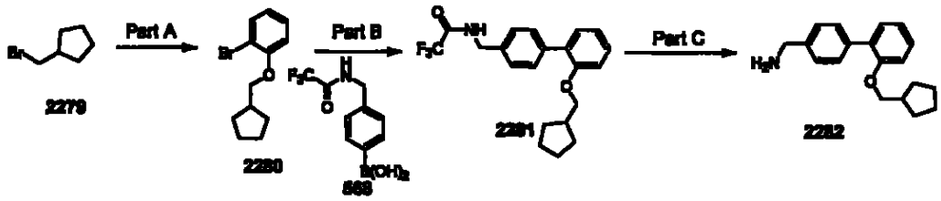
Part A:

Compound **559** (100 mg, 0.35 mmol) was dissolved in dioxane (5 mL). Then boronic acid **2276** (113 mg, 0.52 mmol), $Pd_2(dba)_3$ (27 mg, 0.03 mmol), triphenylphosphine (13.7 mg, 0.052 mmol), potassium phosphate (148 mg, 0.70 mmol) were added to the solution and stirred at reflux overnight. The reaction mixture was cooled to room temperature and filtered, and the toluene was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded **2277** (80 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 1H), 7.45 (m, 2H), 7.30-7.15 (m, 5H), 7.20-7.10 (m, 2H), 7.00-6.90 (m, 3H), 4.30 (d, 2H), 1.45 (s, 9H).

Part B:

Compound **2277** (80 mg, 0.21 mmol) was dissolved in 4 M HCl in dioxane (2 mL) and stirred at room temperature for 1 hr. The reaction was diluted with diethyl ether (5 mL) and **2278** (60 mg) was collected by filtration.

Example 52C:



Part A:

Compound **2279** (500 mg, 3.08 mmol), cesium carbonate (3.0 g, 9.25 mmol), and 2-bromophenol (527 mg, 3.08 mmol) were dissolved in DMF (15 mL) and stirred at 60 °C for 2 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 10% ethyl acetate/hexanes) afforded **2280** (400 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 1H), 7.20 (m, 1H), 6.85 (d, 1H), 6.80 (t, 1H), 3.90 (d, 2H), 2.40 (m, 1H), 1.85 (m, 2H), 1.60-1.45 (m, 4H), 1.40 (m, 2H).

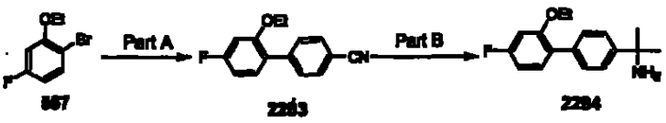
Part B:

Compound **2280** (157 mg, 0.50 mmol), compound **568** (250 mg, 1.02 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.01 mmol), S-PHOS (8.3 mg, 0.02 mmol), potassium fluoride (350 mg, 3.0 mmol) were dissolved in dioxane (8 mL) and stirred at reflux overnight. The reaction mixture was cooled to room temperature and filtered, and the toluene was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 10% ethyl acetate/hexanes) afforded **2281** (200 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.40 (m, 2H), 7.30 (m, 2H), 7.00 (m, 2H), 4.60 (d, 2H), 3.85 (d, 2H), 2.35 (m, 1H), 1.80 (m, 2H), 1.60 (m, 4H), 1.30 (m, 2H).

Part C:

Compound **2281** (100 mg, 0.317 mmol) was dissolved in MeOH (5 mL) and a saturated solution of potassium carbonate (1 mL) was added and the reaction was stirred for 3 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated to afford **2282** (40 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 2H), 7.40 (m, 4H), 7.00 (m, 2H), 4.60 (d, 2H), 3.85 (d, 2H), 2.35 (m, 1H), 1.80 (m, 2H), 1.60 (m, 4H), 1.35 (m, 2H).

Example 52D:



567 2283 2284

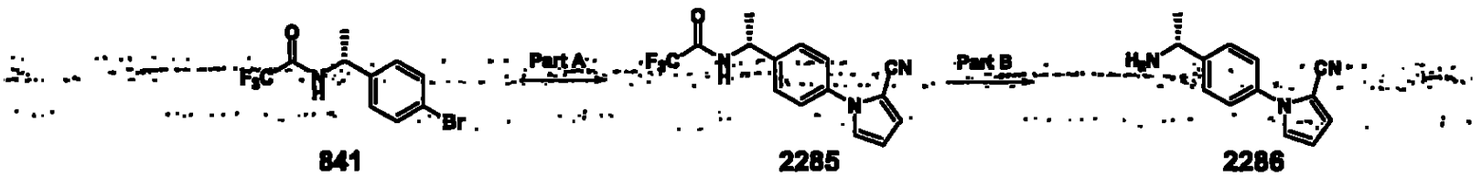
Part A:

Compound **567** (500 mg, 2.29 mmol), 4-cyanophenylboronic acid (483 mg, 3.43 mmol), $Pd_2(dba)_3$ (70 mg, 0.08 mmol), triphenylphosphine (70 mg, 0.26 mmol), potassium phosphate (970 mg, 4.58 mmol) were dissolved in dioxane (15 mL) and stirred at reflux overnight. The reaction mixture was cooled to room temperature and filtered and the dioxane was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 5% ethyl acetate/hexanes) afforded **2283** (240 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.58 (m, 4H), 7.27-7.23 (m, 1H), 6.75-6.70 (m, 2H), 4.05 (q, 2H), 1.38 (t, 3H).

Part B:

Compound **2284** was prepared according to the procedure in *J. Org. Chem.* **1992**, *57*, 4521-4527.

Example 52E:



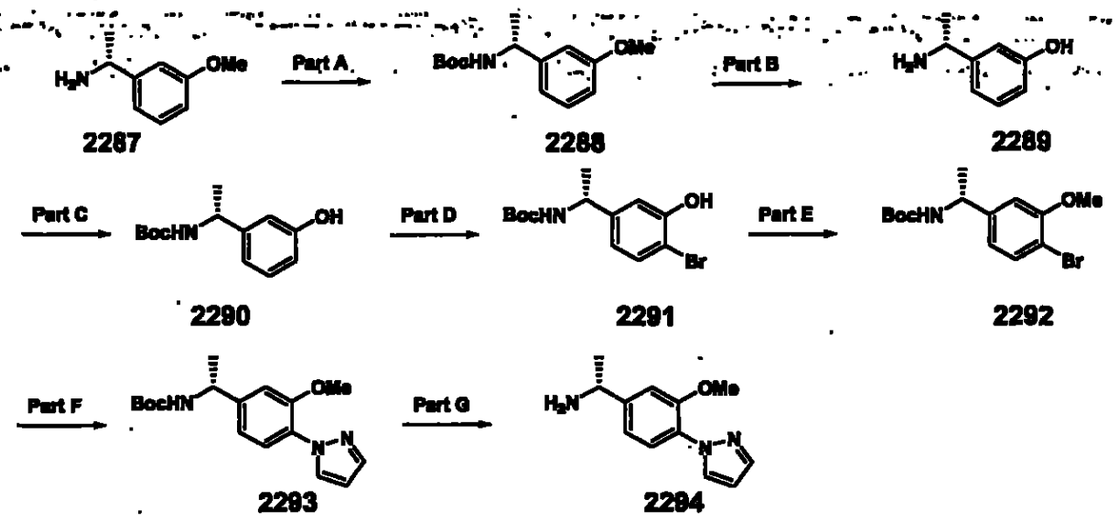
Part A:

To a mixture of compound **841** (2.96 g, 10 mmol), pyrrole-2-carbonitrile (1.1 g, 12 mmol) and 1,10-phenanthroline (1.17 g, 6.5 mmol) in DMA (10 mL) was added cesium carbonate (6.52 g, 20 mmol) and CuI (0.42 g, 2.2 mmol) and the mixture was heated at 150 °C for 18 hours. The mixture was filtered and rinsed with EtOAc (100 mL). The filtrate was washed with water (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated. Purification by column chromatography (SiO_2, 10% EtOAc/hexane followed by 20% EtOAc/hexane) afforded compound **2285** as an oil (0.17 g, 5.7%).

Part B:

A mixture of compound **2285** (0.17 g, 0.57 mmol) and aq. 1M LiOH (1 mL, 1 mmol) in dioxane (3 mL) was stirred at room temperature for 18 hours. The reaction mixture was concentrated and added water (2 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 1% MeOH/ CH_2Cl_2 followed by 5% MeOH/ CH_2Cl_2) afforded compound **2286** as an oil (0.085 g, 71%).

Example 52F:



Part A:

To a solution of compound **2287** (20.6 g, 136.4 mmol) in CH_2Cl_2 (200 mL) was added triethylamine (27.5 g, 272.8 mmol) and the reaction mixture was cooled to 0 °C, and $(Boc)_2O$ (32.7 g, 150 mmol) was added. The mixture was stirred at 0 °C for 10 minutes and then warmed to room temperature and stirred for 4 hours. The reaction mixture was washed with aq. sat. NH_4Cl (100 mL) and dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 10% EtOAc/hexane followed by 15% EtOAc/hexane) afforded the compound **2288** as white solid (32.7 g, 95%).

Part B:

To a solution of compound **2288** (3.95 g, 15.7 mmol) in CH_2Cl_2 (200 mL) at -78 °C was added a solution of 1M BBr_3/CH_2Cl_2 (37 mL) dropwise via a dropping funnel over 15 minutes. The reaction mixture was stirred at -78 °C for 2 hours, then poured carefully into MeOH (100 mL) and concentrated to a brown tar (3.6 g). Trituration with ether (3 x 20 mL) and concentrated afforded compound **2289** as brown tar which was used in next reaction without further purification.

Part C:

The crude compound **2289** was suspended in CH_2Cl_2 (100 mL) and triethylamine (8.8 mL, 63 mmol) was added. The reaction mixture was cooled

to 0 °C and $(Boc)_2O$ (3.77 g, 17.3 mmol) was added. The mixture was stirred at room temperature for 1 hour. The reaction mixture was then washed with water (100 mL), sat. $NaHCO_3$ (25 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 10% EtOAc/hexane followed by 15% EtOAc/hexane and 20% EtOAc/hexane) afforded compound **2290** as an oil (1.85 g, 62% over two steps).

Part D:

To a solution of compound **2290** (0.45 g, 1.9 mmol) in CH_2Cl_2 (10 mL) was added a solution of NBS (0.34 g, 1.9 mmol) in CH_2Cl_2 (10 mL) via a dropping funnel. Stirred at room temperature for 3.5 hours and then washed with aq. 10% H_2SO_4 (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 100% CH_2Cl_2 followed by 1% EtOAc/CH_2Cl_2) afforded compound **2291** (0.13 g, 21%).

Part E:

To a solution of compound **2291** (0.22 g, 0.7 mmol) in acetone (6 mL) was added K_2CO_3 (0.288 g, 2.1 mmol) followed by a solution of methyl iodide (0.065 mL, 1.05 mmol) and the reaction mixture was stirred at room temperature for 18 hours. The mixture was filtered and concentrated to dryness. The residue was dissolved in EtOAc (20 mL) and washed with water (2 mL) followed by brine (2 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to afford the compound **2292** (0.2 g, 86%).

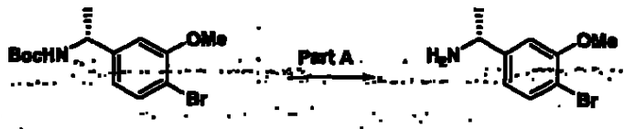
Part F:

Compound **2293** was prepared following the procedure described in Example 52E, Part A.

Part G:

Compound **2294** was prepared from compound **2293** via TFA deprotection as described in Example 1.

Example 52G:

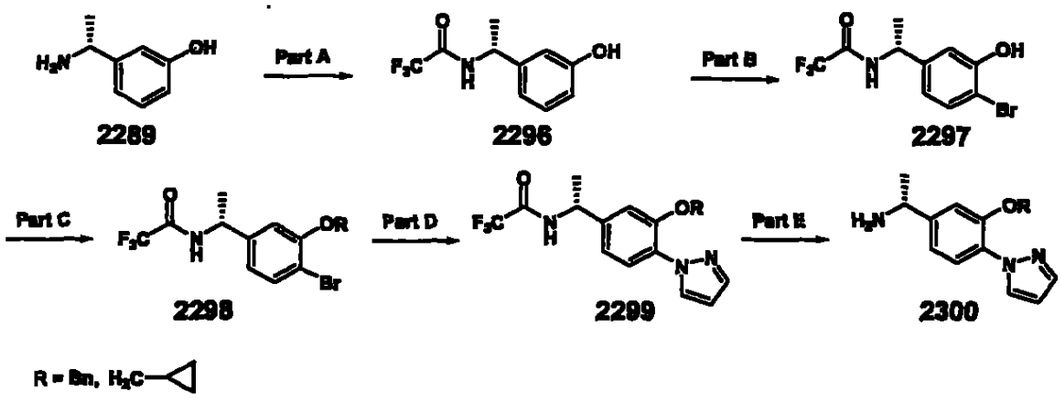


2292 2295

Part A:

Compound **2295** was prepared from compound **2292** **2293** via TFA as described in Example 1.

Examples 52H:



2289 2296 2297

2298 2299 2300

Part A:

Compound **2289** was converted to compound **2296** via the procedure described in Example 52F Part C and using trifluoroacetic anhydride in place of Boc_2O.

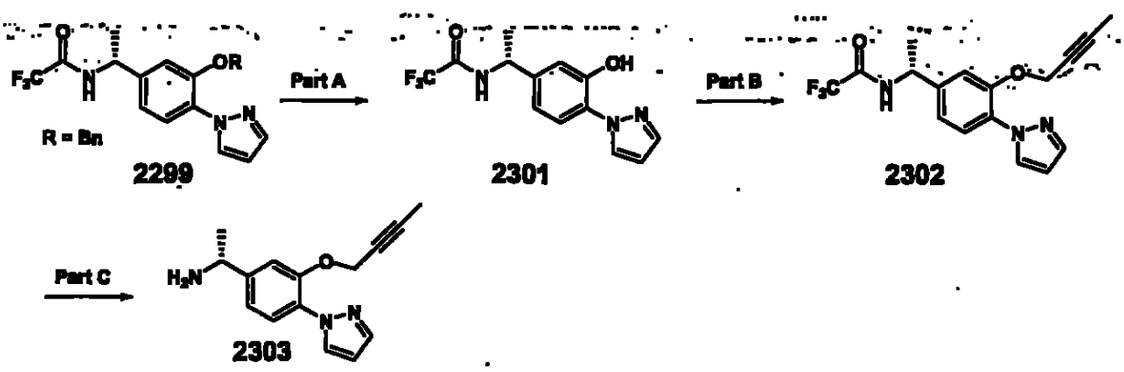
Part B,C,D:

Compounds **2297, 2298** and **2299** were prepared following the procedures described in Example 52F, Part D, E and F using benzyl bromide and cyclopropyl bromide in place of methyl iodide.

Part E:

Compound **2300** were prepared from compound **2299** following the procedures described in Example 52E, Part B.

Example 52I:



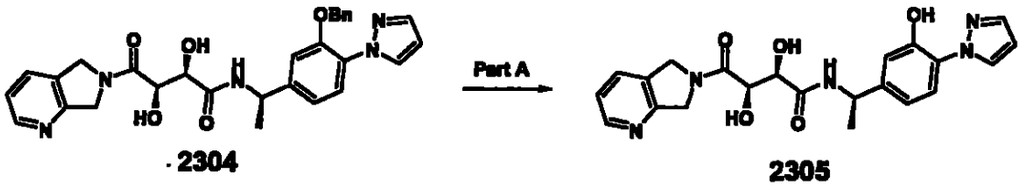
Part A:

A mixture of compound **2299** (0.27 g, 0.69 mmol), 10% Pd-C (0.18 g) and EtOH (25 mL) was stirred under hydrogen atmosphere at 55 psi for 18 hours. Filtered through celite and rinsed with CH_2Cl_2 and concentrated to afford the desired compound **2301** (0.21 g, 100%).

Part B,C:

Compounds **2302** and **2303** were prepared following the procedures described in Example 52H, Part C and E and using 1-bromo-2-butyne as the alkylating reagent.

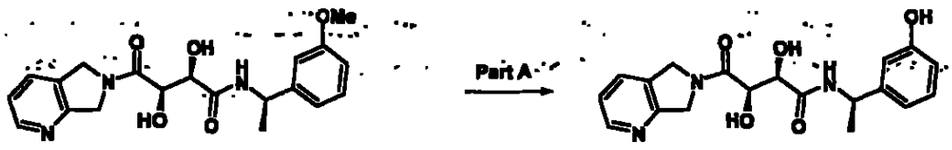
Example 52J:



Part A:

A mixture of compound **2304** (60 mg), 10% Pd-C (30 mg) and MeOH (10 mL) was stirred at room temperature under hydrogen atmosphere for 18 hours. Filtered and rinsed with CH_2Cl_2 and concentrated to afford the desired product **2305** (50 mg).

Example 52K:



2306 2307

Part A:

Compound **2307** was prepared from compound **2306** following the procedure described in Example 52F, Part B.

Example 52L:

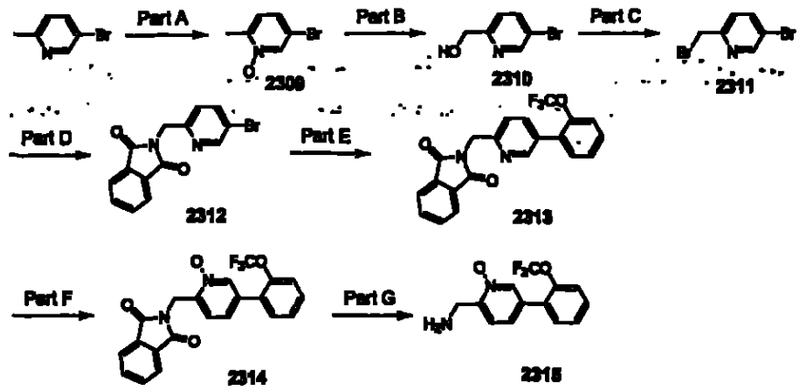


2307 2308

Part A:

To a mixture of **2307** (0.065 g, 0.18 mmol) in acetone (10 mL) was added K_2CO_3 (0.082 g, 0.59 mmol) followed by benzyl bromide (0.022 mL, 0.19 mmol) and the reaction mixture was refluxed for 18 hours. DMF (0.5 mL) was added to the reaction mixture and heated at 70 °C for 18 hours. The reaction mixture was cooled to room temperature and EtOAc (5 mL) was added, then was washed with water (2 x 1 mL) followed by brine (1 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 5% MeOH (NH_3)/CH_2Cl_2) afforded **2308** (0.019 g, 23%).

Example 52M:



Part A:

To a solution of 5-bromopicoline (20 g, 116 mmol) in chloroform (100 mL) at 0 °C was added portionwise 77% mCPBA (28.7 g, 128 mmol) over 20 min. The reaction mixture was allowed to stir at room temperature overnight, after which time the solid was filtered off, the filtrate was washed with saturated Na_2CO_3, dried over Na_2SO_4, and concentrated to afford **2309** (17.83 g, 82%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 2.47 (s, 3H).

Part B:

Compound **2309** (15 g, 80 mmol) was cooled to 0 °C, and trifluoroacetic anhydride (35 mL, 250 mmol) was slowly added under argon. The mixture was allowed to stir at room temperature for 30 min, then at 55 °C for 30 min after which it was cooled to 0 °C in an ice bath. $NaHCO_3$ aqueous solution (10%, 150 mL) was slowly added with caution. After the completion of addition, the mixture was allowed to stir at room temperature for 6 h. The solution was extracted with dichloromethane, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane 50:50), affording product **2310** as a white solid (9.2 g, 61%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 1.9 Hz, 1H), 7.80 (dd, J = 7.9, 2.4 Hz, 1H), 7.19 (dd, J = 8.3, 0.9 Hz, 1H), 4.73 (s, 2H), 3.37 (br s, 1H).

Part C:

To a solution of **2310** (9.0 g, 47.86 mmol) in toluene (40 mL) was added PBr_3 (5 mL, 52.6 mmol) dropwise. After the completion of addition, the mixture was stirred at 100 °C for 2 h. It was cooled to room temperature; the solid was

collected by filtration to afford **2311** as a yellow solid (HBr salt, 14.83 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (br, 1H), 8.66 (d, *J* = 1.8 Hz, 1H), 8.06 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.19 (dd, *J* = 8.3, 0.9 Hz, 1H), 4.67 (s, 2H).

Part D:

To a solution of **2311** (14.83 g, 44.7 mmol) in DMF at 0 °C was slowly added Cs_2CO_3 (29.1 g, 89.4 mmol) and potassium phthalimde (9.1 g, 49.2 mmol). The reaction mixture was allowed to stir at room temperature for 6h after which the solvent was evaporated to dryness. The resulting solid was washed with H_2O. The solid cake was recrystallized in hot EtOH, affording compound **2312** (7.64 g, 54%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, *J* = 1.9 Hz, 1H), 8.00 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.90-7.83 (m, 4H), 7.41 (d, *J* = 7.8 Hz, 1H), 4.88 (s, 2H).

Part E:

A mixture of $Pd(OAc)_2$ (45 mg, 0.2 mmol), 2-bis(tert-butyl)phosphino-biphenyl (120 mg, 0.4 mmol), compound **2312** (3.17 g, 10 mmol), 2-trifluoromethoxyphenyl boronic acid (2.47 g, 12 mmol) and KF (2.1 g, 36 mmol) was charged into a 250-mL round bottom flask. Then THF (30 mL) was added under argon, and the reaction mixture was allowed at stir at 50 °C overnight, after which it was cooled to room temperature, filtered through celite and concentrated. Flash column chromatography on silica gel (EtOAc/hexane (5:95) provided compound **2313** (3.27 g, 82%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 1.5 Hz, 1H), 7.91-7.89 (m, 2H), 7.77-7.73 (m, 3H), 7.44-7.34 (m, 5H), 5.08 (s, 2H).

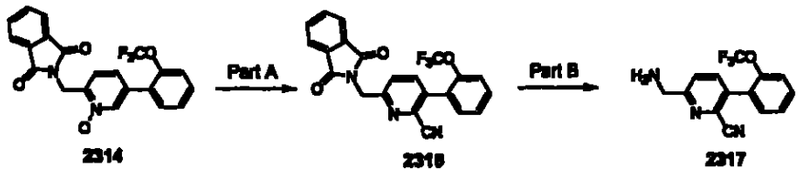
Part F:

Compound **2314** was prepared according to the same procedure as in Example 52M Part A. HPLC-MS t_R = 1.74 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{13}F_3N_2O_4$ 414.1, observed LCMS m/z 415.0 (M+H).

Part G:

To a solution of compound **2314** (210 mg, 0.51 mmol) in EtOH (10 mL) was added with hydrazine (0.5 mL). The solution was refluxed for 3 h, then cooled to room temperature. After removing the precipitate by filtration, the solution was concentrated. The resulting residue was extracted with Et_2O and concentrated, affording compound **2315** as a pale yellow oil (160 mg, 91%). HPLC-MS t_R = 1.74 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{11}F_3N_2O_2$ 284.1, observed LCMS m/z 285.1 (M+H).

Example 52N:



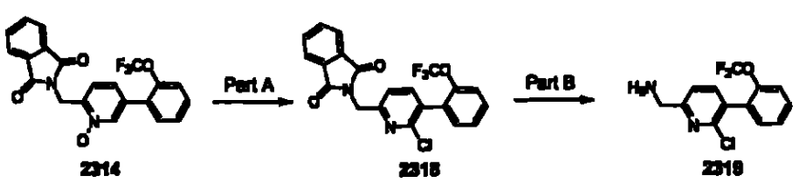
Part A:

To compound **2314** (200 mg, 0.48 mmol) in acetonitrile (1 mL) was added Et_3N (0.094 mL, 0.672 mmol) and Me_3SiCN (0.225 mL, 1.69 mmol) subsequently under argon. The reaction mixture was stirred at 80 °C for 48 h, after which it was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. Flash column chromatography (EtOAc/hexane 40:60) afforded compound **2316** (130 mg, 64%). HPLC-MS t_R = 2.06 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{12}F_3N_3O_3$ 423.1, observed LCMS m/z 424.0 (M+H).

Part B:

Compound **2317** was prepared using the procedure described in Example 52M Part G. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.47-7.42 (m, 4H), 4.12 (s, 2H). 1.98 (br s, 2H).

Example 52O:



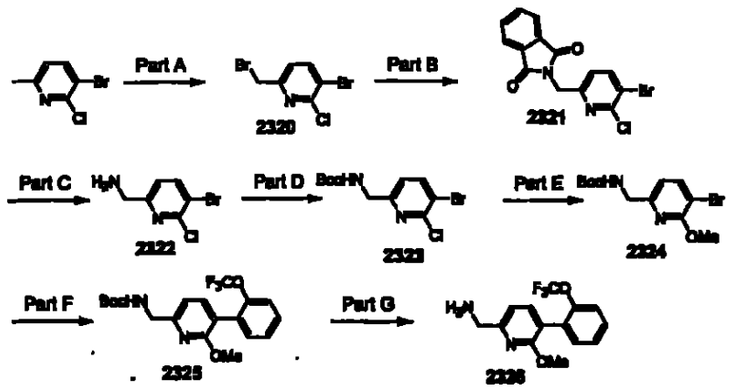
Part A:

Phosphorous trichloride (0.330 mL, 3.62 mmol) was added to a solution of **2314** (300 mg, 0.72 mmol) in $CHCl_3$ (1 mL). The reaction mixture was stirred at 60 °C overnight, after which it was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. Flash column chromatography (EtOAc/hexane 30:70) afforded **2318** (180 mg, 58%). HPLC-MS t_R = 2.33 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{12}ClF_3N_2O_3$ 432.1, observed LCMS m/z 433.0 (M+H).

Part B:

Compound **2319** was prepared using the procedure described in Example 52M Part G. HPLC-MS t_R = 1.26 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{10}ClF_3N_2O$ 302.0, observed LCMS m/z 303.0 (M+H).

Example 52P:



Part A:

3-Bromo-2-chloro-6-picoline (1.0 g, 4.84 mmol) and NBS (1.20 g, 6.78 mmol) were dissolved in CCl_4 (20 mL). The solution was briefly flushed with argon, then AIBN (16 mg, 0.097 mmol) was added. The mixture was stirred at room temperature overnight, after which the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane 5:95) providing compound **2320** as a white solid (1.28 g, 92%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 4.19 (s, 2H).

Part B:

Compound **2321** was prepared according to the procedure described in Example 52M, Part D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.92-7.84 (m, 4H), 7.41 (d, *J* = 8.0 Hz, 1H), 4.86 (s, 2H).

Part C:

Compound **2322** was prepared according to the procedure described in Example 52M, Part G. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 3.93 (s, 2H), 1.78 (br s, 2H).

Part D:

Compound **2322** (370 mg, 1.67 mmol) in THF (10 mL) was added dropwise into the solution of Boc_2O (437 mg, 2.0 mmol) in THF (10 mL), followed by DIEA (300 mL). The mixture was stirred at room temperature overnight and concentrated. Column chromatography on silica gel (EtOAc/hexane 20:80) provided compound **2323** (450 mg, 84%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 5.35 (br s, 1H), 4.37 (d, *J* = 5.9 Hz, 2H), 1.47 (s, 9H).

Part E:

Sodium (4 pellets) was dissolved in MeOH (15 mL). The mixture was stirred at room temperature for 10 min until all the sodium had reacted. To this solution was added compound **2323** (450 mg, 1.4 mmol) in MeOH (5 mL) via syringe. The reaction mixture was stirred at 60 °C for 48 h and concentrated. The residue was dissolved with EtOAc and 1N NH_4Cl solution, washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (SiO_2, EtOAc/hexane 20:80) afforded compound **2324** as a white solid (350 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.3 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 5.26 (br s, 1H), 4.32 (d, *J* = 5.1 Hz, 2H), 4.02 (s, 3H), 1.48 (s, 9H).

Part F:

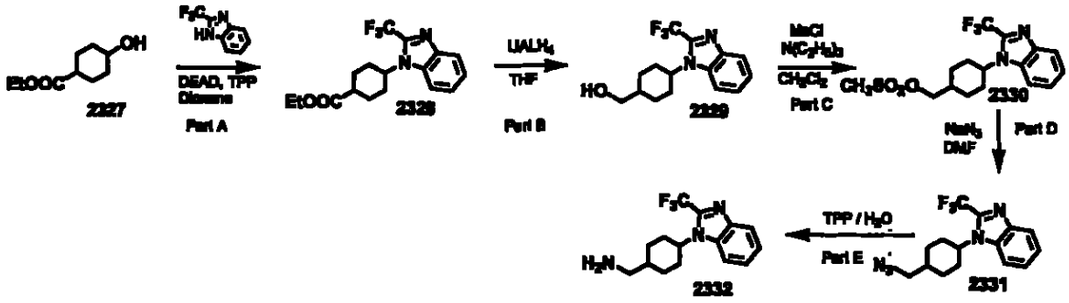
Compound **2325** was prepared according to the same procedure as in Example 52M Part E for the Suzuki coupling. HPLC-MS t_R = 2.35 min (UV_{254}

nm); mass calculated for formula $C_{19}H_{21}F_3N_2O_4$ 398.2, observed LCMS m/z 399.1 (M+H).

Part G:

Compound **2325** was deprotected with TFA in CH_2Cl_2. HPLC-MS t_R = 1.12 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{13}F_3N_2O_2$ 298.1, observed LCMS m/z 299.0 (M+H).

Example 52Q:



Part A:

Ethyl-4-hydroxycyclohexylcarboxylate (2327) (cis/trans mixture) (4.3 g, 25 mmol), 2-trifluoromethylbenzimidazole (4.65 g, 25 mmol), and triphenylphosphine (9.8 g, 37.5 mmol) were dissolved in dioxane (60 mL). The resulting solution was treated with diethyldiazodicarboxylate (6.5 g, 37.5 mmol), dropwise, over a period of 1h and stirred for 16h. The reaction mixture was diluted with ethyl acetate (200 mL) and washed in sequence with water (2 X 100 mL) and brine (1 X 100 mL). The organics were dried and concentrated to yield a crude which was subjected to silica-gel column chromatography (10% ethyl acetate/hexane) to yield pure **2328** (0.2 g, 0.6 mmol).

Part B:

$LiAlH_4$ was added to dry THF (40 mL) and the mixture was then cooled to 0 °C. Then ester **2328** (0.2 g, 0.6 mmol) in THF (5 mL) was added to the mixture dropwise. The reaction mixture was allowed to warm to ambient temperature and stirred for 48 h, then cooled back to 0 °C and quenched by the sequential addition of 1 mL of water, 2 mL of 0.5 N NaOH, and 1 mL of water. The resulting mixture was stirred vigorously for 2 h and then filtered

through Celite. The filtrate was concentrated to yield pure **2329** as an oil (0.2 g, 0.6 mmol).

Part C:

Alcohol **2329** (0.2 g, 0.6 mmol) and triethylamine (0.18 g, 1.8 mmol) were dissolved in CH_2Cl_2 (200 mL) and cooled to 0 °C. The cooled solution was stirred, and CH_3SO_2Cl (as a CH_2Cl_2 solution; 0.2 g, 1.8 mmol, 5 mL CH_2Cl_2) was added dropwise, and the stirring was continued for 24 h. The reaction mixture was then washed two times with 50 mL of water and two times with 50 mL of brine. The organic and aqueous phases were separated, and the organic phase was dried, and concentrated to provide pure product **2330** as an oil (0.21 g).

Part D:

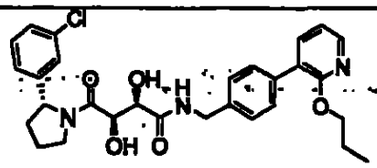
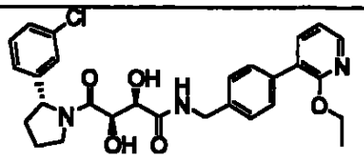
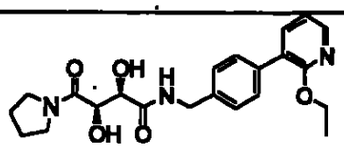
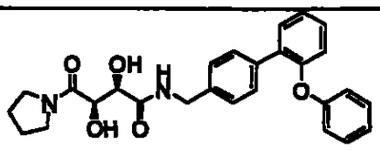
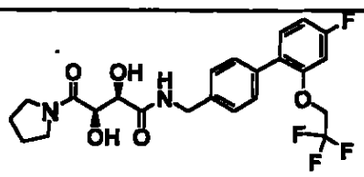
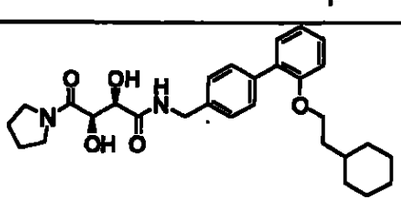
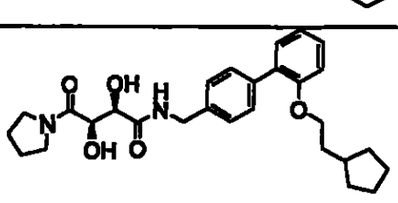
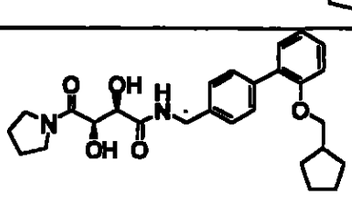
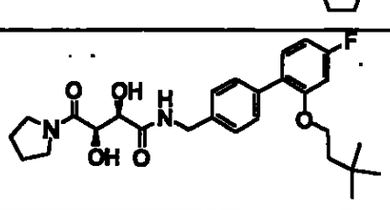
The mesylate **2330** was dissolved in DMF (10 mL) and treated with NaN_3 (0.23 g, 1.8 mmol), and the mixture was stirred vigorously for 36-72 h. The reaction mixture was then diluted with 100 mL water and extracted with ethyl acetate (2 x 100 mL). The organic phases were combined, dried, and concentrated to yield pure azide **2331** (0.19 g, 87%).

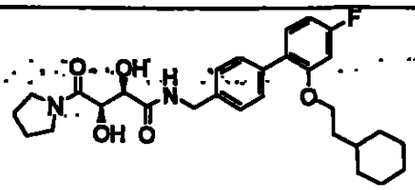
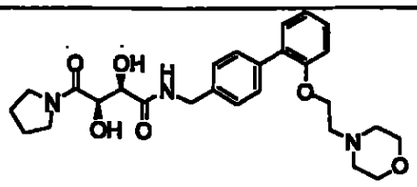
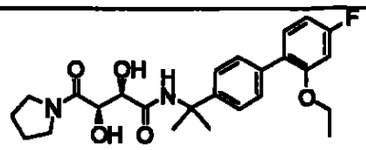
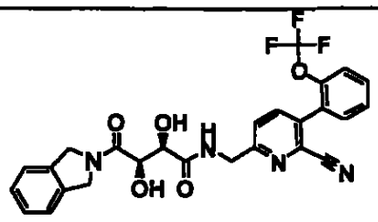
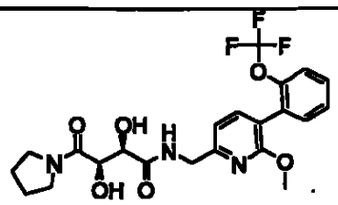
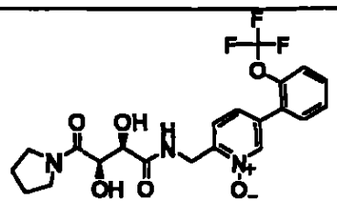
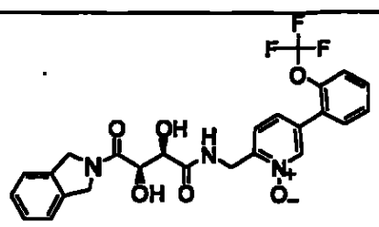
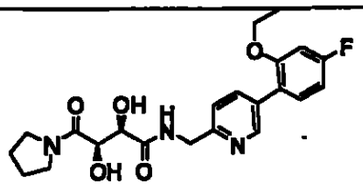
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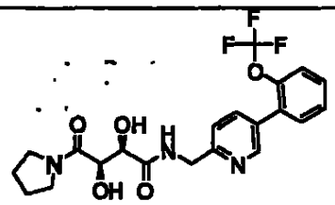
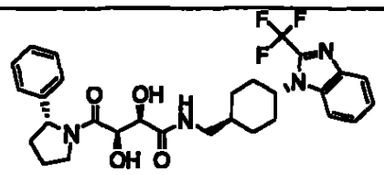
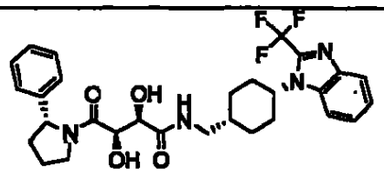
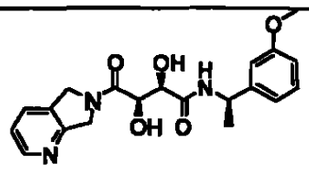
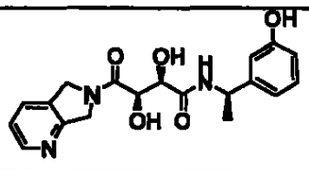
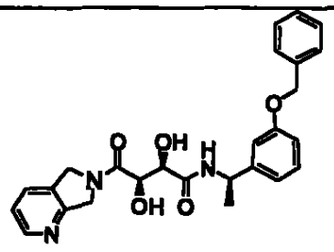
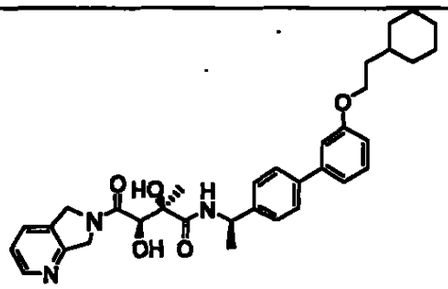
The azide **2331** (0.19 g, 0.6 mmol)) and triphenylphosphine (0.15 g, 0.6 mmol) were dissolved in 5 mL of THF, and then water (0.6 mL, 33.3 mmol) was added. The resulting mixture was stirred vigorously for 16-24 h. The solvent was removed and the crude amine **2332** was taken to the next step without further purification.

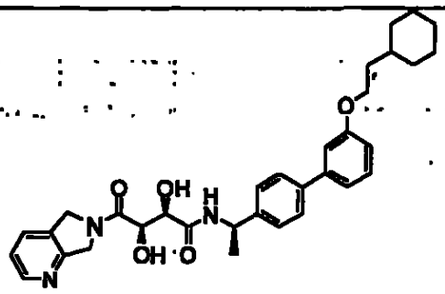
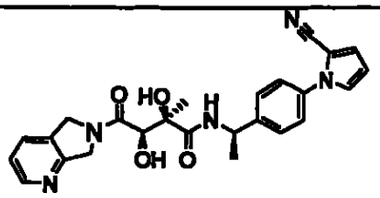
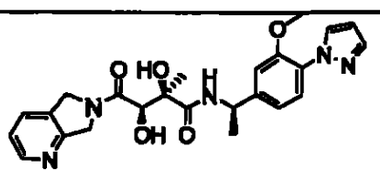
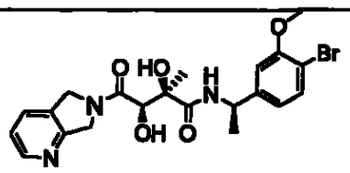
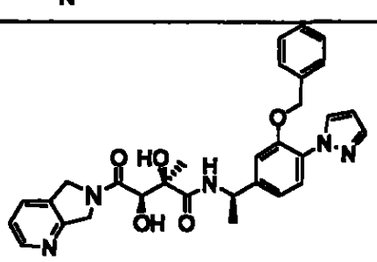
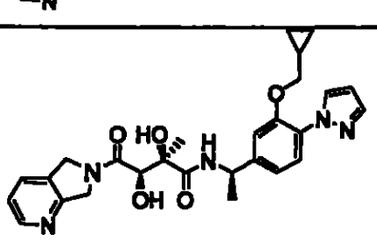
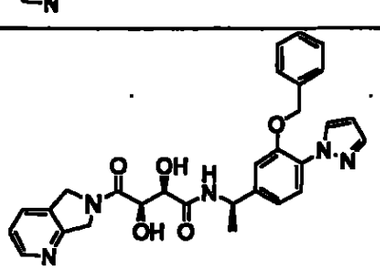
The following compounds were prepared using previously described procedures.

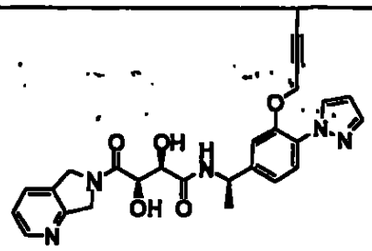
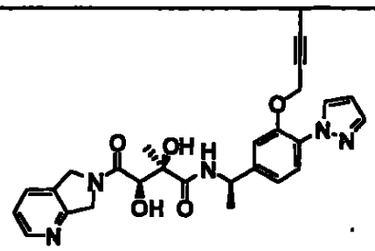
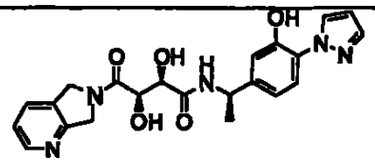
Compound #	Structure	Exact mass	MS m/z (M+H)

2333		537.2	538.1
2334		523.2	524.1
2335		413.2	414.2
2336		460.2	461.0
2337		484.2	485.2
2338		494.3	495.2
2339		480.3	481.1
2340		466.3	467.2
2341		486.3	487.2

2342		512.3	513.2
2343		497.3	498.2
2344		458.2	459.2
2345		526.2	527.0
2346		483.2	484.0
2347		469.2	470.0
2348		517.2	518.0
2349		431.2	432.1

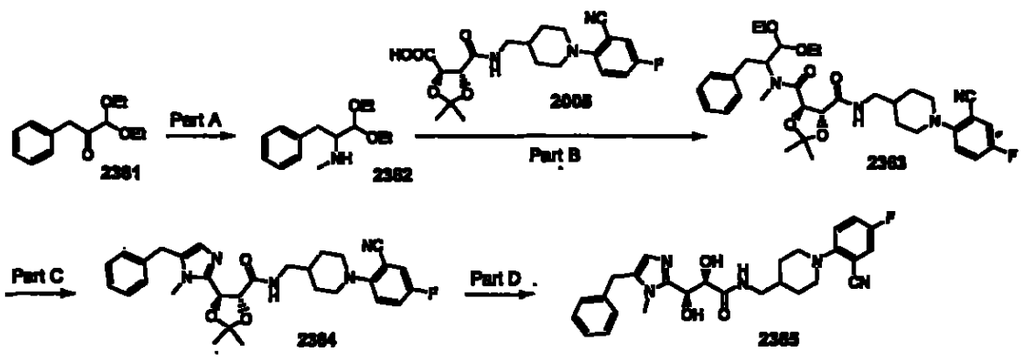
2350		453.2	454.1
2351		558.2	559.1
2352		558.2	559.1
2306		385.2	386.1
2307		371.2	372.1
2308		461.2	462.1
2353A		571.3	572.3

2353B		557.3	558.1
2354		459.2	460.1
2355		465.2	466.3
2356		477.1	478.3
2357		541.2	542.3
2358		505.2	506.3
2304		527.2	528.3

2359		489.2	490.3
2360		503.2	504.3
2305		437.2	438.1

Example 53:

Example 53A:



Part A:

Compound **2361** was prepared using procedures described in Adamczyk, M. et al. *Synth. Commun.* 2002, *32*, 3199-3205.

According to a modification of a procedure by Neidigh, K. A. et al. *(J. Chem. Soc. Perkin Trans. 1* **1998**, 2527-2531) a mixture of ketone **2361** (1.56 g, 7 mmol), titanium (IV) isopropoxide (4.1 mL, 14 mmol), methylamine hydrochloride (0.94 g, 14 mmol) and triethylamine (1.95 mL, 14 mmol) in ethanol (15 mL) was stirred at rt overnight. Then sodium borohydride (0.4 g, 10.5 mmol) was added and the resulting mixture was stirred at rt for 8 h. The reaction mixture was then poured into aqueous ammonium hydroxide (40 mL), the resulting white inorganic precipitate was filtered off, and washed several times with dichloromethane. The organic layer was separated, and the aqueous phase was extracted with dichloromethane. Combined dichloromethane extracts were washed with brine, concentrated and chromatographed (SiO_2, 5% methanol/dichloromethane) to give **2362** (1.03 g, 62%). ^{1}H NMR (400 Mhz, $CDCl_3$) δ 7.30-7.17 (m, 5H), 4.31-4.30 (d, 1H), 3.78-3.62 (m, 2H), 3.57-3.47 (m, 2H), 2.97-2.70 (m, 3H), 2.43 (s, 3H), 1.27-1.20 (m, 6H).

Part B:

Compound **2005** was prepared using procedures described in Example 27. Compound **2363** was prepared using the coupling conditions described in Example 1. HPLC-MS t_R = 2.42 min ($UV_{254\ nm}$); mass calculated for formula C34H45FN4O6 624.3, observed LCMS m/z 625.2 (M+H).

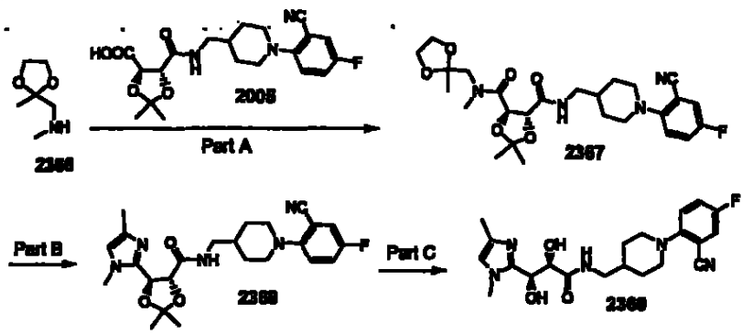
Part C:

Compound **2364** was prepared using the cyclization conditions described in Example 29. HPLC-MS t_R = 1.66 min ($UV_{254\ nm}$); mass calculated for formula C30H34FN5O3 531.3, observed LCMS m/z 532.2 (M+H).

Part D:

Compound **2364** was deprotected using procedures described in Example 29. Purification by prep-LC and conversion to a hydrochloric salt afforded **2365** as an off-white solid. HPLC-MS t_R = 3.54 min (10 min; $UV_{254\ nm}$); mass calculated for formula C27H30FN5O3 491.2, observed LCMS m/z 492.1 (M+H).

Example 53B:



Part A:

Compound **2366** was prepared using procedures described in Waldvogel, E. et al. *Helv. Chim. Acta.* **1997**, *80*, 2084-2099.

Compound **2367** was prepared using the coupling conditions described in Example 1. HPLC-MS t_R = 1.88 min ($UV_{254\ nm}$); mass calculated for formula C26H35FN4O6 518.2, observed LCMS m/z 519.2 (M+H).

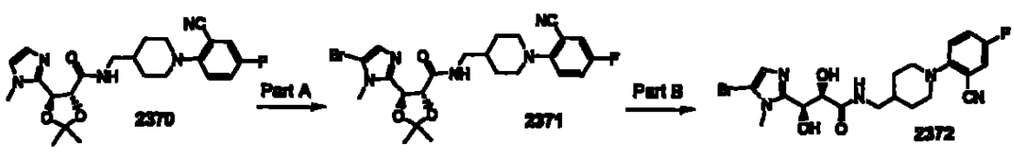
Part B:

Compound **2368** was prepared using the cyclization conditions described in Example 29. HPLC-MS t_R = 1.40 min ($UV_{254\ nm}$); mass calculated for formula C24H30FN5O3 455.2, observed LCMS m/z 456.1 (M+H).

Part C:

Compound **2368** was deprotected using procedures described in Example 29. Purification by prep-LC and conversion to a hydrochloric salt afforded **2369** as an off-white solid. HPLC-MS t_R = 2.99 min (10 min; $UV_{254\ nm}$); mass calculated for formula C21H26FN5O3 415.2, observed LCMS m/z 416.2 (M+H).

Example 53C:



Part A:

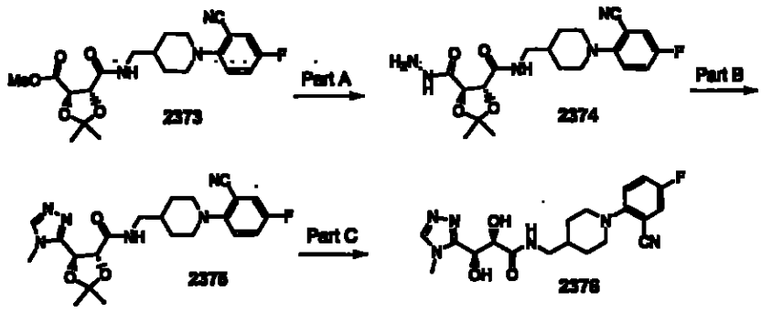
Compound **2370** was prepared using previously described procedures in Example 29. HPLC-MS t_R = 1.30 min ($UV_{254\ nm}$); mass calculated for formula C23H28FN5O3 441.2, observed LCMS m/z 442.1 (M+H).

According to a modification of a procedure by Miller, R. D. et al. *(Chem. Mater.* **1994**, *6*, 1023-1032) to an ice cold solution of compound **2370** (104 mg, 0.23 mmol) and pyridine (0.039 mL, 0.48 mmol) in dichloromethane (3 mL) was added dropwise a solution of bromine (0.016 mL, 0.31 mmol) in dichloromethane (1 mL) and the resulting solution was stirred at 0 °C for 20 min. The reaction mixture was quenched with 10% sodium thiosulfate solution, and extracted with dichloromethane. Combined organic extracts were dried, concentrated and chromatographed (SiO_2, gradient elution 50% to 80% ethyl acetate/hexane, ethyl acetate followed by 5% methanol/ethyl acetate) to give **2371** as a white solid (35 mg, 37% based on reacted starting material). HPLC-MS t_R = 1.94 min ($UV_{254\ nm}$); mass calculated for formula C23H27BrFN5O3 519.1, observed LCMS m/z 520.0 (M+H).

Part B:

Compound **2371** was deprotected using procedures described in Example 29. Purification by prep-LC and conversion to a hydrochloric salt afforded **2372** as a white solid. HPLC-MS t_R = 3.1 min (10 min; $UV_{254\ nm}$); mass calculated for formula C20H23BrFN5O3 479.1, observed LCMS m/z 480.0 (M+H).

Example 53D:



Part A:

Compound **2373** was prepared using previously described procedures in Examples 1 and 27.

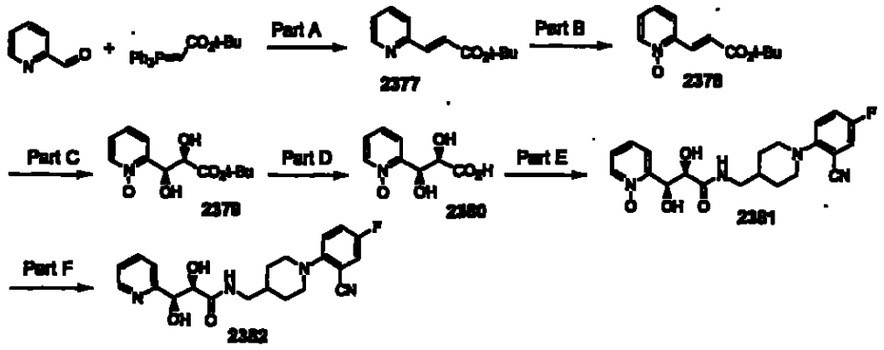
To a solution of **2373** (300 mg, 0.71 mmol) in methanol (7 mL) was added hydrazine monohydrate (0.35 mL; 7.1 mmol) and the resulting mixture was heated at 70 °C in a sealed tube overnight. The mixture was then cooled to rt, concentrated, diluted with ethyl acetate, washed with water, brine and concentrated to give **2374** (220 mg, 73%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.24 (m, 1H), 7.22-7.17 (m, 1H), 7.00 (t, 1H, NH), 6.99-6.96 (m, 2H), 4.62-4.57 (dd, 2H), 3.51-3.48 (d, 2H), 3.38-3.24 (m, 2H), 2.80-2.74 (m, 2H), 1.88-1.84 (d, 2H), 1.79-1.69 (m, 1H), 1.61-1.50 (m, 2H), 1.53 (s, 3H), 1.52 (s, 3H). HPLC-MS t_R = 1.49 min ($UV_{254\ nm}$); mass calculated for formula C20H26FN5O4 419.2 observed LCMS m/z 420.1 (M+H).

Part B:
According to a modification of a procedure by Stocks, M. J. et al. *(Org. Lett.* **2004**, *17*, 2969-2971) to a solution of hydrazide **2374** (110 mg, 0.26 mmol) in acetonitrile (1 mL) was added N,N-dimethylformamide dimethyl acetal (0.035 mL; 0.26 mmol) and the mixture was heated at 50 °C for 50 min. Then methylamine (0.18 mL of 2 M solution in THF, 0.36 mmol) was added, followed by acetic acid (1 mL) and the resulting mixture was heated at 80 °C overnight. The reaction mixture was then concentrated and chromatographed (SiO_2, 9:1:90 methanol:triethylamine:dichloromethane) to give **2375**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.27-7.24 (m, 1H), 7.21-7.18 (m, 1H), 7.02-6.97 (m, 1H), 6.92 (t, 1H, NH), 5.48-5.37 (dd, 2H), 3.51-3.47 (m, 2H), 3.36-3.23 (m, 2H), 2.80-2.74 (m, 2H), 1.88-1.81 (m, 2H), 1.76-1.70 (m, 1H), 1.58-1.54 (m, 2H), 1.58 (s, 3H), 1.43 (s, 3H). HPLC-MS t_R = 1.58 min ($UV_{254\ nm}$); mass calculated for formula C22H27FN6O3 442.2 observed LCMS m/z 443.2 (M+H).

Part C:
Compound **2375** was deprotected with 4 M HCl in dioxane (3 mL) and water (0.3 mL) at 55 °C for 1 hour. Purification by prep-LC and conversion to a hydrochloric salt afforded **2376** as an off-white solid (20 mg). HPLC-MS t_R =

1.23 min ($UV_{254\ nm}$); mass calculated for formula C19H23FN6O3 402.2, observed LCMS m/z 403.1 (M+H).

Example 53E:



Part A:

(*tert*-Butoxycarbonylmethylene)triphenylphosphorane (15.1 g, 40 mmol) was added portionwise to a solution of 2-pyridinecarboxaldehyde (4.28 g, 40 mmol) in THF (60 mL) at 0 °C over a period of 5 min. The reaction mixture was allowed to stir at room temperature overnight. The solution was concentrated, extracted with hexane (120 mL). After filtration to remove the solid, the filtrate was concentrated to give a yellow oil. Purification by flash chromatography on silica gel (EtOAc/hexane 15:85) yielded the desired product **2377** (4.5 g, 55%) as slightly yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.9 Hz, 1H), 7.69 (td, *J* = 6.6, 1.7 Hz, 1H), 7.58 (d, *J* = 15.5 Hz, 1H), 7,41(dd, *J* = 7.8, 0.6 Hz, 1H), 7.23 (m, 1H), 6.82 (d, *J* = 16.1 Hz, 1H), 1.54 (s, 9H).

Part B:

Compound **2377** (4.5 g, 21.92 mmol) was dissolved in dry DCM (40 mL) and cooled to 0 °C, then 77% *m*-CPBA (5.41 g, 24.12 mmol) was added in three portions over 5 min. The reaction mixture was allowed to stir overnight at room temperature. It was poured into saturated aqueous $NaHCO_3$ (100 mL) and the product was extracted into DCM. The organic layer was washed with water and brine and dried (Na_2SO_4). Flash chromatography on silica gel (MeOH/DCM 5:95) afforded compound **2378** as a pale yellow solid (3.2 g,

66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (m, 1H), 7.96 (d, *J* = 16.0 Hz, 1H), 7.51 (m, 1H); 7.22 (m, 1H); 6.85 (d, *J* = 16.0 Hz, 1H); 1.55 (s, 1H).

Part C:

A 250-mL round bottom flask filled with H_2O (30 mL) was cooled to 0 °C in an ice bath. Reagents $K_3[Fe(CN)_6]$ (9.88 g, 30 mmol), K_2CO_3 (6.91 g, 50 mmol), and $MeSO_2NH_2$ (0.95 g, 10 mmol) were subsequently added, followed by $K_2[OsO_2(OH)_4]$ (14.7 mg, 0.04 mmol), (DHQ)PHAL (233.7 mg, 0.3 mmol), compound **2378** (2.21 g, 10 mmol) and *t*-BuOH (20 mL). The reaction mixture was stirred at 0 °C for 24 h. The solid was filtered off and washed with excess EtOAc. The organic layer was separated. The aqueous solution was concentrated to dryness, and the resulting solid was extracted with CH_2Cl_2. The above EtOAc and CH_2Cl_2 solutions were combined and concentrated. Flash chromatography on silica gel (MeOH/CH_2Cl_2 10:90) provided compound **2379** as a white solid (2.2 g, 86%). Recrystallization from EtOAc afforded analytically pure material (1.51 g, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.24 (d, *J* = 6.5 Hz, 1H), 7.54 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.30 (m, 1H), 5.41 (d, *J* = 2.6 Hz, 1H), 4.69 (d, *J* = 2.7 Hz, 1H), 1.54 (s, 9H).

Part D:

Compound **2379** (1.0 g, 3.9 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (4 mL). The solution was allowed to stir at room temperature for 2 h, and then concentrated to afford compound **2380** as a white solid (750 mg, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (dd, *J* = 6.3, 1.2 Hz, 1H), 7.54 (dd, *J* = 6.4, 2.2 Hz, 1H), 7.37 – 7.32 (m, 2H), 5.38 (d, *J* = 2.1 Hz, 1H), 4.62 (d, *J* = 2.3 Hz, 1H).

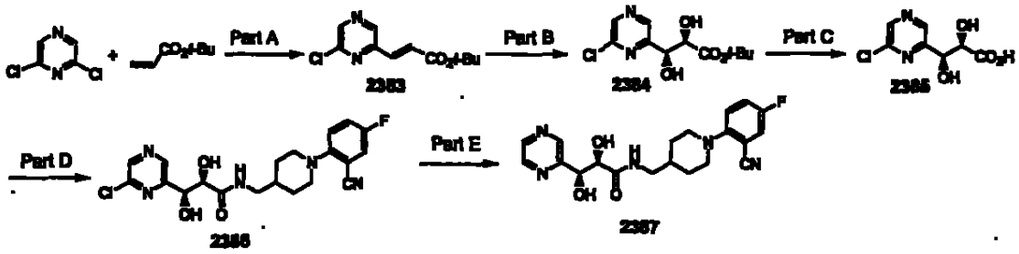
Part E:

Compound **2381** was prepared using the coupling conditions described in Example 1. Purification by prep-LC afforded **2381** as a white solid (63 mg). HPLC-MS t_R = 1.30 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{23}FN_4O_4$, 414.2, observed LCMS m/z 415.1 (M+H).

Part F:

To compound **2381** (25 mg, 0.06 mmol) in EtOH (5 mL) was added with saturated NH_4Cl aqueous solution (5 mL) and indium (16.6 mg, 0.072 mmol). The reaction mixture was allowed to reflux for 24 h. After cooling to room temperature, it was concentrated and extracted with DCM. The DCM extract was filtered and concentrated. Purification by column chromatography on silica gel (Et_3N / MeOH / EtOAc 5:5:95) afforded compound **2382** as a white solid (8.5 mg, 35%). HPLC-MS t_R = 1.16 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{23}FN_4O_3$, 398.2, observed LCMS m/z 399.1 (M+H).

Example 53F:



Part A:

Under argon, to a mixture of $Pd_2(dba)_3$ (384 mg, 0.42 mmol), tri(t-butyl)phosphinium tetrafluoroborate (243 mg, 0.84 mmol), and 2,6-dichloropyrizine (5.0 g, 33.56 mmol) were added sequentially NMP (10 mL), *t*-butyl acrylate (2.46 mL, 16.78 mmol) and Et_3N (3.51 mL, 25.17 mmol). The reaction mixture was allowed to stir at 50 °C for 12 h. After cooling to room temperature, the mixture was diluted with EtOAc and water, filtered through a pad of celite, washed with water, brine, dried (Na_2SO4), and concentrated. Flash column chromatography on silica gel (EtOAc / hexane 15:85) afforded compound **2383** as a pale yellow solid (2.32 g, 57%). ^1H NMR (400 MHz, acetone-d_6) δ 8.84 (s, 1H), 8.68 (s, 1H), 7.61 (d, *J* = 15.7 Hz, 1H), 6.92 (d, *J* = 15.5 Hz, 1H), 1.55 (s, 9H).

Part B:

A 50-mL round bottom flask filled with H_2O (9 mL) was cooled to 0 °C in an ice bath. Reagents $K_3[Fe(CN)_6]$ (1.29 g, 3.93 mmol), K_2CO_3 (905 mg, 6.55

mmol), and $MeSO_2NH_2$ (124.6 mg, 1.31 mmol) were subsequently added, followed by $K_2[OsO_2(OH)_4]$ (2.0 mg, 0.005 mmol), (DHQ)PHAL (31.0 mg, 0.04 mmol), compound **2383** (315 mg, 1 mmol) and *t*-BuOH (6 mL). The reaction mixture was stirred at 0 °C for 36 h. Then EtOAc and H_2O were added to dissolve the solid. The organic layer was separated and the aqueous layer was back extracted with EtOAc. The EtOAc extracts were combined, washed with water and brine, dried (Na_2SO_4), and concentrated. Flash chromatography on silica gel (EtOAc/hexane 40:60) provided compound **2384** as a white solid (285 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.54 (s, 1H), 5.13 (d, *J* = 2.3 Hz, 1H), 4.55 (d, *J* = 2.9 Hz, 1H), 1.55 (s, 9H). HPLC-MS t_R = 1.73 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{15}ClN_2O_4$, 274.1, observed LCMS m/z 275.0 (M+H).

Part C:

Compound **2384** (285 mg, 1.04 mmol) in dioxane (5 mL) was treated with 4N HCl in dioxane (5 mL). After stirring at room temperature for 2 h, the solution was concentrated to afford compound **2385** (200 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.66 (s, 1H), 5.00 (d, *J* = 2.6 Hz, 1H), 4.31 (d, *J* = 2.2 Hz, 1H), 1.55 (s, 9H).

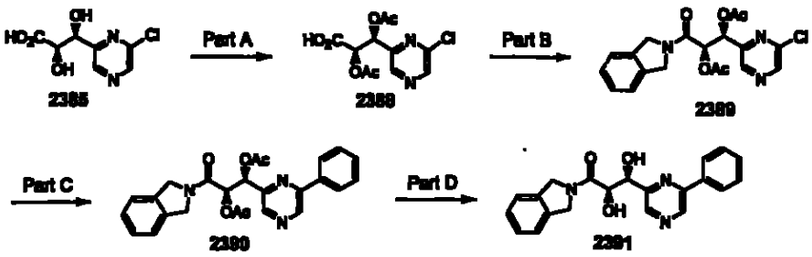
Part D:

Compound **2386** was prepared using the coupling conditions described in Example 1. Purification by prep-LC afforded **2386** as a white solid (42 mg). HPLC-MS t_R = 1.55 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{21}ClFN_5O_3$, 433.1, observed LCMS m/z 434.0

Part E:

Compound **2386** (20 mg, 0.046 mmol) along with 10% Pd/C (20 mg) in EtOAc (10 mL) was stirred at room temperature for 12 h under hydrogen atmosphere (1 atm). The solution was filtered through celite and concentrated. Purification by prep-LC afforded **2387** as a white solid (15 mg, 81%). HPLC-MS t_R = 1.35 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{22}FN_5O_3$, 399.2, observed LCMS m/z 400.1

Example 53G:



Part A:

To compound **2385** (150 mg, 0.69 mmol) in acetic acid (2 mL) was added acetic anhydride (0.5 mL). The reaction mixture was stirred at room temperature for 2 h, and then concentrated. The residue was dissolved in EtOAc, washed with H_2O, brine, dried over Na_2SO_4, and concentrated, giving rise to compound **2388** as oily solid (180 mg, 86%). HPLC-MS t_R = 1.10 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{11}ClN_2O_6$ 302.0, observed LCMS m/z 303.0 (M+H).

Part B:

To compound **2388** (180 mg, 0.59 mmol) and HATU (269 mg, 0.71 mmol) in DMF (4 mL) was added isoindoline (84 mg, 0.71 mmol). The reaction mixture was stirred at room temperature for 12 h, and concentrated. The residue was dissolved with EtOAc and water, washed with saturated bicarbonate solution, and brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography on silica gel (EtOAc/hexane 60:40) afforded the desired product **2389** as a pale yellow solid (150 mg, 63%). ^1H NMR (400 MHz, CDCl3) δ 8.67 (s, 1H), 8.51 (s, 1H), 7.29 (m, 4H), 6.39 (d, *J* = 7.1 Hz, 1H), 5.93 (d, *J* = 6.7 Hz, 1H), 5.21 (d, *J* = 5.4 Hz, 1H), 5.05 (d, *J* = 4.1 Hz, 1H), 4.78 (d, *J* = 5.6 Hz, 1H), 4.52 (d, *J* = 4.7 Hz; 1H), 2.18 (s, 3H), 2.16 (s, 3H). HPLC-MS t_R = 1.70 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{18}ClN_3O_5$ 403.1, observed LCMS m/z 404.0 (M+H).

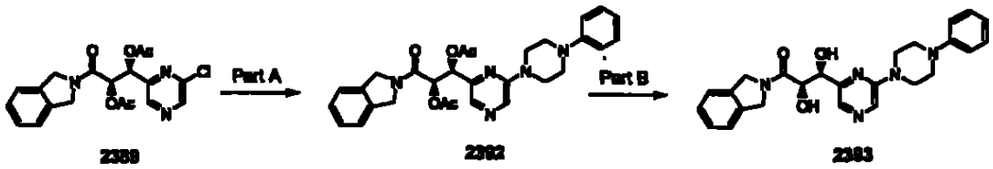
Part C:

A 4-mL vial was charged with $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol), tri(t-butyl)phosphonium tetrafluoroborate (1.5 mg, 0.0025 mmol), compound **2389** (20 mg, 0.05 mmol), phenylboronic acid (9.1 mg, 0.075 mmol) and potassium fluoride (13 mg, 0.225 mmol). Under argon, dioxane (1 mL) was added via syringe. The vial was sealed with a Teflon coated screw cap and placed into an oil bath preheated to 80 °C. The reaction mixture was allowed to stir at 80 °C for 12 h. LC-MS indicated the reaction was completed. After cooling to room temperature, the reaction mixture was filtered through celite with the aid of EtOAc. The filtrate was washed with saturated NaHCO3, brine, dried over Na2SO4, and concentrated. The resulting solid (21 mg) was used for next step without purification. HPLC-MS t_R = 1.89 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{23}N_3O_5$ 445.1, observed LCMS m/z 446.0 (M+H).

Part D:

Compound **2390** (21 mg) was deprotected using procedures described in Example 2. Purification by prep-LC afforded **2391** as an off-white solid (8.3 mg). HPLC-MS t_R = 4.02 min (10 min method) ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{19}N_3O_5$ 361.1, observed LCMS m/z 362.0 (M+H).

Example 53H:



2389 2392 2393

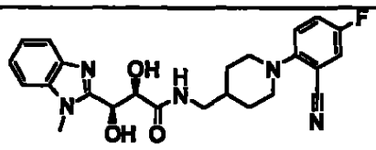
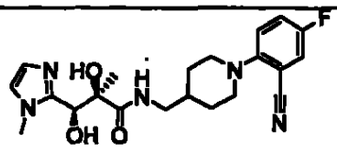
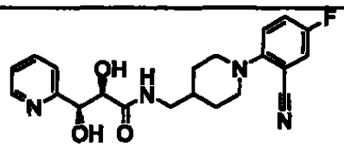
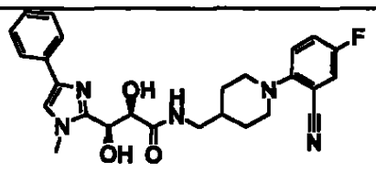
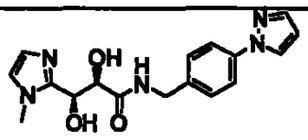
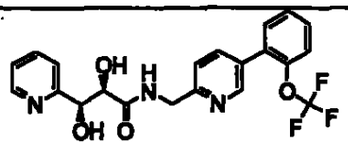
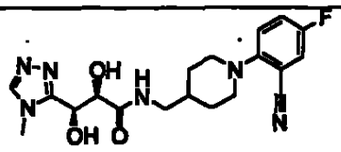
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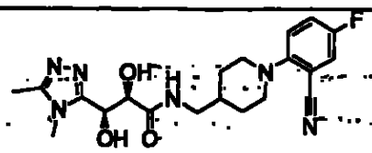
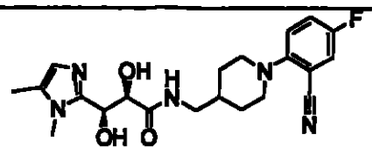
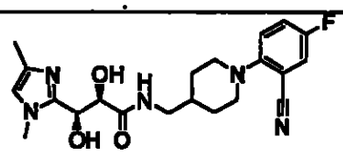
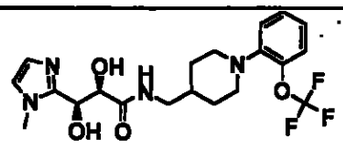
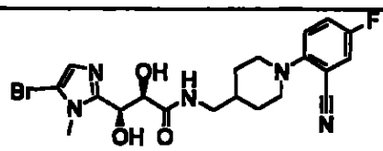
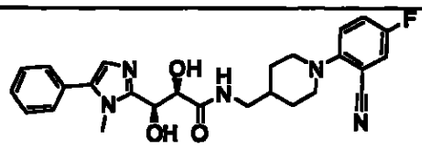
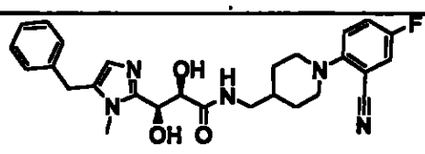
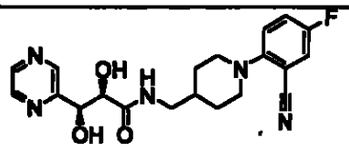
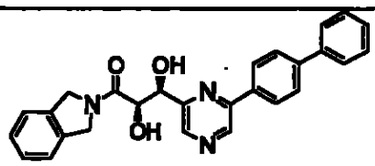
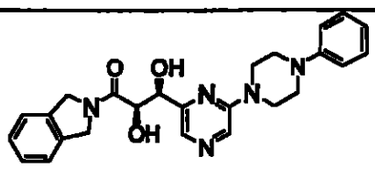
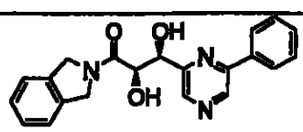
To compound **2389** (50 mg, 0.12 mmol) in NMP (1 mL) was added 4-N-phenylpipyzine (29 mg, 0.18 mmol) and DIEA (0.032 mL, 0.18 mmol). The reaction mixture was allowed to stir at 80 °C for 16 h. After cooling to room temperature, the solution was diluted with EtOAc, washed with water and brine, dried over Na2SO4, and concentrated. The resulting oily solid (52 mg) was utilized for next step without further purification. HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); mass calculated for formula $C_{29}H_{31}N_5O_5$ 529.2, observed LCMS m/z 530.2 (M+H).

Part B:

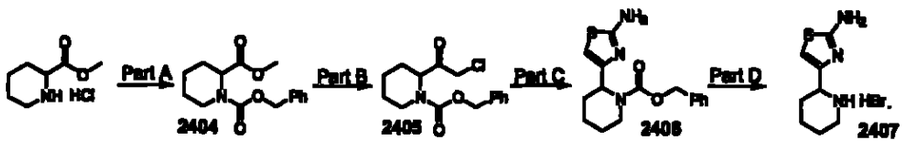
Compound **2392** (52 mg) was deprotected using procedures described in Example 2. Purification by prep-LC afforded **2393** as an off-white solid (15 mg). HPLC-MS t_R = 1.60 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{27}N_5O_3$ 445.2; observed LCMS m/z 446.1 (M+H).

The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2394		451.2	452.2
2395		415.2	416.2
2382		398.2	399.1
2396		477.2	478.2
2397		341.2	342.1
2398		433.1	434.0
2376		402.2	403.1

2399		416.2	417.1
2400		415.2	416.2
2369		415.2	416.2
2401		442.2	443.2
2372		479.1	480.0
2402		477.2	478.1
2365		491.2	492.1
2387		399.2	400.1
2403		437.2	438.0
2393		445.2	446.1
2391		361.1	362.0

Example 54:



Part A:

Methyl pipecolinate hydrochloride (2.0 g, 11 mmol) was dissolved in THF (20 mL) and saturated sodium bicarbonate (20 mL) and cooled in an ice bath. Benzyl chloroformate (1.5 mL, 11 mmol) was added dropwise and the reaction was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated sodium bicarbonate, water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 10% ethyl acetate/hexane to 15% ethyl acetate/hexane) afforded **2404** as a clear oil (2.9 g, 93%).

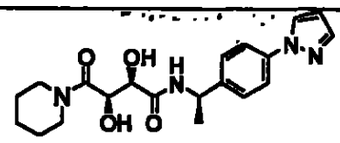
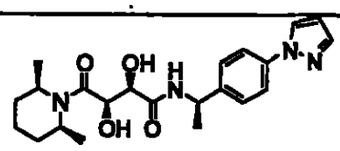
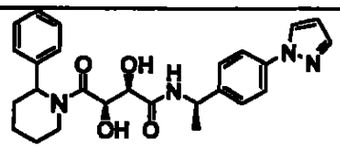
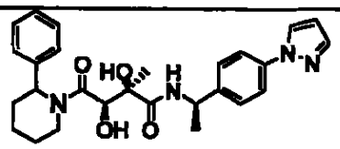
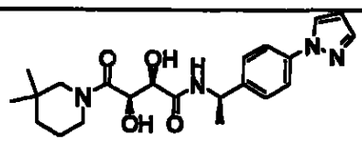
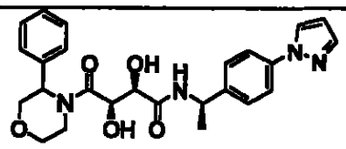
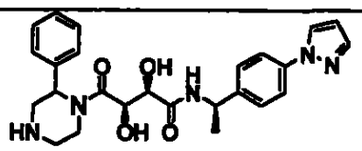
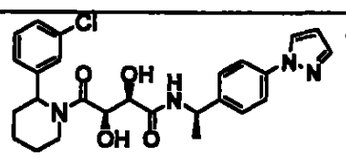
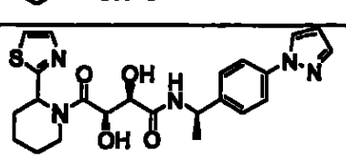
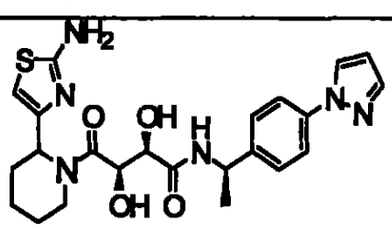
Part B and C:

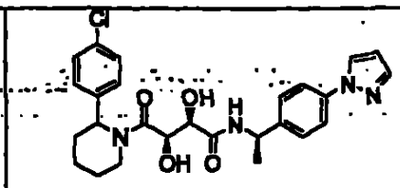
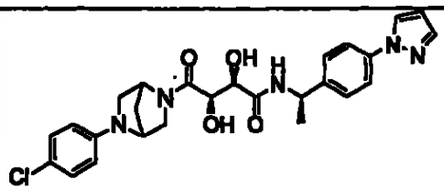
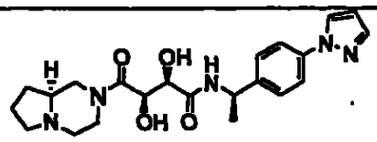
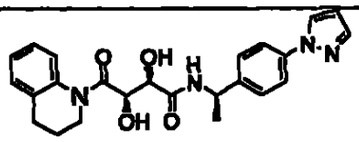
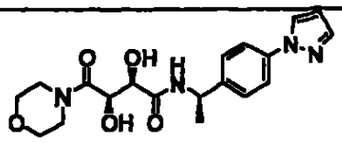
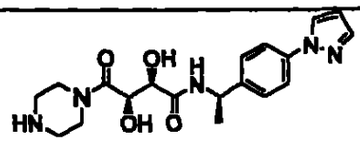
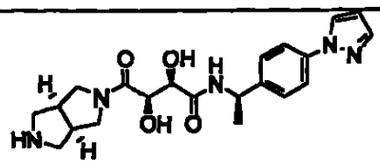
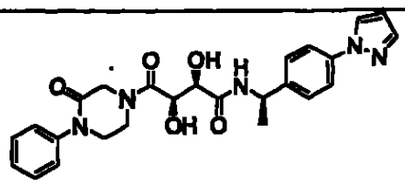
Compounds **2405** and **2406** were prepared following the procedures described in Example 10B part A and part B. Compound **2406**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 6.11 (s, 1H), 5.36 (m, 1H), 5.18 (s, 2H), 3.72 (m, 1H), 3.00 (m, 1H), 2.33 (m, 1H), 1.90 – 1.40 (m, 7H). HPLC-MS t_R = 1.34min ($UV_{254\ nm}$); Mass calculated for C16H19N3O2S 317.4, observed LSMS m/z 318.1 (M+H).

Part D:

Compound **2406** (75 mg, 0.24 mmol) was stirred in 30% HBr in acetic acid (2 mL) for 1 hour at room temperature. The solvent was evaporated and the residue was dissolved in water and lyophilized to afford **2407** (66 mg) as a red solid.

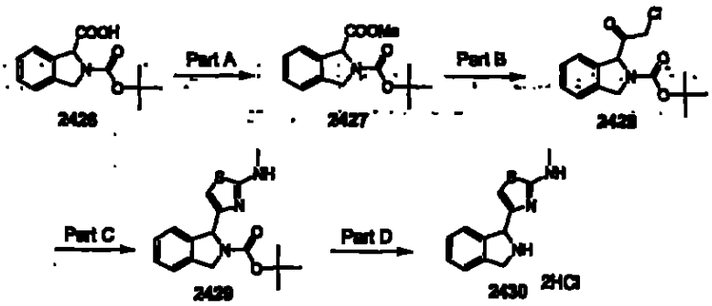
The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2408		386.2	387.1
2409		414.2	415.1
2410		462.2	463.1
2411		476.2	477.1
2412		414.2	415.1
2413		464.2	465.1
2414		463.2	464.2
2415		496.2	497.0
2416		469.2	470.0
2417		484.2	485.0

2418		496.2	497.0
2419		509.2	510.1
2420		427.2	428.2
2421		434.2	435.1
2422		388.2	389.1
2423		387.2	388.1
2424		413.2	414.1
2425		477.2	478.1

Example 55:

Example 55A:



Part A:

To an ice cold solution of acid **2426** (1.0 g, 3.8 mmol) in 1:1 methanol:toluene (10 mL) was added dropwise TMS-diazomethane (3.2 mL of 2 M solution in hexane, 6.4 mmol) and the resulting solution was stirred at rt for 1 h. The reaction mixture was concentrated, partitioned between ethyl acetate and water and extracted with ethyl acetate. The combined organic extracts were washed with saturated sodium bicarbonate solution, brine, dried and evaporated to give ester **2427** as an off-white solid (0.907 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.28 (m, 4H), 5.53-5.46 (dd, 1H), 4.86-4.69 (m, 2H), 3.77-3.75 (d, 3H), 1.54-1.49 (d, 9H).

Part B:

Chloroketone **2428** was prepared using procedures described in Example 10. ^{1}H NMR (400 MHz, CDCl3) δ 7.46-7.30 (m, 4H), 5.65-5.48 (d of d, 1H), 4.90-4.71 (m, 2H), 4.42-4.06 (m, 2H), 1.57-1.52 (d, 9H).

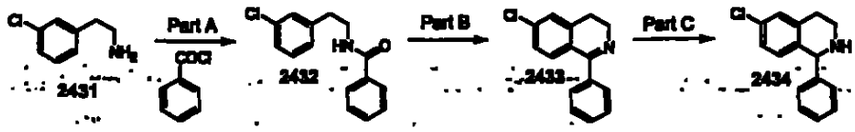
Part C:

Compound **2429** was prepared using procedures described in Example 10. HPLC-MS t_R = 1.51 min ($UV_{254\ nm}$); mass calculated for formula C17H21N3O2S 331.1, observed LCMS m/z 332.1 (M+H).

Part D:

Compound **2430** was prepared using procedures described in Example 10. HPLC-MS t_R = 0.80 min ($UV_{254\ nm}$); mass calculated for formula C12H13N3S 231.1, observed LCMS m/z 232.1 (M+H).

Example 55B:



Part A:

According to a modification of a procedure by Mach, U. R. et al. (*ChemBioChem* 2004, *5*, 508-518) to a mixture of 3-chlorophenethylamine **2431** (3.89 g, 25 mmol) and 2 M potassium hydroxide solution (35 mL) was added dropwise benzoyl chloride (3.48 mL, 30 mmol). Within minutes a white precipitate formed, it was filtered and washed thoroughly with water, dried (air) and recrystallized (ethanol) to give amide **2432** as a white solid (4.22 g, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (t, 1H, NH), 7.78-7.76 (d, 2H), 7.50-7.17 (m, 7H), 3.50-3.46 (m, 2H), 2.85 (t, 2H). HPLC-MS t_R = 1.81 min ($UV_{254\ nm}$); mass calculated for formula C15H14ClNO 259.1, observed LCMS m/z 260.0 (M+H).

Part B:

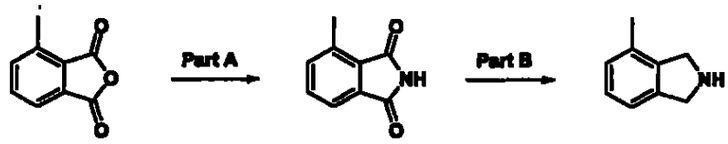
According to a modification of a procedure by Mach, U. R. et al. (*ChemBioChem* 2004, *5*, 508-518) to a mixture of amide **2432** (1.79 g, 6.9 mmol) and powder zinc chloride (3.29 g, 24.1 mmol) in toluene (30 mL) was added dropwise phosphorus oxychloride (4.4 mL, 48.3 mmol) and the mixture was heated at reflux for 2 h, during which time a polymer-like residue formed. The reaction mixture was cooled in an ice bath, quenched by the addition of 2 M sodium hydroxide solution, extracted and sonicated with dichloromethane (the residue dissolved). The combined dichloromethane extracts were concentrated to a solid residue, which was then triturated with THF. The resulting white solid was filtered and dried to give compound **2433** (1.23 g, 74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82-7.67 (m, 6H), 7.58-7.55 (dd, 1H), 7.41-7.39 (d, 1H), 3.98 (t, 2H), 3.23 (t, 2H). HPLC-MS t_R = 0.96 min ($UV_{254\ nm}$); mass calculated for formula C15H12ClN 241.1, observed LCMS m/z 242.1 (M+H).

Part C:

According to a modification of a procedure by Mach, U. R. et al. (*ChemBioChem* 2004, *5*, 508-518) to a solution of imine **2433** (760 mg, 3.14

mmol) in ethanol (50 mL) was added portionwise sodium borohydride (300 mg; 7.86 mmol) and the resulting mixture was heated at reflux overnight. The reaction mixture was cooled, quenched with water, concentrated, partitioned between ethyl acetate and water, and extracted with ethyl acetate. The combined organic extracts were dried and concentrated to give amine **2434** (418 mg, 55%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33-7.04 (m, 7H), 6.62-6.60 (d, 1H), 5.00 (s, 1H), 3.36-3.26 (m, 1H), 3.11-3.06 (m, 1H), 2.98-2.73 (m, 2H). HPLC-MS t_R = 1.14 min ($UV_{254\ nm}$); mass calculated for formula C15H14ClN 243.1, observed LCMS m/z 244.1 (M+H).

Example 55C:



2435 **2436** **2437**

Part A:

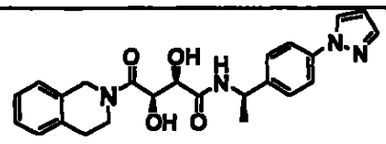
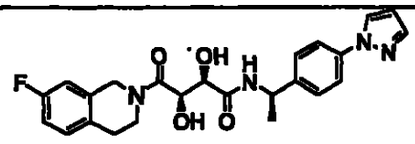
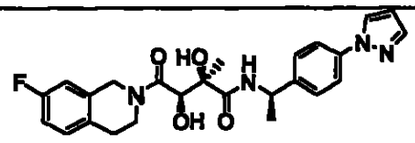
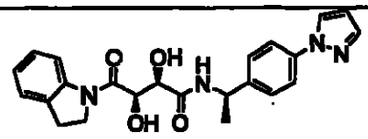
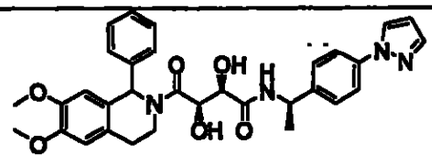
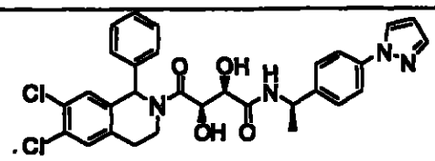
A mixture of compound **2435** (6 g, 36.5 mmol) and urea (1.95 g, 32.5 mmol) was heated over a sand bath at 350 °C for 30 minutes. The resulting black tar was cooled down to 100 °C and water (25 mL) was carefully added. This mixture was stirred for 1 hour. The solid was collected by filtration, dissolved in DMF (40 mL) and stirred with Darco (1 g) for 1 hour. The mixture was filtered and water (100 mL) was added to the filtrate to precipitate out a brown solid. The solid was collected by filtration and air dried. The the solid was dissolved in boiling MeOH (120 mL) with Darco (1 g). The mixture was filtered and the filtrate was concentrated to dryness. The residue was suspended in EtOAc and filtered to afford the desired compound **2436** as brown solid (2.5 g, 43%).

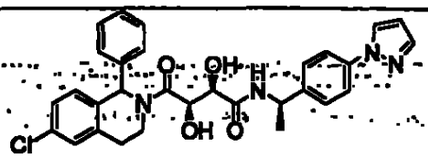
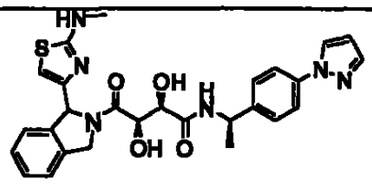
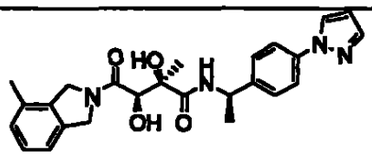
Part B:

Compound **2436** (1 g, 6.2 mmol) was added to a solution of 1M borane/THF (21 mL, 21 mmol) at 0 °C and the mixture was warmed to room temperature and then refluxed for 18 hours. The reaction mixture was cooled to room temperature and 6N HCl (50 mL) was added dropwise. The reaction mixture

was concentrated to remove THF and then cooled to 0 °C and sodium hydroxide pellets (13 g) were added carefully to the reaction mixture. The reaction mixture was extracted with CH_2Cl_2 (1 x 50 mL, 1 x 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 3% MeOH(NH_3)/CH_2Cl_2, followed by 5% MeOH(NH_3)/CH_2Cl_2) afforded the desired compound **2437** as tan solid (64 mg, 7.7%).

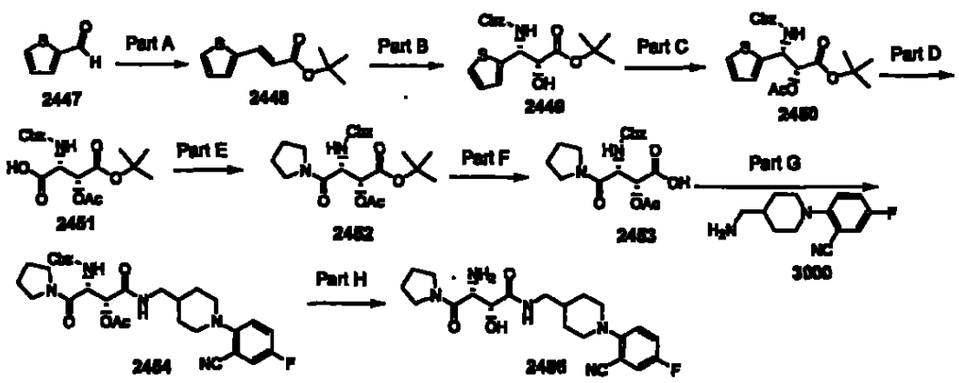
The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2438		434.2	435.1
2439		452.2	453.1
2440		466.2	467.0
2441		420.2	421.1
2442		570.2	571.1
2443		578.2	579.1

2444		544.2	545.0
2445		532.2	533.0
2446		448.2	449.1

Example 56:

Example 56A:



Parts A-D:

Compounds **2448-2451** were prepared according to the procedures in *Syn. Lett.* **1999**, 12, 1907-1910.

Part E:

Compound **2451** (200 mg, 0.52 mmol), HATU (260 mg, 0.68 mmol), pyrrolidine (0.052 mL, 0.624 mmol), and DIEA (0.1 mL) were dissolved in DMF (5 mL). The reaction mixture was stirred overnight at room temperature and then partitioned between ethyl acetate and water. The organic layers were washed with 1 M HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography

(SiO_2, 50% ethyl acetate/hexanes) afforded the desired product (200 mg). HPLC-MS t_R = 1.91 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{30}N_2O_7$ 434.21, observed LCMS m/z 435.1 (M+H).

Part F:

Compound **2452** (200 mg, 0.46 mmol) was dissolved in methylene chloride (4 mL) and trifluoroacetic acid (1 mL). The reaction mixture was stirred at room temperature for 4 hours. The solvent was evaporated and the material was used without further purification (160 mg). HPLC-MS t_R = 1.31 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{22}N_2O_7$ 434.21, observed LCMS m/z 379.1 (M+H).

Part G:

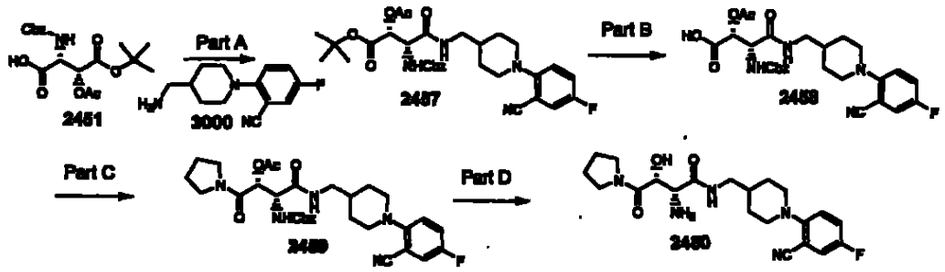
Compound **2453** (160 mg, 0.423 mmol), compound **3000** (prepared as described in Example 27A) (122 mg, 0.423 mmol), HATU (210 mg, 0.55 mmol), and DIEA (0.5 mL) were dissolved in DMF (10 mL). The reaction mixture was stirred overnight at room temperature and then partitioned between ethyl acetate and water. The organic layers were washed with 1 M HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes to 100% ethyl acetate) afforded the desired product (175 mg). HPLC-MS t_R = 1.94 min ($UV_{254\ nm}$); mass calculated for formula $C_{31}H_{38}FN_5O_8$ 593.2, observed LCMS m/z 594.2 (M+H).

Part H:

Compound **2454** (50 mg, 0.084 mmol) was dissolved in 7 M ammonia in MeOH (0.5 mL) and MeOH (2 mL) and stirred for 30 minutes. The solvent was removed under reduced pressure. The residue was dissolved in MeOH (5 mL) and acetic acid (0.3 mL) and Pd-C (100 mg) was added under an argon atmosphere. The reaction was stirred under a hydrogen atmosphere for 3 hours and then filtered through a pad of celite. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The combined organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. The residue

was dissolved in ethyl acetate (2 mL) and treated with 4 M HCl in dioxane (0.1 mL). The solids were filtered and washed several times with ethyl acetate to obtain the desired product as an HCl salt (23 mg). HPLC-MS t_R = 1.15 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{28}FN_5O_3$ 417.2, observed LCMS m/z 418.1 (M+H).

Example 56B:



Part A:

Compound **2451** (200 mg, 0.52 mmol), compound **3000** (194 mg, 0.68 mmol), HATU (260 mg, 0.68 mmol), and DIEA (0.5 mL) were dissolved in DMF (5 mL). The reaction mixture was stirred overnight at room temperature and then partitioned between ethyl acetate and water. The organic layers were washed with 1 M HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 33% ethyl acetate/hexanes to 100% ethyl acetate) afforded the desired product (230 mg). HPLC-MS t_R = 2.20 min ($UV_{254\ nm}$); mass calculated for formula $C_{31}H_{37}FN_4O_7$ 596.2, observed LCMS m/z 597.2 (M+H).

Part B:

Compound **2457** (230 mg, 0.386 mmol) was dissolved in methylene chloride (4 mL) and trifluoroacetic acid (1 mL). The reaction mixture was stirred at room temperature for 4 hours. The solvent was evaporated and **2458** (190 mg) was used without further purification. HPLC-MS t_R = 1.77 min ($UV_{254\ nm}$); mass calculated for formula $C_{27}H_{29}FN_4O_7$ 540.2, observed LCMS m/z 541.2 (M+H).

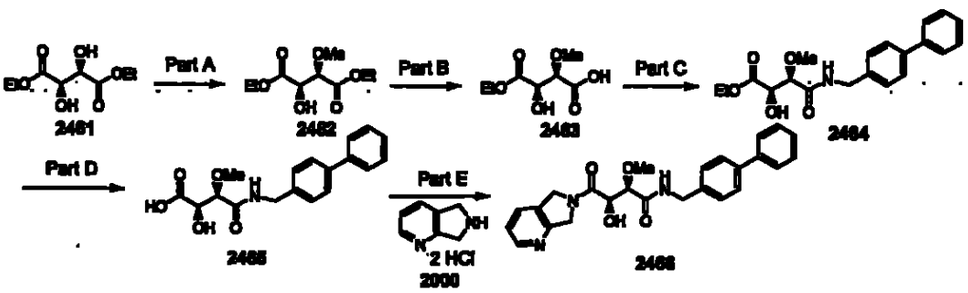
Part C:

Compound **2458** (190 mg, 0.32 mmol), HATU (160 mg, 0.416 mmol), pyrrolidine (0.035 mL, 0.416 mmol), and DIEA (0.5 mL) were dissolved in DMF (5 mL). The reaction mixture was stirred overnight at room temperature and then partitioned between ethyl acetate and water. The organic layers were washed with 1 M HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes to 100% ethyl acetate) afforded the desired product (200 mg). HPLC-MS t_R = 1.92 min ($UV_{254\ nm}$); mass calculated for formula $C_{31}H_{39}FN_5O_8$ 593.2, observed LCMS m/z 594.2 (M+H).

Part D:

Compound **2459** (55 mg, 0.092 mmol) was dissolved in 7 M ammonia in MeOH (0.5 mL) and MeOH (2 mL) and stirred for 30 minutes. The solvent was removed under reduced pressure. The residue was dissolved in MeOH (5 mL) and acetic acid (0.3 mL) and Pd-C (100 mg) was added under an argon atmosphere. The reaction was stirred under a hydrogen atmosphere for 3 hours and then filtered over a bed of celite. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The combined organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. The residue was dissolved in ethyl acetate (2 mL) and treated with 4 M HCl in dioxane (0.1 mL). The solids were filtered and washed several times with ethyl acetate to obtain **2460** as an HCl salt (29 mg). HPLC-MS t_R = 1.15 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{28}FN_5O_3$ 417.2, observed LCMS m/z 418.1 (M+H).

Example 56C:



Part A:

Compound **2462** was prepared using a modification of the procedure in *Chem. Pharm. Bull.* **1991**, 39, 8, 1972-1982. Compound **2461** (1.06 g, 5.14 mmol) and Bu_2SnO (1.28 g, 5.14 mmol) were dissolved in toluene (20 mL) and stirred at reflux for 1.5 hours using a Dean-Stark trap to azeotrope the water formed in the reaction. The solvent was evaporated under reduced pressure and placed under vacuum for 1 hr. Cesium fluoride (1.08 g, 6.68 mmol) was added to the residue and placed under vacuum for an additional 2 hours. The mixture was then dissolved in DMF (20 mL) and iodomethane (2.99 g, 22.1 mmol) and stirred overnight at room temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with 1 N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 33% ethyl acetate/hexanes) afforded the desired product (800 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 (d, 1H), 4.30 (m, 4H), 4.15 (d, 1H), 3.50 (s, 3H), 1.35 (t, 6H).

Part B:

Compound **2463** was prepared using a modification to a procedure found in *Tetrahedron* **1993**, 49, 37, 8381-8396. The diester **2462** (0.837 g, 3.6 mmol) was suspended in pH 8 phosphate buffer (75 mL) and pH was monitored at 8.33. Pig liver esterase (20 mg) was added to the suspension and the reaction mixture was stirred at room temperature. The pH of the reaction was maintained between 7.9-8.2 by the dropwise addition of 1M NaOH (3.27 mL, 3.24 mmol) over 1.5 hours. The reaction mixture was partitioned between diethyl ether and water. The aqueous layer was acidified to pH 2 and extracted with ethyl acetate. The combined ethyl acetate layers were dried over sodium sulfate and evaporated to provide the desired product as a 4.5:1 mixture of inseparable acids (275 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 (d, 1H), 4.40 (m, 2H), 4.25 (d, 1H), 3.50 (s, 3H), 1.35 (t, 3H).

Part C:

Compound **2463** (130 mg, 0.65 mmol), HATU (322 mg, 0.845 mmol), 4-phenylbenzylamine (153 mg, 0.845 mmol), and DIEA (0.2 mL) were dissolved in DMF (6 mL). The reaction mixture was stirred overnight at room

temperature and then partitioned between ethyl acetate and water. The organic layers were washed with 1 M HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Recrystallization from ethyl acetate provided pure product (50 mg) and slightly impure product (150 mg). HPLC-MS t_R = 1.70 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{23}NO_5$ 357.1, observed LCMS m/z 358.1 (M+H).

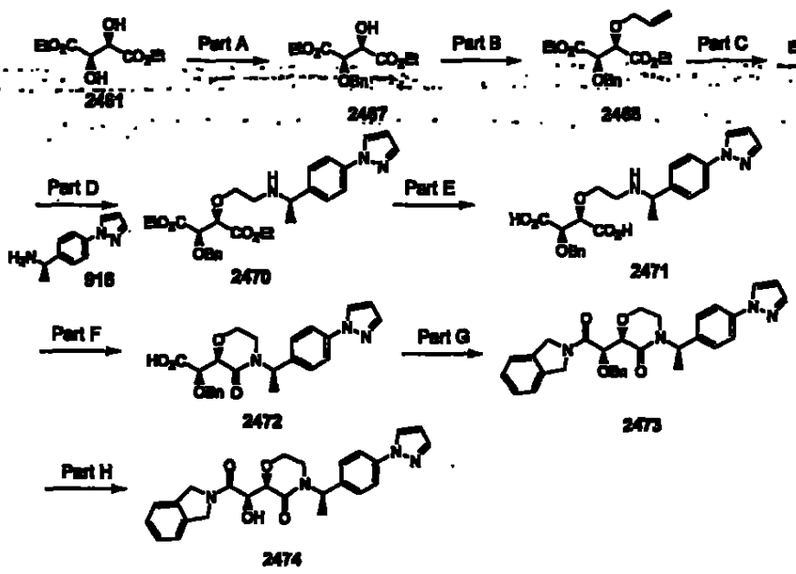
Part D:

Compound **2464** (50 mg, 0.140 mmol) was dissolved in 1 M LiOH (0.151 mL, 0.151 mmol) and THF (5 mL) and stirred for 1 hour. The reaction mixture was partitioned between ethyl acetate and water and the aqueous layer was acidified to pH 2 using 1N HCl. The organic layers were dried over sodium sulfate and concentrated to provide the desired product (46 mg). HPLC-MS t_R = 1.43 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{19}NO_5$ 329.1, observed LCMS m/z 330.1 (M+H).

Part E:

Compound **2465** (46 mg, 0.140 mmol), HATU (70 mg, 0.182 mmol), compound **2000** (35 mg, 0.182 mmol), and DIEA (0.12 mL) were dissolved in DMF (6 mL). The reaction mixture was stirred overnight at room temperature and then partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Recrystallization from ethyl acetate provided pure product (30 mg). HPLC-MS (10 min) t_R = 3.51 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{25}N_3O_4$ 431.2, observed LCMS m/z 432.1 (M+H).

Example 56D:



Part A:

Compound **2467** was prepared according to a modified literature procedure (Nagashima, N. and Ohno, M., *Chem. Pharm. Bull.*, **1991**, *39*, 1972-1982.)

L-Diethyl tartrate (2461) (6.18 g, 30 mmol) and dibutyltin oxide (7.47 g, 30 mmol) in toluene (100 mL) was heated under reflux for 1h, removing water formed as the azotropic mixture. The solution was evaporated to complete dryness *in vacuo* to afford a white solid. To this solid was added dry CsF (8.66 g, 59 mmol) and DMF (60 mL). The resulting mixture was cooled to 0 °C, and benzyl bromide (6 mL, 51 mmol) was added dropwise via a syringe. After the completion of addition, the reaction mixture was allowed to stir rigorously at room temperature for 12 h. The solvent was removed under vacuum and the obtained residue was dissolved in EtOAc and H_2O. The organic layer was washed with $NaHCO_3$ aqueous solution, brine, dried over Na_2SO_4, and concentrated. Purification by flask column chromatography on silica gel (EtOAc / hexane 30:70) afforded compound **2467** as colorless liquid (8.10 g, 91%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 4.87 (d, J = 12.0 Hz, 1H), 4.58 (br s, 1H), 4.02 (d, J = 12.0 Hz, 1H), 4.34 – 4.25 (m, 3H), 4.23-4.21 (m, 1H), 4.08 – 4.03 (m, 1H), 3.12 (br s, 1H), 1.35 (t, J = 7.0 Hz, 3H), 1.19 (t, J = 6.9 Hz, 3H).

Part B:

To compound **2467** (2.96 g, 10 mmol) in toluene (10 mL) was added with Ag_2O (4.63 g, 20 mmol) and allyl bromide (1.31 mL, 15 mmol). The reaction mixture was allowed to stir at 110 °C for 16 h and cooled to room temperature. After filtering through a pad of celite, the solution was concentrated. Flash column chromatography on silica gel (EtOAc / hexane 20: 80) afforded the desired product **2468** (2.65 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 5H), 4.87 (d, *J* = 12.0 Hz, 1H), 5.89-5.79 (m, 1H), 5.26-5.15 (m, 2H), 4.87 (d, *J* = 11.4 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.41-4.38 (m, 2H), 4.34 – 3.92 (m, 6H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H).

Part C:

To an ice-cold mixture of compound **2468** (1.0 g, 3 mmol) and N-methylmorpholine monohydrate (703 mg, 6 mmol) in THF / H_2O 3:1 (20 mL) was added OsO_4 (2.5 wt% in *t*-BuOH, 610 mg, 0.06 mmol). After stirring for 30 min, the ice bath was removed and the reaction mixture was stirred at room temperature overnight. Solid $NaHSO_3$ (750 mg, 7.2 mmol) was added, and the mixture was stirred for an additional 30 min. The mixture was filtered through a pad of silica and the solution was concentrated *in vacuo* giving rise to an oil. This material was dissolved in THF/H_2O 3:1 (20 mL) and $NaIO_4$ (1.28 g, 6 mmol) was added. The mixture was allowed to stir at room temperature for 1 h. It was filtered through silica, and the solvent was evaporated. Flash column chromatography on silica gel (EtOAc/ hexane 50:50) provided the aldehyde **2469** (760 mg, 75%) as a colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.35-7.26 (m, 5H), 4.89 (d, *J* = 11.8 Hz, 1H), 4.52-4.48 (m, 2H), 4.45 – 4.04 (m, 7H), 1.34 (t, *J* = 7.7 Hz, 3H), 1.19 (t, *J* = 7.4 Hz, 3H).

Part D:

Compound **2469** (340 mg, 1 mmol) and amine **916** (187 mg, 1 mmol) in 1,2-dichloroethane (5 mL) were stirred at room temperature for 5 min, after which sodium tri(acetoxyl)borohydride (254 mg, 1.2 mmol) was added slowly. The reaction mixture was allowed to stir at room temperature overnight. The

solution was concentrated, the crude residue was purified by flash column chromatography on silica gel (MeOH/EtOAc 10:90), affording desired product **2470** (350 mg, 69%) as a colorless oil. HPLC-MS t_R = 1.49 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{35}N_3O_8$ 509.2, observed LCMS m/z 510.1 (M+H).

Part E:

To a solution of compound **2470** (170 mg, 0.33 mmol) in dioxane / water 1:1 (10 mL) was added LiOH (1M, 1.32 mL, 1.32 mmol) dropwise. The mixture was stirred at room temperature for 2h after which it was neutralized with 1 M HCl and concentrated. The residue was utilized for the following step without further purification. HPLC-MS t_R = 1.12 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{27}N_3O_8$ 453.2, observed LCMS m/z 454.1 (M+H).

Part F:

The crude compound **2471** was dissolved in DMF (10 mL) and cooled to 0 °C in an ice bath, HATU (304 mg, 0.8 mmol) was added slowly and the reaction mixture was stirred at 0 °C for 2h. LC-MS indicated the disappearance of diacid and the formation of the cyclized product **2472**. HPLC-MS t_R = 1.65 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{25}N_3O_5$ 435.2, observed LCMS m/z 436.1 (M+H).

Part G:

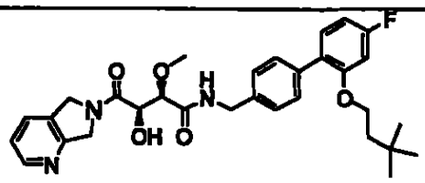
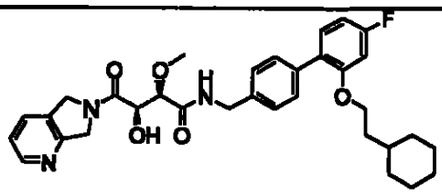
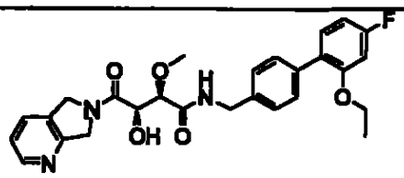
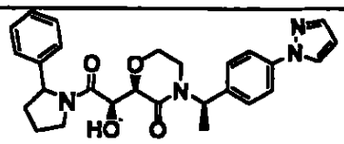
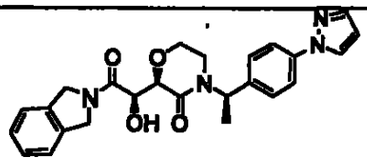
To the above solution at 0 °C was added isoindoline (48 mg, 0.4 mmol) and the reaction mixture was stirred at room temperature overnight. The DMF was evaporated, the residue was dissolved inn EtOAc and water, washed with 1N HCl, saturated NaHCO3 and brine, dried over Na2SO4 and concentrated to afford **2437** as an oily solid (85 mg, 47% yield over three steps). HPLC-MS t_R = 2.00 min ($UV_{254\ nm}$); mass calculated for formula $C_{32}H_{32}N_4O_4$ 536.1, observed LCMS m/z 537.1 (M+H).

Part H:

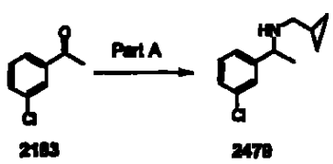
Crude compound **2473** was dissolved in EtOH (20 mL), and palladium on carbon (10%, 40 mg) was added. The mixture was hydrogenated (atmospheric pressure) at room temperature overnight. The suspension was

filtered through celite and concentrated. The resulting residue was purified by preparative LC affording 2474 as a white solid (9.4 mg). HPLC-MS t_R = 3.57 min (10 min method, $UV_{254\ nm}$); mass calculated for formula $C_{25}H_{26}N_4O_4$ 446.2, observed LCMS m/z 447.1 (M+H).

The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2475		549.3	550.2
2476		575.3	576.1
2477		493.2	494.2
2478		474.2	475.1
2474		446.2	447.1

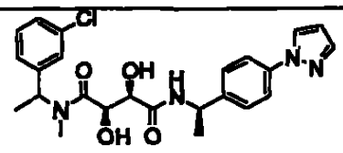
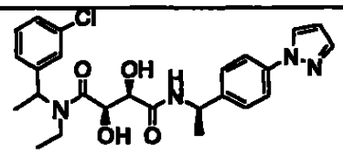
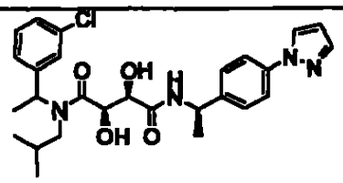
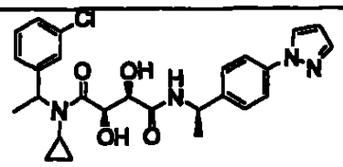
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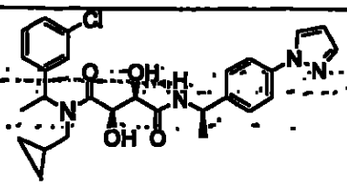
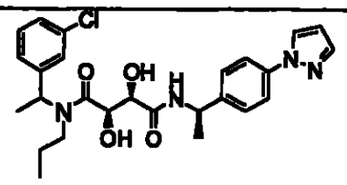
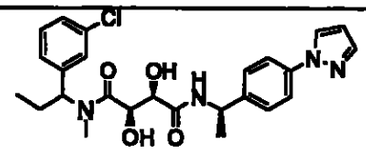
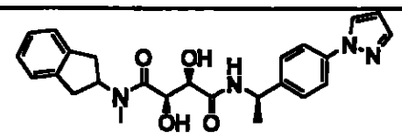


Part A:

Compound 2183 (200 mg, 1.3 mmol) and cyclopropylmethyl-amine (0.16 mL) were dissolved in MeOH (5 mL) and stirred at 50 °C overnight. Then sodium borohydride (42 mg, 1.3 mmol) was added and the mixture was stirred for 2 hours. The solvent was removed under reduced pressure and the residue was partitioned between diethyl ether and 1 N HCl. The aqueous layer was made basic and extracted with ethyl acetate. The combined ethyl acetate layers were dried over sodium sulfate and concentrated to provide the desired product **2479** (130 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 1H), 7.28-7.18 (m, 3H), 3.79 (m, 1H), 2.50-2.25 (m, 2H), 1.38 (d, 3H), 1.00-0.90 (m, 1H), 0.50-0.45 (m, 2H), 0.10-0.00 (m, 2H).

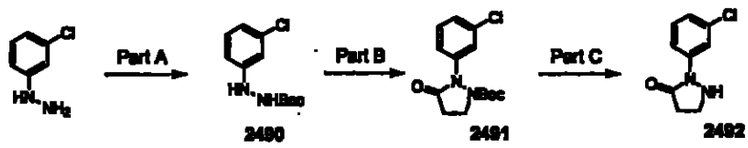
The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2480		470.2	471.1
2481		484.2	485.0
2482		512.2	513.1
2483		496.2	497.0

2485		510.2	511.1
2486		498.2	499.1
2487		484.2	485.0
2489		448.2	449.1

Example 58:

Example 58A:



Part A:

To a solution of Boc_2O (6.1 g, 28 mmol) and Et_3N (7.8 mL, 56 mmol) in DMF (20 mL) at 0 °C was added portionwise 3-chlorophenylhyrazine hydrocloride (5.0 g, 28 mmol) in DMF (20 mL). The reaction mixture was allowed to stir at room temperature for 2 h and concentrated. The residue was dissolved in EtOAc and H_2O, washed with 1N citric acid and saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated, affording **2490** (17.83 g, 97%) as a off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, J = 8.3 Hz, 1H), 6.86-6.81 (m, 2H), 6.70-6.66 (m, 1H), 6.36 (br s, 1H), 1.48 (s, 10H).

Part B:

3-Chloropropionyl chloride (0.400 mL, 4.12 mmol) was added dropwise into a solution of compound **2490** (1.0 g, 4.12 mmol) and K_2CO_3 (1.14 g, 8.24 mmol) in DMF (10 mL) at 0 °C. The reaction mixture was allowed to stir at 80°C overnight and concentrated. The residue was dissolved in EtOAc and H_2O, washed with 1N citric acid and saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated. Column chromatography (EtOAc/hexane 25:75) provided compound **2491** (600 mg, 49%) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (t, *J* = 2.3 Hz, 1H), 7.51-7.48 (m, 1H), 7.27 (t, *J* = 8.3 Hz, 1H), 7.12-7.09 (m, 1H), 4.16 (t, *J* = 7.2 Hz, 2H), 2.77 (t, *J* = 7.3 Hz, 2H), 1.34 (s, 9H).

Part C:

Compound **2491** was deprotected with TFA in CH_2Cl_2. The material was used without further purification.

Example 58B:

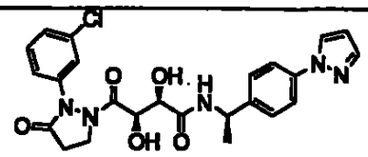
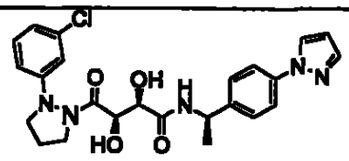
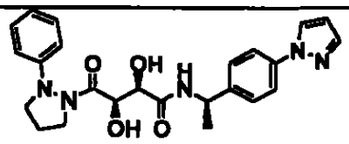


2493

Part A:

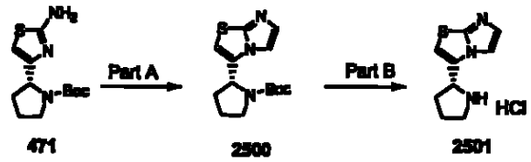
To a suspension of NaH (60% in mineral oil, 1.56 g, 39 mmol) in benzene (40 mL) at 0 °C was added with 3-chlorophenylhyrazine (2.13 g, 15 mmol). The mixture was stirred at 80 °C for 1 h, after which 1,3-dibromopropane (2.0 g, 10 mmol) was added slowly via syringe. It was stirred at 80 °C overnight and quenched by adding water (20 mL). The organic layer was separated, washed with water and brine, dried over Na_2SO_4, and concentrated. Column chromatography (DCM) provided compound **2493** (850 mg, 47%) as pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, *J* = 8.2 Hz, 1H), 7.04 (t, *J* = 2.3 Hz, 1H), 6.84-6.81 (m, 1H), 6.74-6.71 (m, 1H), 3.75 (bs, 1H), 3.35 (t, *J* = 7.5 Hz, 2H), 3.00 (t, *J* = 6.7 Hz, 2H), 2.16-2.11 (m, 2H).

The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2494		497.2	498.1
2495		483.2	484.1
2496		449.2	450.1

Example 59:

Example 59A:



471 2500 2501

Part A:

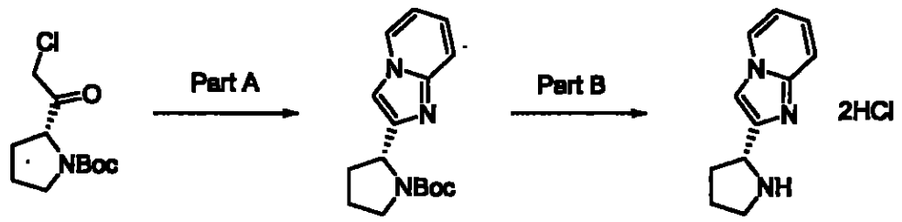
To compound 471 (100 mg, 0.37 mmol) in EtOH (2 mL) was added chloroacetaldehyde (50 wt.% in water, 233 mg, 1.48 mmol). The reaction mixture was allowed to stir at 90 °C overnight and concentrated. The residue was dissolved in EtOAc , washed with water and brine, dried (Na_2SO_4) and concentrated. The crude product 2500 (90 mg, 82%) was used without further purification. HPLC-MS t_R = 1.10 min; Mass calculated for formula $C_{14}H_{19}N_3O_2S$ 293.1, observed m/z 294.1(M+H).

Part B:

Compound 2500 (90 mg) was dissolved in 2 mL of 4 N HCL in dioxane/H2O (1:1). After stirring at room temperature for 1 h, the solution was

concentrated, affording a brown solid (80 mg, 90%). HPLC-MS t_R = 0.22 min; Mass calculated for formula $C_9H_{11}N_3S$ 193.1, observed m/z 194.1 (M+H).

Example 59B:



470 2502 2503

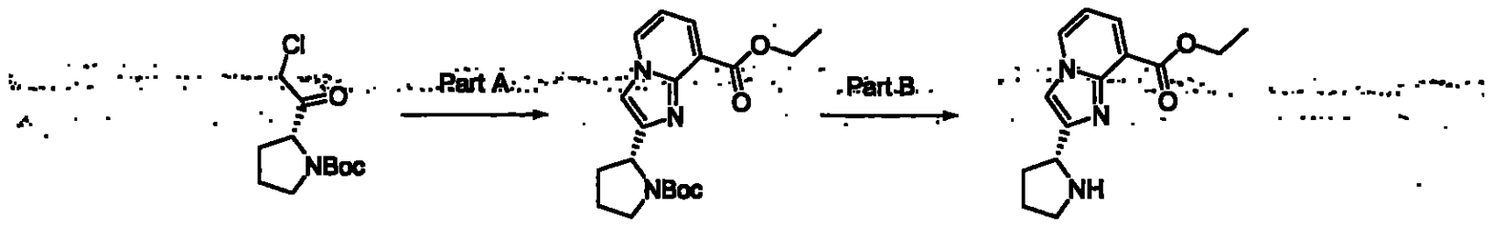
Part A:

A mixture of chloroketone **470** (200 mg, 0.81 mmol) and 2-aminopyridine (77 mg, 0.82 mmol) in ethanol (5 ml) was heated to reflux and stirred overnight. The reaction mixture was concentrated and purified by prep-HPLC to afford **2502** (103 mg). HPLC-MS t_R = 1.00 min ($UV_{254\ nm}$); mass calculated for formula C16H21N3O2 287.2, observed LCMS m/z 288.3 (M+H).

Part B:

To a solution of imidazopyridine **2502** (103 mg, 0.56 mmol) in dioxane (2 mL) was added HCl (4N in dioxane, 4 mL) and water (0.5 mL). The mixture was stirred at room temperature for 1 hour and concentrated. The resulting residue **2503** (81 mg) was dried under vacuum and used in the next step without further purification. HPLC-MS t_R = 0.19 min ($UV_{254\ nm}$); mass calculated for formula C11H13N3 187.1, observed LCMS m/z 188.1 (M+H).

Example 59C:



470 2504 2505

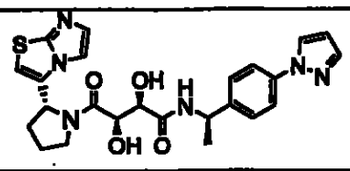
Part A:

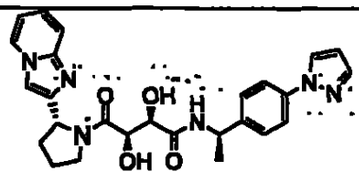
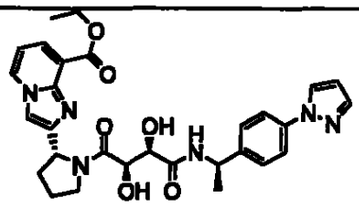
A mixture of chloroketone 471 (200 mg, 0.81 mmol) and 2-aminopyridine (140 mg, 0.81 mmol) in ethanol (5 ml) was heated up to reflux and stirred overnight. The reaction mixture was concentrated and purified by prep-HPLC to afford 2504 (119 mg). HPLC-MS t_R = 1.22 min ($UV_{254\ nm}$); mass calculated for formula C19H25N3O4 359.2, observed LCMS m/z 360.1 (M+H).

Part B:

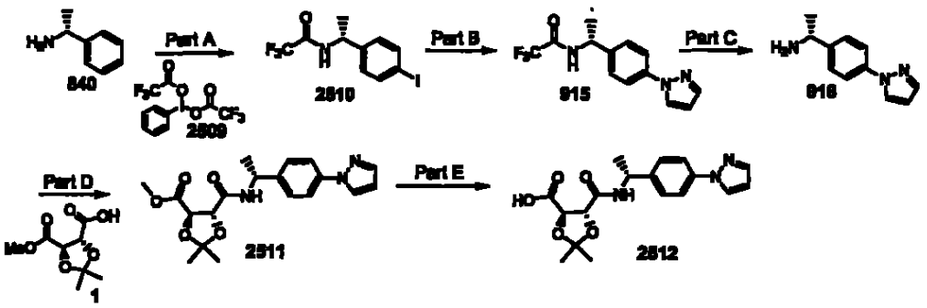
To a solution of imidazopyridine 2504 (119 mg, 0.33 mmol) in dioxane (2 mL) was added HCl (4N in dioxane, 4 mL) and water (0.5 mL). The mixture was stirred at room temperature for 1 hour and concentrated. The resulting residu 2505 (83 mg) was dried under vacuum and used in the next step without further purification. HPLC-MS t_R = 0.70 min ($UV_{254\ nm}$); mass calculated for formula C14H17N3O2 259.1, observed LCMS m/z 260.1 (M+H).

The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2506		494.2	495.1

2507		488.2	489.1
2508		560.2	561.2

Example 60:



Part A:

Trifluoroacetic anhydride (16 mL, 115.1 mmol) was dissolved in methylene chloride (60 mL) and cooled in an ice bath. Compound **840** (10.0 g, 82.6 mmol) was added dropwise in methylene chloride (40 mL) and stirred at room temperature for one hour. The solution was cooled in an ice bath and iodine (11.0 g, 43.2 mmol) and compound **2509** (9.8 g, 22 mmol) were added and stirred for 12 hours in the dark (cover flask with aluminum foil). Additional compound **2509** (9.5 g, 20 mmol) was added and stirring was continued for 12 hours. The reaction mixture was added to a cooled solution of methylene chloride and 5% sodium bisulfite and stirred for one hour. The organic layer was washed with saturated sodium bicarbonate, filtered through a pad of silica, and concentrated. The residue was suspended in diethyl ether (30 mL) and hexanes (90 mL) and stirred for 30 minutes. The mixture was filtered to

provide compound **2510** as a white solid (15.5 g). The product was stored in the dark at room temperature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 2H), 7.06 (d, 2H), 5.10 (m, 1H), 1.60 (d, 3H).

Part B:

Compound **2510** (4.0 g, 11.66 mmol), pyrazole (0.953 g, 14 mmol), copper (I) iodide (444 mg, 2.33 mmol), cesium carbonate (7.6 g, 23.3 mmol), 1,10 phenanthroline (844 mg, 4.66 mmol) and dimethylacetamide (40 mL) were combined in a 80 mL screw-capped vial and stirred in the dark at 120 °C for 12 hours. The reaction mixture was poured into ethyl acetate (200 mL) and filtered. The organic layer was washed with water several times followed by 1N citric acid solution. The organic layer was dried over sodium sulfate and concentrated. The residue was recrystallized from ethyl acetate and hexanes to provide 2.45 g of compound **915**. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.92 (m, 1H), 7.70 (m, 2H), 7.40 (d, 1H), 6.45 (t, 1H), 5.20 (m, 1H), 1.65 (d, 3H).

Part C:

Compound **915** (2.43 g, 9.13 mmol) was dissolved in methanol (20 mL) and 1N lithium hydroxide (20 mL) and stirred for 6 hours. The reaction mixture was poured into ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated to provide compound **916** (1.45 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.90 (d, 1H), 7.70 (d, 1H), 7.64 (d, 2H), 7.43 (d, 2H), 6.46 (t, 1H), 1.44 (d, 3H).

Part D:

Compound **916** (1.45 g, 7.7 mmol), compound **1** (1.5 g, 7.35 mmol), HATU (3.63 g, 9.55 mmol), and diisopropylethylamine (1.28 mL, 7.35 mmol) were dissolved in DMF (20 mL) at 0 °C. The reaction mixture was stirred for 12 hours and then diluted with water and extracted with ethyl acetate. The combined organic layers were washed with 1N HCl, saturated sodium bicarbonate, brine and water, dried over sodium sulfate and concentrated. The residue was purified by column chromatography (2:1 hexanes/ethyl

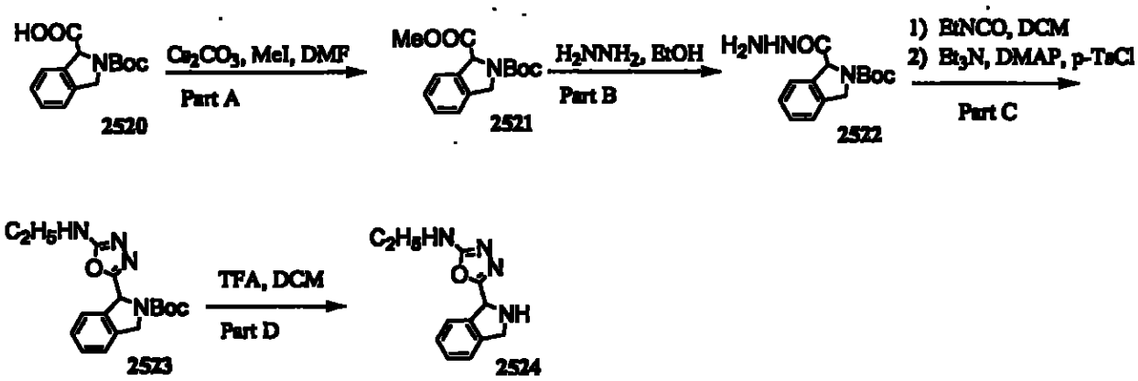
acetate) to provide compound **2511** (2.15 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.90 (d, 1H), 7.72 (m, 1H), 7.66 (d, 2H), 7.40 (d, 2H), 6.75 (d, 1H), 6.49 (d, 1H), 5.20 (m, 1H), 4.82-4.75 (dd, 2H), 3.83 (s, 3H), 1.57 (d, 3H), 1.54 (s, 3H), 1.50 (s, 3H).

Part E:

Compound **2511** (2.15 g, 5.76 mmol) was dissolved in THF (20 mL) and 1N lithium hydroxide and stirred for 2 hours. Diethyl ether was added and the aqueous layer was acidified to pH 2 with 1 N HCl and extracted with ethyl acetate. The combined ethyl acetate layers were dried over sodium sulfate and concentrated to provide compound **2512** as a white solid (1.95 g). 1H NMP (400MHz, $CDCl_3$) δ7.9 (d, 1H), 7.74 (m, 1H), 7.70 (d, 2H), 7.42 (d, 2H), 6.96 (d, 1H), 6.49 (t, 1H), 5.2 (m, 1H), 4.60-4.50 (dd, 2H), 1.64 (d, 3H), 1.54 (d, 3H).

Example 61:

Example 61A:



Part A:

(R,S)-BOC-1,3-Dihydro-2H-Isoindole carboxylic acid **2520** (3.0 g, 11.39 mmol) and cesium carbonate (4.05 g, 12.43 mmol) were stirred together in DMF (25mL) at r.t. for one hour. Iodomethane (1.05 mL, 16.86 mmol) was added and the reaction mixture was stirred at ambient temperature overnight. The

reaction mixture was diluted with ethyl acetate then washed several times with water, brine (1 x 50 mL), dried over Na_2SO_4 and concentrated to give light yellow oil. Purification by column chromatography (SiO_2, 25% ethyl acetate / hexane) afforded **2521** (2.66 g, 84 %) as white solid.

Part B:

A mixture of **2521** (0.2 g, 0.72 mmol) and hydrazine (0.22 mL, 7.0mmol) in ethanol (20 mL) was heated at 70 °C for 5 hours. The solvent was removed under reduced pressure and the resulting residue was dissolved in ethyl acetate, washed with water (2 x 30mL), brine (1 x 20 mL), dried over Na_2SO_4 and concentrated to provide **2522** (0.18 g, 86%) as an yellow oil, which was used in the next step without further purification.

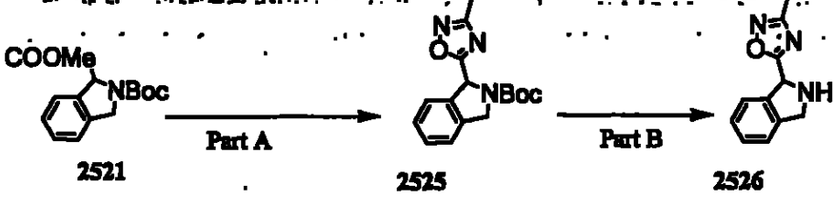
Part C:

A mixture of **2522** (0.2 g, 0.72 mmol) and ethyl isocyanate (0.077 g, 1.083 mmol) in DCM (5 mL) was stirred at r.t. for 16 hours. Additional ethyl isocyanate (0.077 g, 1.083 mmol) was added and reaction was stirred for another two hours. The solvent was removed under reduced pressure to provide the crude product as a white gum. It was dissolved in DCM (20 mL) and treated triethyl amine (0.5 mL, 3.6 mmol) , DMAP (0.017 g, 0.139 mmol) and *p*-toluene sulphonyl chloride (0.16 g, 0.83 mmol). The mixture was stirred at room temperature for 64 hours and the solvent was removed. The residue was purified by preparative chromatography using 5% $MeOH/CH_2Cl_2$, to provide the product which was again purified using ethyl acetate/Hexane (3/1) to yield intermediate **2523** (0.1 g, 44%) as a light brown solid.

Part D:

Intermediate **2523** (0.05 g, 0.15 mmol) was dissolved in DCM (10 mL) then trifluoroacetic acid (0.06 mL, 0.77 mmol) was added. Reaction was stirred at ambient temperature for 3 hours and then concentrated. The residue was dissolved in DCM and washed with saturated sodium bicarbonate solution (1 x 0.8 mL), saline(1 x 0.8 mL), dried over sodium sulfate and concentrated under vacuum to provide amine **2524** (0.03 g, 86%) as a brown oil. It was used in the next step without additional purification.

Example 61B:



2521 2525 2526

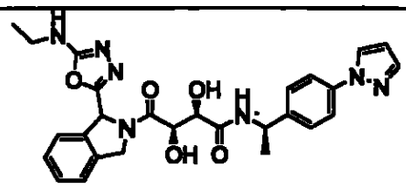
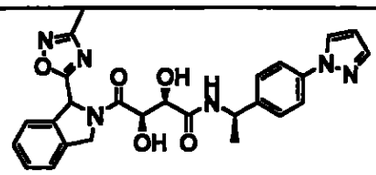
Part A:

Intermediate **2525** was prepared by known methods (Showell , G.A.; Gibbons, T.L.; Kneen, C.O.; Macleod, A.M..; Merchant, K.; Saunders, J.; Freedman, S.B.; Patel, S; Baker, R.. *J Med Chem.* **1991**, *34* (3), 1086-1094).

Part B:

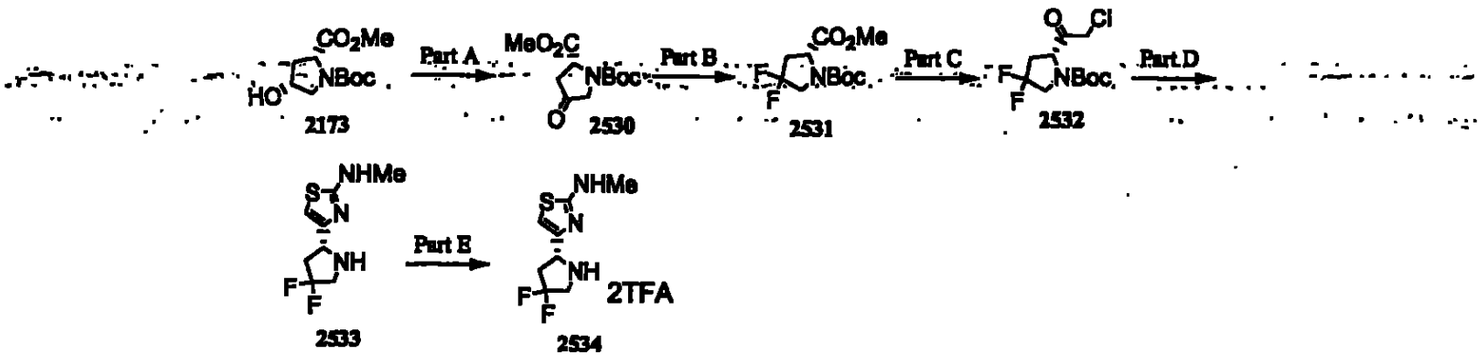
Intermediate **2526** was prepared using the method described in Example 61A Part D.

The following compounds were prepared using previously described procedures.

Compound #	SCH	Structure	Exact mass	MS m/z (M+H)
2527	786656		531.2	532.2
2528	7867566		502.2	503.2

Example 62:

Example 62A:



Part A:

A mixture of **2173** (1.54 g, 6.28 mmol) and Dess-Martin periodinane (2.72 g, 6.41 mmol) in DCM (30 ml) was stirred at room temperature overnight. To the reaction mixture was add saturated sodium bicarbonate solution and the mixture was stirred for 2 hours. The solids were removed by filtration. The filtrate was separated and the organic layer was washed with brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 30% ethyl acetate / hexane) afforded **2530** (939 mg, 61%) as an oil. HPLC-MS t_R = 1.10 min (MS); Mass calculated for formula C11H17NO5 243.1, observed m/z 266.1 (M+Na).

Part B:

To ketone **2530** (939 mg, 3.86 mmol) in DCM (30 mL) at -78 oC under argon was added (diethylamino)sulfur trifluoride (2.53 mL, 19.3 mmol). The bath was slowly warmed to room temperature while the mixture was stirred overnight. The reaction mixture was poured into saturated sodium bicarbonate and the layers were separated. The organic layer was washed with brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 10% to 30% ethyl acetate / hexane) afforded **2531** (751 mg, 74%) as an oil. HPLC-MS t_R = 4.72 min (10 min, MS); Mass calculated for formula C11H17F2NO4 265.1, observed m/z 288.1 (M+Na).

Part C:

Compound **2531** (751 mg, 2.83 mmol) was converted to **2532** (418 mg, 52 %) using the procedures described in Example 10 Part A. HPLC-MS t_R = 1.85

min (MS); Mass calculated for formula C11H16ClF2NO3 283.1, observed m/z 228.1 (M-55).

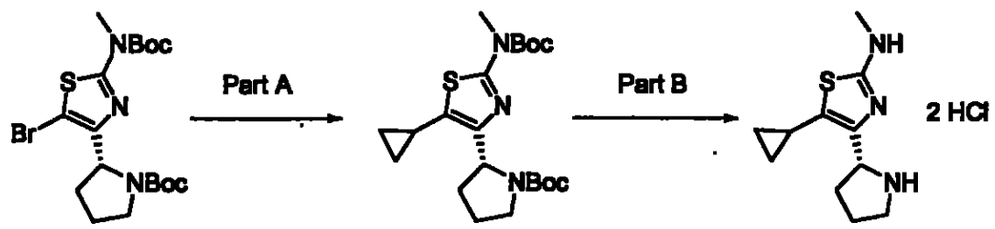
Part D:

Compound **2532** (418 mg, 1.47 mmol) was cyclized with N-methylthiourea according to the procedures described in Example 51B Part C to afford **2533** (200 mg, 42%). HPLC-MS t_R = 1.38 min (UV $_{254\ nm}$); Mass calculated for formula C8H11F2N3S 319.1, observed m/z 320.1 (M+H).

Part E:

Compound **2534** was synthesized in quantitative yield using the procedure described in Example 51D Part H. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H), 4.98 (dd, 1H, J = 7.2, 11.7 Hz), 3.89 (m, 1H), 3.72 (m, 1H), 3.13 (s, 3H), 3.09-2.85 (m, 2H).

Example 62B:



2209A **2535** **2536**

Part A:

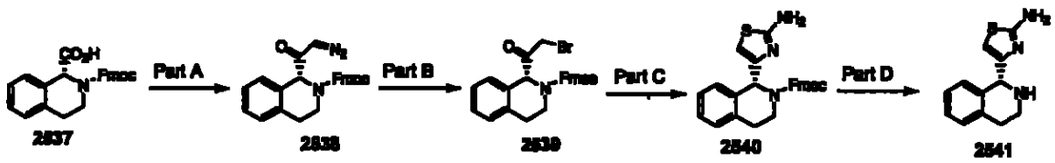
The mixture of 5-bromothiazole **2209A** (210 mg, 0.45 mmol), cyclopropylboronic acid (80 mg, 1.0 mmol), $Pd(dppf)Cl_2$ (41 mg, 0.05 mmol) and K_3PO_4 (424 mg, 2.0 mmol) in 20-ml vial was flushed with argon for 3 min. Under the argon, dioxane (5 mL) was added and the vial was sealed under the argon atmosphere. The mixture was heated to 80 °C and stirred overnight. After cooling to room temperature, ethyl acetate (30 mL) was added to the reaction mixture and the solution was filtered through celite. The filtrate was concentrated and purified by column chromatography (SiO_2, 10% ethyl acetate/hexanes) to afford 5-cyclopropylthiazole **2535** (166 mg) as oil. HPLC-

MS t_R = 2.65 min ($UV_{254\ nm}$); mass calculated for formula C21H33N3O4S 423.2, observed LCMS m/z 424.1 (M+H).

Part B:

To the solution of 5-cyclopropylthiazole **2535** (166 mg, 0.39 mmol) in dioxane (2 mL), HCl (4N in dioxane, 4 mL) was added followed by the addition of water (0.5 mL). The mixture was stirred at room temperature for 1 hour and concentrated. The resulting residue **2536** (111 mg) was dried under vacuum and used in the next step without further purification. HPLC-MS t_R = 0.86 min ($UV_{254\ nm}$); mass calculated for formula C11H17N3S 223.1, observed LCMS m/z 224.1 (M+H).

Example 62C:



Part A:

To Fmoc-D-Tiq-OH (**2537**) (1.0 g, 2.5 mmol) in dichloromethane (20 mL) at 0 °C was added $(COCl)_2$ (0.262 mL, 3.0 mmol) and DMF (2 drops, catalytic) under argon. The reaction mixture was stirred at 0 °C for 2 hr and concentrated to dryness in *vacuo*. The resulting syrup was dissolved in dry THF (20 mL) and cooled to 0 °C. Trimethylsilyldiazomethane (2.0 M in Et2O, 5 mL, 10 mmol) was added dropwise under argon during a period of 30 min. After the completion of addition, the solution was stirred at 0 °C for 3 hr and concentrated under reduced pressure. Flash column chromatography on silica (EtOAc/hexane 25:75) afforded **2538** (630 mg, 60%) as a yellow oily solid. HPLC-MS t_R = 2.23 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{21}N_3O_3$ 423.2, observed LCMS m/z 446.2 (M+Na).

Part B:

Compound **2538** (630 mg, 1.49 mmol) in Et_2O (20 mL) was cooled to 0 °C. To this solution was added 2.15 M hydrobromide acid in Et_2O (830 µL, 1.79 mmol) dropwise. The reaction mixture was stirred for 20 min at 0 °C and concentrated. The residue was dissolved in EtOAc, the solution was than washed with saturated bicarbonate solution, brine, dried (Na_2SO_4) and concentrated in *vacuo* to afford **2539** (630 mg, 89%) as an off white solid. HPLC-MS t_R = 2.40 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{22}BrNO_3$ 475.1, observed LCMS m/z 476.0 (M+H).

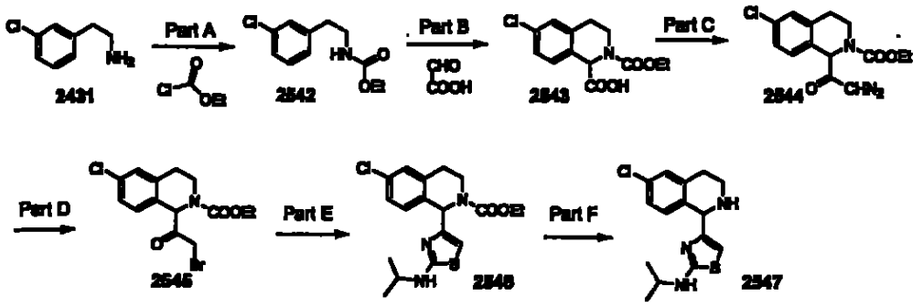
Part C:

Compound **2539** (150 mg, 0.31 mmol) and thiourea (36 mg, 0.47 mmol) in DMF (2 mL) was allowed to stir at room temperature for 3 hr. The solution was concentrated and the residue was dissolved with EtOAc and saturated $NaHCO_3$ solution. The organic phase was washed with H_2O, brine, dried over Na_2SO_4, and concentrated. Flash column chromatography on silica (EtOAc / hexane 60:40) afforded **2540** (120 mg, 84%) as a white solid. HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); mass calculated for formula $C_{27}H_{23}N_3O_2S$ 453.2, observed LCMS m/z 454.1 (M+H).

Part D:

Compound **2540** (150 mg, 0.26 mmol) was treated with 20% piperidine in DMF (10 mL). The solution was stirred at room temperature for 2 hr and concentrated. LC-MS indicated the clean deprotection of the Fmoc group. HPLC-MS t_R = 0.72 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{13}N_3S$ 231.1, observed LCMS m/z 232.1 (M+H).

Example 62D:



Part A:

According to a modification of a procedure by Ortwine, D. F. et al. (*J. Med. Chem.* **1992**, 35, 1345-1370) to an ice-cold solution of 3-chlorophenethylamine **2431** (10 g, 64.6 mmol) and triethylamine (6.46 mL, 67.8 mmol) in DCM (200 mL) was added dropwise ethyl chloroformate (9.45 mL, 67.8 mmol), and the resulting solution was stirred at 0 °C for 1 h, and then at rt for 1.5 h. The reaction mixture was washed with saturated sodium bicarbonate solution, brine, dried and concentrated to give ethyl carbamate **2542** as a colorless oil (14.36 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.19 (m, 3H), 7.09-7.07 (d, 1H), 4.66 (s, broad, NH), 4.12 (q, 2H), 3.44 (q, 2H), 2.81 (t, 2H), 1.25 (t, 3H).

Part B:

According to a modification of a procedure by Ortwine, D. F. et al. (*J. Med. Chem.* **1992**, 35, 1345-1370) to an ice-cold mixture of carbamate **2542** (6.81 g, 29.9 mmol) and 3:1 glacial acetic acid:sulfuric acid (64 mL) was added (in two portions) glyoxylic acid monohydrate (3.03 g, 32.9 mmol) and the mixture was stirred at rt overnight. The reaction mixture was poured in ice, and extracted with dichloromethane (5 times). The combined dichloromethane extracts were dried and concentrated to an oily residue, which was then taken in toluene and concentrated (3 times) and dried under vacuum overnight to give compound **2543** (7.91 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.9 (s, broad, COOH), 7.50-7.12 (m, 3H), 5.42 (s, 1H), 4.12-4.03 (m, 2H), 3.77-3.50 (m, 2H), 2.89-2.79 (m, 2H), 1.24-1.16 (m, 3H). HPLC-MS t_R = 1.68 min ($UV_{254\ nm}$); mass calculated for formula C13H14ClNO4 283.1, observed LCMS m/z 284.0 (M+H).

Part C:

Diazoketone **2544** was prepared using procedures described in Example 62C Part A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.18 (m, 3H), 5.60-5.41 (m, 2H), 4.26-4.22 (m, 2H), 3.90-3.65 (m, 2H), 2.97-2.82 (m, 2H), 1.36-1.32 (m, 3H). HPLC-MS t_R = 1.8 min ($UV_{254\ nm}$); mass calculated for formula

C14H14ClN3O3 307.1, observed LCMS m/z 280.1 (M-N2+H), and 330.1 (M+Na).

Part D:

Bromoketone **2545** was prepared using procedures described in Example 62C Part B. ^{1}H NMR (400 MHz, CDCl3) δ 7.31-7.20 (m, 3H), 5.87-5.81 (m, 1H), 4.25-4.04 (m, 4H), 3.90-3.82 (m, 1H), 3.60-3.51 (m, 1H), 2.98-2.79 (m, 2H), 1.34-1.31 (m, 3H). HPLC-MS t_R = 2.07 min ($UV_{254\ nm}$); mass calculated for formula C14H15BrClNO3 359.0, observed LCMS m/z 360.0 (M+H).

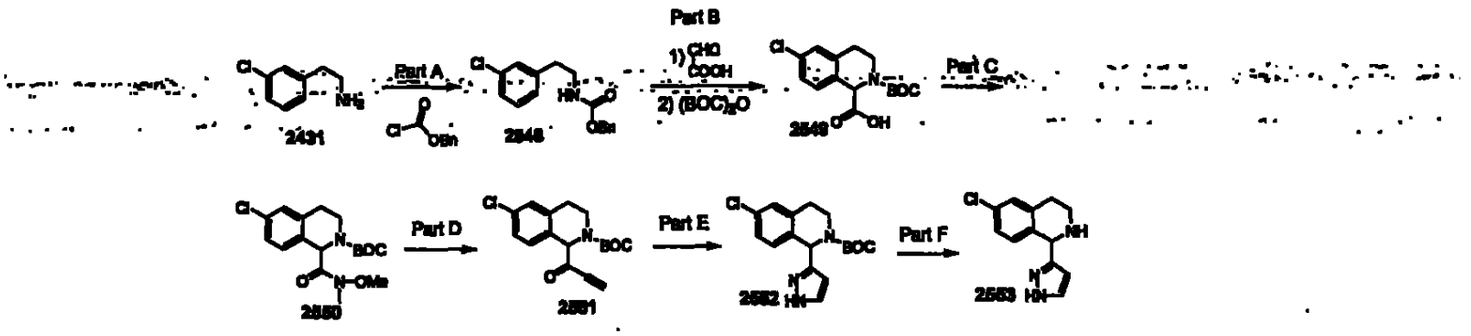
Part E:

Thiazole **2546** was prepared using procedures described in Example 10. HPLC-MS t_R = 2.05 min ($UV_{254\ nm}$); mass calculated for formula C18H22ClN3O2S 379.1, observed LCMS m/z 380.1 (M+H).

Part F:

To a solution of thiazole **2546** (117 mg, 0.31 mmol) in chloroform (1.5 mL) was added iodotrimethylsilane (0.32 mL, 2.24 mmol) and the resulting mixture was heated at 50 °C for 2 h. The reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate, brine and concentrated to give amine **2547** as a dark yellow solid (93 mg, 97%). ^{1}H NMR (400 MHz, CDCl3) δ 7.12-6.97 (m, 3H), 6.01(s, 1H), 5.26 (s, broad, 1H), 5.15 (s, 1H), 3.60-3.53 (m, 1H), 3.18-2.80 (m, 4H), 1.28-1.26 (d of d, 6H). HPLC-MS t_R = 1.24 min ($UV_{254\ nm}$); mass calculated for formula C15H18ClN3S 307.1, observed LCMS m/z 308.2 (M+H).

Example 62E:



Part A:

According to a modification of a procedure by Ortwine, D. F. et al. (*J. Med. Chem.* 1992, 35, 1345-1370) to an ice-cold solution of 3-chlorophenethylamine **2431** (11.6 g, 75 mmol) and triethylamine (10.9 mL, 78.7 mmol) in DCM (300 mL) was added dropwise benzyl chloroformate (11.1 mL, 78.1 mmol), and the resulting solution was stirred at 0 °C for 30 min, and then at rt overnight. The reaction mixture was washed with saturated sodium bicarbonate solution, brine, dried and concentrated to give benzyl carbamate **2548** as a colorless oil (21.4 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 5H), 7.23-7.05 (m, 4H), 5.1 (s, 2H), 4.75 (s, broad, NH), 3.46 (q, 2H), 2.82 (t, 2H).

Part B:

According to a modification of a procedure by Ortwine, D. F. et al. (*J. Med. Chem.* 1992, 35, 1345-1370) to an ice-cold mixture of benzyl carbamate **2548** (8.6 g, 31.4 mmol) and 3:1 glacial acetic acid:sulfuric acid (64 mL) was added (in two portions) glyoxylic acid monohydrate (3.0 g, 32.6 mmol) and the mixture was stirred at rt overnight. The reaction mixture was poured in ice, and washed with dichloromethane (4 times). The aqueous phase was concentrated, diluted with tetrahydrofuran (200 mL), and treated with 6M NaOH solution (130 mL) to pH 12-13, followed by di-tert-butyl dicarbonate (7.94 g, 36.4 mmol), and then stirred at rt overnight. The reaction mixture was concentrated, diluted with water, acidified with 2 M HCl solution to pH 2, and

extracted with ethyl acetate. The combined organic extracts were concentrated and chromatographed (SiO_2; 5% methanol/dichloromethane) to give compound **2549** (0.95 g, 15% based on reacted starting material). ^1H NMR (400 MHz, $CDCl_3$) δ 7.54-7.27 (m, 3H), 5.67-5.50 (d, 1H), 3.87-3.79 (m, 2H), 3.01-2.88 (m, 2H), 1.61-1.57 (9H).

Part C:

Weinreb amide **2550** was prepared using procedures described in Example 51I, Part A. ^1H NMR (400 MHz, CDCl3) δ 7.37-7.14 (m, 3H), 6.1-5.88 (d, 1H), 4.0 (s, 3H), 3.84-3.67 (m, 2H), 3.21 (s, 3H), 3.17-3.09 (m, 1H), 2.79-2.72 (m, 1H), 1.5 (s, 9H). HPLC-MS t_R = 2.15 min ($UV_{254\ nm}$); mass calculated for formula C17H23ClN2O4 354.1, observed LCMS m/z 255.1 (M-BOC+H).

Part D:

Acetylene **2551** was prepared using procedures described in Example 51I, Part B. HPLC-MS t_R = 2.22 min ($UV_{254\ nm}$); mass calculated for formula C17H18ClNO3 319.1, observed LCMS m/z 264.0 (M-(t-butyl)).

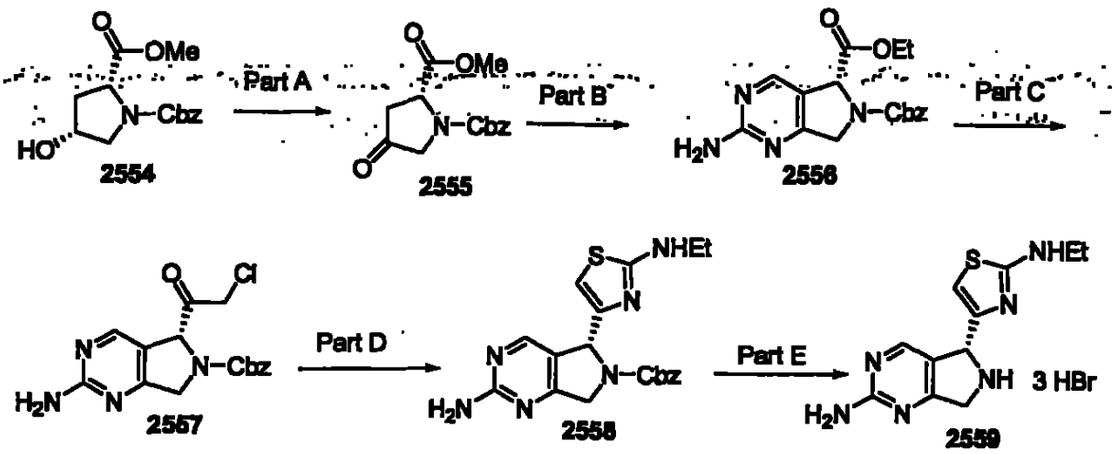
Part E:

Pyrazole **2552** was prepared using procedures described in Example 62G Part A. HPLC-MS t_R = 1.97 min ($UV_{254\ nm}$); mass calculated for formula C17H20ClN3O2 333.1, observed LCMS m/z 234 (M-BOC+H).

Part F:

Amine **2553** was prepared using a procedure similar to that described in Example 51I, Part D. HPLC-MS t_R = 0.89 min ($UV_{254\ nm}$); mass calculated for formula C12H12ClN3 233.1, observed LCMS m/z 234.1 (M+H).

Example 62F:



Part A:

Compound **2554** (3.7 g, 13.4 mmol) was dissolved in methylene chloride (35 mL) and Dess-Martin periodinane (8.55 g, 20.18 mmol) was added and stirred at room temperature overnight. The reaction was quenched with saturated sodium bicarbonate and stirred for 1 hour. The reaction mixture was filtered through celite. The aqueous layer was extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded **2555** (1.75 g). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5 H), 5.25-5.20 (m, 2H), 4.90-4.80 (m, 1H), 4.00-3.80 (m, 2H), 3.80-3.60 (m, 3H), 3.00 (m, 1H), 2.60 (m, 1H).

Part B:

Compound **2556** was prepared according to the procedure in *Bioorg. Med. Chem.* **2002**, *10*, *5*, 1197-1206. ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.4-7.3 (m, 5 H), 5.3-5.15 (m, 3H), 4.7-4.55 (m, 2H), 4.3-4.2 (m, 2H), 1.3 (t, 3H).

Part C:

Compound **2557** was prepared from compound **2556** according to the procedure described in Example 10B Part B. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 1H), 7.60-7.40 (m, 5H), 5.30-5.20 (m, 2H), 5.10 (m, 2H), 4.80-4.60 (m, 1H).

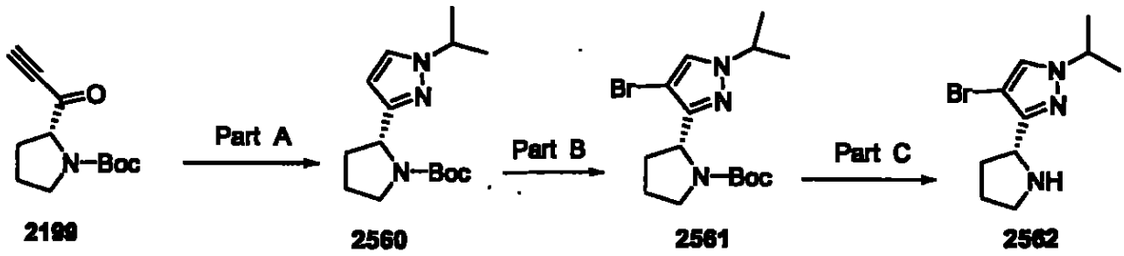
Part D:

Compound **2558** was prepared as described in Example 51B-Part C from compound **2557**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.40-7.20 (m, 5H), 6.20 (s, 1H), 5.30-5.00 (m, 3H), 4.70 (m, 2H), 3.25 (m, 2H), 1.30 (m, 3H).

Part E:

Compound **2558** (80 mg, 0.202 mmol) was dissolved in 30% HBr in acetic acid (3 mL) and stirred for 2 hours. The solvent was removed and the residu was dissolved in water and washed with ethyl acetate. The aqueous layer was lyophilized to provide **2559** as a red solid (100 mg). HPLC-MS t_R = 0.414 min ($UV_{254\ nm}$); mass calculated for formula C11H14N6S 262.1, observed LCMS m/z 263.1 (M+H).

Example 62G:



2199 **2560** **2561** **2562**

Part A:

Compound **2199** (1.11 g, 3.7 mmol), isopropyl hydrazine hydrochloride (616 mg, 5.55 mmol), and sodium carbonate (980 mg, 9.25 mmol) were dissolved in ethanol (12 mL) and stirred at 80 °C for 5 hours. The reaction mixture was cooled to room temperature and diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 33% ethyl acetate/hexanes) afforded **2560** (750 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, 1 H), 6.00 (d, 1H), 5.10-4.90 (m, 1H), 4.50 (m, 1H), 3.60-3.40 (m, 2H), 2.30-2.10 (m, 1H), 2.10-1.80 (m, 3H), 1.50 (m, 9H), 1.30 (s, 6H).

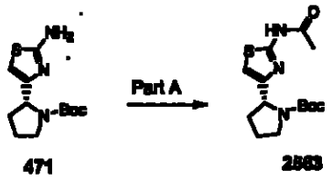
Part B:

Compound **2560** (541 mg, 1.93 mmol) was dissolved in chloroform (10 mL) and N-bromosuccinimide (412 mg, 2.31 mmol) was added and stirred at room temperature overnight. The reaction was diluted with methylene chloride and water. The organic layer was washed with 1N NaOH, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 15% ethyl acetate/hexanes) afforded **2561** (350 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1 H), 5.00-4.80 (m, 1H), 4.40 (m, 1H), 3.60-3.40 (m, 2H), 2.30-2.20 (m, 1H), 2.10-2.00 (m, 1H), 2.00-1.80 (m, 2H), 1.40 (m, 9H), 1.20 (s, 6H).

Part C:

Compound **2561** (86 mg, 0.238 mmol) was dissolved in 4M HCl in dioxane (2.0 mL) and stirred for 1 hour. The solvent was removed to provide **2562** as a white solid (82 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 9.60 (bs, 1H), 8.80 (bs, 1H), 8.18 (s, 1 H), 4.60 (m, 1H), 4.50 (m, 1H), 3.25 (m, 2H), 2.35 (m, 1H), 2.10-1.90 (m, 3H), 1.40 (d, 6H).

Example 62H:



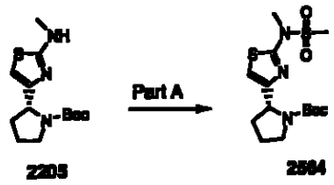
471 2563

Part A:

To **471** (81 mg, 0.30 mmol) and DIEA (0.156 mL, 0.90 mmol) in dichloromethane (5 mL) was added slowly acetyl chloride (0.052 mL, 0.72 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 hr and concentrated. The residue was then dissolved in EtOAc and H_2O, washed with 1N citric acid, $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. The resulting sticky solid was dissolved in methanol (5 mL) and stirred with solid K_2CO_3 (100 mg) for 2 hr. After removing the solvent, the residue was dissolved in EtOAc and H_2O, washed with H_2O, brine, dried (Na_2SO_4) and concentrated to afford **2563** (82 mg, 87 %) as an oily solid.

HPLC-MS t_R = 1.60 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{21}N_3O_4S$ 311.1, observed LCMS m/z 312.1 (M+H).

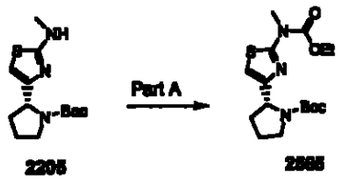
Example 62I:



Part A:

To compound **2205** (100 mg, 0.35 mmol) and DIEA (0.092 mL, 0.53 mmol) in dichloromethane (5 mL) was slowly added methylsulfonic chloride (0.033 mL, 0.42 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 hr and concentrated. The residue was dissolved in EtOAc, washed with water, 1N citric acid, $NaHCO_3$, and brine, dried over Na_2SO_4 and concentrated to afford **2564** (120 mg, 94%) as an oily solid. HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{23}N_3O_4S_2$ 361.1, observed LCMS m/z 362.0 (M+H).

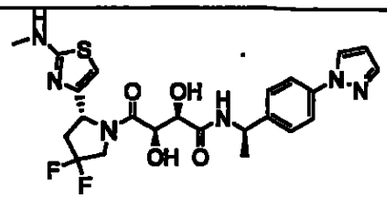
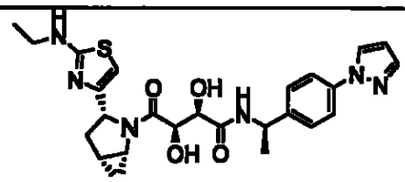
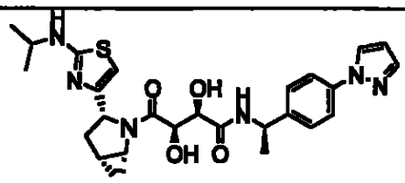
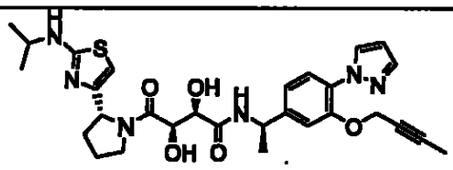
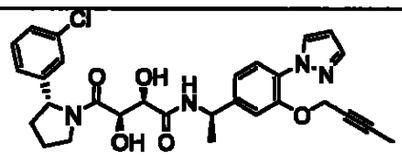
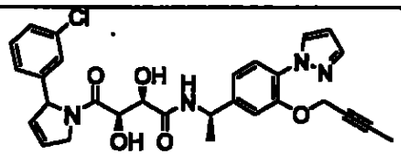
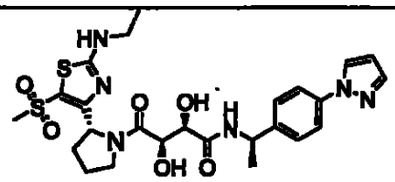
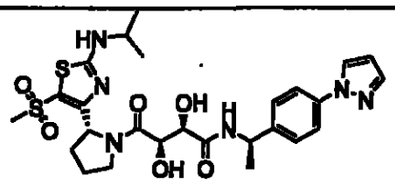
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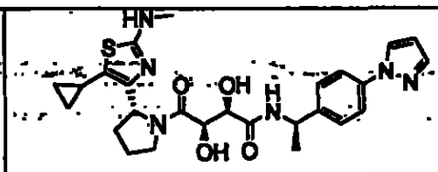
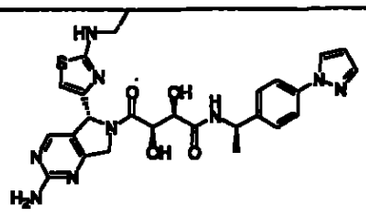
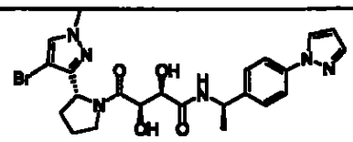
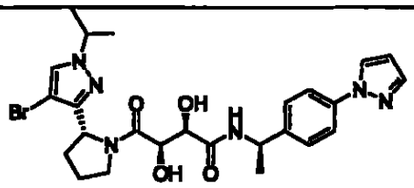
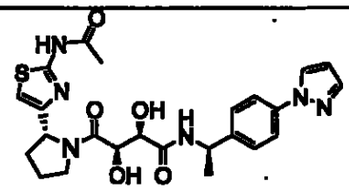
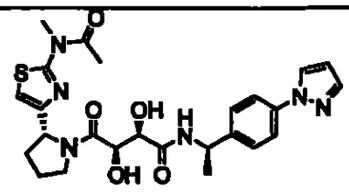
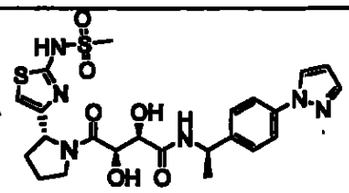
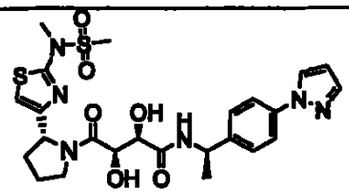


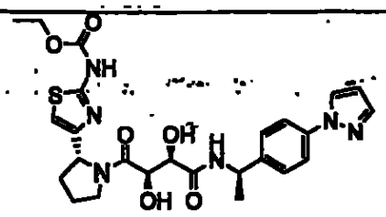
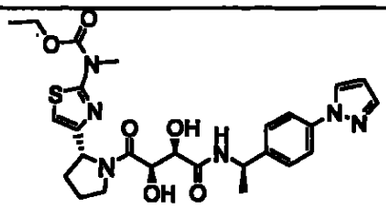
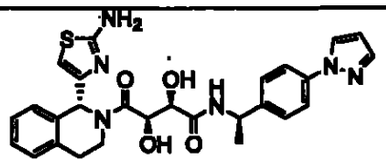
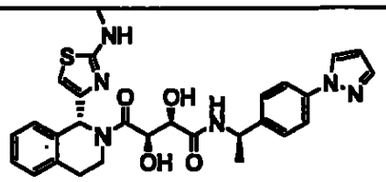
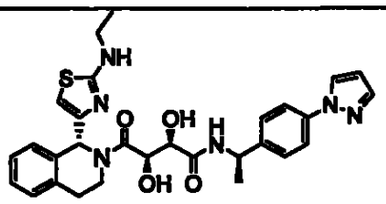
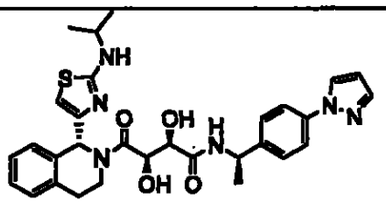
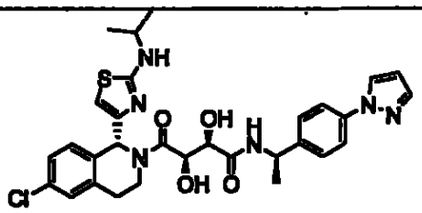
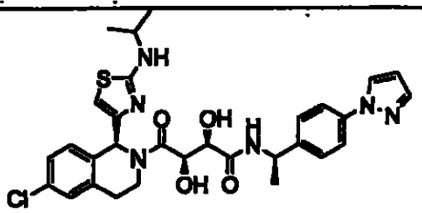
Part A:

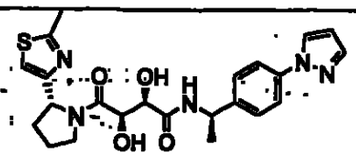
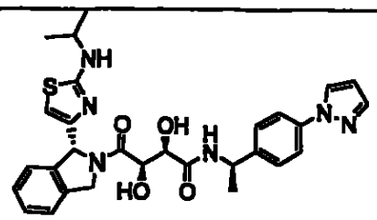
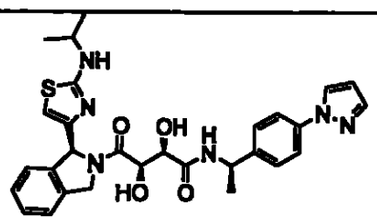
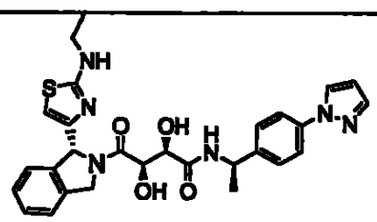
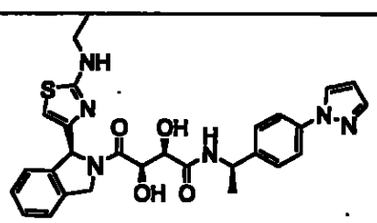
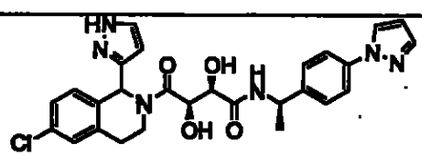
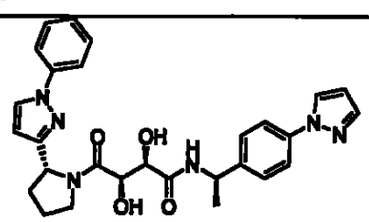
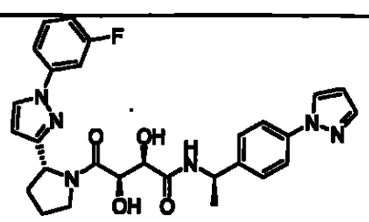
To compound **2205** (80 mg, 0.28 mmol) and DIEA (0.098 mL, 0.56 mmol) in dichloromethane (5 mL) was added slowly ethyl chloroformate (0.054 mL, 0.56 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 hr and concentrated. The residue was dissolved in EtOAc, washed with water, 1N citric acid, $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to afford **2565**(88 mg, 88%) as an oily solid. HPLC-MS t_R = 2.23 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{25}N_3O_4S$ 355.2, observed LCMS m/z 356.2 (M+H).

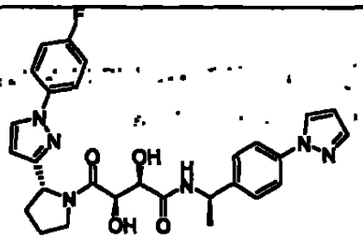
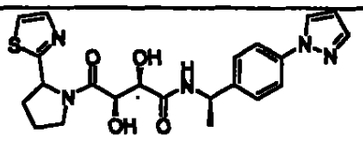
The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2567		520.17	521.0
2568		510.2	511.1
2569		524.2	525.3
2570		580.2	581.2
2571		550.2	551.0
2572		548.2	549.2
2573		576.2	577.3
2574		590.2	591.3

2575		524.2	525.2
2576		563.2	564.2
2577		530.1	531.1
2578		558.2	559.2
2579		512.2	513.2
2580		526.2	527.2
2581		548.2	549.2
2582		562.2	563.2

2583		542.2	543.2
2584		556.2	557.2
2585		532.2	533.2
2586		546.2	547.2
2587		560.2	561.1
2588		574.2	575.2
2589		608.2	609.2
2590		608.2	609.2

2591		469.2	470.2
2592		560.2	561.1
2593		560.2	561.1
2594		546.2	547.2
2595		546.2	547.2
2596		534.2	535.2
2597		514.2	515.2
2598		532.2	533.2

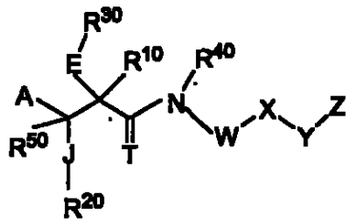
2599		532.2	533.2
2600		455.2	456.2

It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications that are within the spirit and scope of the invention, as defined by the appended claims.

Claims

What is claimed is:

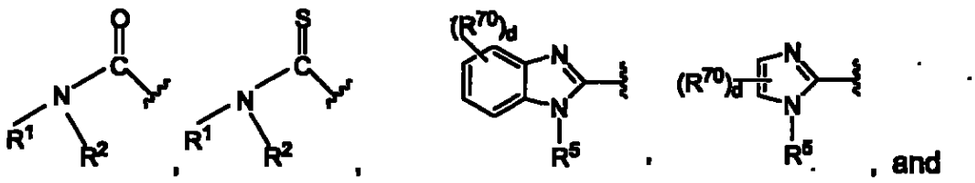
1. A compound of formula (I):



formula (I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

A is selected from the group consisting of:



, and

$-CO_2R^1$;

d is 0 to 4;

J is selected from the group consisting of O, S, and NR^5;

E is selected from the group consisting of: O, S, and NR^5;

T is O or S;

R^1 and R^2 are the same or different, each being independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; or alternatively R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, heteroaryl and 4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more

moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^{10} is selected from the group consisting of H, alkyl, and fluoroalkyl;

R^{20} is selected from the group consisting of H, alkyl, and fluoroalkyl;

R^{30} is H or alkyl, or alternatively R^{30} and R^{40} taken together with the N to which R^{40} is shown attached to in Formula I, are joined to form a 4-7 membered heterocylic ring, wherein said heterocylic ring is unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^{40} is H or alkyl;

R^{60} is H or alkyl;

W is $-(CR^{13}_2)_n-$, wherein n is 0 to 5 or a covalent bond, or alternatively two R^{13} groups can fuse to form a 3-8 membered cycloalkyl, wherein said 3-8 membered cycloalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^6 moieties below;

X is absent or present, and if present X is selected from the group consisting of a covalent bond, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

Y is absent or present, and if present Y is selected from the group consisting of a covalent bond, $-[C(R^6)_2]_n-$ wherein n is 1 or 2, -O-, -S-, $-NR^1-$, $-SO_v-$ wherein v is 1 to 2, $-SO_n(CR^6_2)_p-$ wherein n is 1 or 2 and p is 1 to 4, $-O(CR^6_2)_q-$ or $-(CR^6_2)_qO-$ wherein q is 1 to 4, $-N(R^7)S(O)_n-$ or $-S(O)_nN(R^7)-$ wherein n is 1 or 2, and $-N(R^7)C(O)-$ or $-C(O)N(R^7)-$;

Z is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, said cycloalkyl, heterocyclyl, aryl, and heteroaryl being optionally fused with aryl, heterocyclyl, heteroaryl or cycloalky; wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl,

aryl, and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^6 is selected from the group consisting of hydrogen, alkyl, and alkylaryl;

each R^8 is the same or different and is independently selected from the group consisting of hydrogen, halogen, $-SR^{15}$, $-S(O)_qR^{15}$ wherein q is 1 to 2, alkyl, cycloalkyl, heterocyclyl, alkoxyl, hydroxy, nitro, cyano, amino, alkenyl, alkynyl, arylalkyl, aminocarbonyl, alkylcarbonyl, and alkoxycarbonyl;

each R^7 is the same or different and is independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, alkenyl, alkynyl, arylalkyl, alkylcarbonyl, and alkoxycarbonyl, wherein each of the aryl, heteroaryl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^{13} is the same or different and is independently selected from the group consisting of hydrogen, halogen, -OH, $-OR^{14}$, alkyl, cycloalkyl, heterocyclyl, alkenyl, alkynyl, alkylaryl, alkylamino, and alkylcarbonyl;

R^{14} is alkyl;

each R^{70} is a substituent for H where indicated and is the same or different and is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, $-CF_3$, $-OCF_3$, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)_qN(R^{15})(R^{16})$ wherein q is 1 to 2, $-C(=NOR^{15})R^{16}$, $-N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{17})S(O)_2N(R^{16})(R^{15})$, $-N(R^{17})S(O)N(R^{16})(R^{15})$, $-N(R^{17})C(O)N(R^{16})(R^{15})$, $-CH_2-N(R^{17})C(O)N(R^{16})(R^{15})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, and

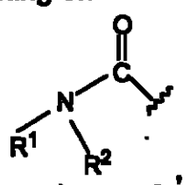
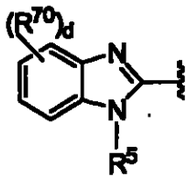
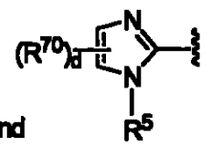
$-S(O)_qR^{15}$ wherein q is 1 to 2; and wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl are independently unsubstituted or substituted by 1 to 5 groups independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, $-CF_3$, -CN, $-OR^{15}$, $-N(R^{15})(R^{16})$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, and $-N(R^{15})S(O)R^{16}$; and

each R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, or alternatively R^{15} and R^{16} taken together with the N to which they are shown attached, are joined to form a 4-8 membered heterocylic ring, wherein said 4-8 membered cycloalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{75} moieties below;

each R^{75} is independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl, and wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl are independently unsubstituted or substituted by 1 to 5 groups independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, $-CF_3$, -CN, $-OR^{19}$, $-N(R^{19})_2$, $-C(O)OR^{19}$, $-C(O)N(R^{19})_2$, and $-N(R^{19})S(O)R^{19}$; and

each R^{19} is independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl.

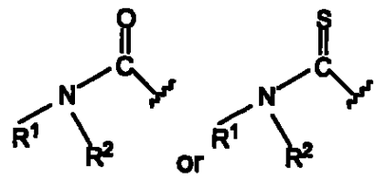
2. The compound of claim 1 wherein A is selected from the group consisting of:



and


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said

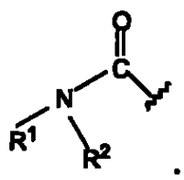
4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

3. The compound of claim 1 wherein A is

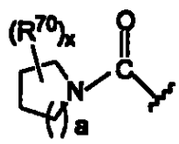


wherein R^1 and R^2 are the same or different, each being independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; wherein said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

4. The compound of claim 3 wherein A is



5. The compound of claim 2 wherein A is

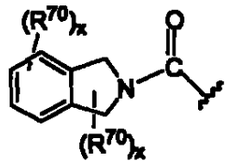


wherein

a is 0 to 4; and

x is 0 to 4.

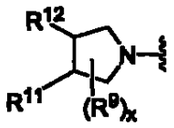
6. The compound of claim 2 wherein A is:



wherein

each x idependently is 0 to 4.

7. The compound of claim 2 wherein a ring is formed from $-NR^1R^2$ and said ring is



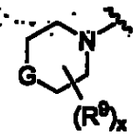
wherein

each R^9 is a substituent for H where indicated and can be the same or different, each being independently selected from the group consisting of -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

$R^{11}$and R^{12} taken together with the carbon to which each $R^{11}$and R^{12} are shown attached are fused heteroaryl or fused cycloalkyl, wherein said fused heteroaryl and fused cycloalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; and

x is 0 to 4, and when x is greater than 1, each R^9 moiety can be the same or different, each moiety being independently selected from the group of R^9 moieties.

8. The compound of claim 2 wherein a ring is formed from $-NR^1R^2$ and said ring is



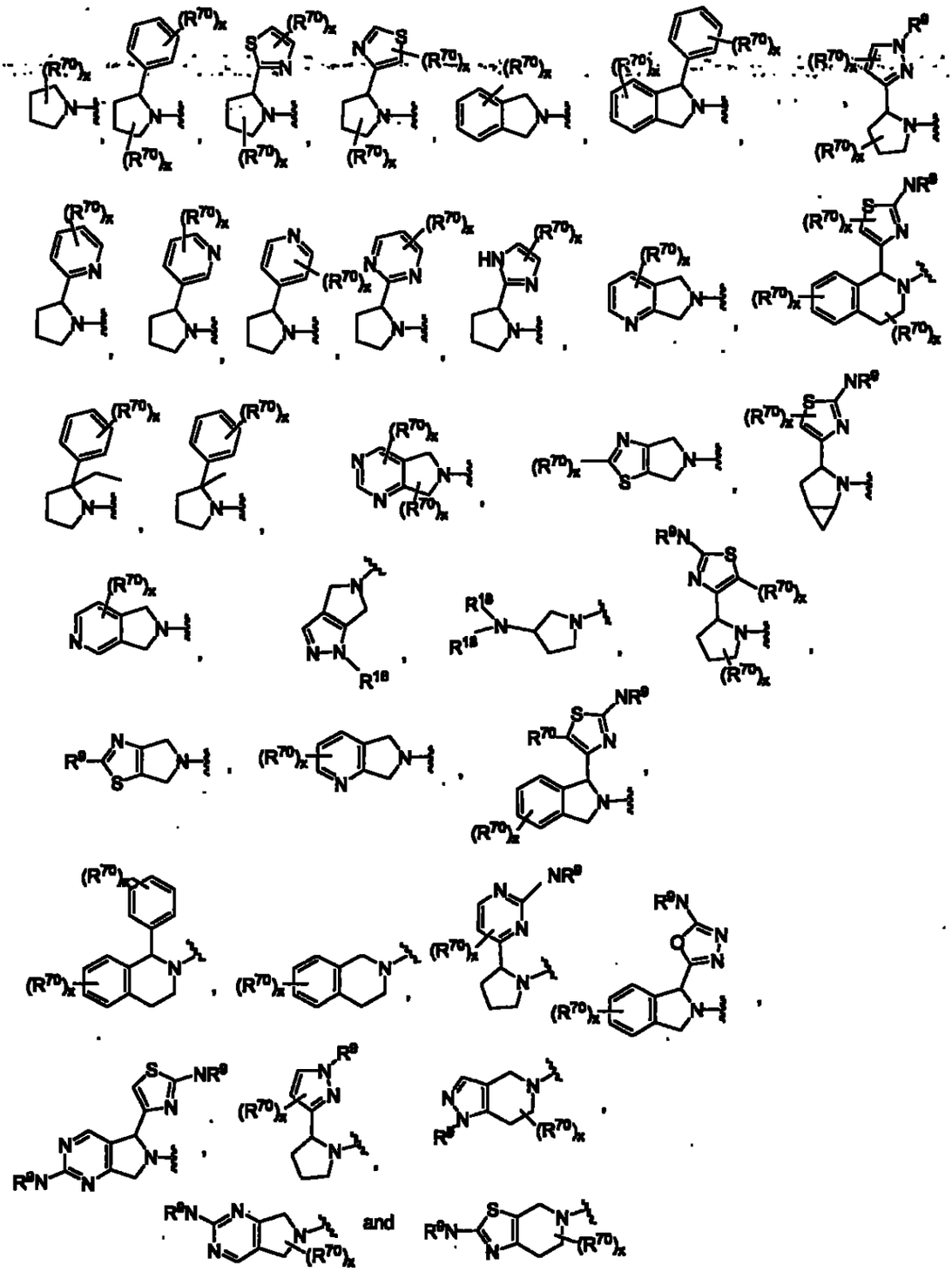
wherein

each R^9 is a substituent for H where indicated and can be the same or different, each being independently selected from the group consisting of -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

x is 0 to 4, and when x is greater than 1, each R^9 moiety can be the same or different, each moiety being independently selected from the group of R^9 moieties; and

G is selected from the group consisting of CH_2, NR^7, O, S, or SO_2.

9. The compound of claim 2 wherein a ring is formed from $-NR^1R^2$ and said ring is selected from the group consisting of

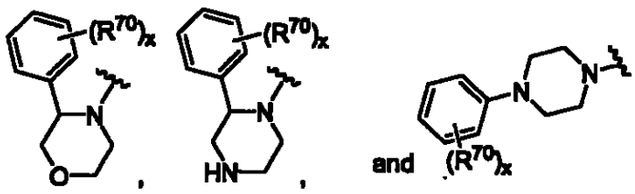


wherein

x is 0 to 4, and when x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties; and

each R^{18} is the same or different and is independently H or alkyl.

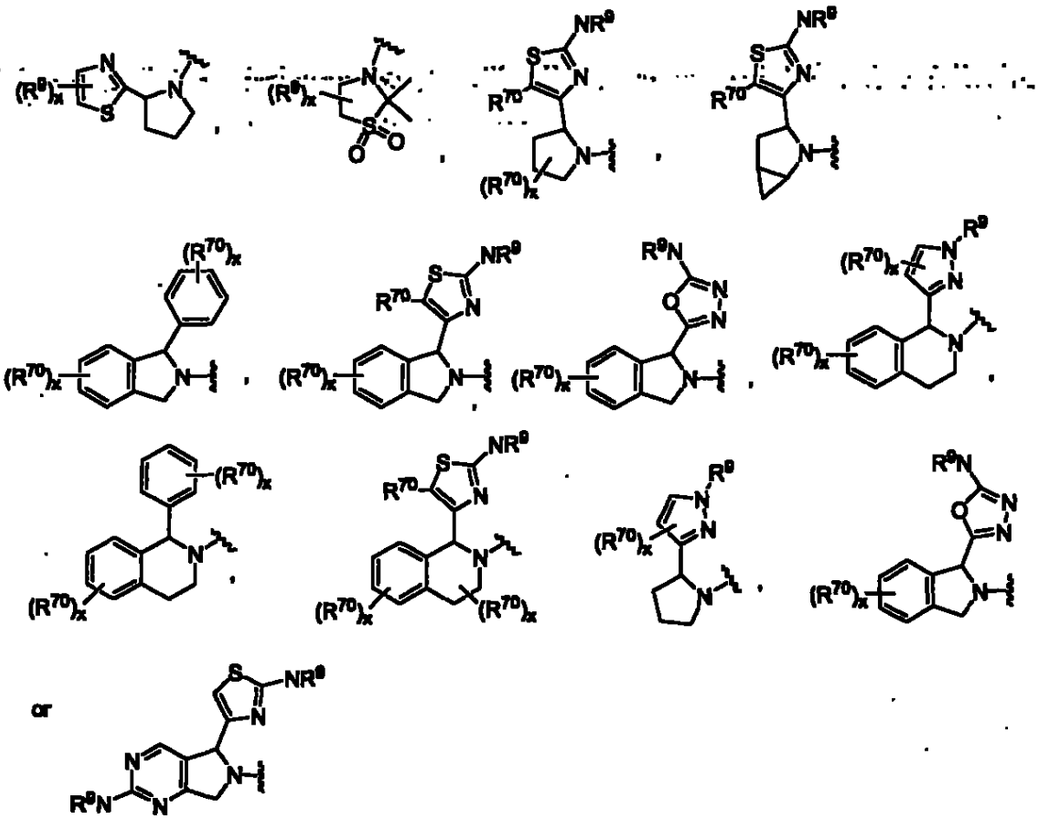
10. The compound of claim 2 wherein a ring is formed from $-NR^1R^2$ and said ring is selected from the group consisting of:



wherein

x is 0 to 4, and when x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

11. The compound of claim 2 wherein a ring is formed from $-NR^1R^2$ and is



or

wherein

each R^9 is a substituent for H where indicated and can be the same or different, each being independently selected from the group consisting of -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; and

x is 0 to 4, and when x is greater than 1, each R^9moiety can be the same or different, each moiety being independently selected from the group of R^9moieties.

12. The compound of claim 2 wherein J is O.

13. The compound of claim 2 wherein E is O.

14. The compound of claim 2 wherein R^{10} is H or alkyl.

15. The compound of claim 2 wherein R^{20} is H.

16. The compound of claim 2 wherein R^{30} is H.

17. The compound of claim 2 wherein R^{40} is H.

18. The compound of claim 2 wherein R^{50} is H.

19. The compound of claim 2 wherein R^{13} is H or alkyl.

20. The compound of claim 19 wherein R^{13} is H or $-CH_3$.

21. The compound of claim 2 wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-6 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, wherein R^{70} is aryl.

22. The compound of claim 2 wherein Y is a covalent bond or $-[C(R^6)_2]_n-$ wherein n is 1 to 2.

23. The compound of claim 2 wherein Y is selected from the group consisting of a covalent bond, $-CH_2-$, -C(H)(OH)-, -C(O)- and –O-.

24. The compound of claim 23 wherein Y is a covalent bond or $-CH_2-$.

25. The compound of claim 24 wherein Y is a covalent bond.

26. The compound of claim 2 wherein W is $-(CR^{13}_2)_n-$, in which n is 1-5 and each R^{13} is H, or alkyl.

27. The compound of claim 2 wherein W is selected from the group consisting of $-CH_2-$, $-C(H)(CH_3)-$, $-C(CH_3)_2-$ and $-CH_2CH_2-$.

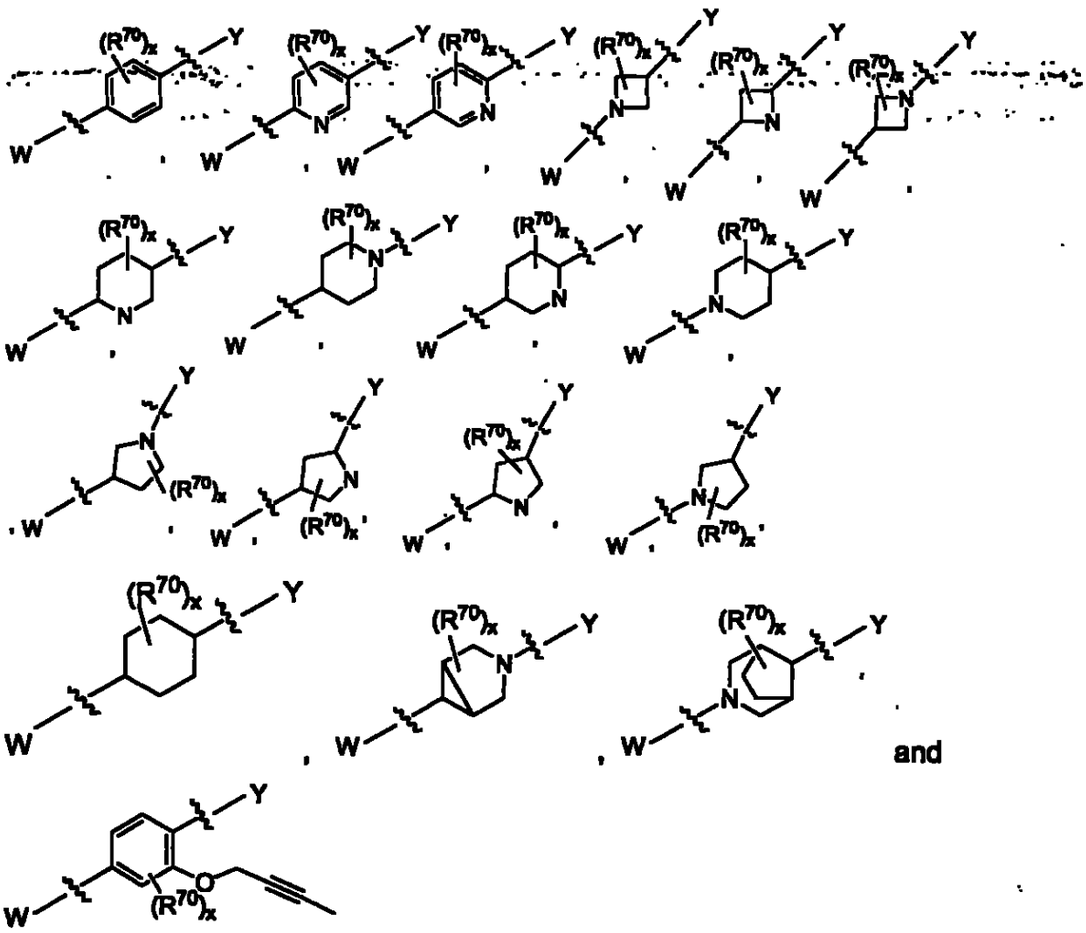
28. The compound of claim 27 wherein W is $-CH_2-$ or $-C(H)(CH_3)-$.

29. The compound of claim 2 wherein X is selected from the group consisting of alkyl, aryl, heterocyclyl and heteroaryl.

30. The compound of claim 29 wherein X is selected from the group consisting of phenyl, azetidinyl, pyrrolidinyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl.

31. The compound of claim 30 wherein X is selected from the group consisting of phenyl, piperidinyl and pyridinyl.

32. The compound of claim 29 wherein X is selected from the group consisting of

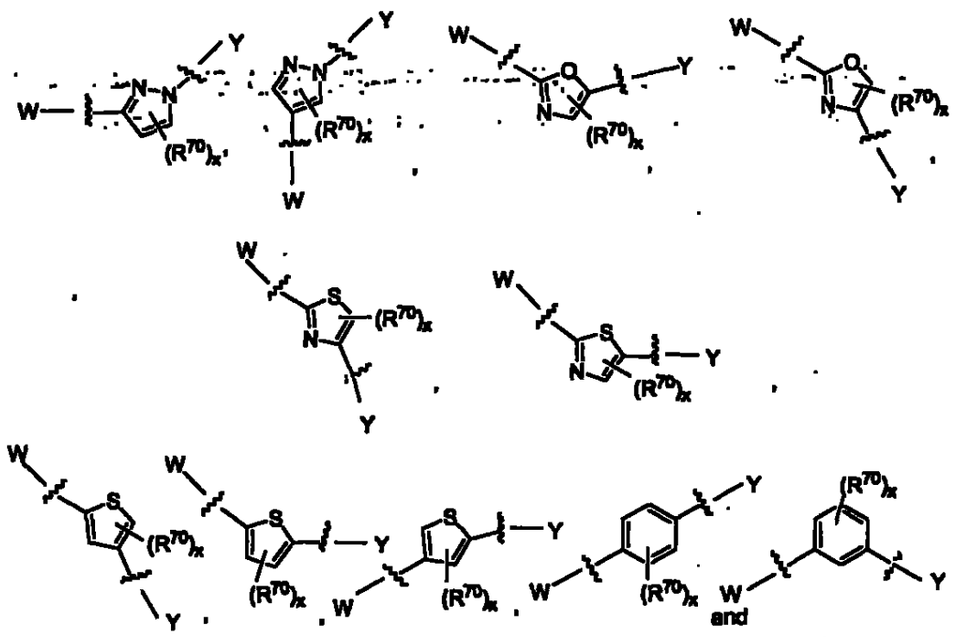


and

wherein

x is 0 to 4, and wherein x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

33. The compound of claim 29, wherein X is selected from the group consisting of



and

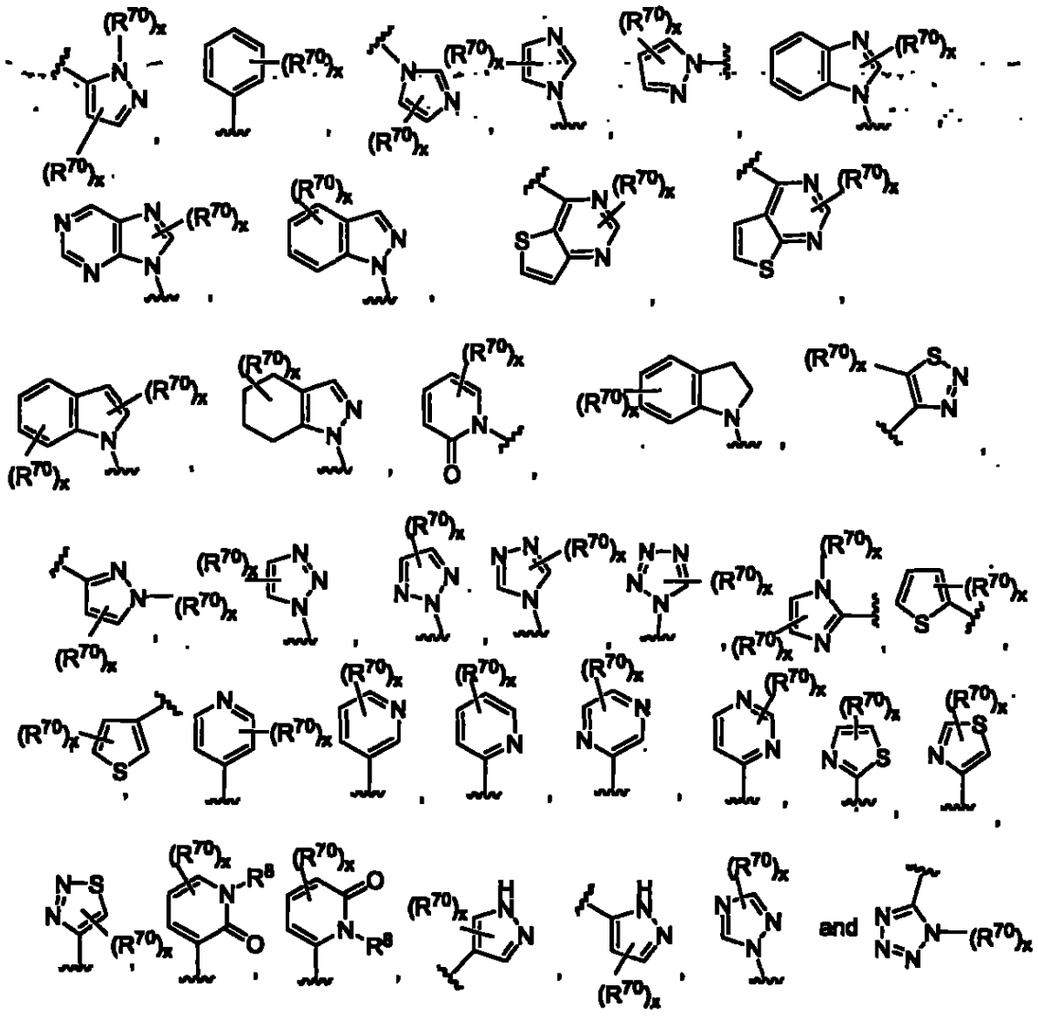
wherein

x is 0 to 4, and when x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

34. The compound of claim 2 wherein Z is selected from the group consisting of H, aryl and heteroaryl.

35. The compound of claim 34 wherein Z is selected from the group consisting of H, phenyl, indolyl, benzimidazolyl, pyrazolyl, thienyl, pyridinyl, thiazolyl, thiadiazolyl, imidazolyl, pyrrolidinyl, pyrazinyl, triazolyl, tetrazolyl and tetrazinyl, wherein said phenyl, indolyl, benzimidazolyl, pyrazolyl, thienyl, pyridinyl, thiazolyl, thiadiazolyl, imidazolyl, pyrrolidinyl, pyrazinyl, triazolyl, tetrazolyl and tetrazinyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of R^{70} moieties.

36. The compound of claim 35 wherein Z is selected from the group consisting of



wherein

x is 0 to 4, and when x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

37. The compound of claim 35 wherein Z is phenyl.

38. The compound of claim 37 wherein said phenyl is substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

39. The compound of claim 35 wherein Z is thienyl.

40. The compound of claim 39 wherein said thienyl is substituted with at least one substituent selected from the group consisting of cyano,

alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

41. The compound of claim 35 wherein Z is pyrazolyl.

42. The compound of claim 41 wherein said pyrazolyl is substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

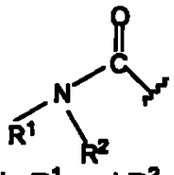
43. The compound of claim 35 wherein Z is pyridinyl.

44. The compound of claim 43 wherein said pyridinyl is substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

45. The compound of claim 35 wherein Z is imidazolyl.

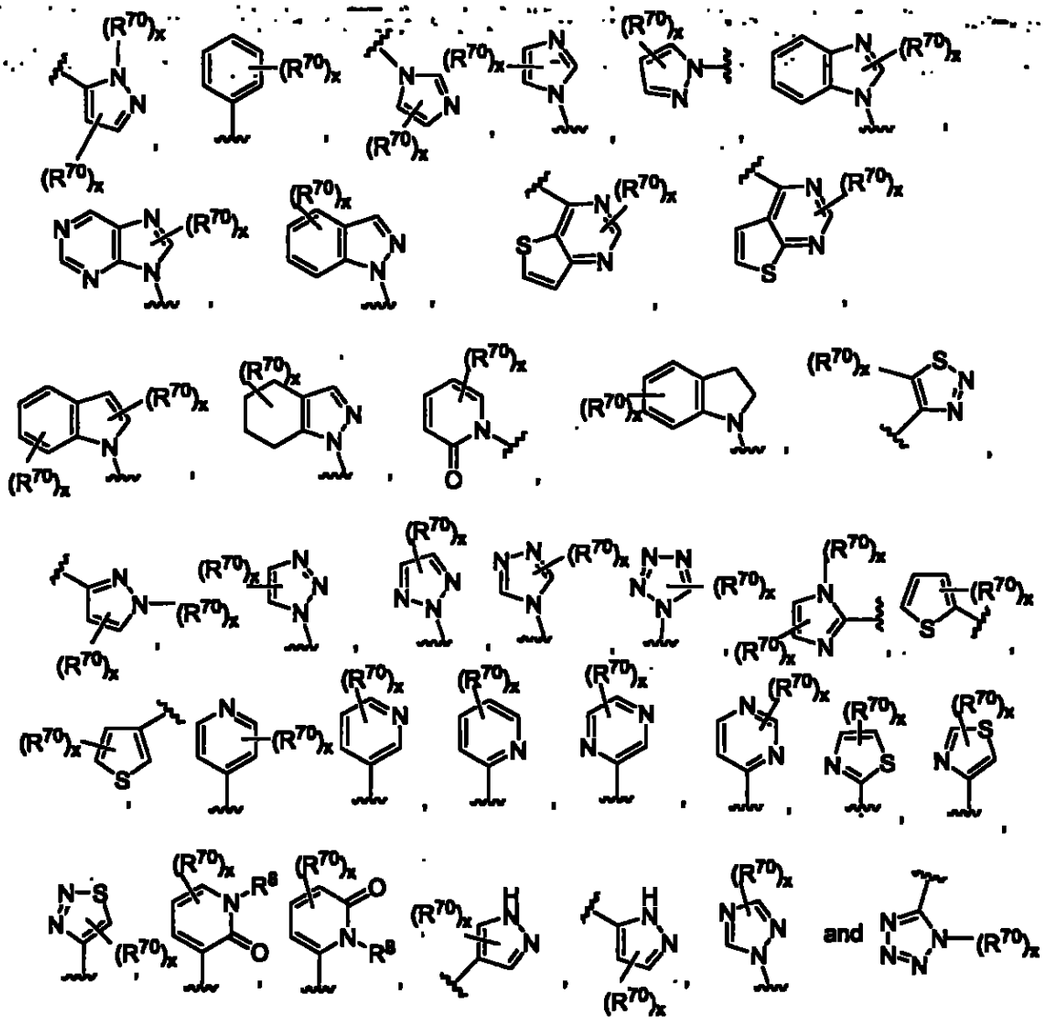
46. The compound of claim 45 wherein said imidazolyl is substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

47. The compound of claim 2 wherein A is

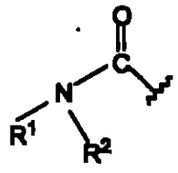


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^{13}{}_2)_n-$, wherein n is 0 to 5; X is selected from the group consisting of aryl, heteroaryl and heterocyclyl; Y is selected from the group consisting of a covalent bond, $-[C(R^6)_2]_n-$ wherein n is 1 to 2, -O-, -S-, and $-NR^1-$; and Z is selected from the

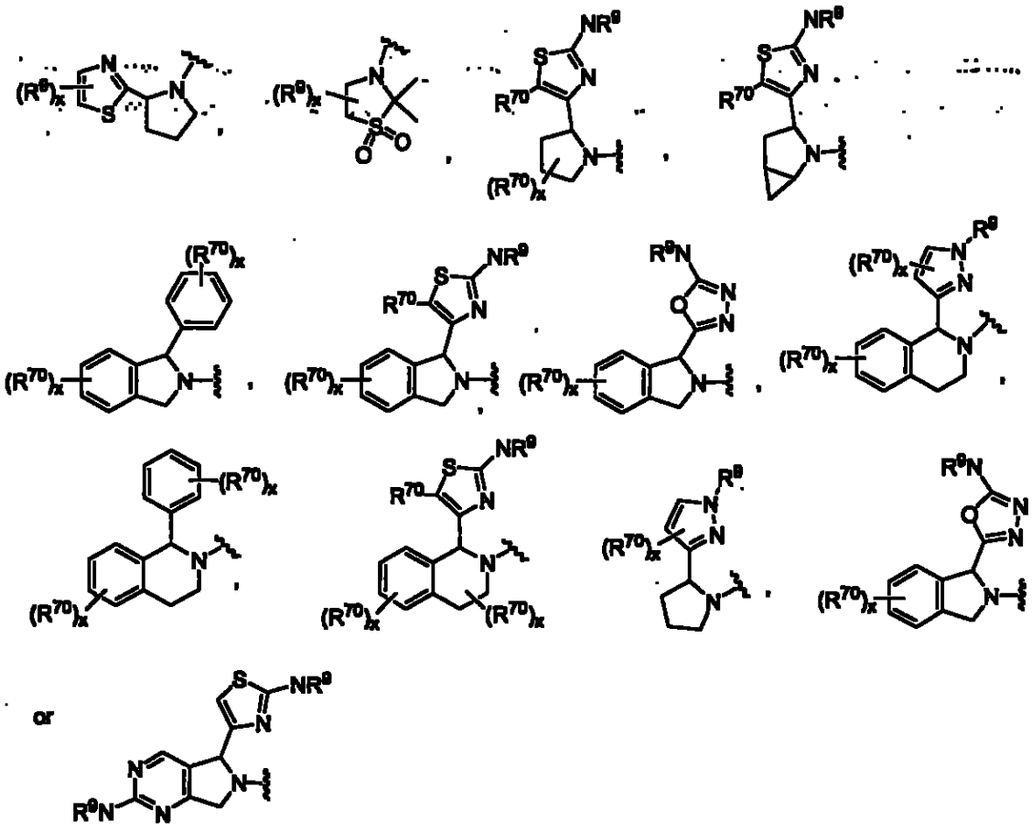
group consisting of



48. The compound of claim 47 wherein the $-NR^1R^2$ of



is



wherein

each R^9 is a substituent for H where indicated and can be the same or different, each being independently selected from the group consisting of -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; and

x is 0 to 4, and when x is greater than 1, each R^9moiety can be the same or different, each moiety being independently selected from the group of R^9moieties.

49. The compound of claim 47 wherein X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl, and pyrazolyl.

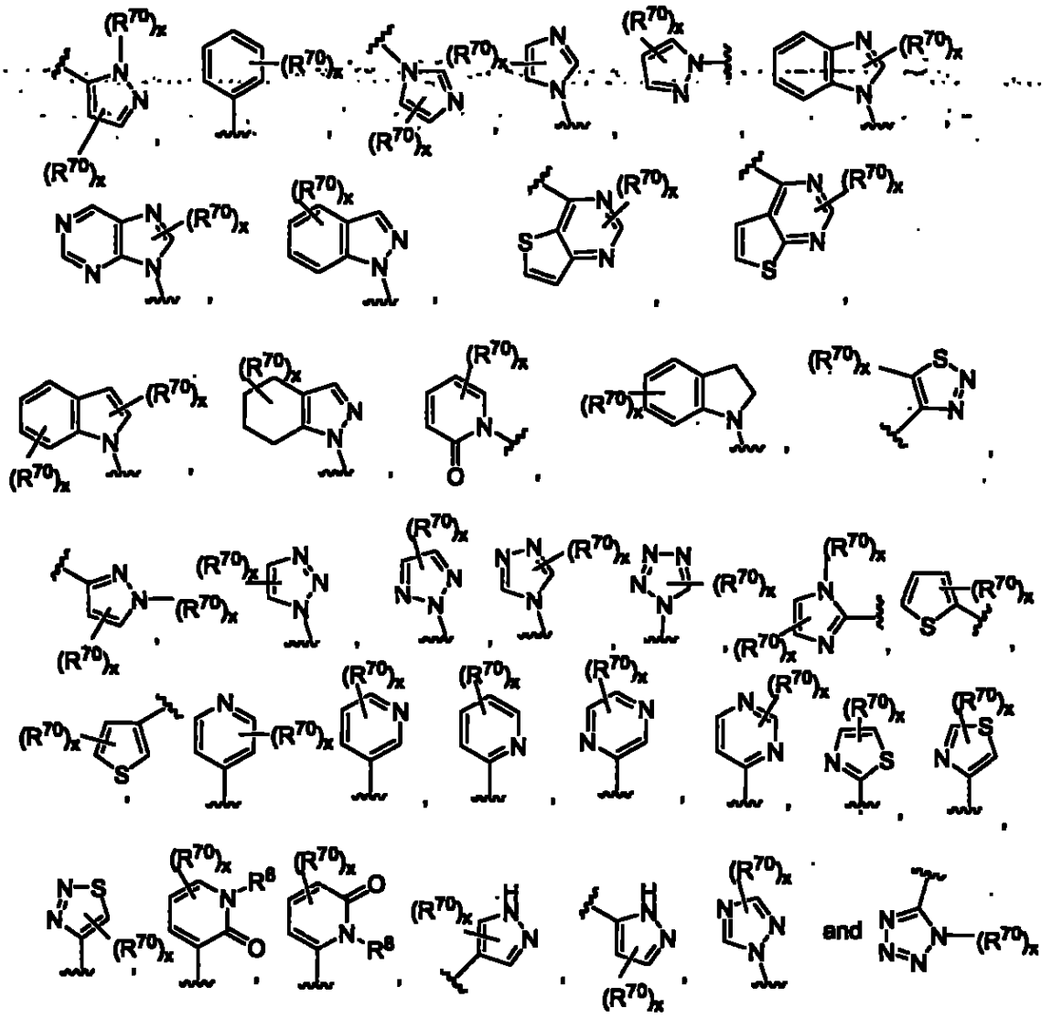
50. The compound of claim 48 wherein X is selected from the group consisting of phenyl, piperidinyl, thienyl, and pyridinyl and Y is selected from the group consisting of a covalent bond, $-[C(R^6)_2]_n-$ wherein n is 1 to 2 and -O-.

51. The compound of claim 48 wherein X is piperidinyl, Y is a covalent bond, and Z is aryl or heteroaryl having two substituents which can be the same or different, each moiety being independently selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy and amino.

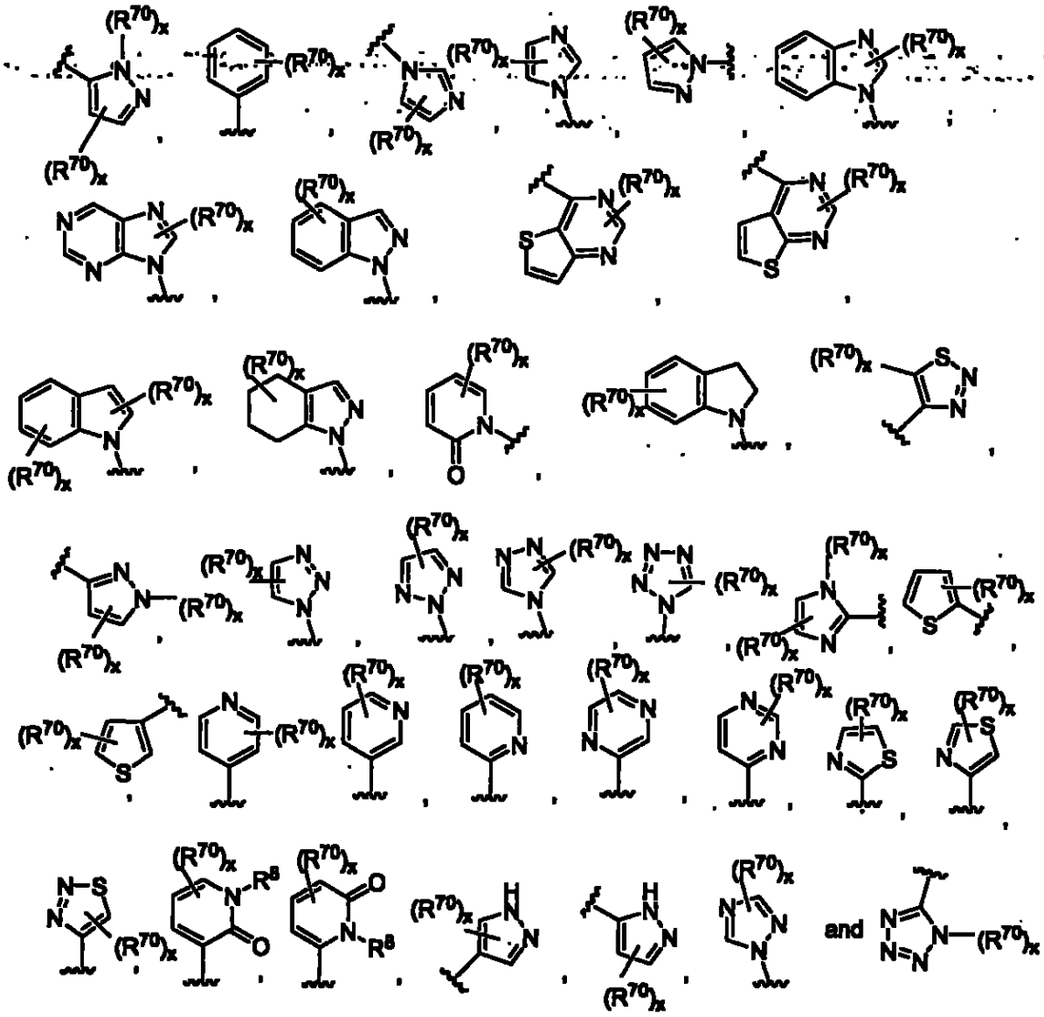
52. The compound of claim 47 wherein W is selected from the group consisting of $-CH_2-$, $-C(H)CH_3-$, $-C(CH_3)_2-$ and Y is a covalent bond.

53. The compound of claim 47 wherein W is $-CH_2-$ or $-C(H)(CH_3)-$ and Y is $-CH_2-$.

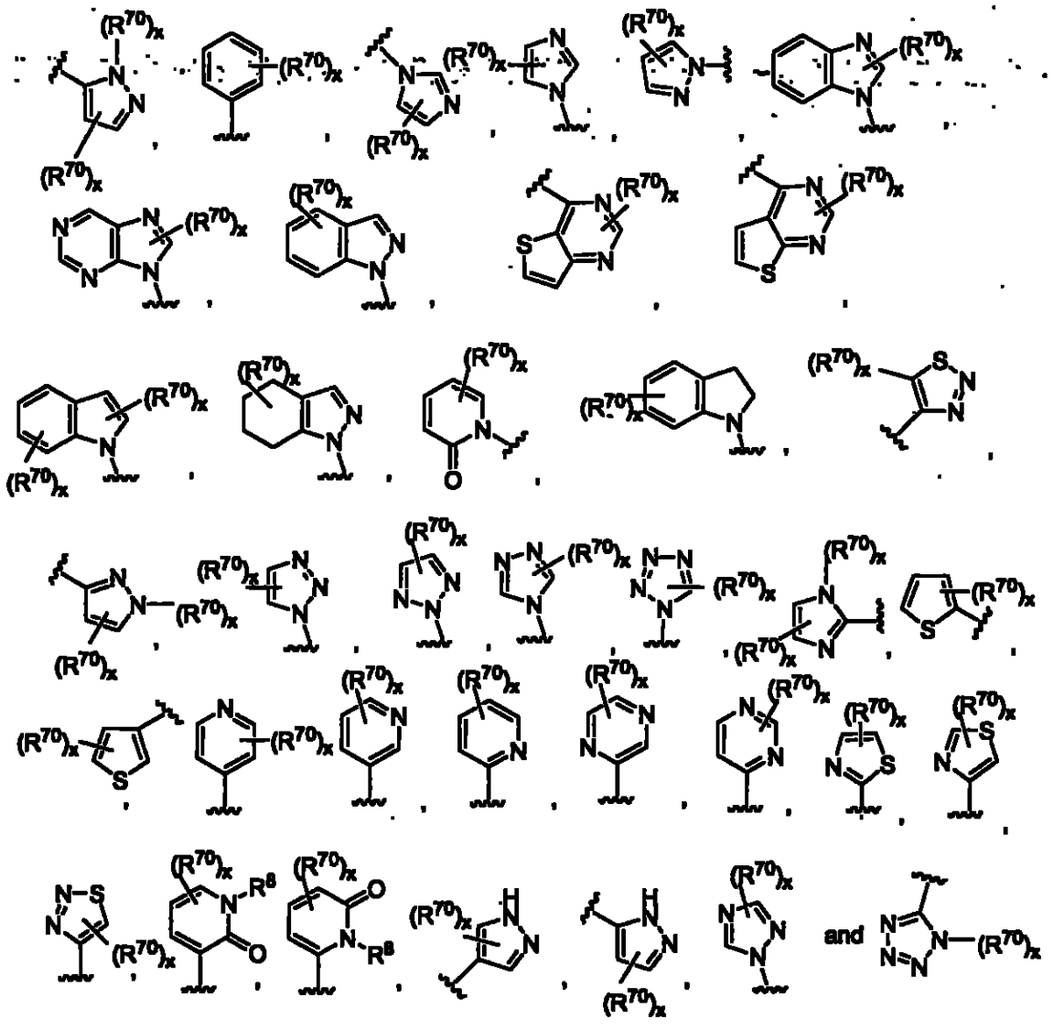
54. The compound of claim 47 wherein X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is $-[C(R^6)_2]_n-$ wherein n is 1 to 2; and Z is selected from the group consisting of



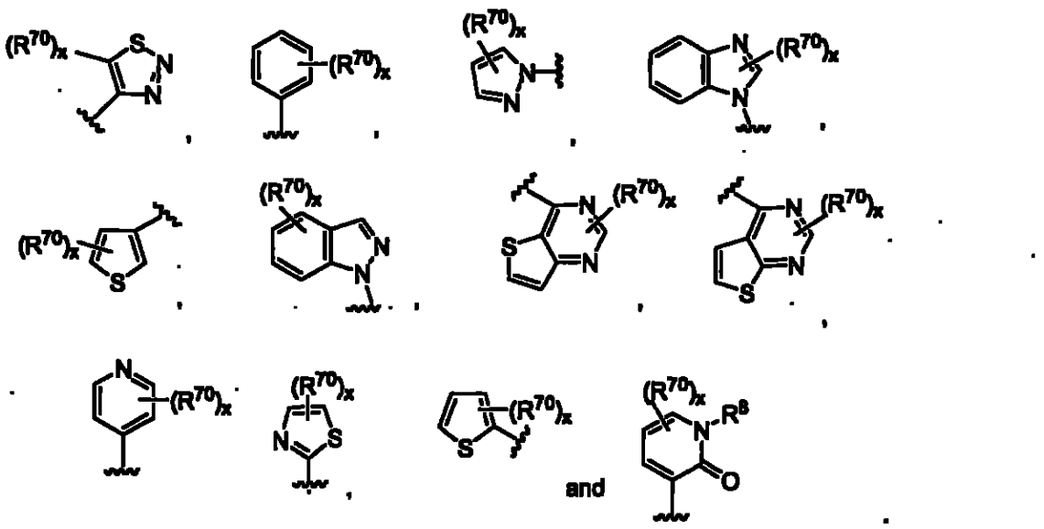
55. The compound of claim 47 wherein X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is selected from the group consisting of O-, -S-, and -NR^1-; and Z is selected from the group consisting of



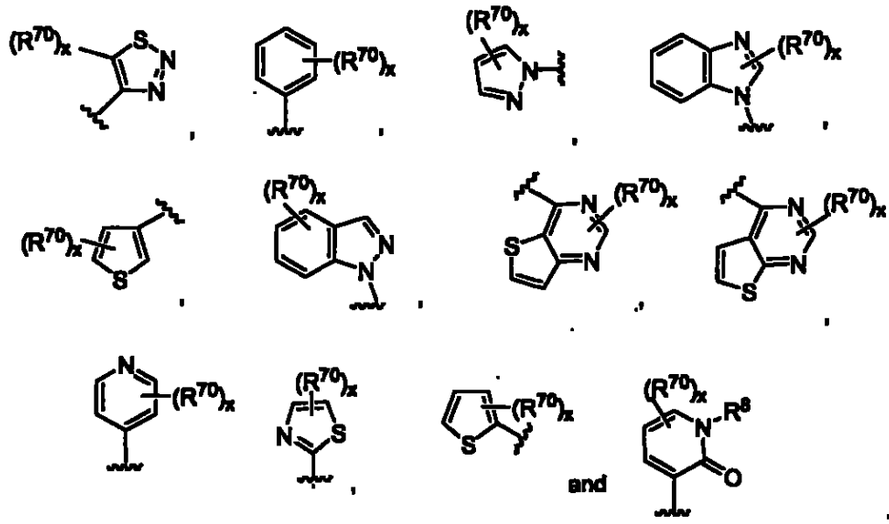
56. The compound of claim 47 wherein W is -$(CR^{13}_2)_n$- wherein n is 1 or 2; X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is a covalent bond and Z is selected from the group consisting of



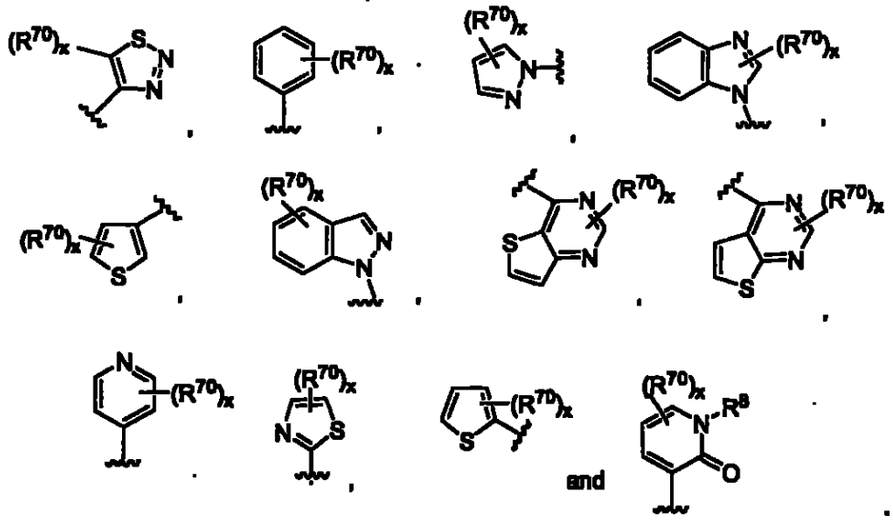
57. The compound of claim 53 wherein Z is selected from the group consisting of



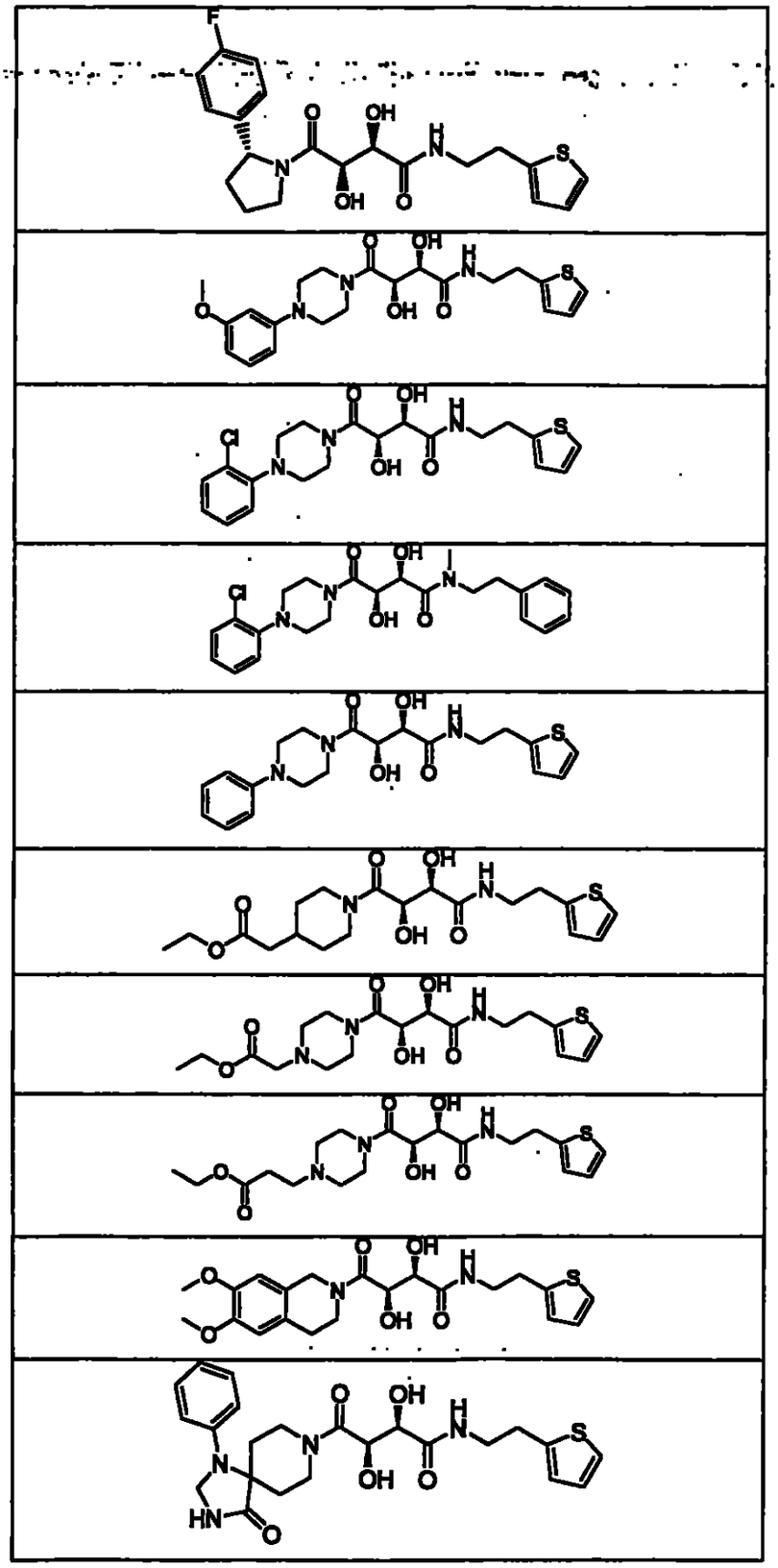
58. The compound of claim 54 wherein Z is selected from the group consisting of

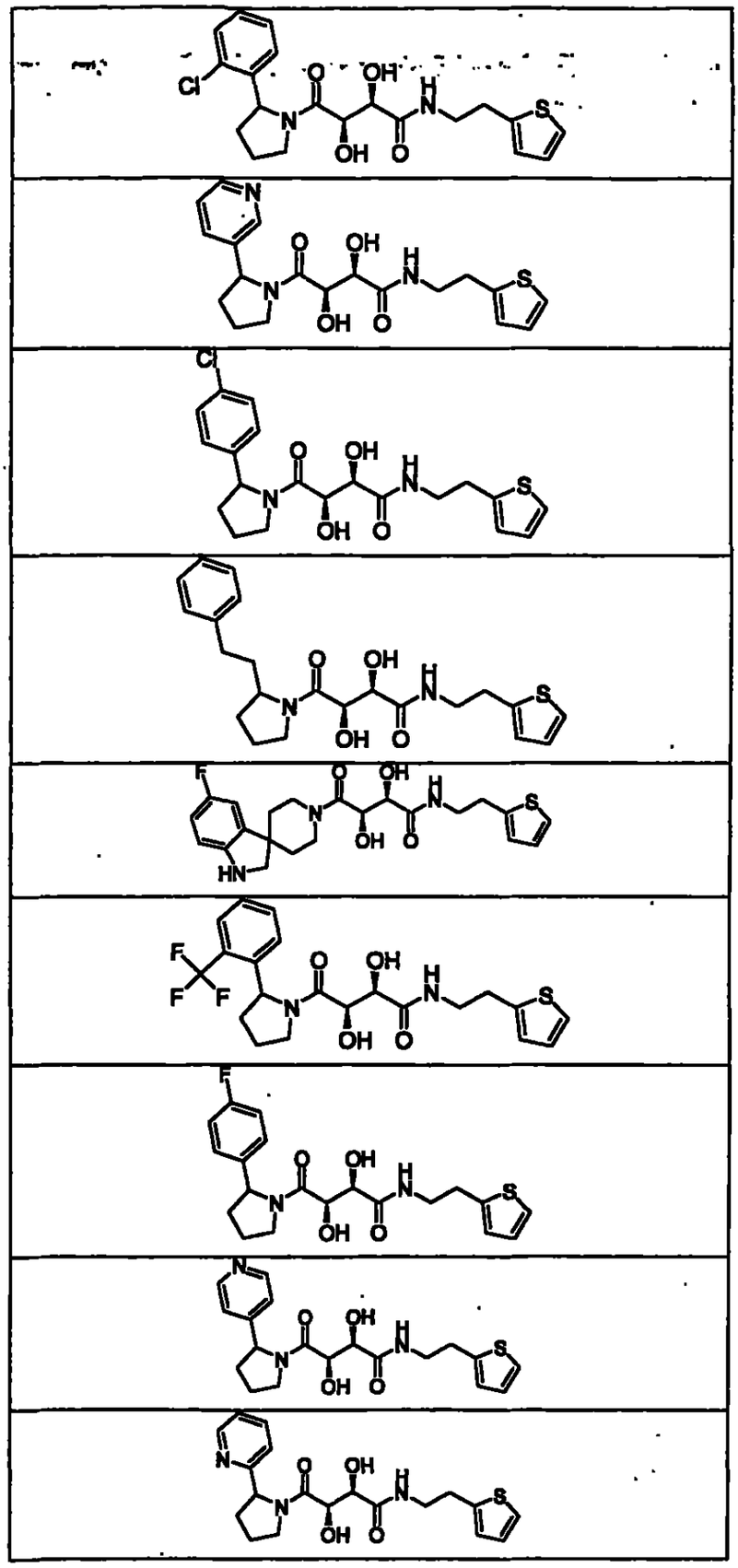


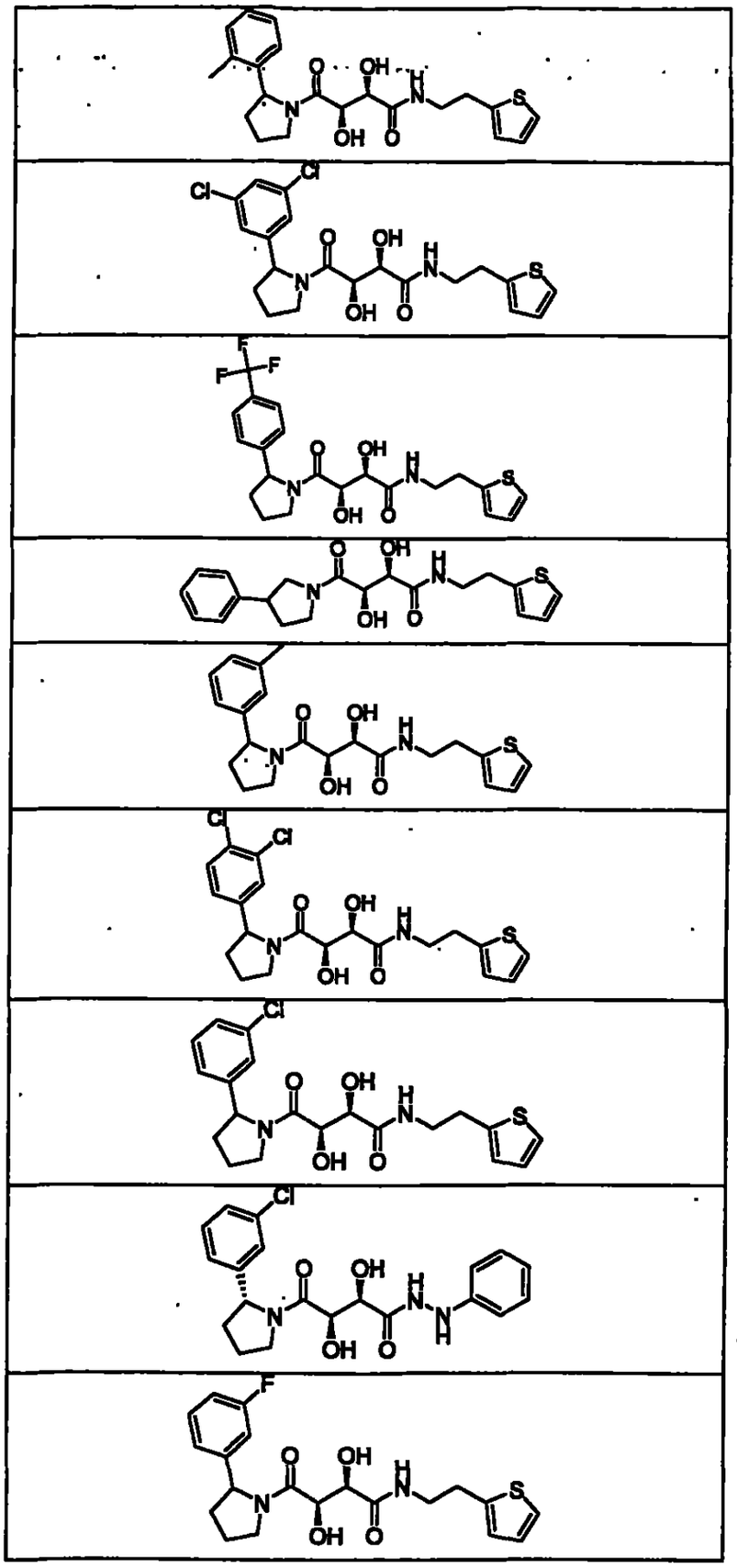
59. The compound of claim 55 wherein Z is selected from the group consisting of

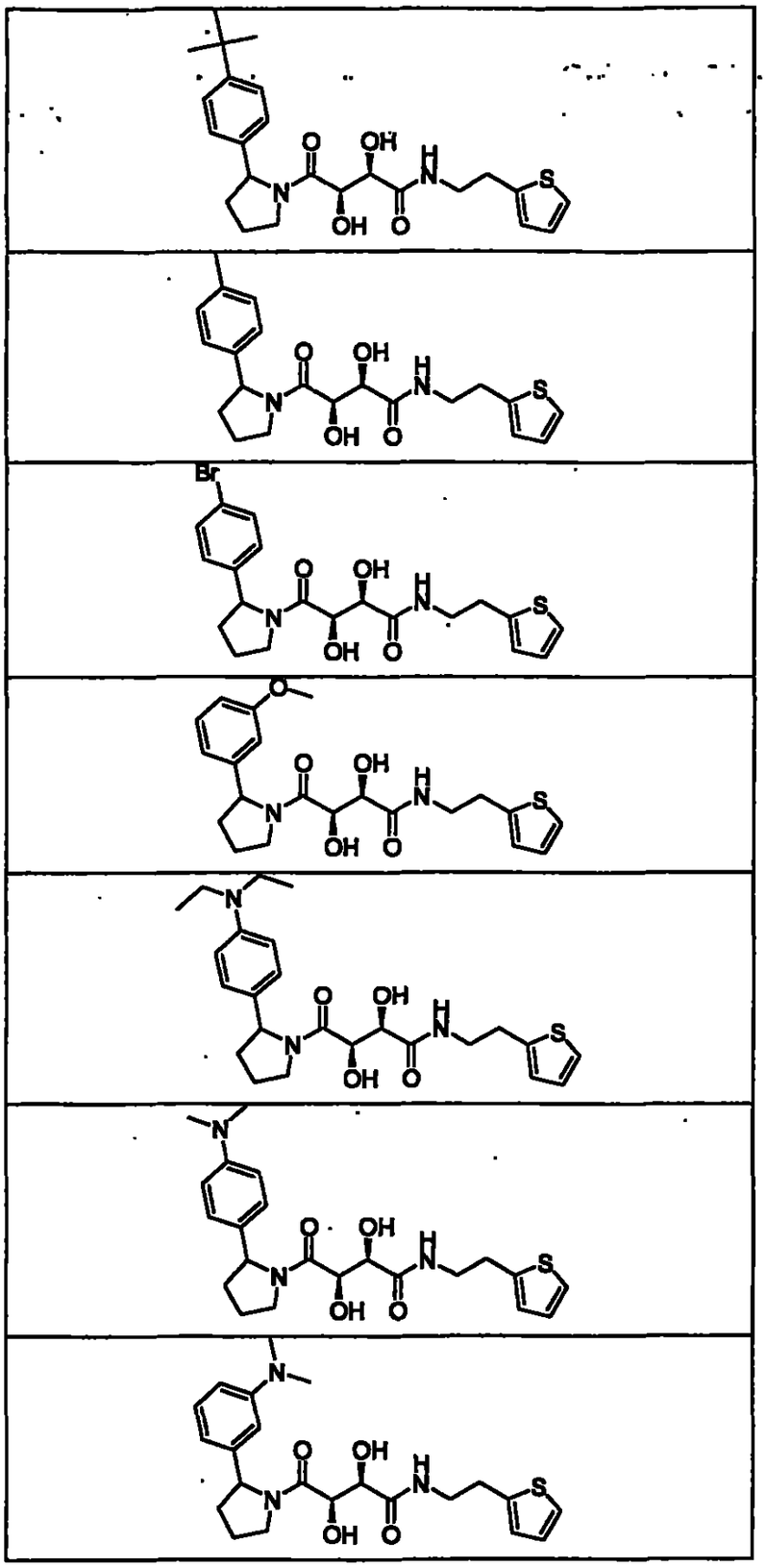


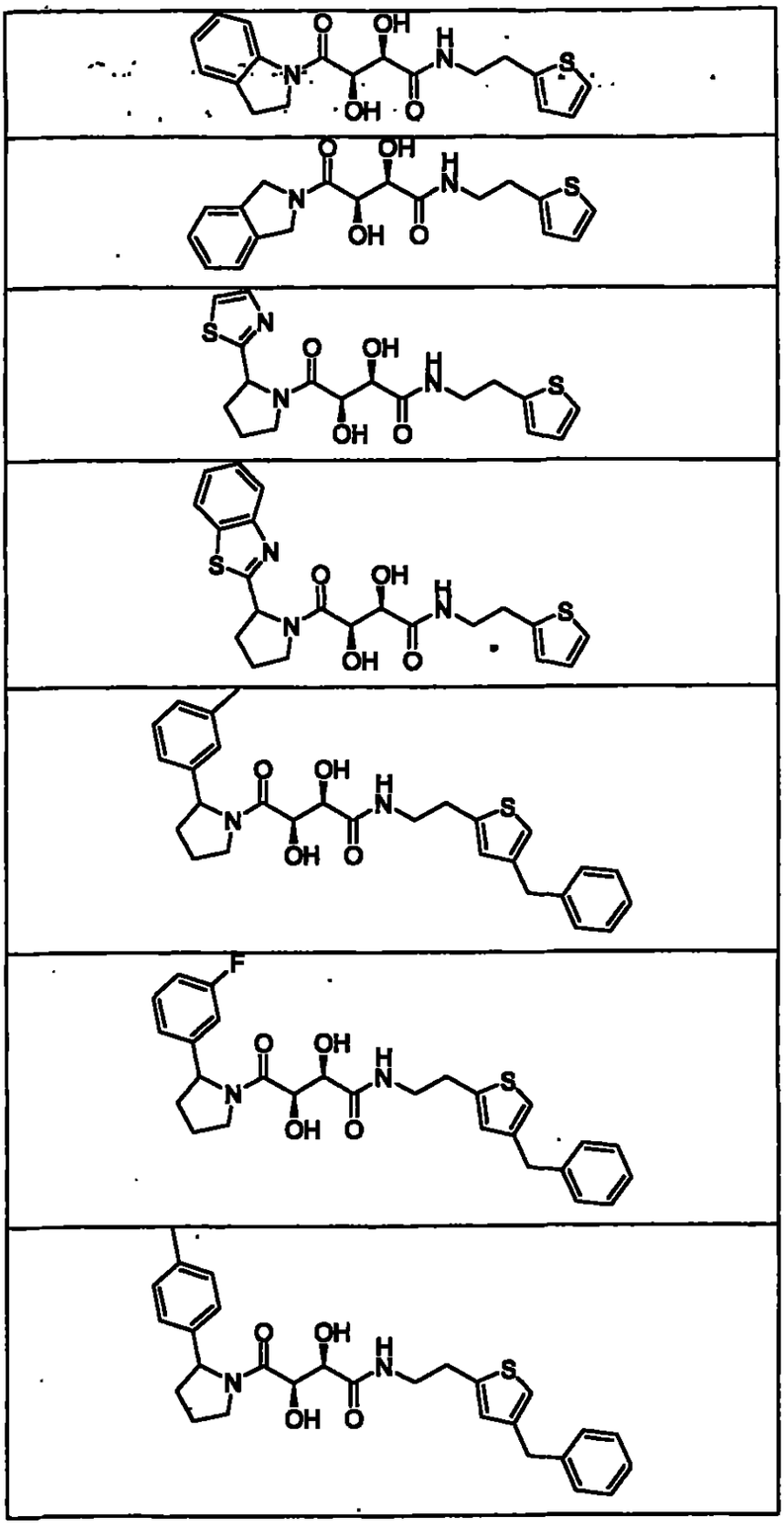
60. A compound exhibiting TACE, TNF-α, MMP or any combination thereof inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the compounds of structures listed below:

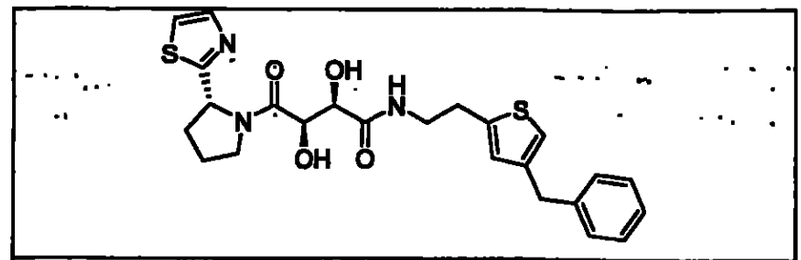


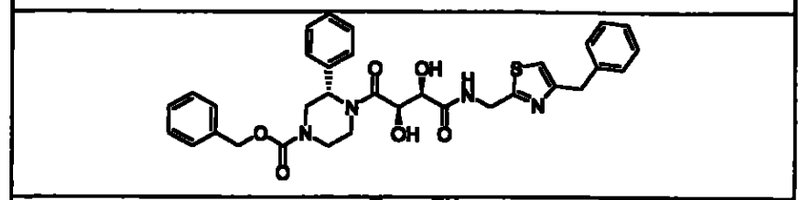


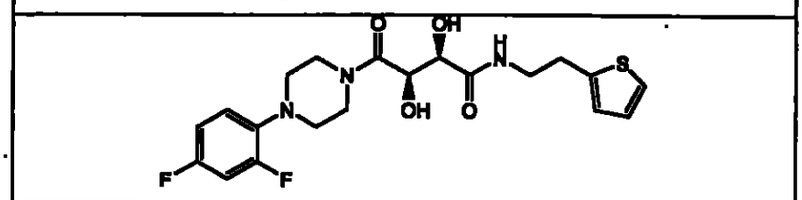


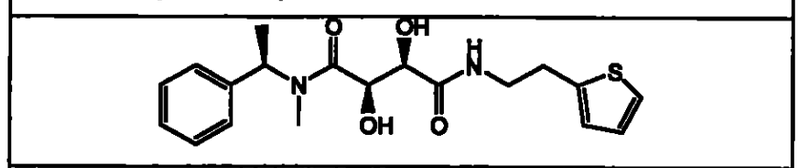


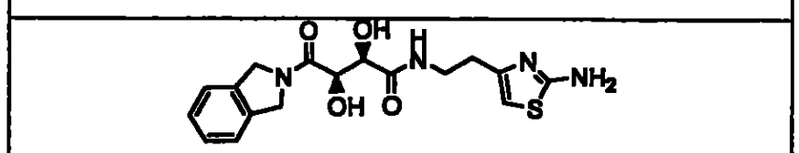


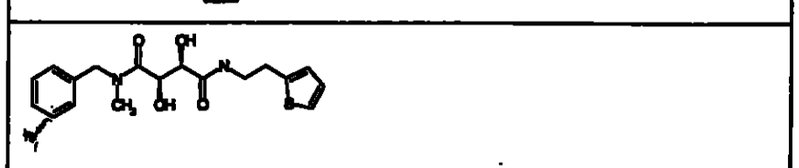


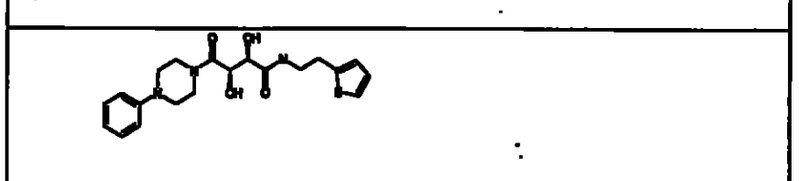


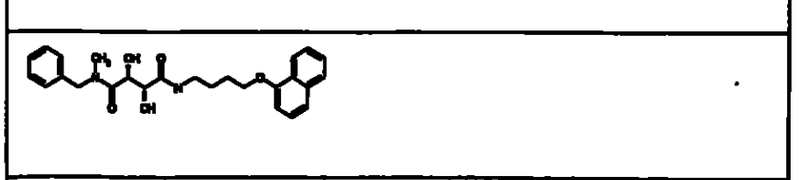




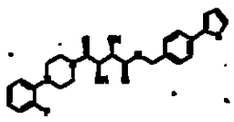
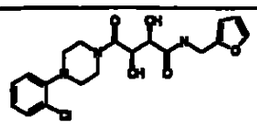
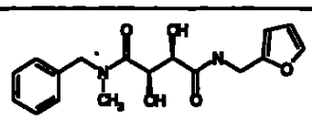
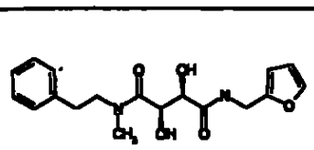
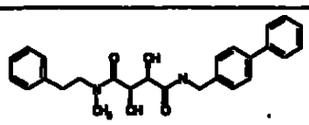
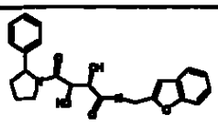
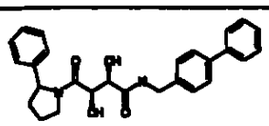
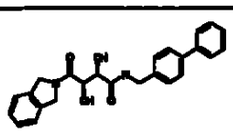
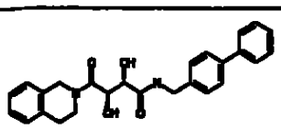


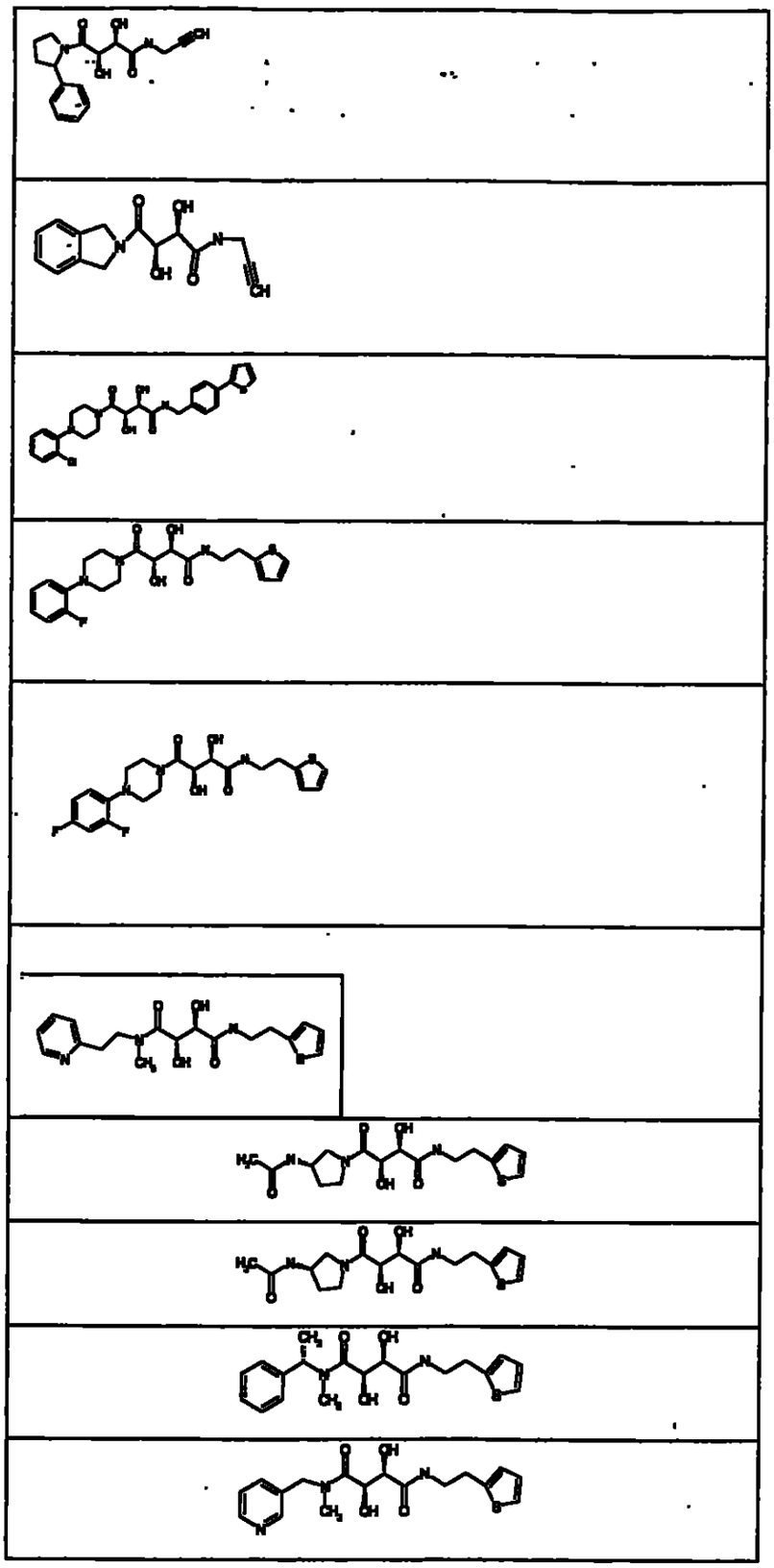


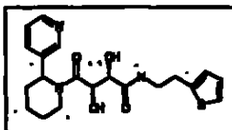
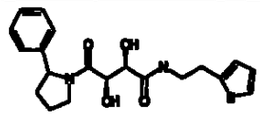
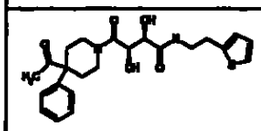
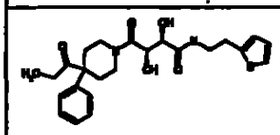
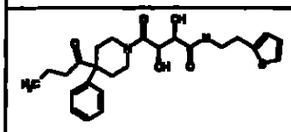
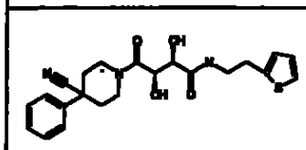
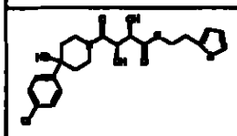
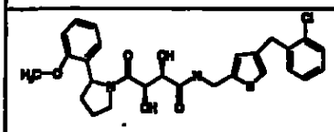
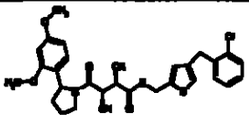


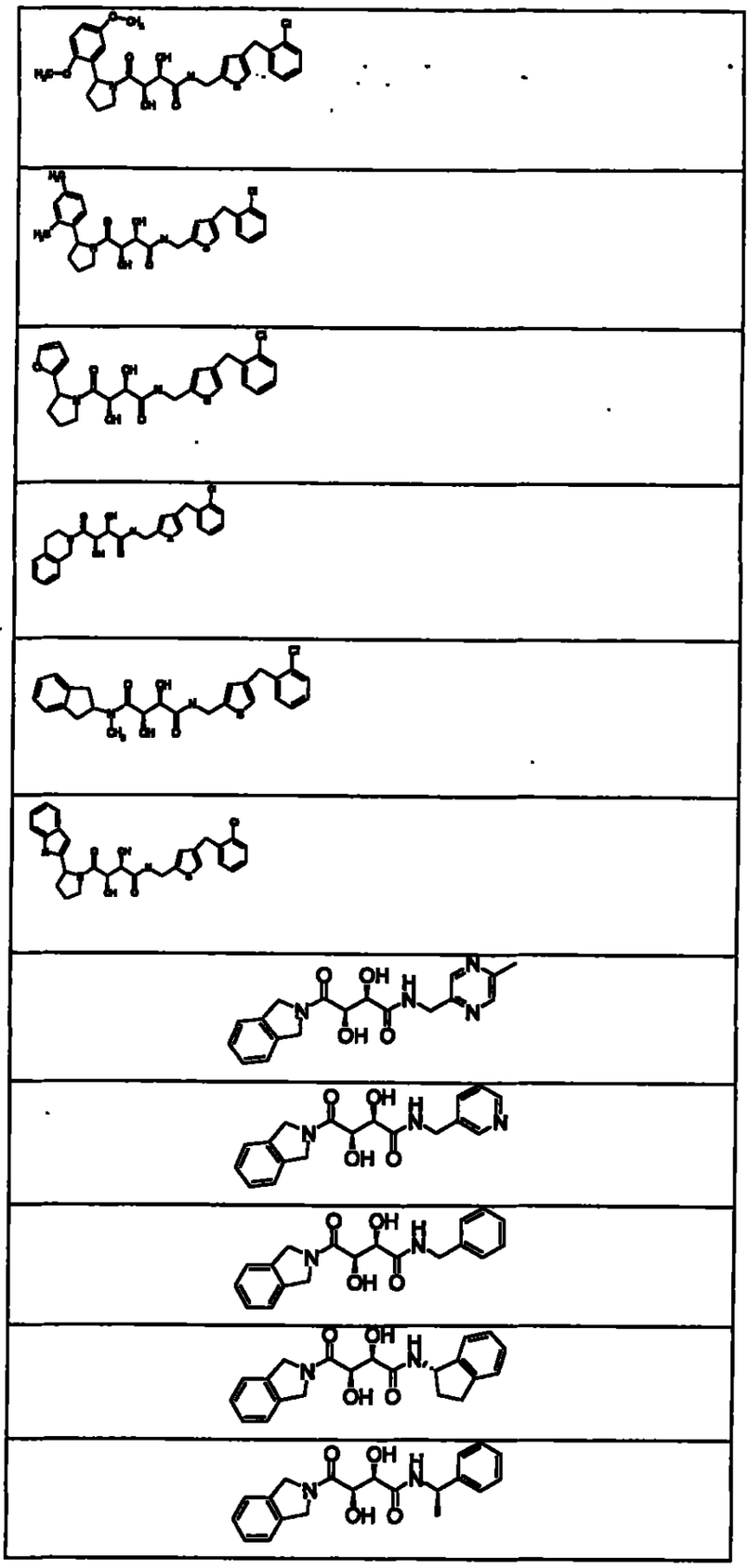


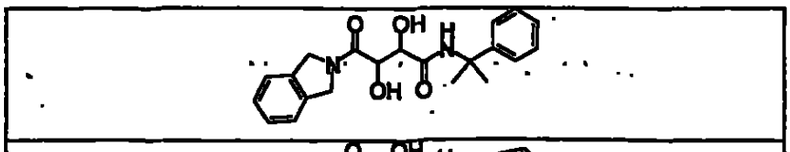


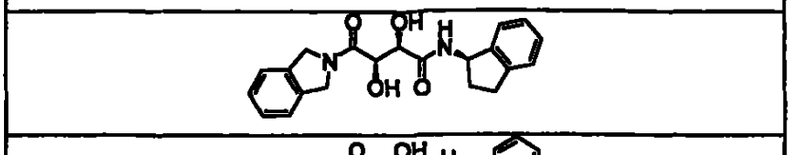










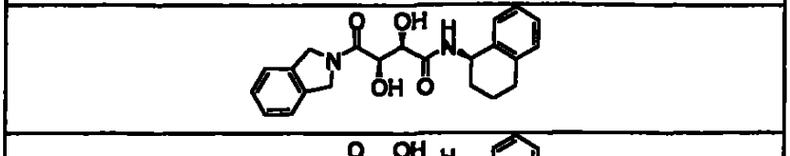


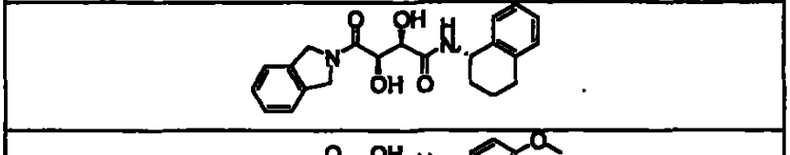










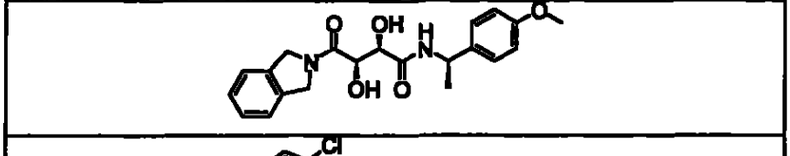


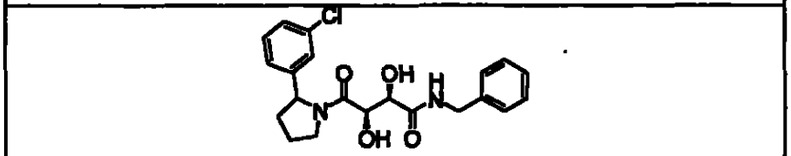


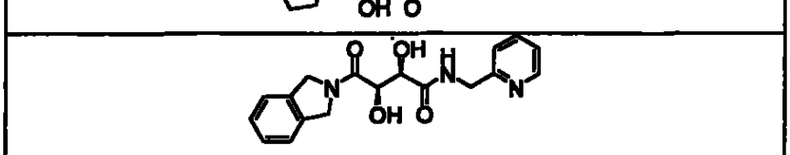


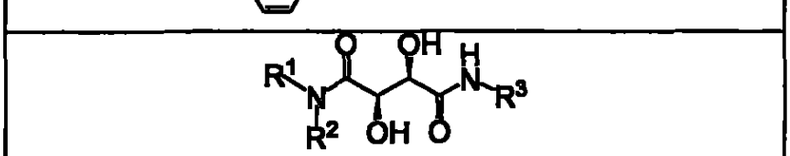




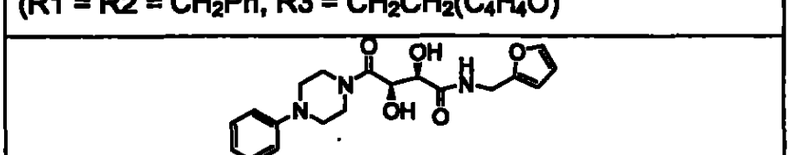


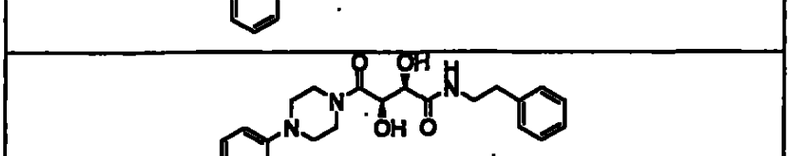


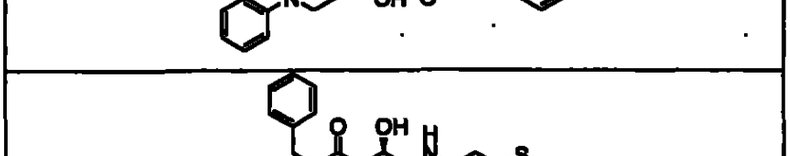


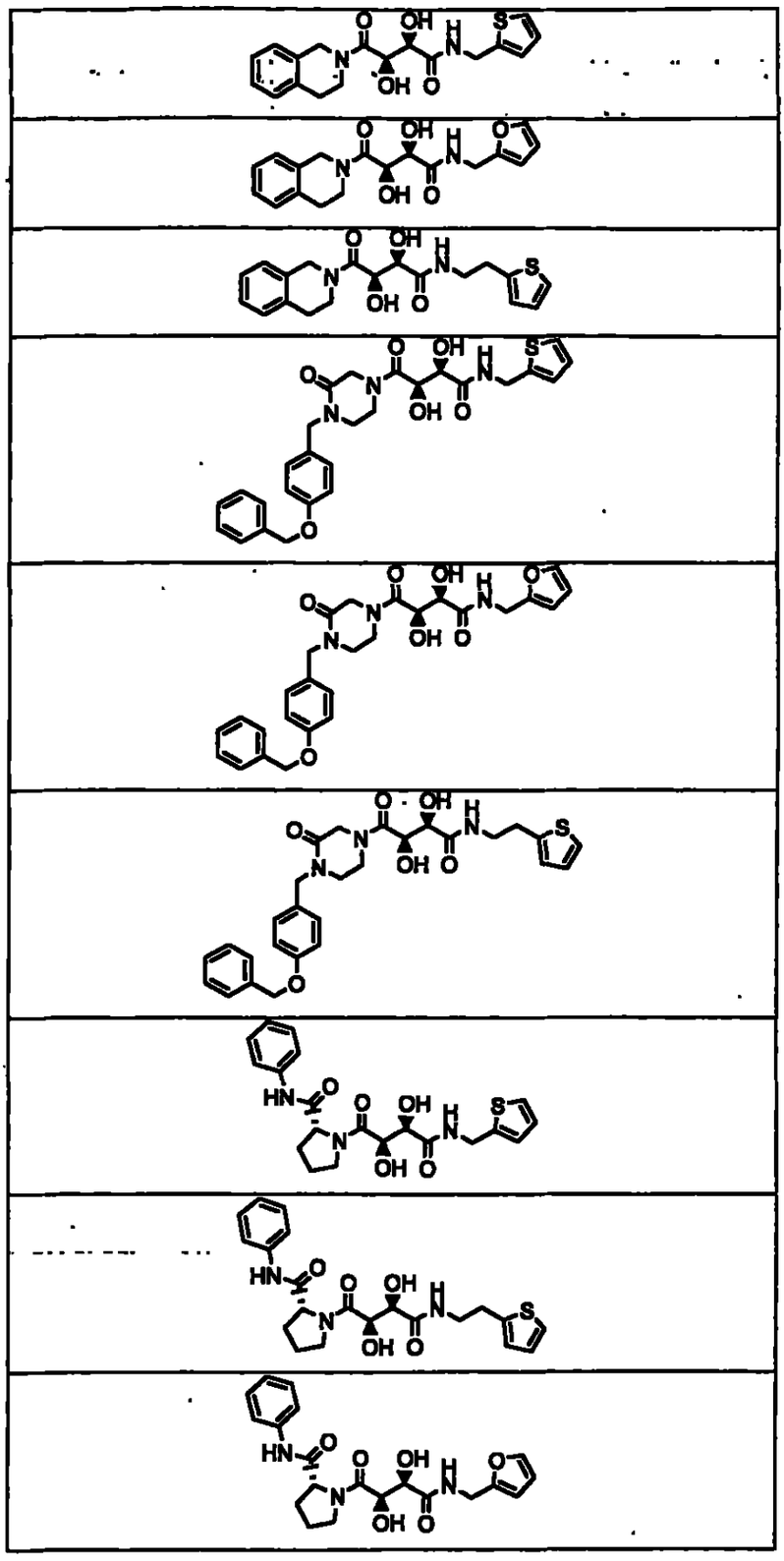


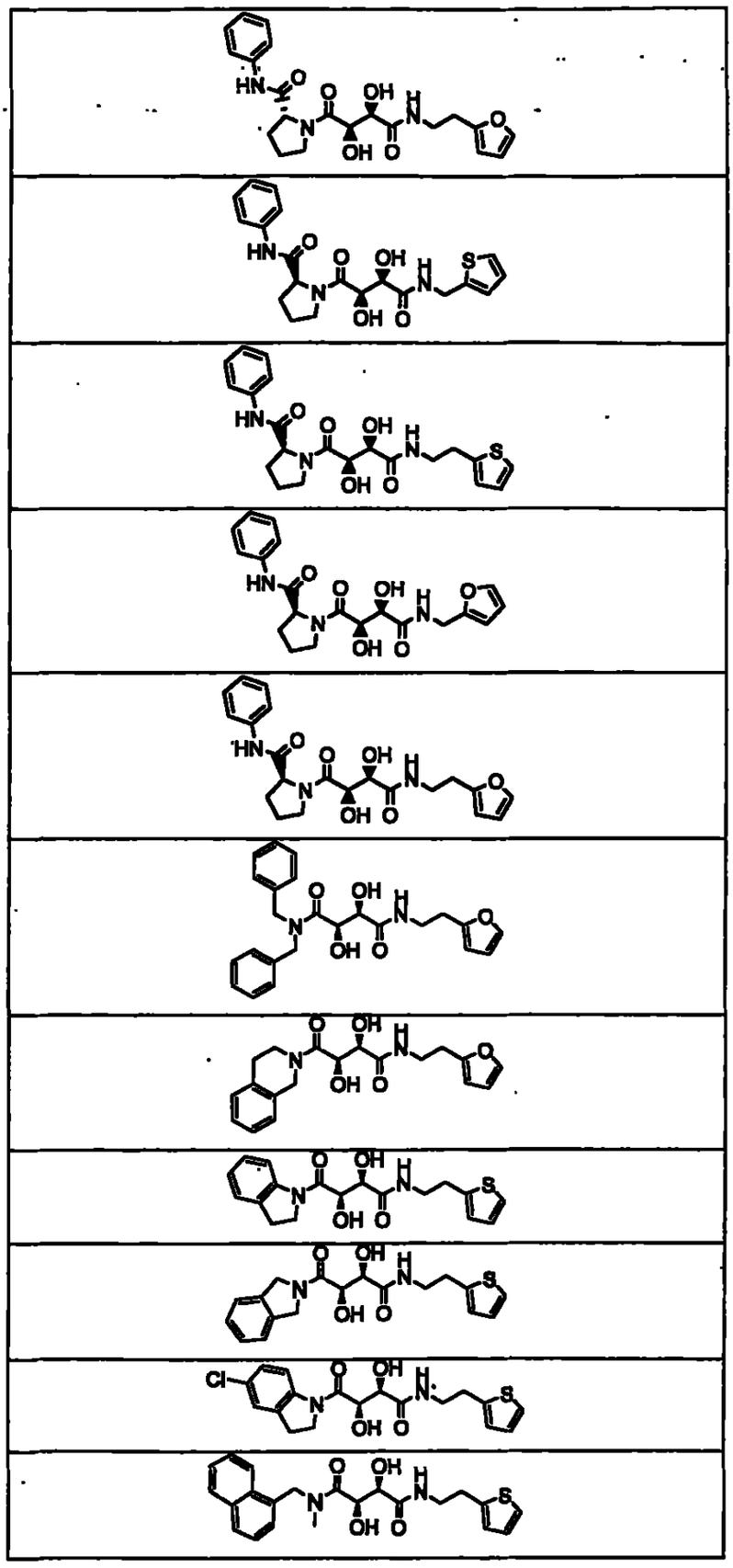
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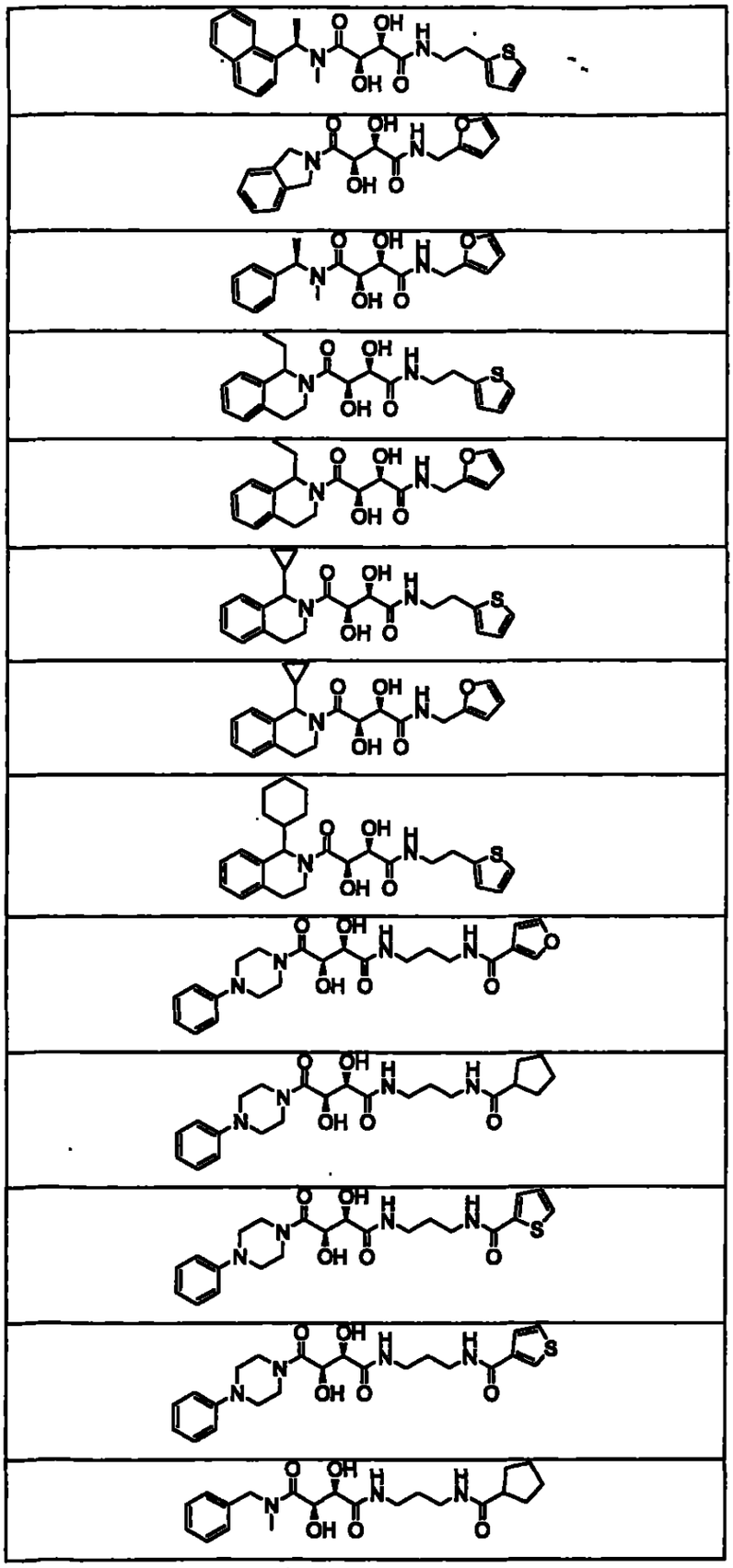


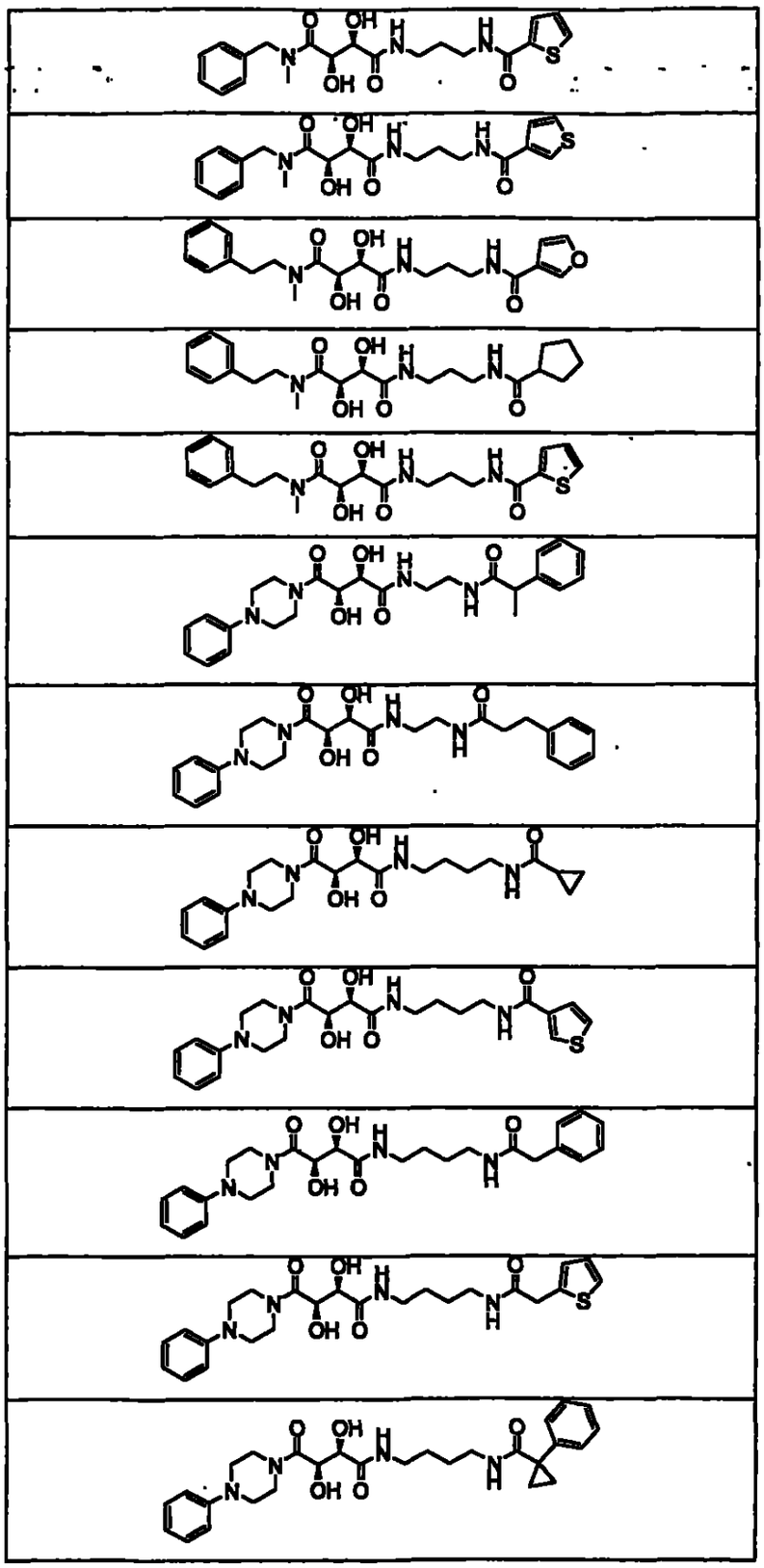


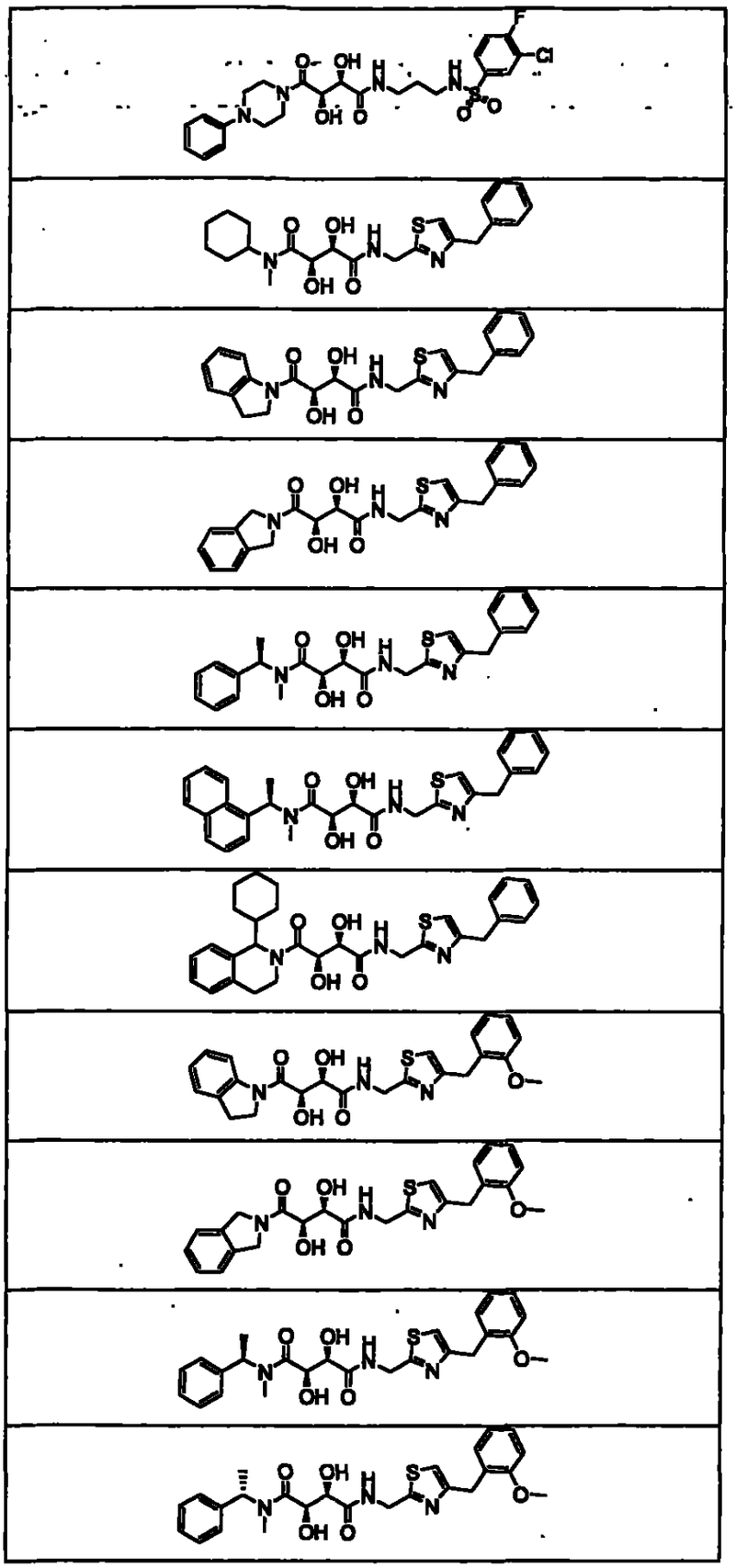


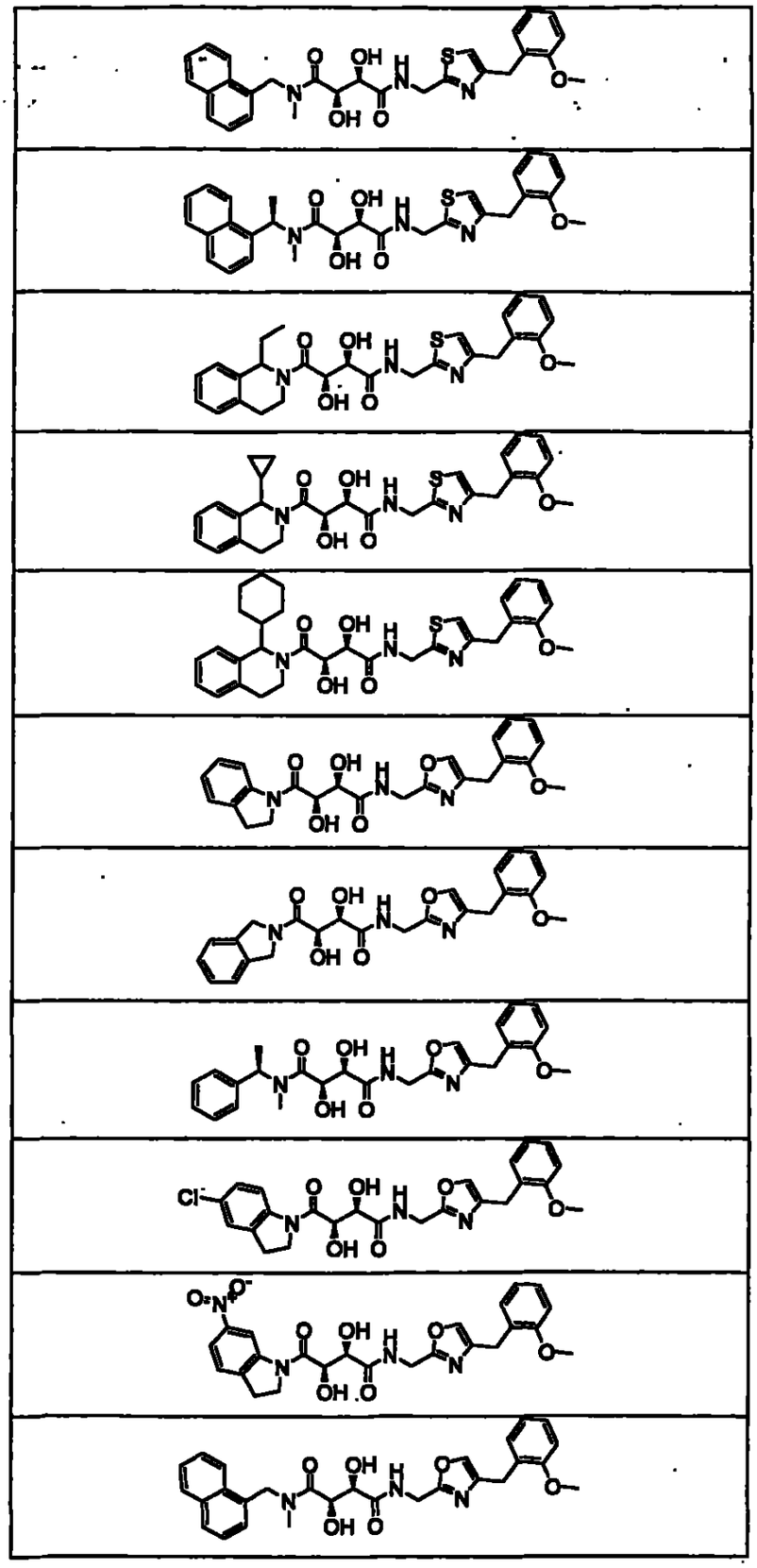


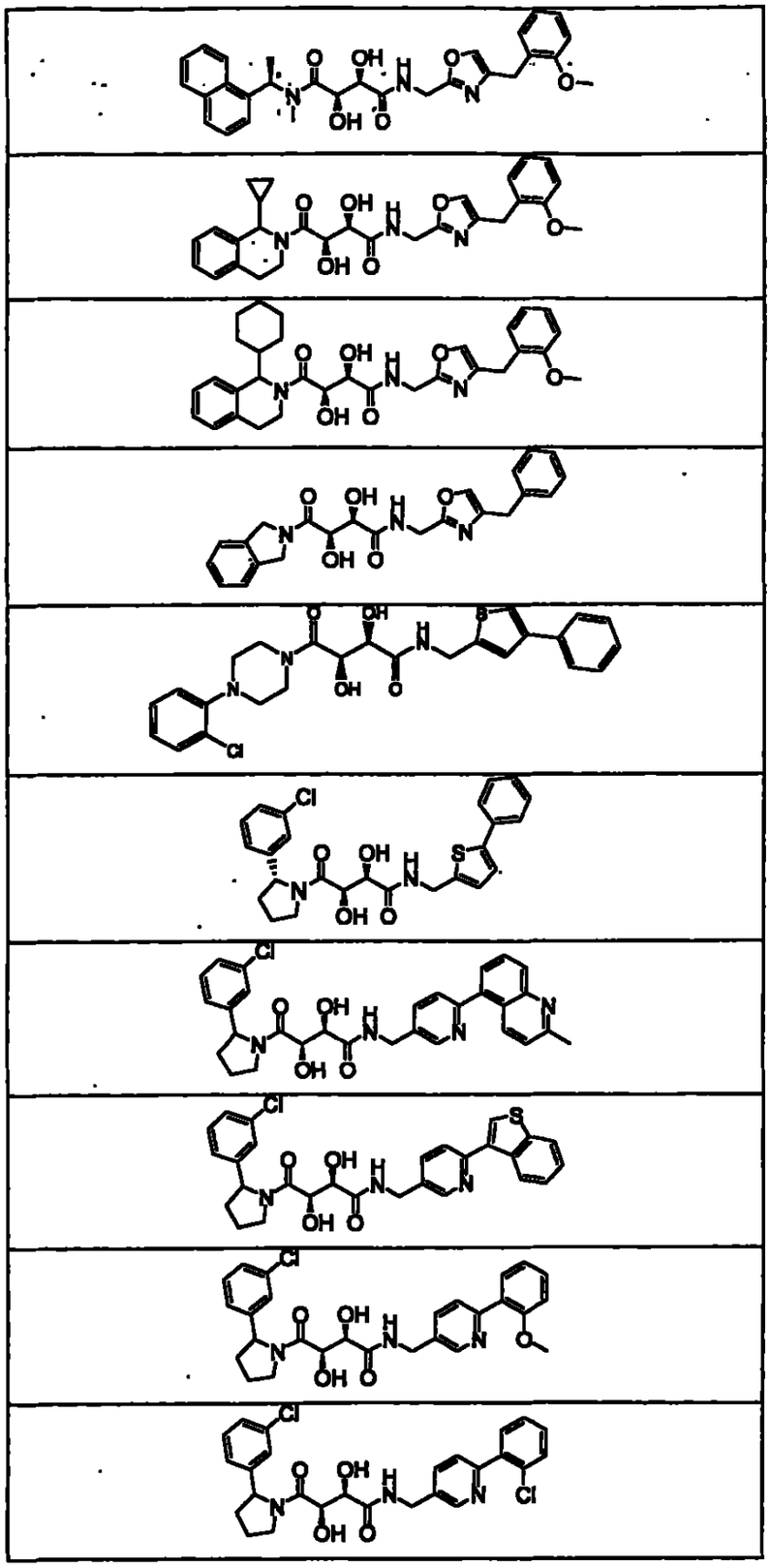


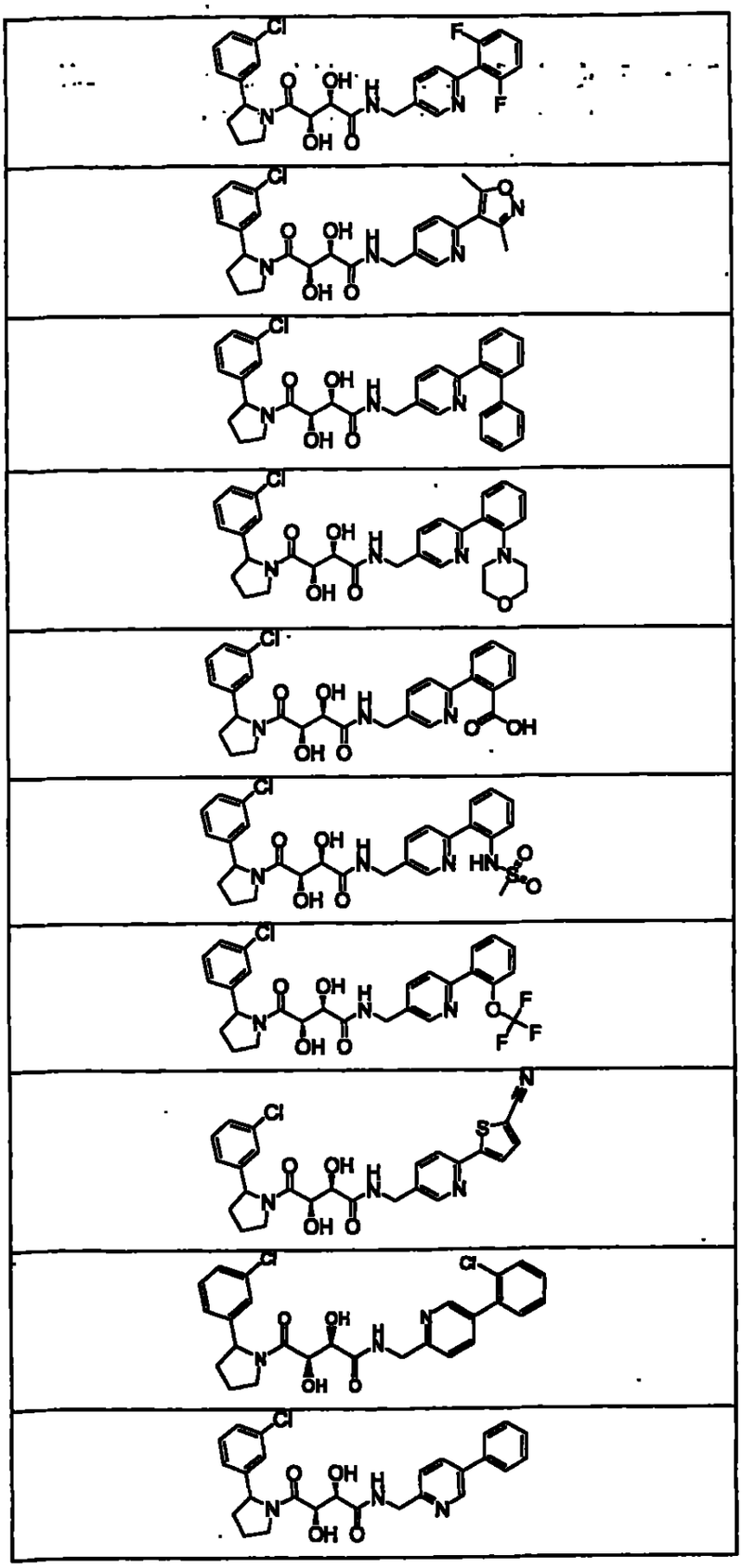


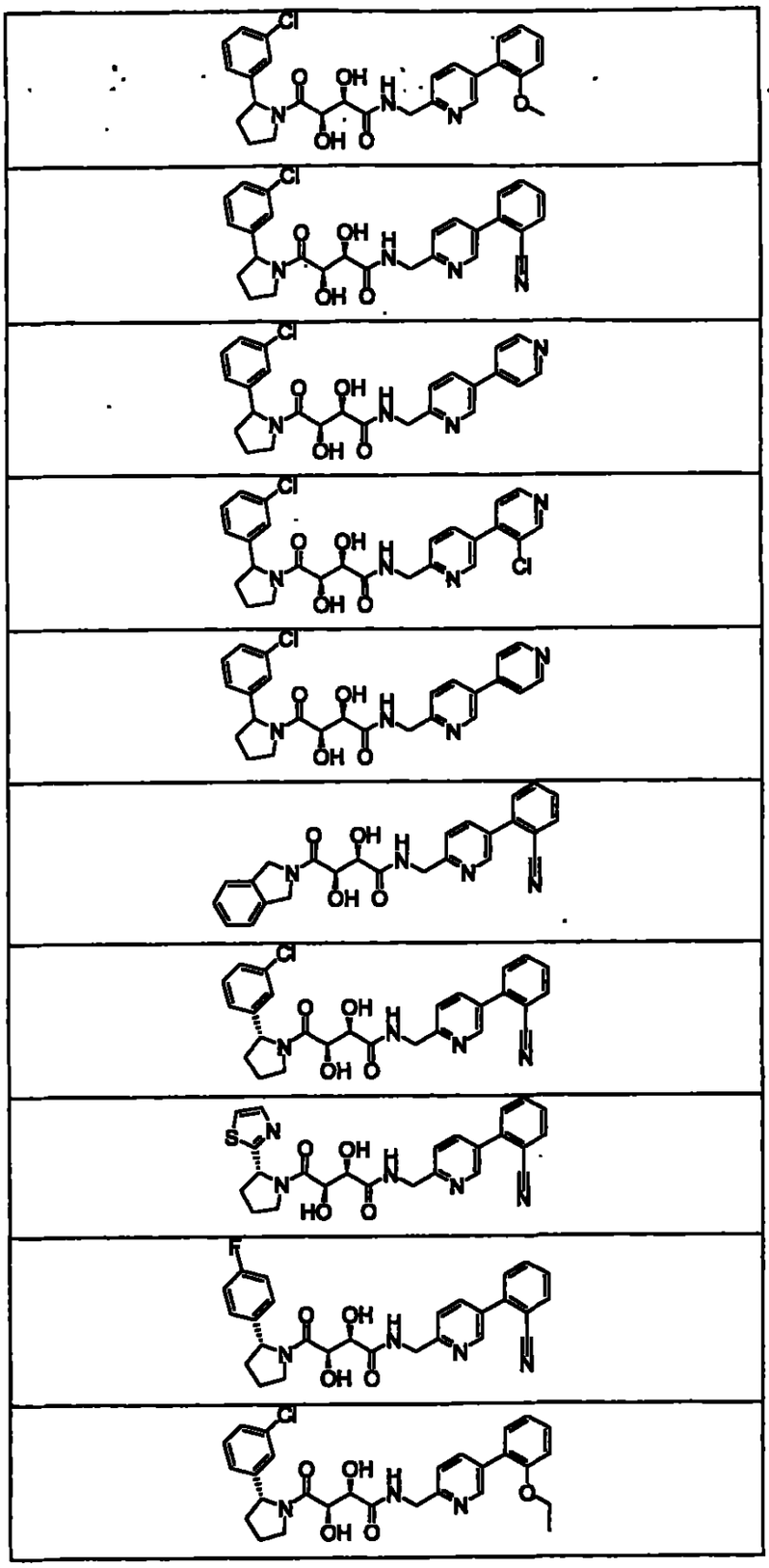


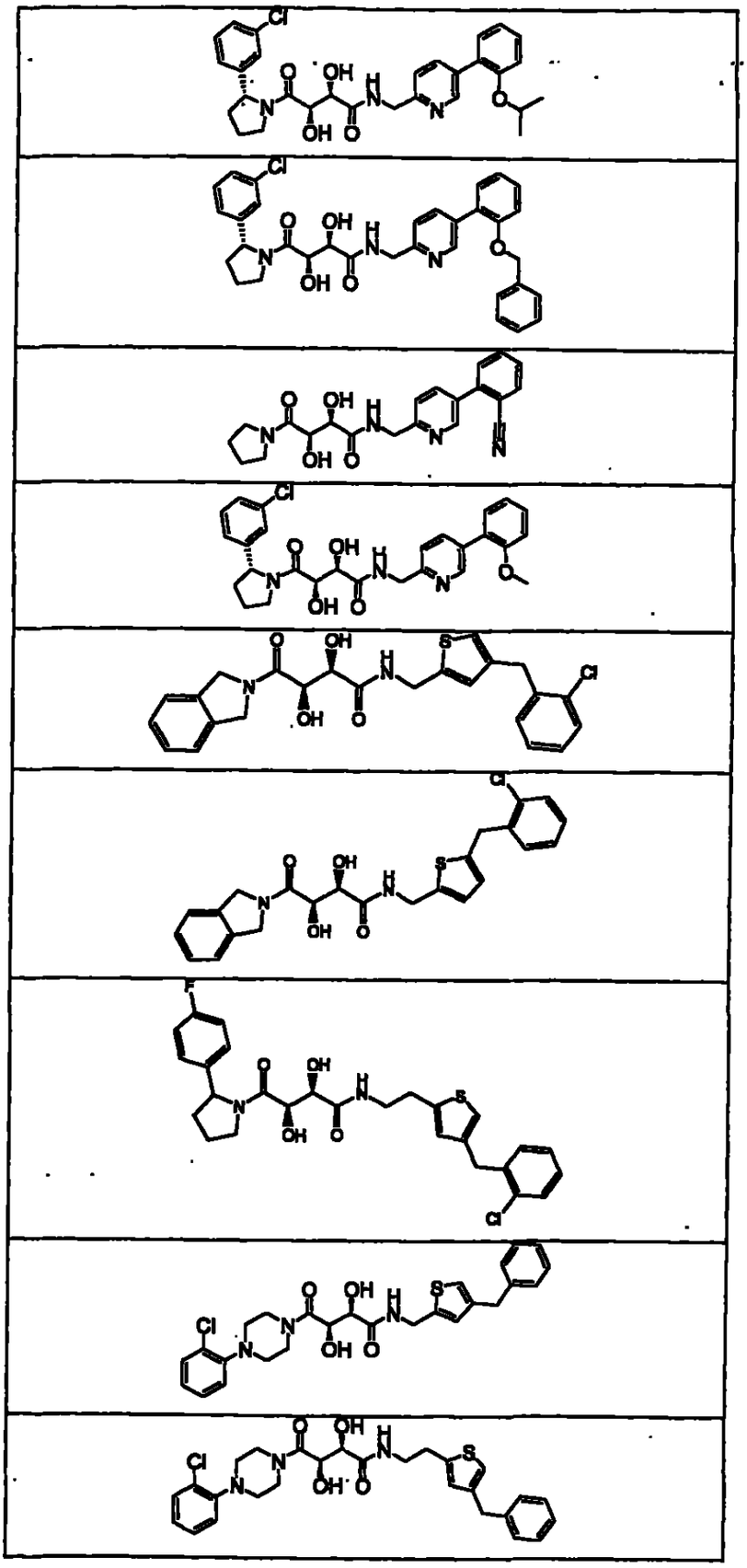


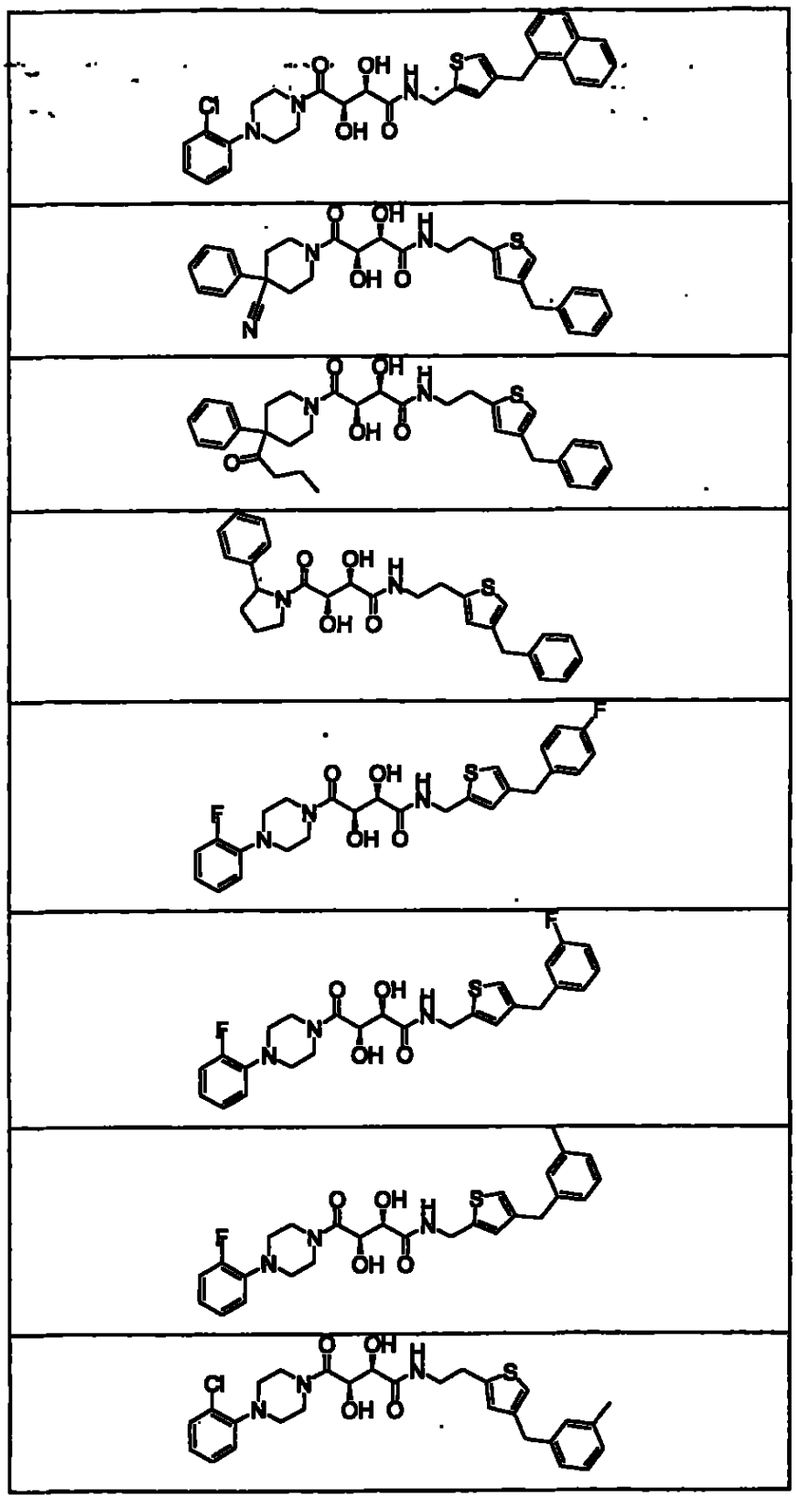


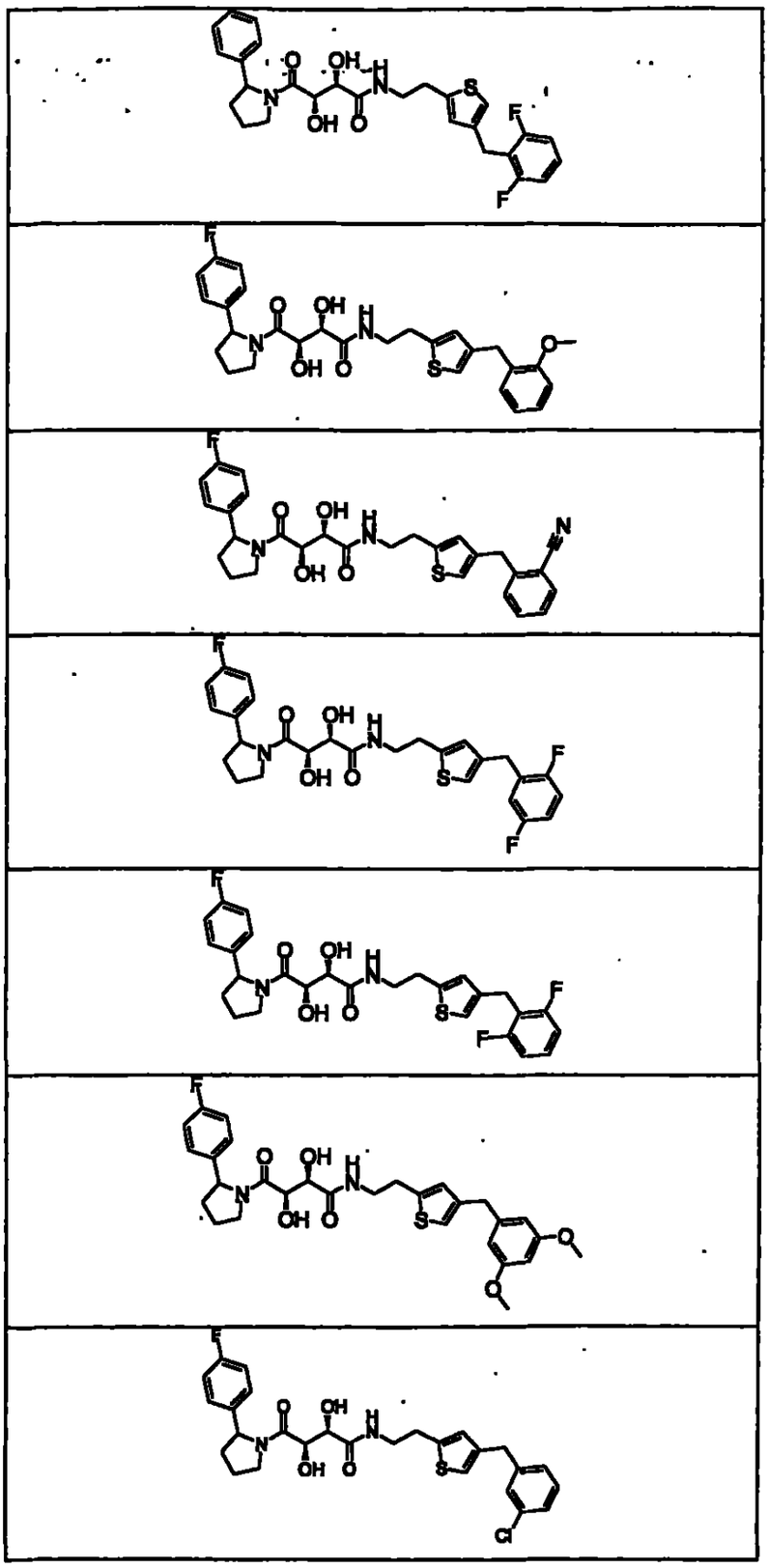


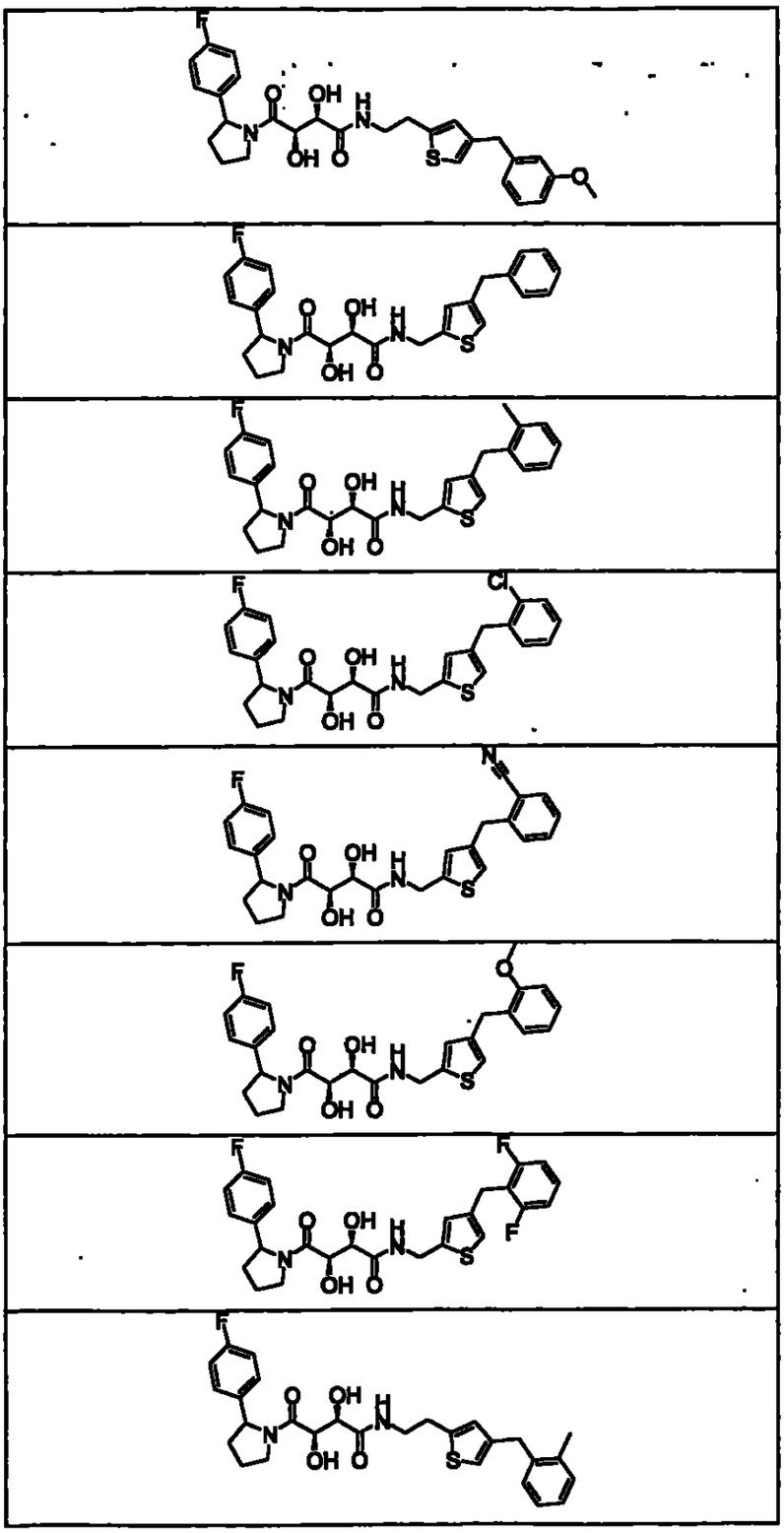


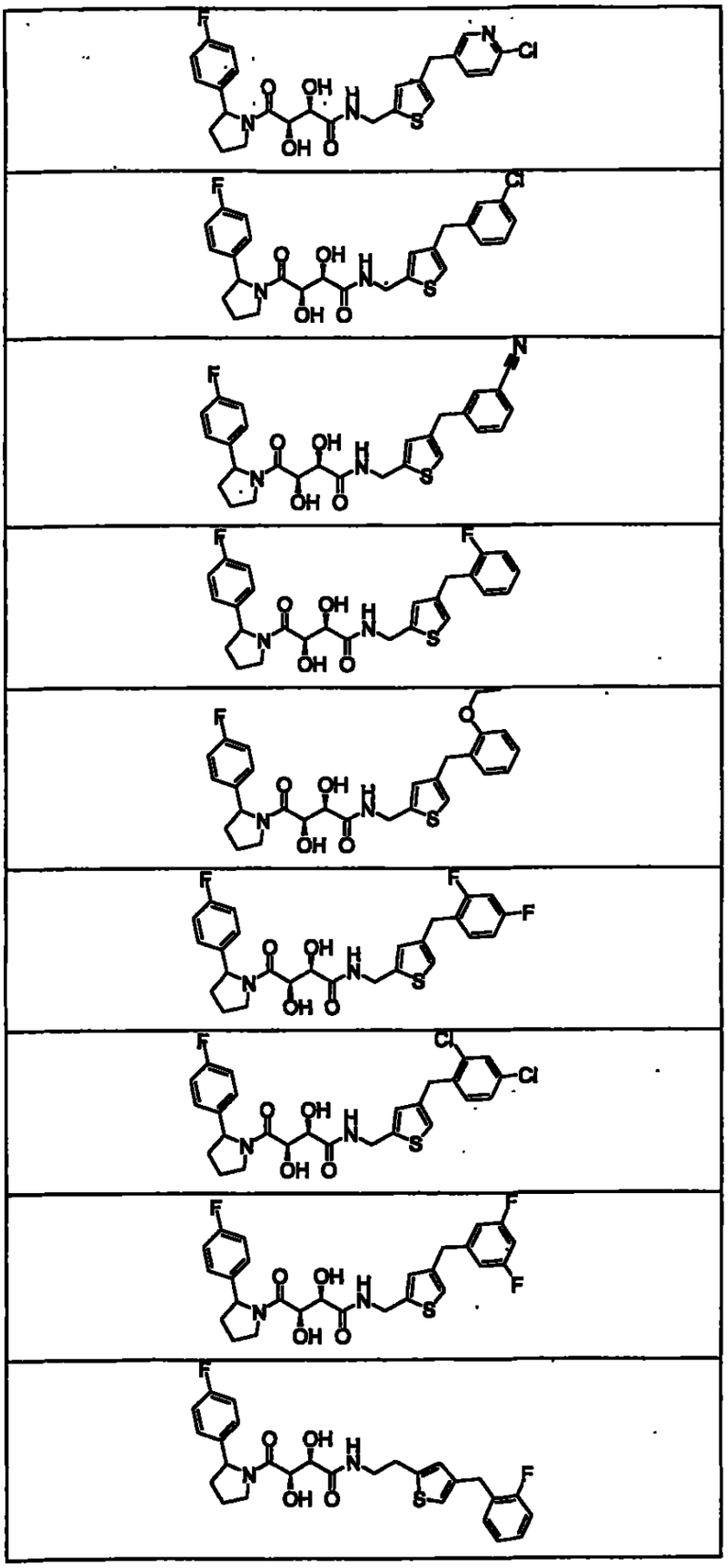


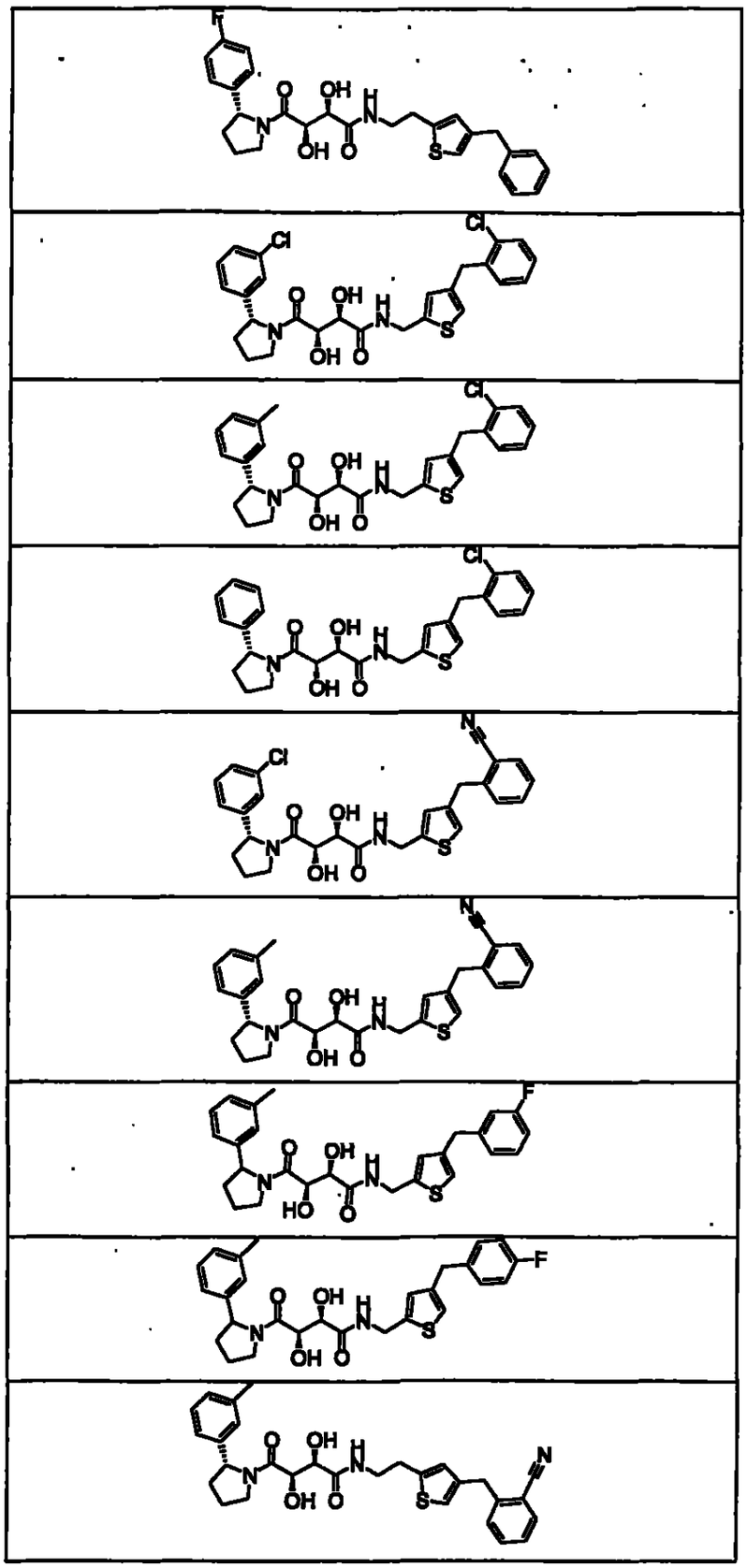


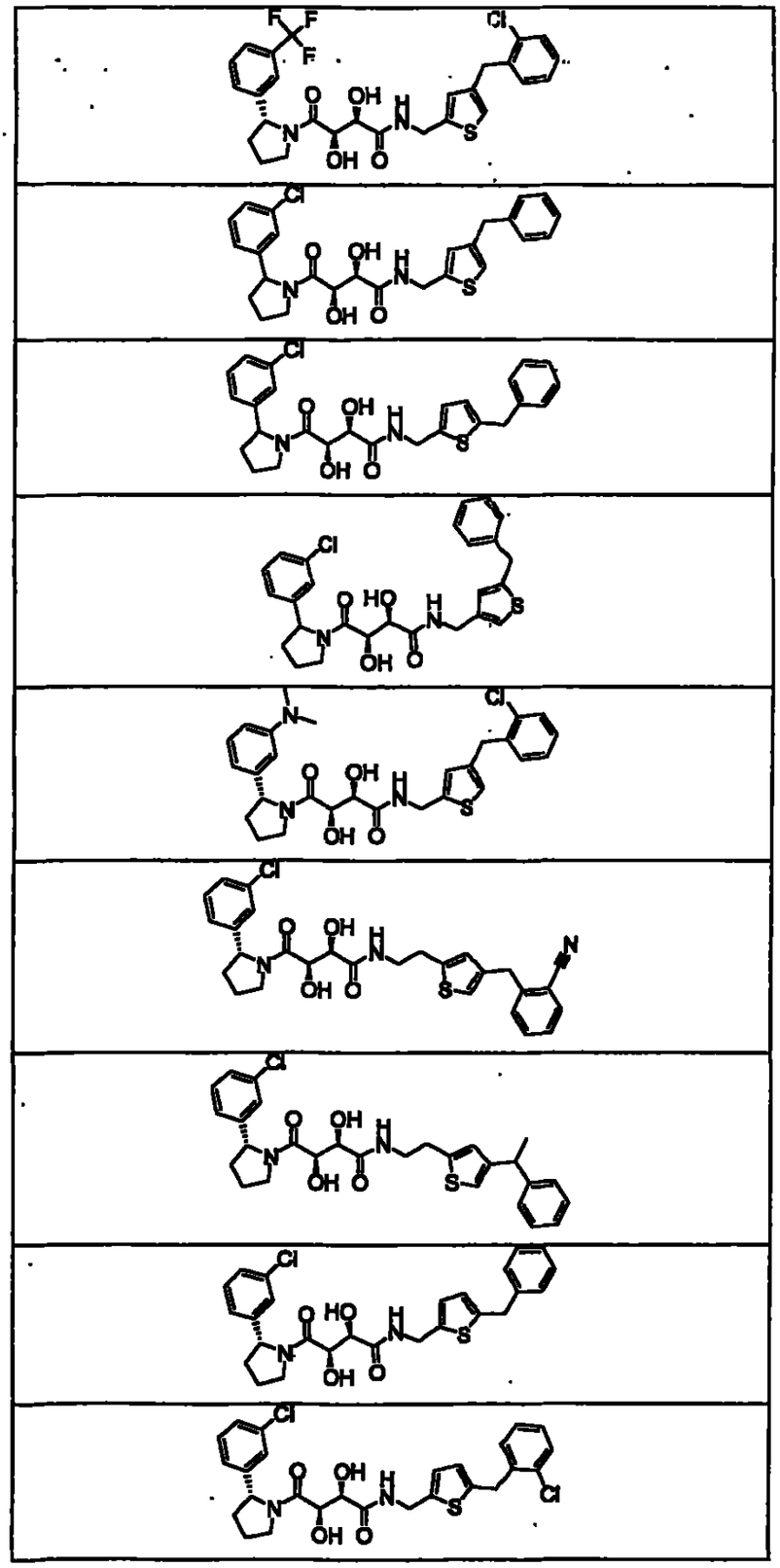


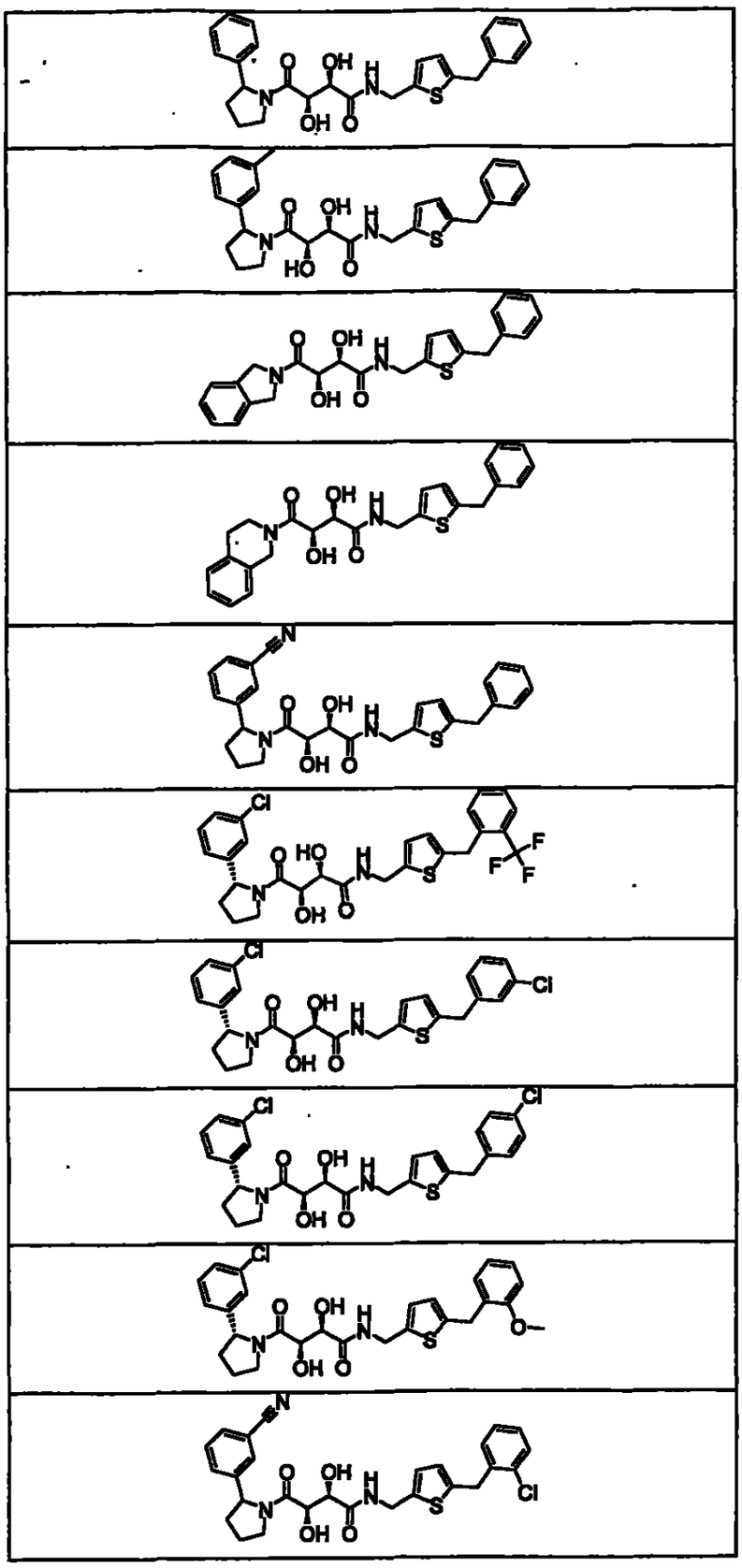


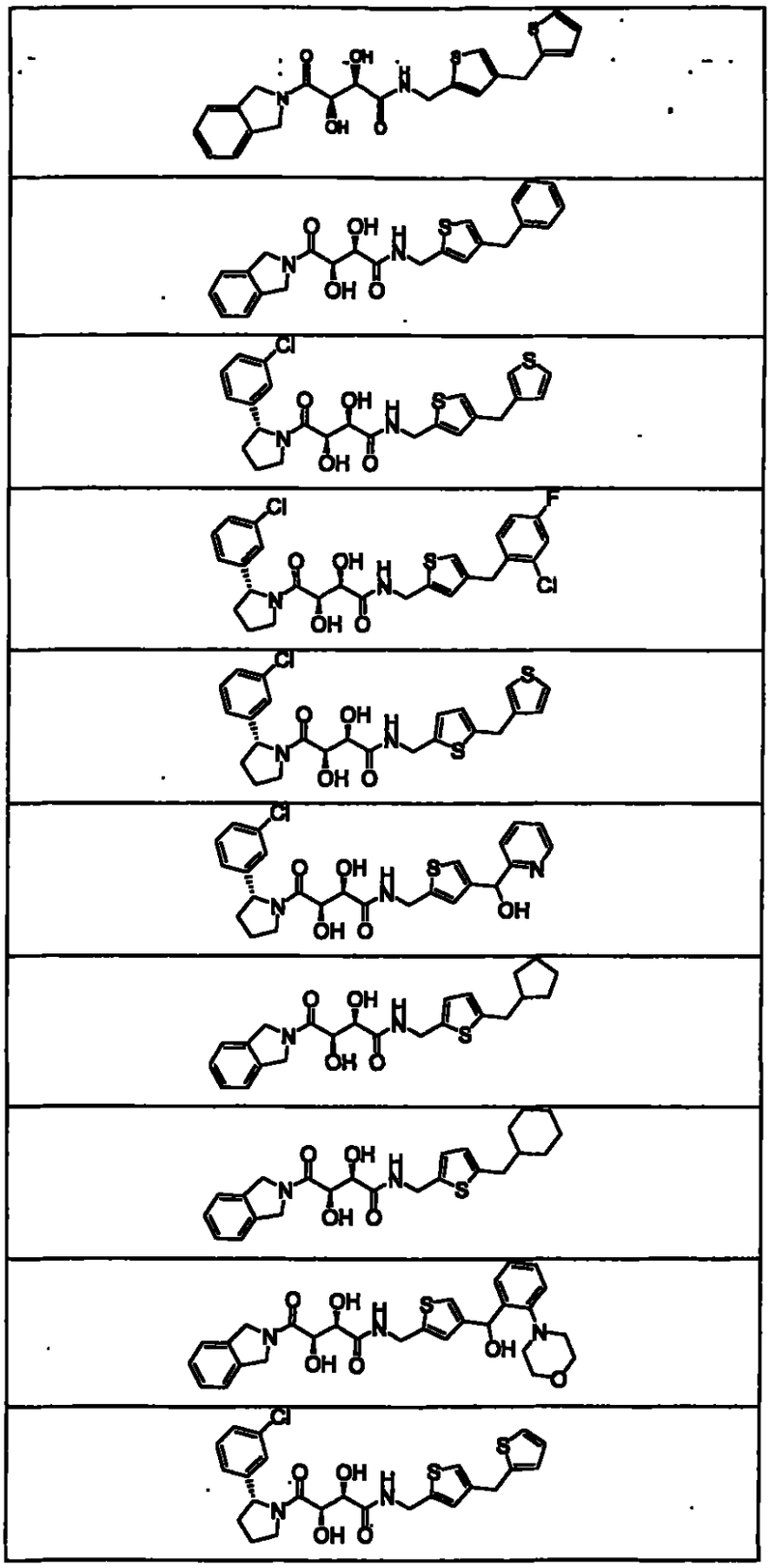


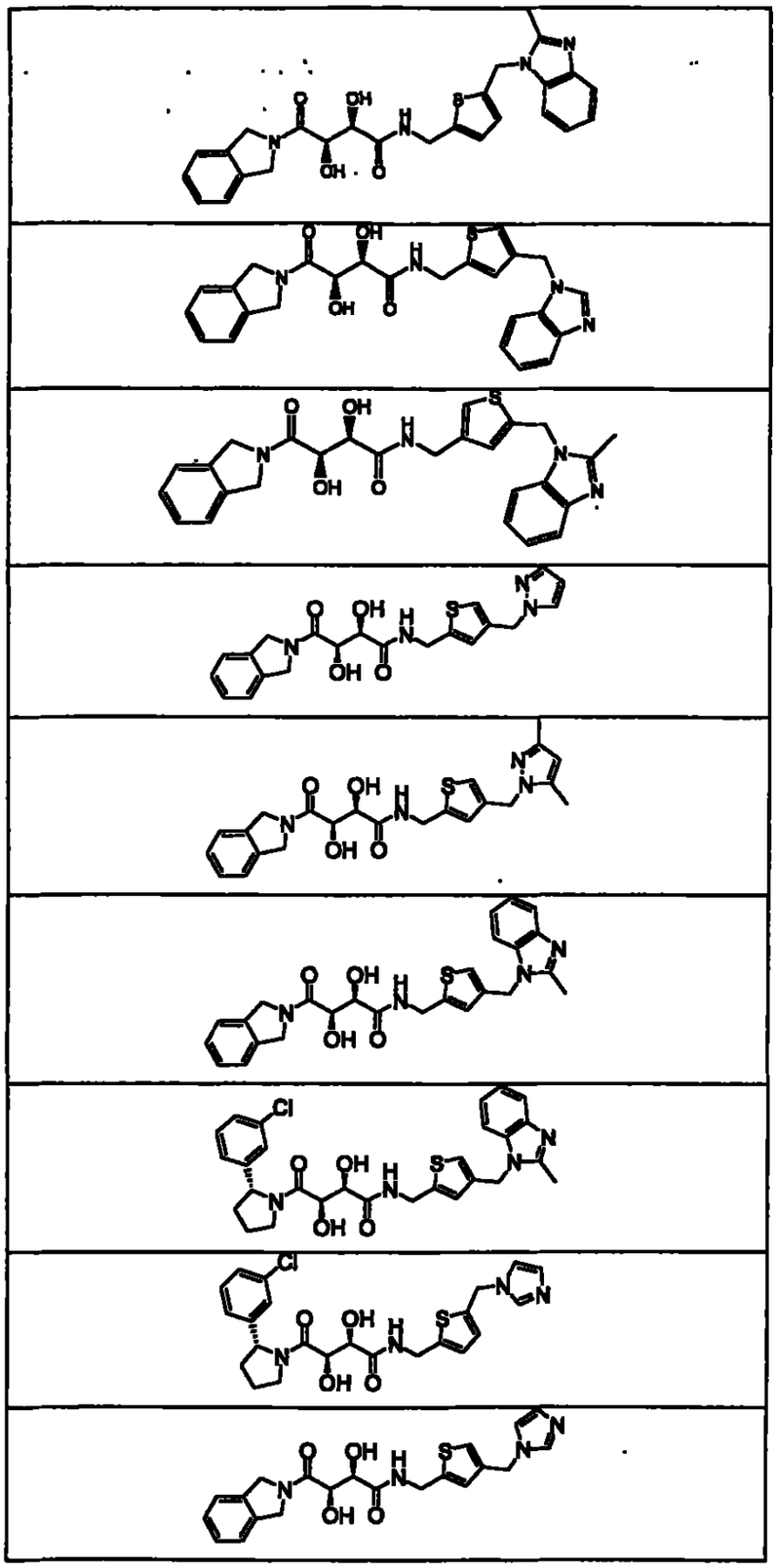


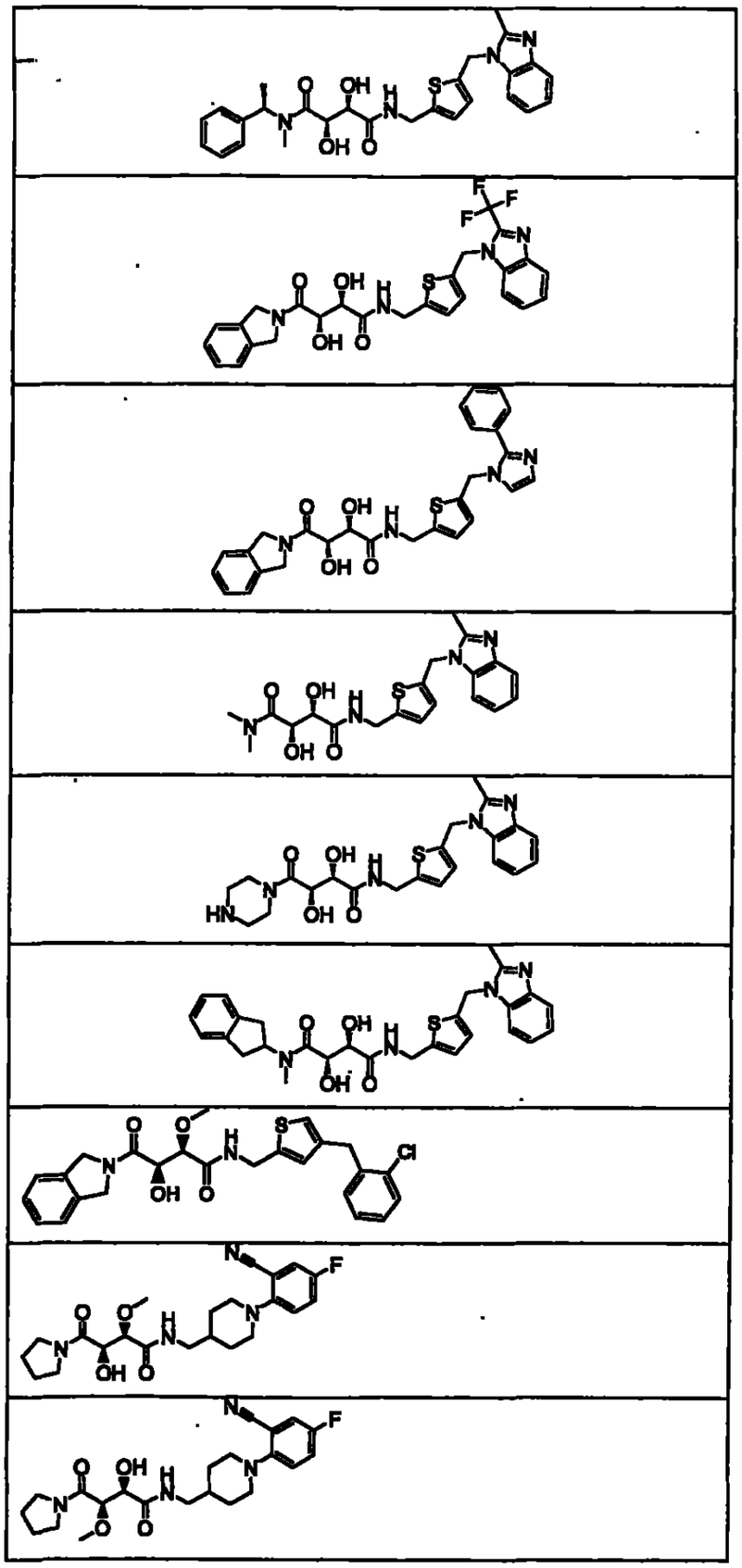


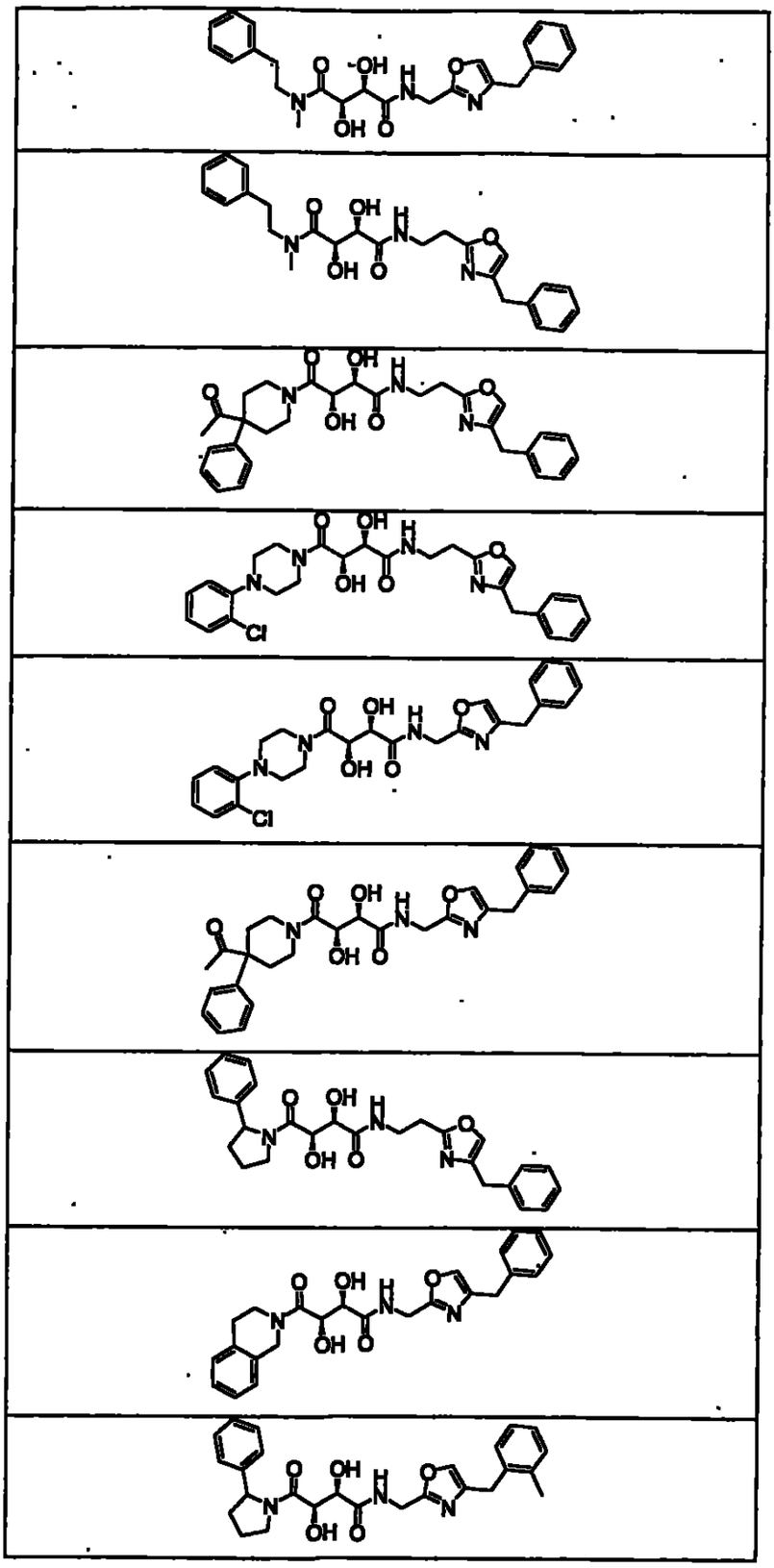


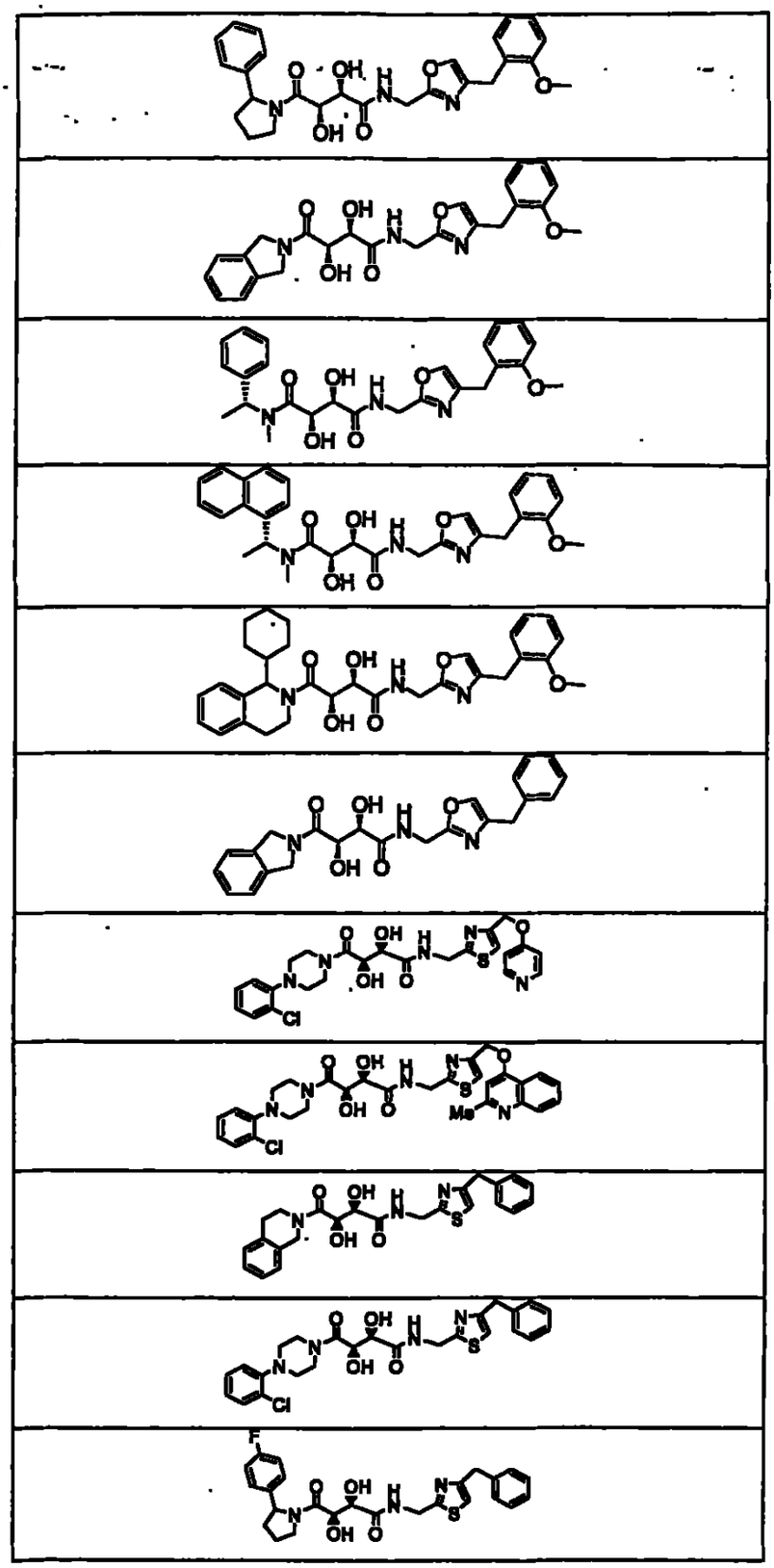


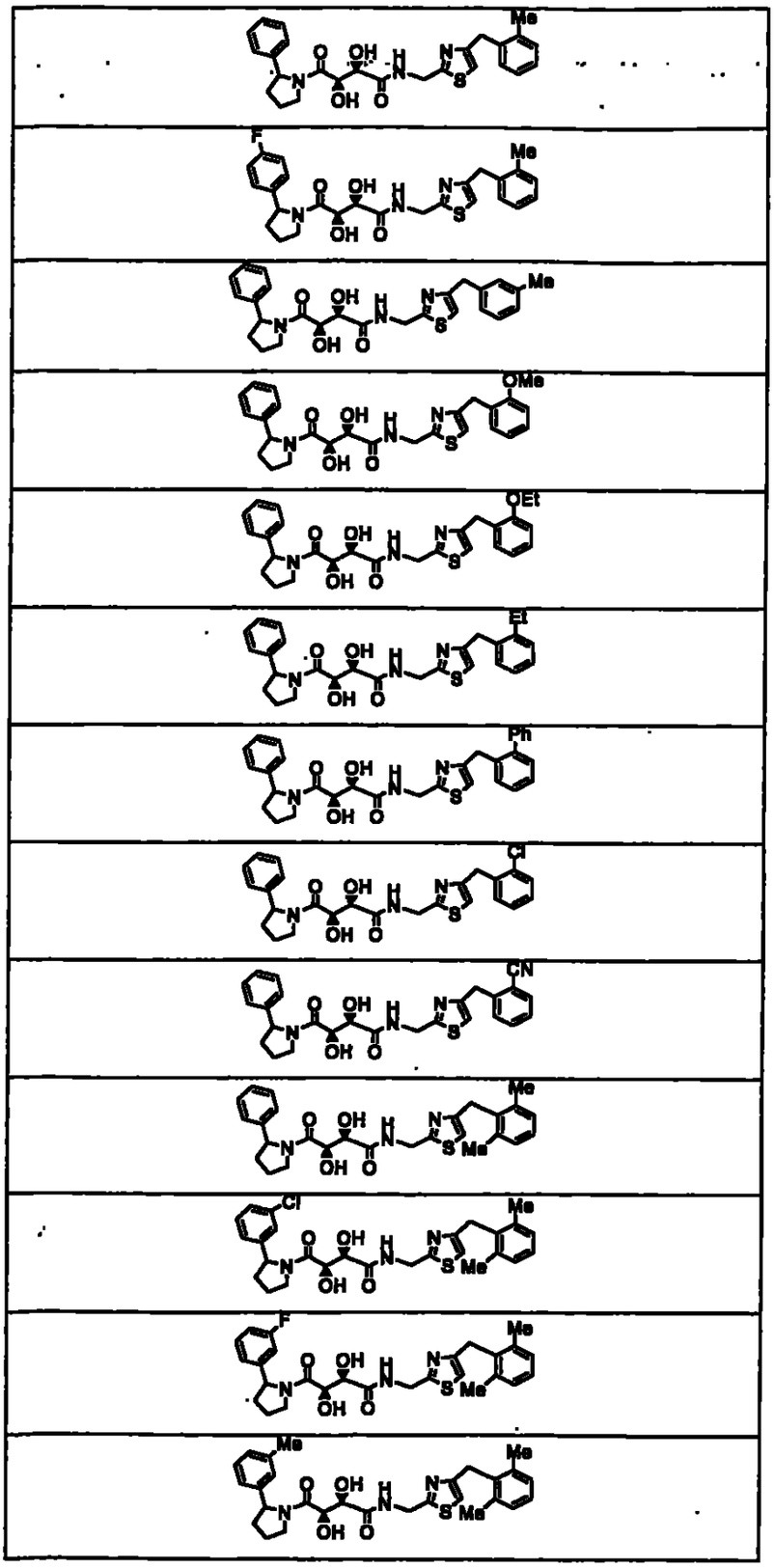


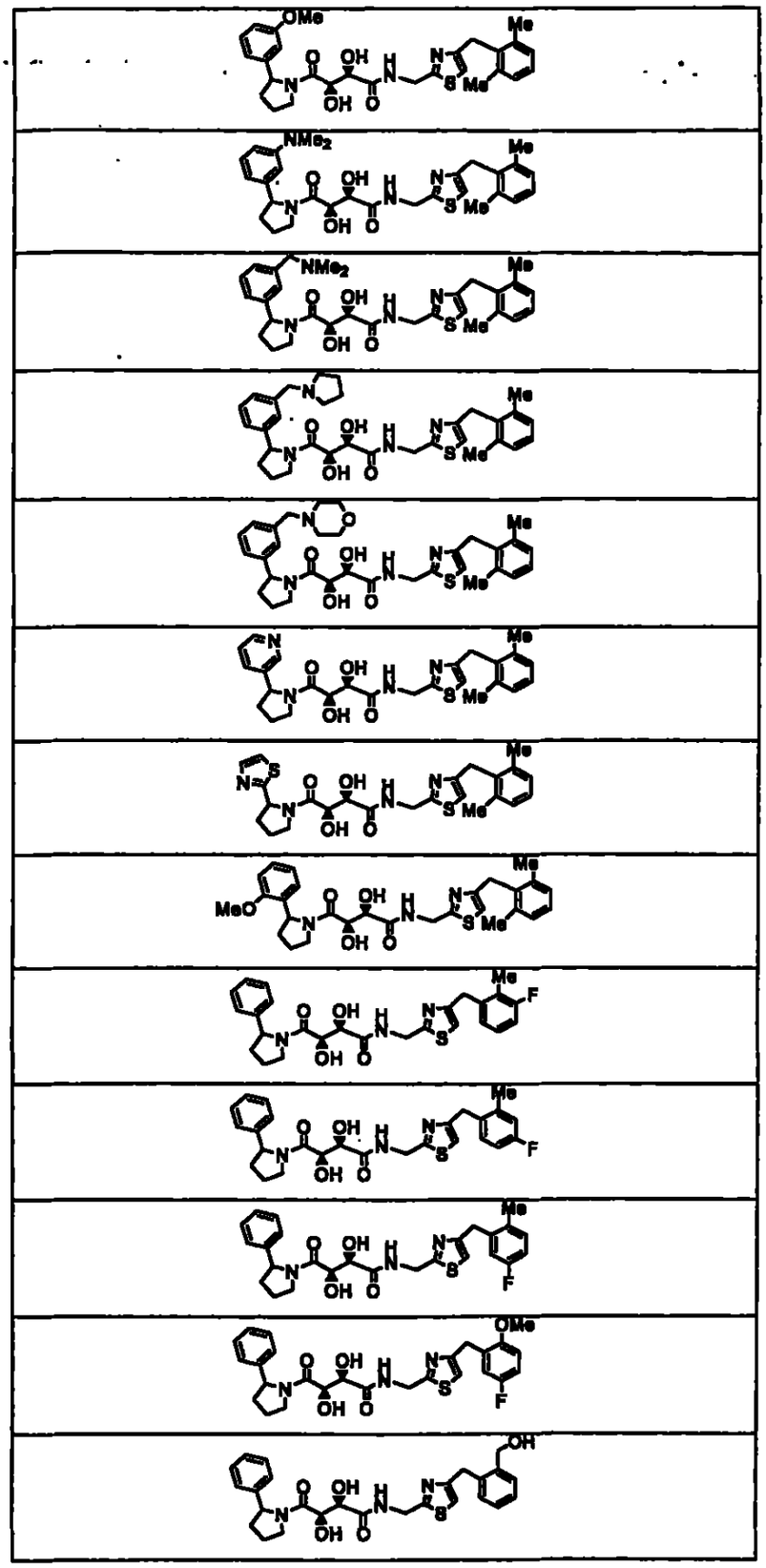


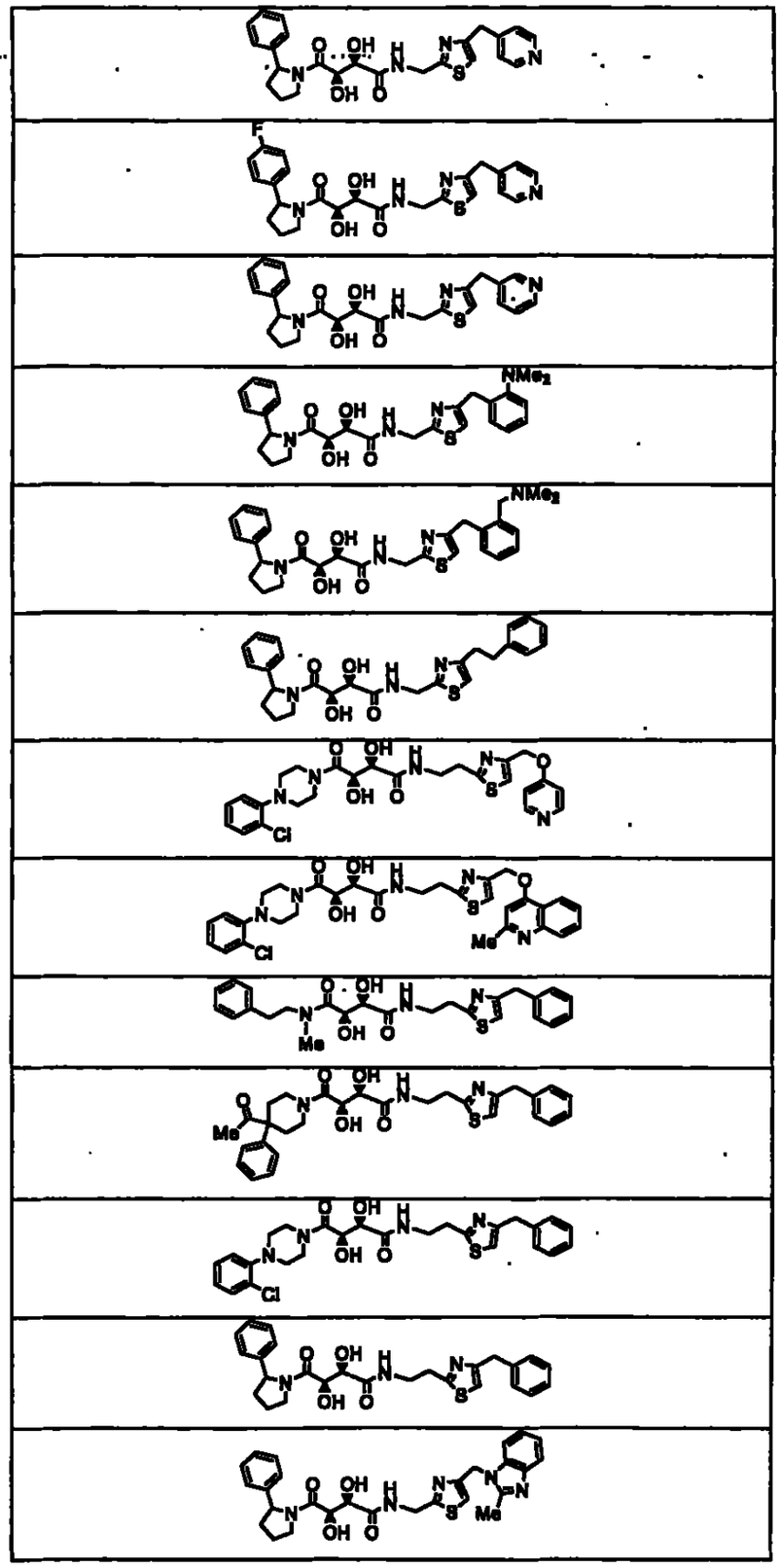


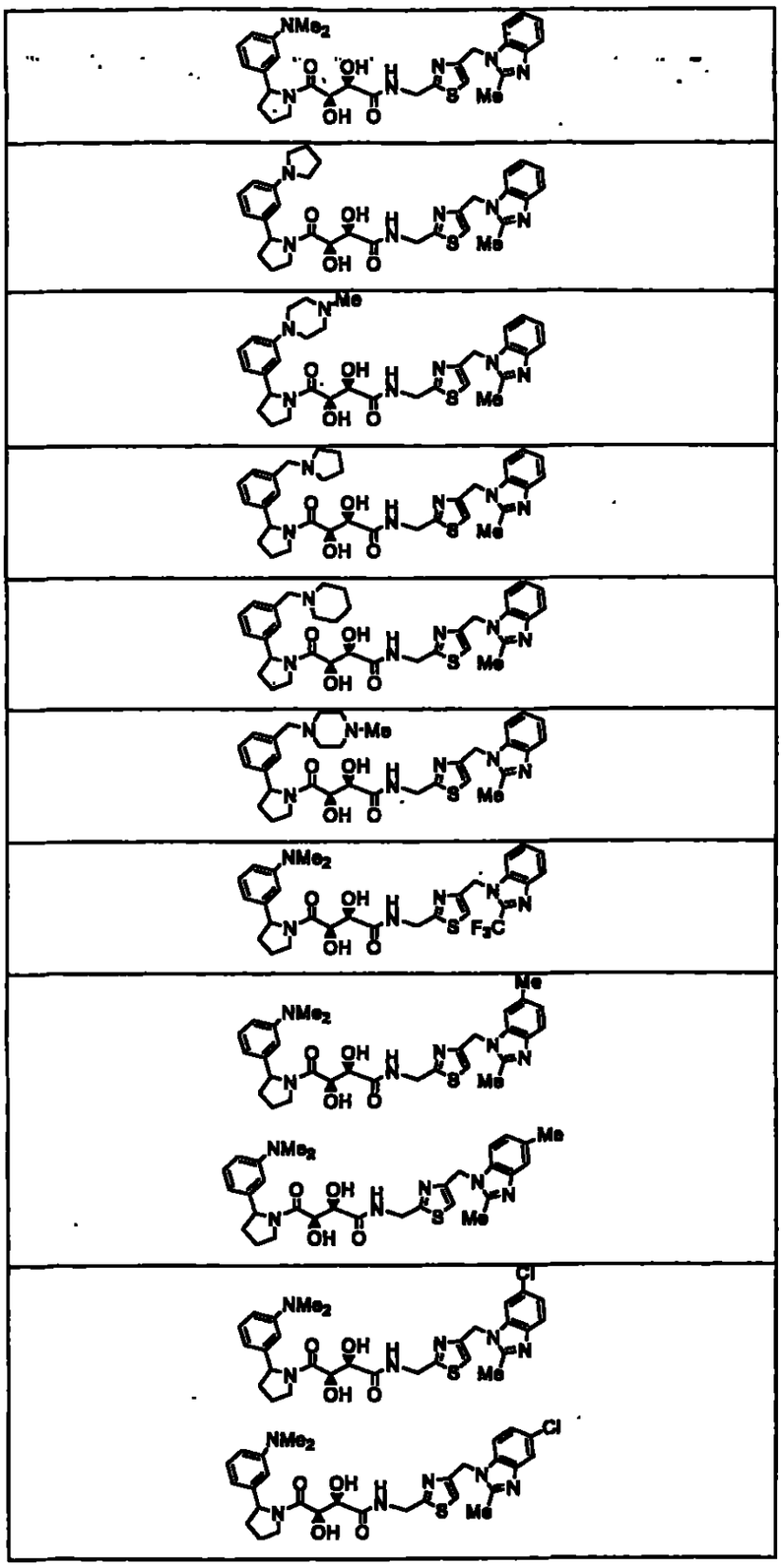


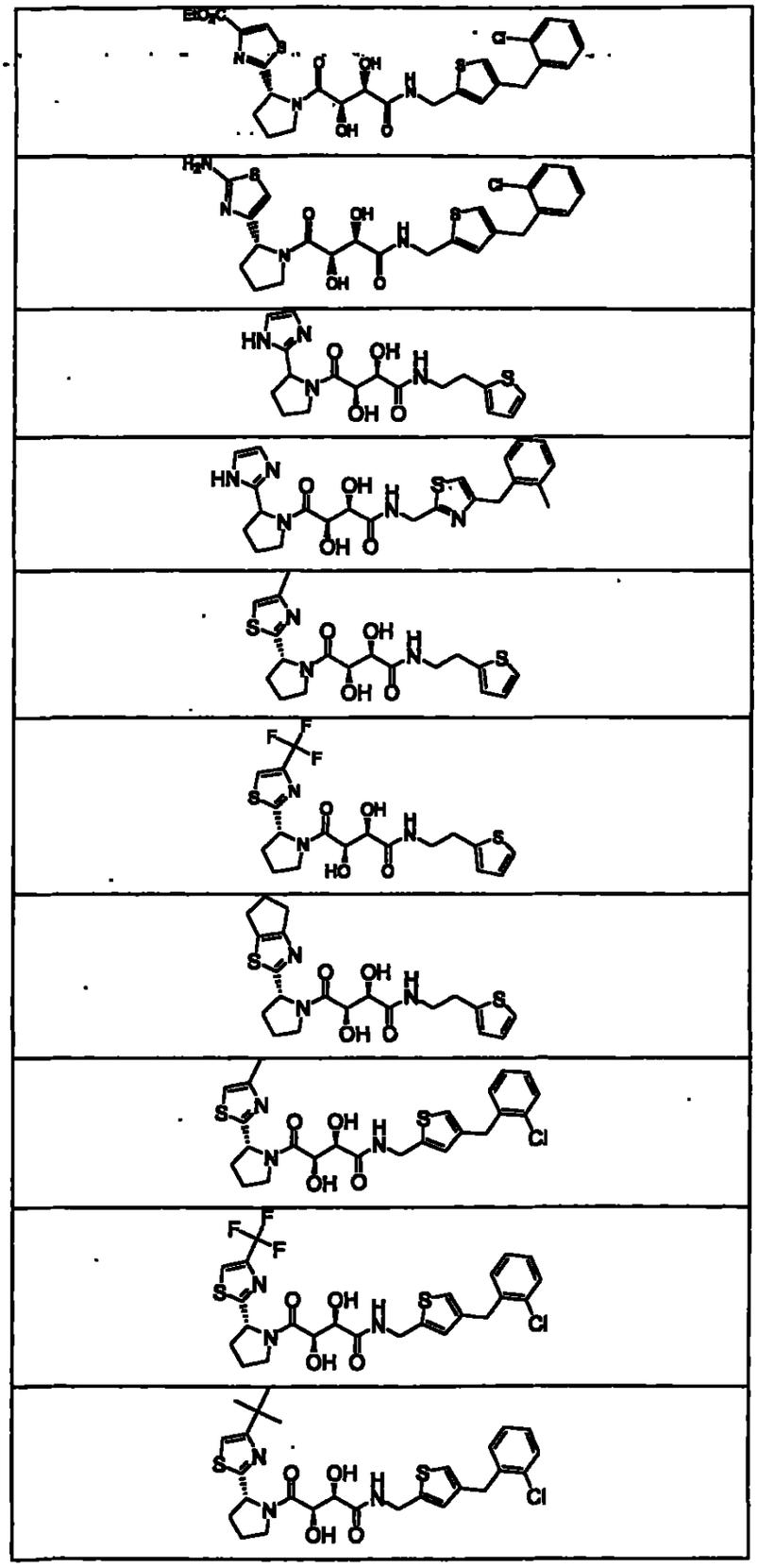


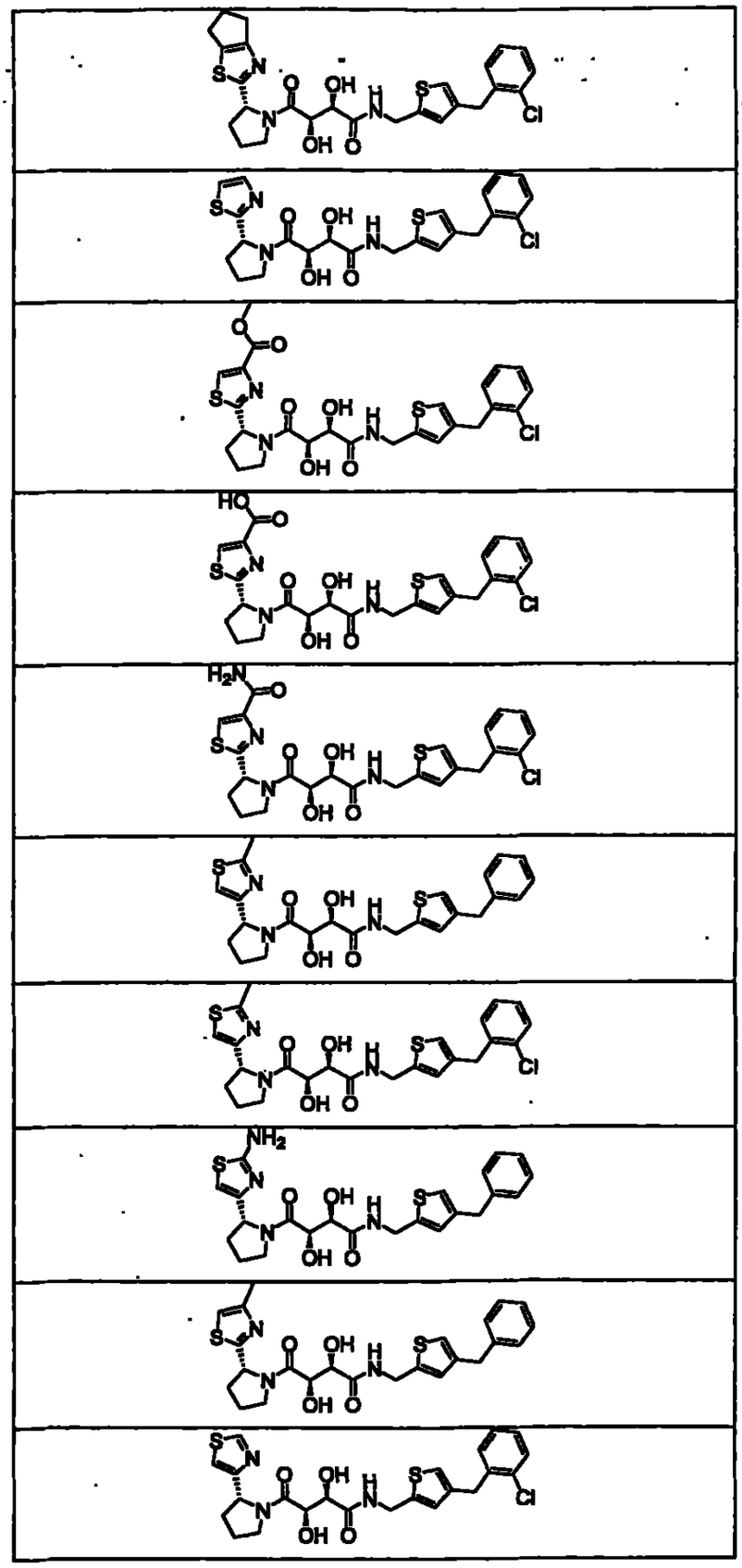


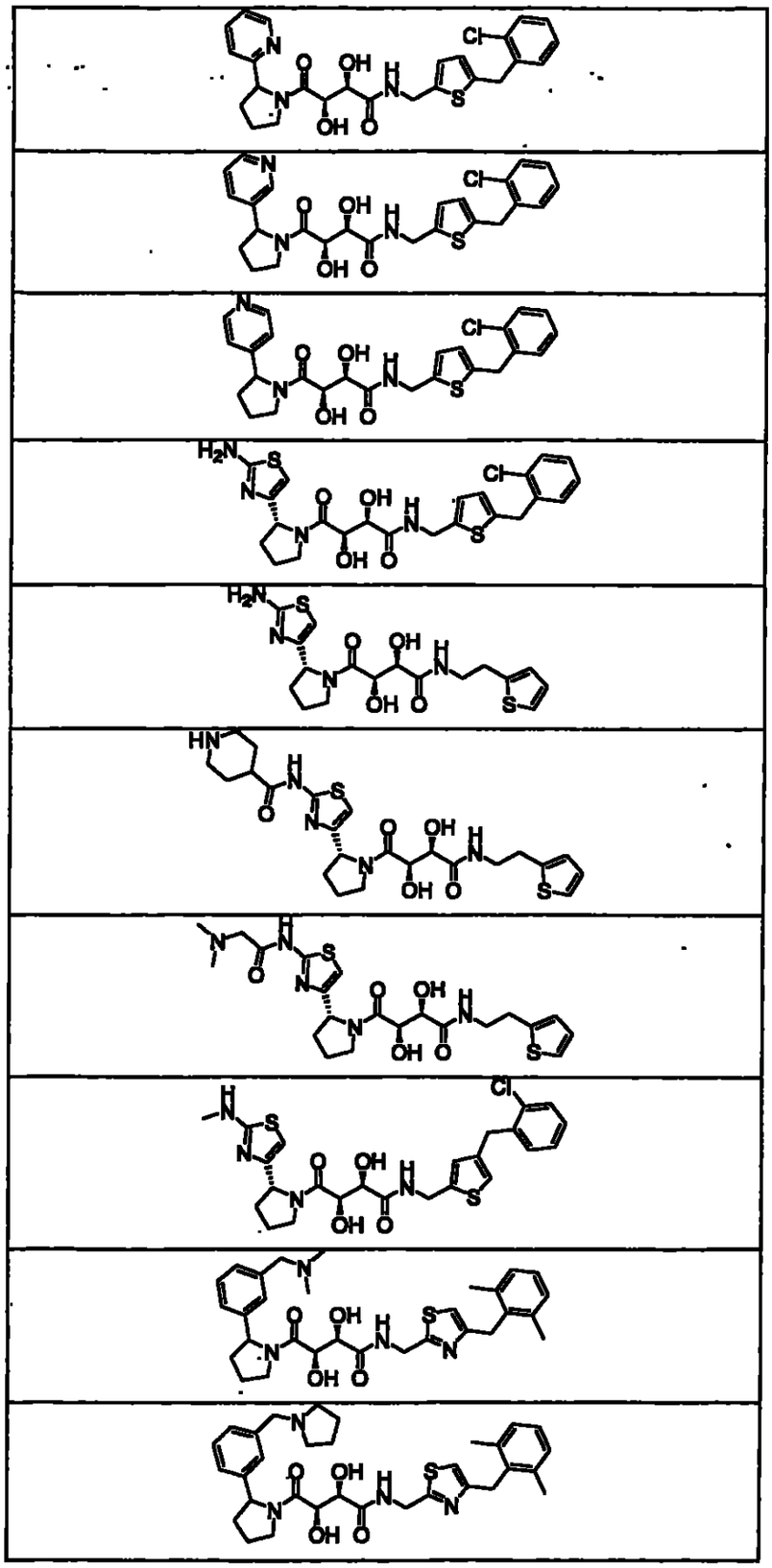


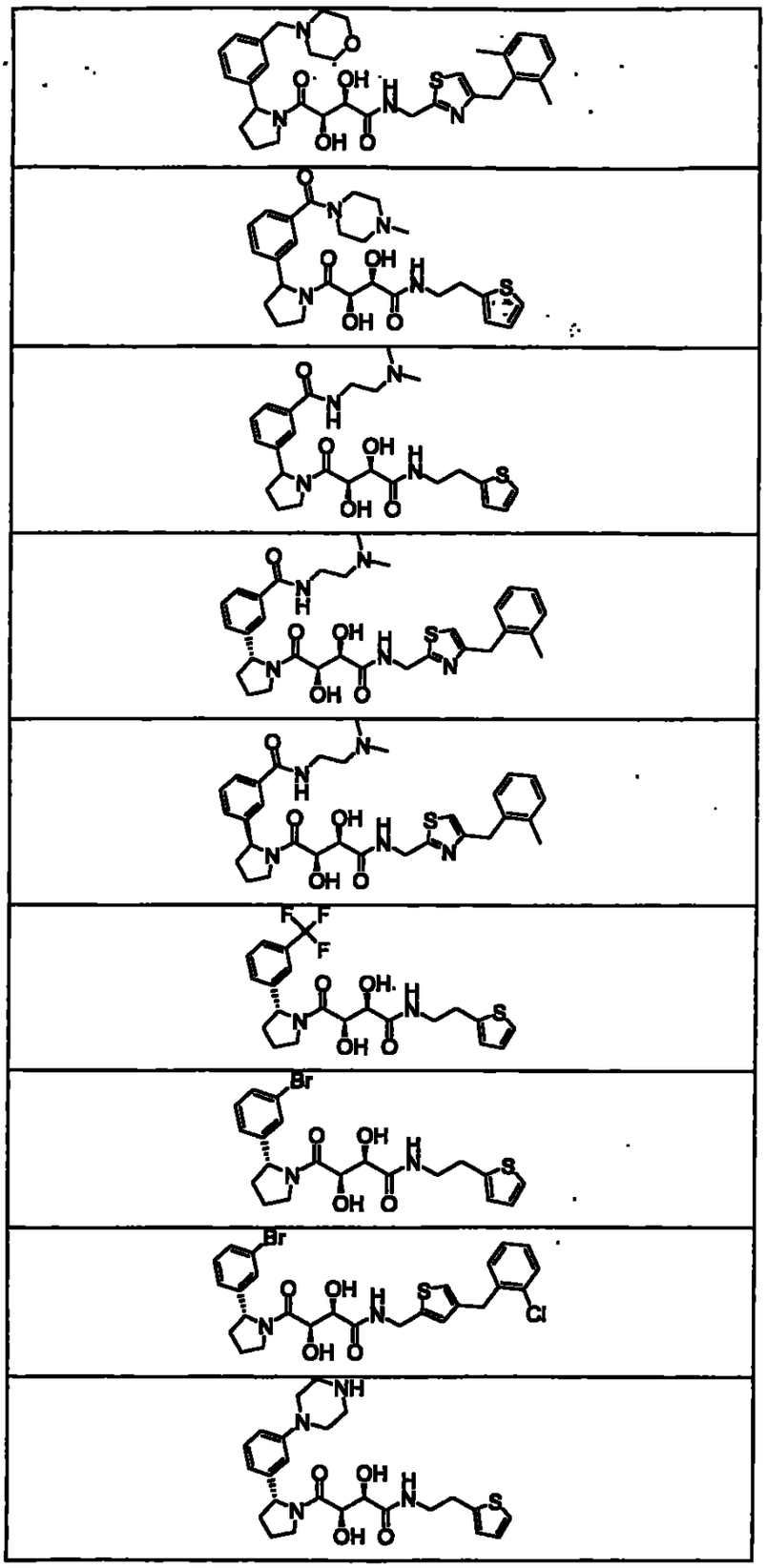


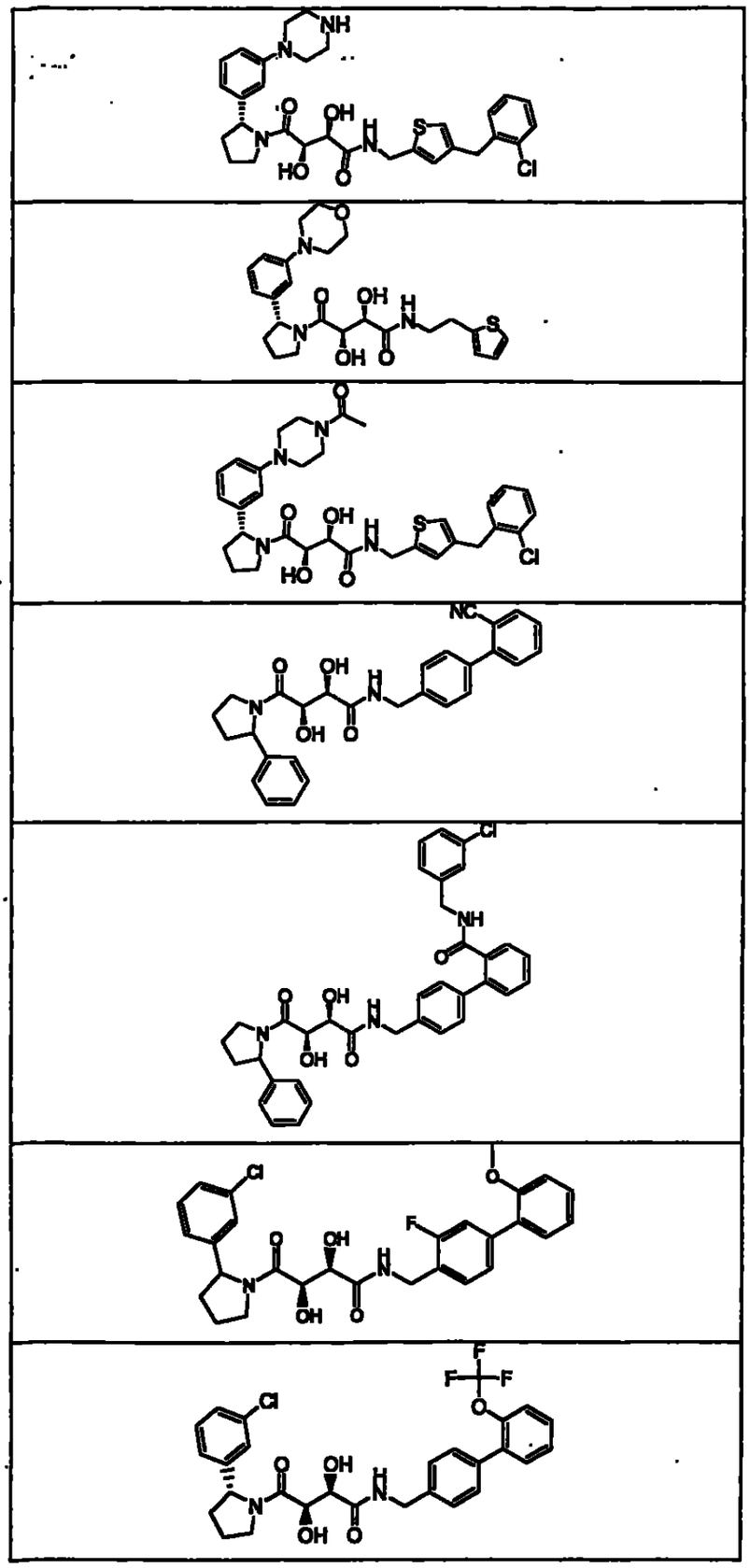


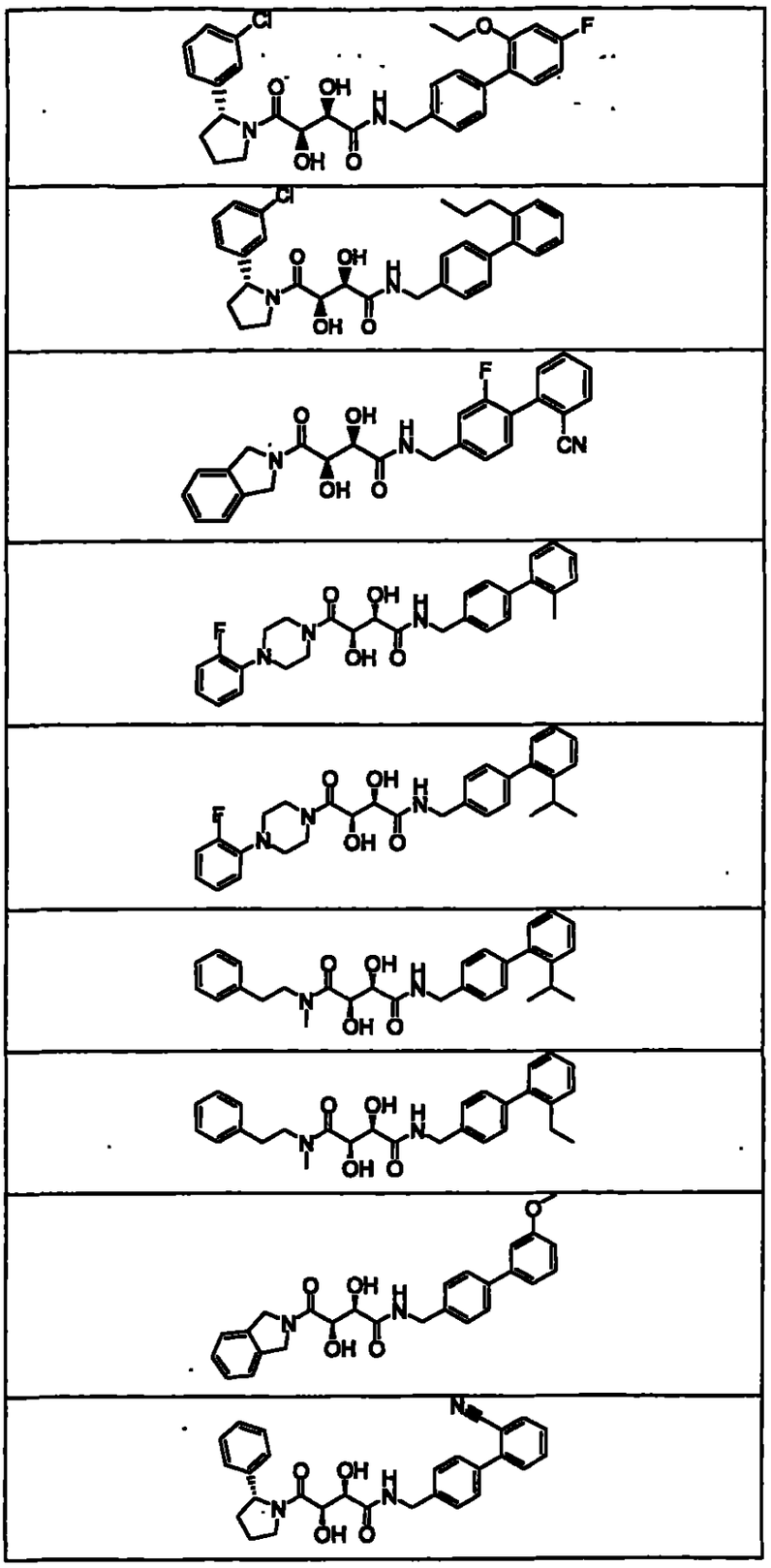


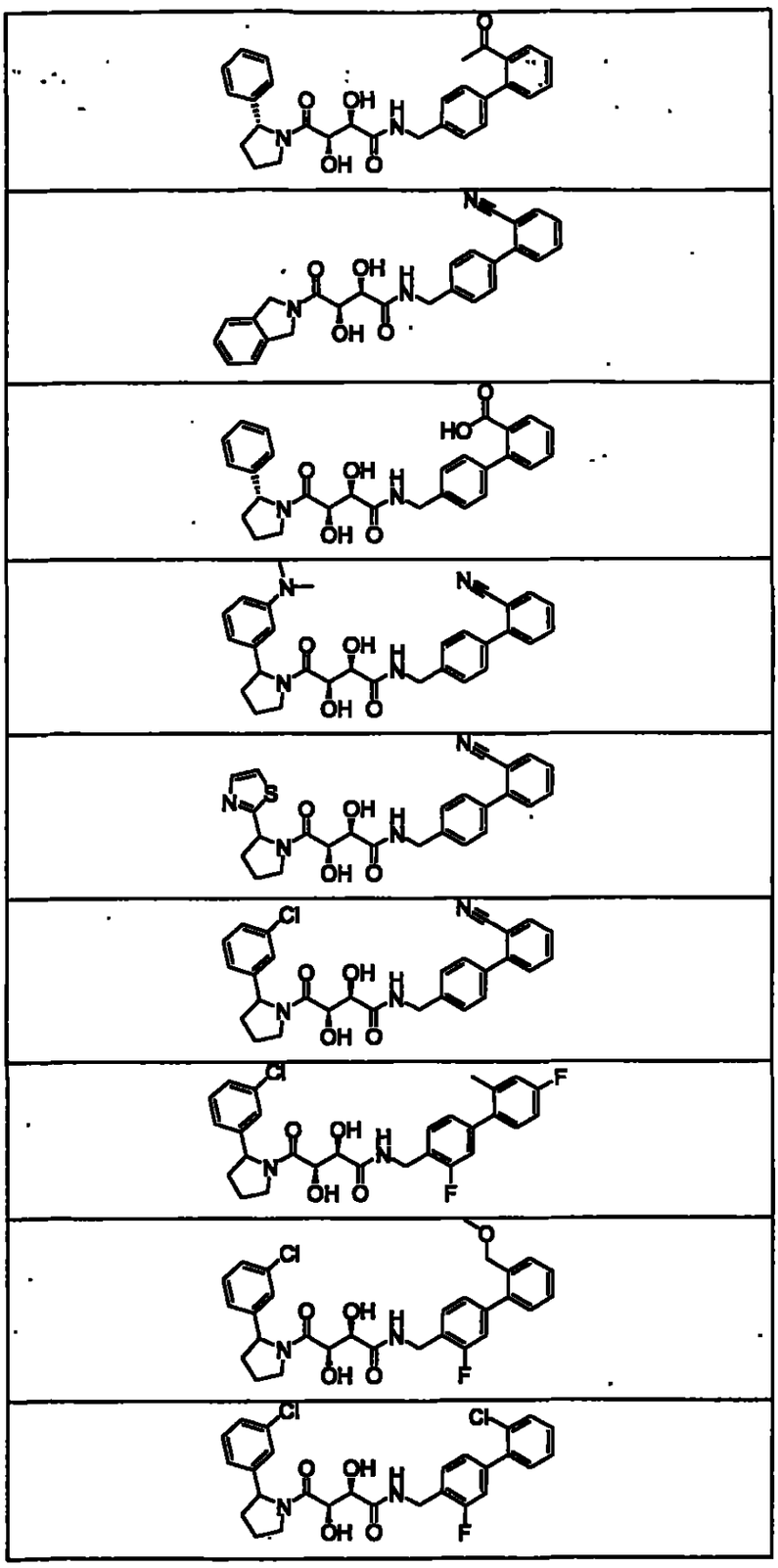


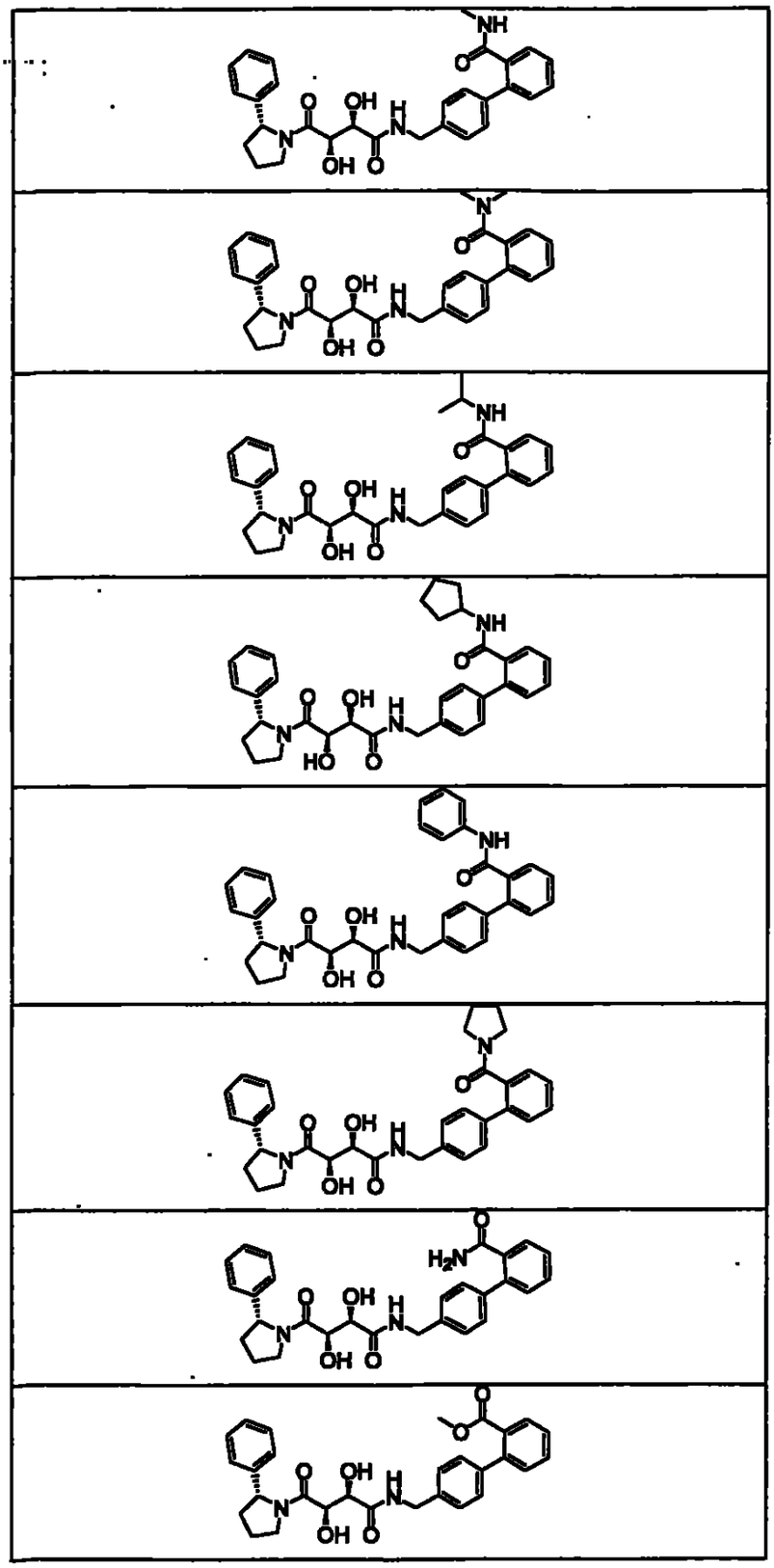


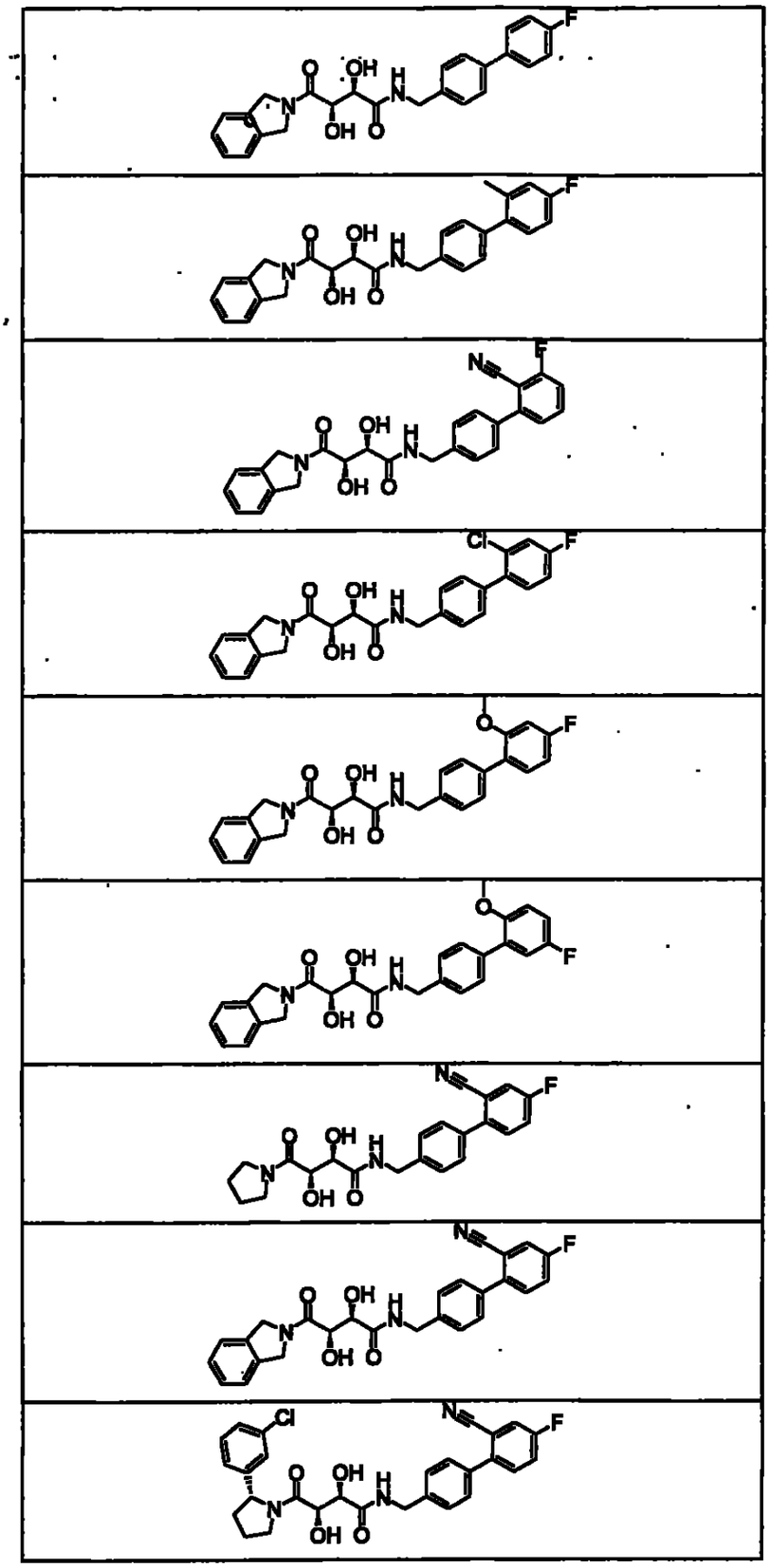


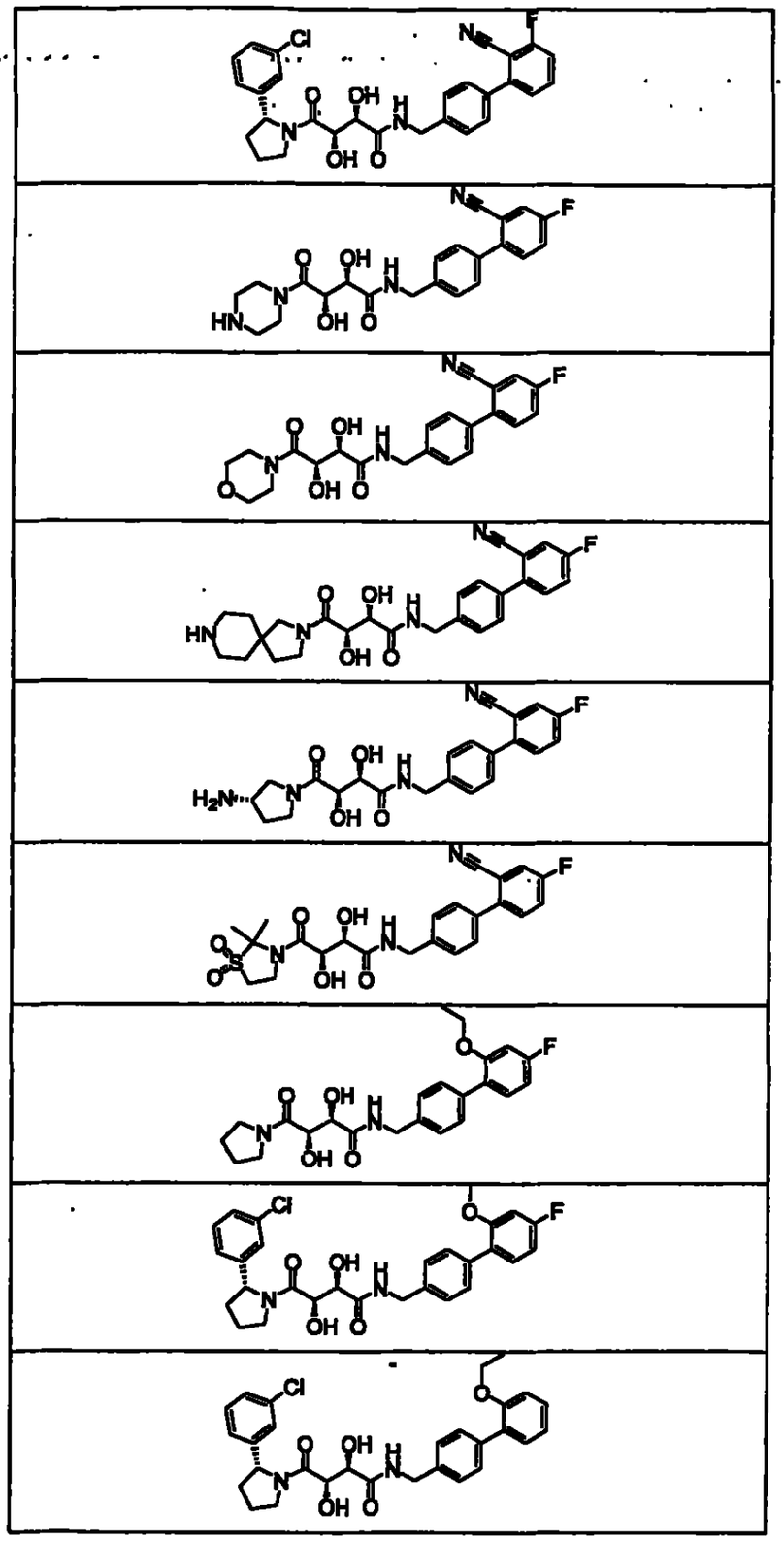


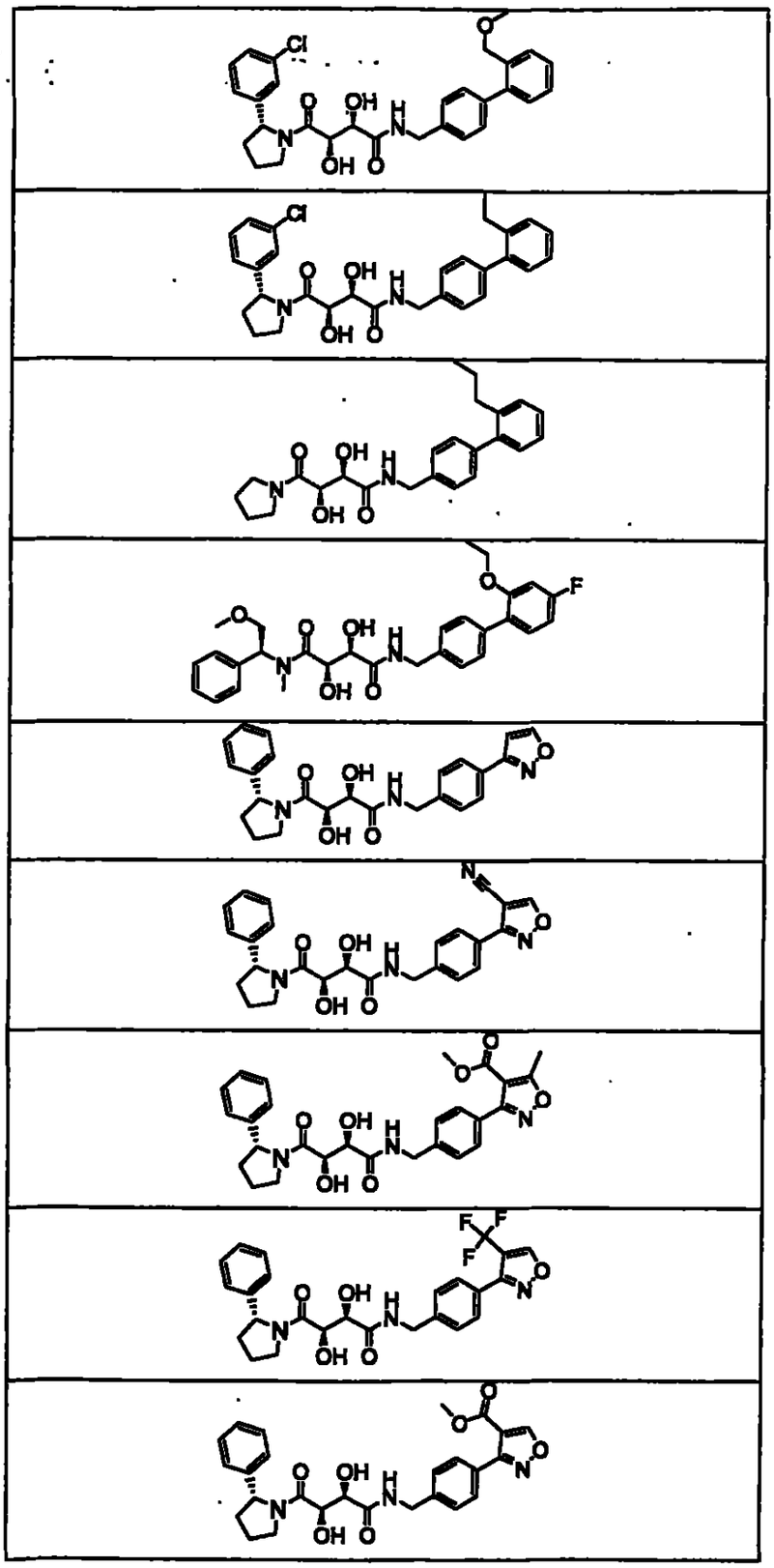


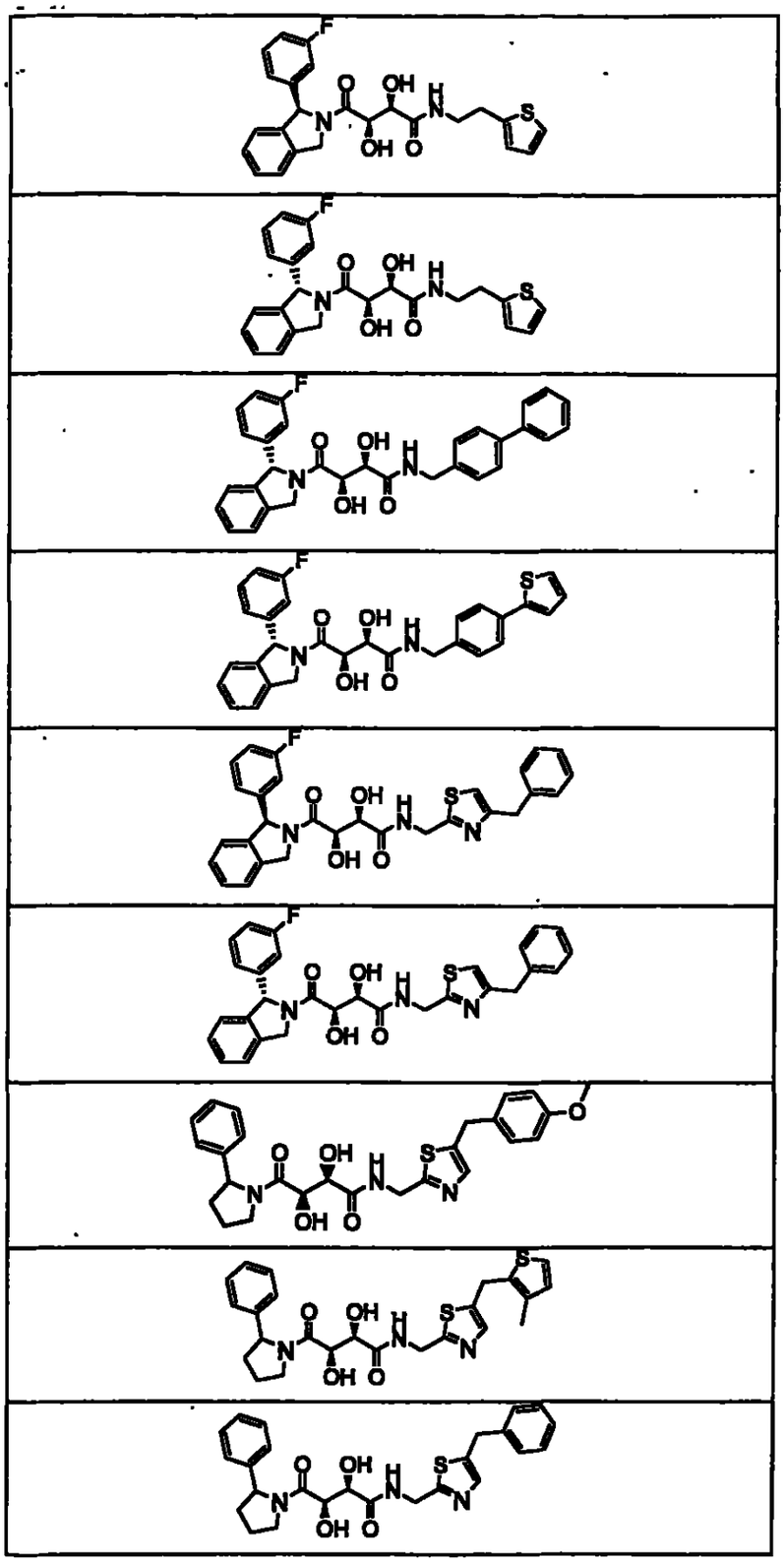


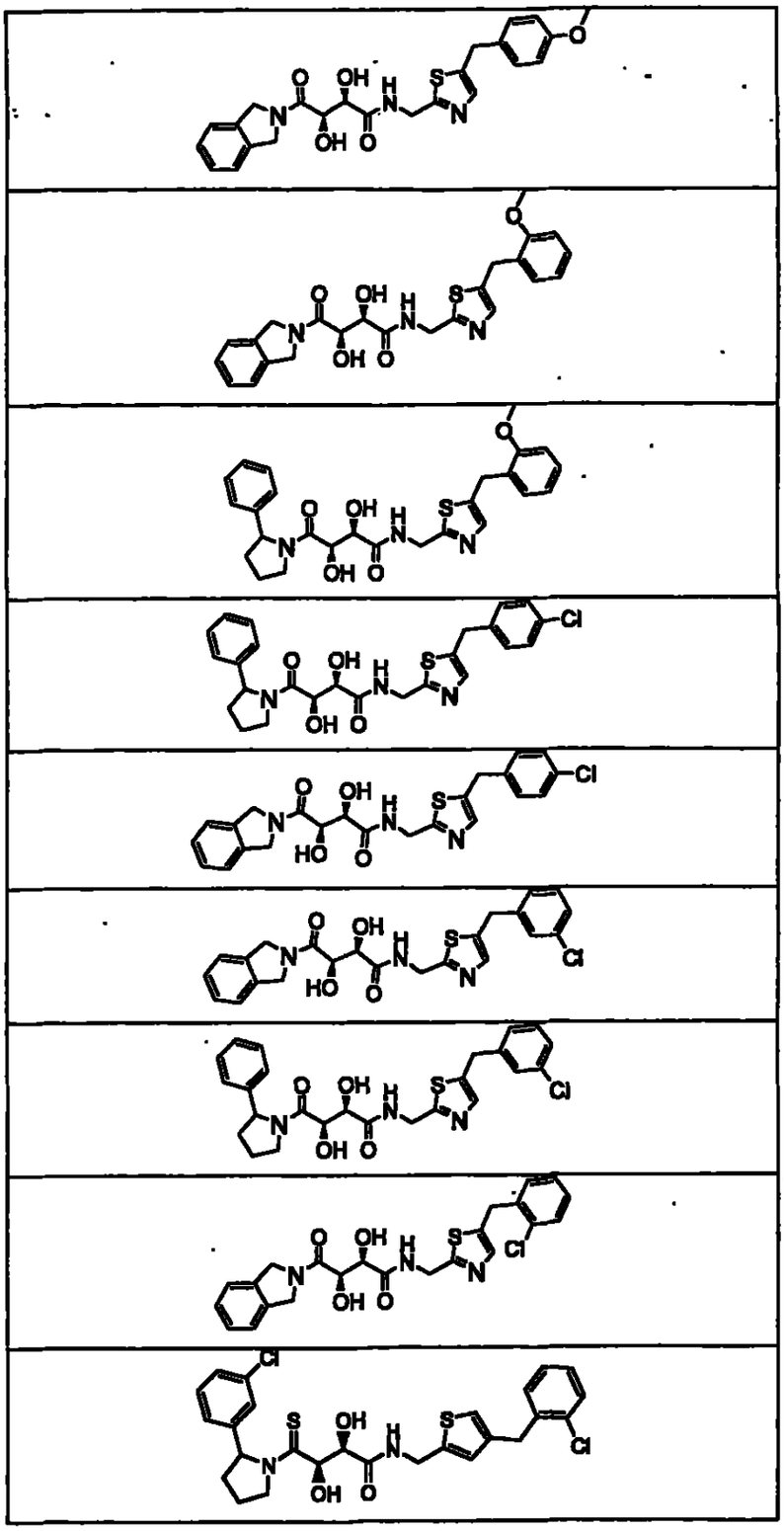


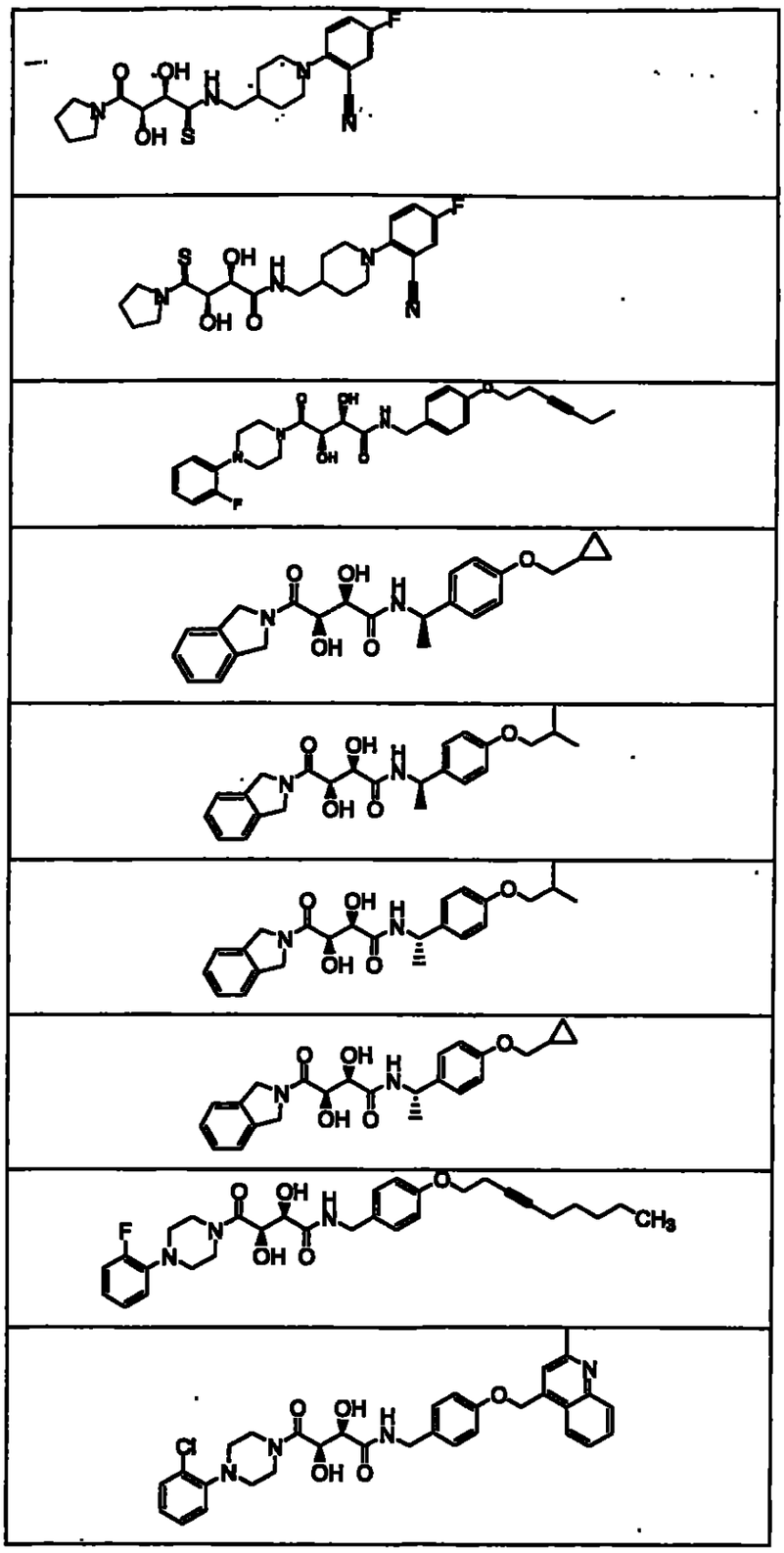


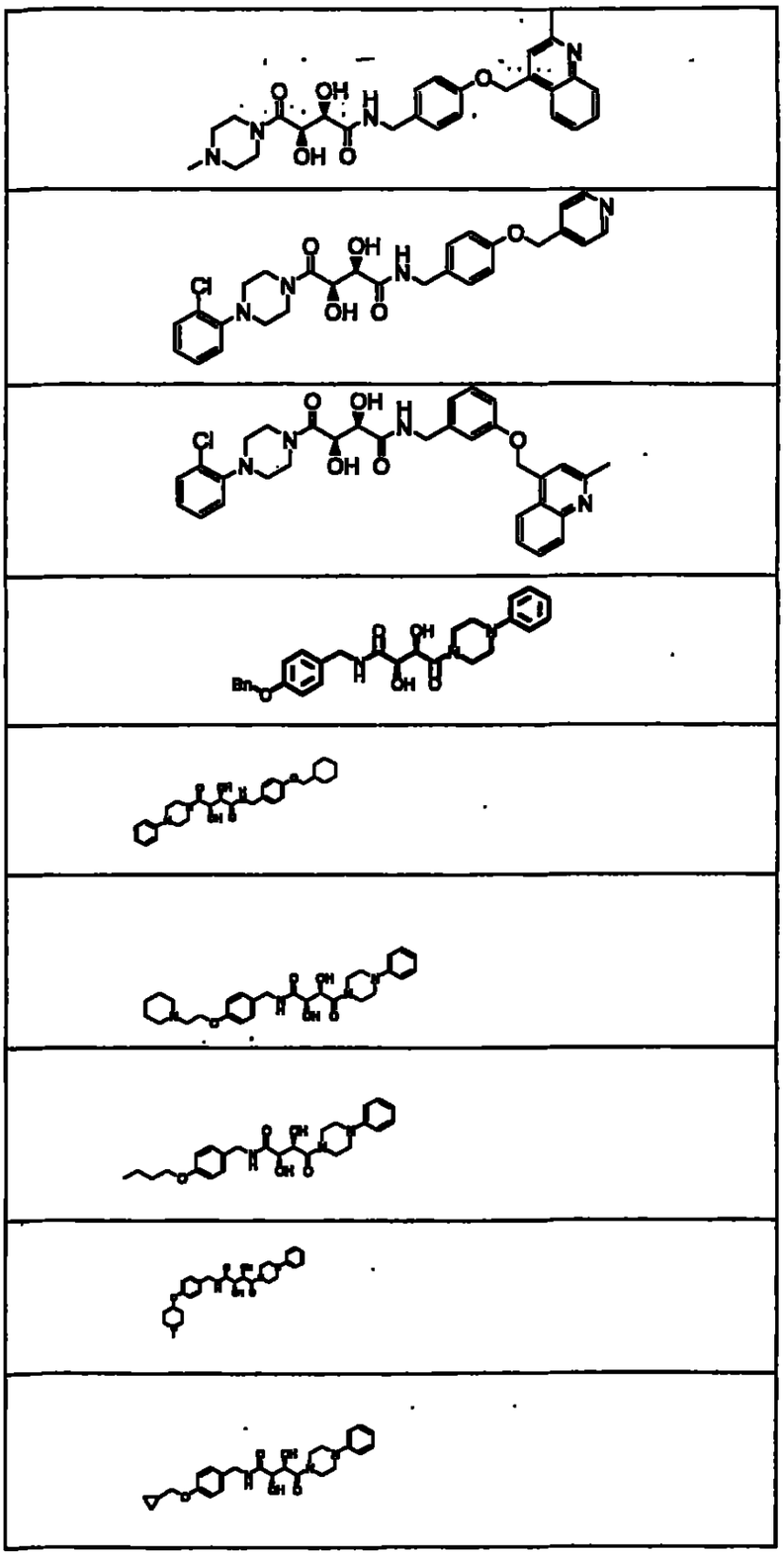


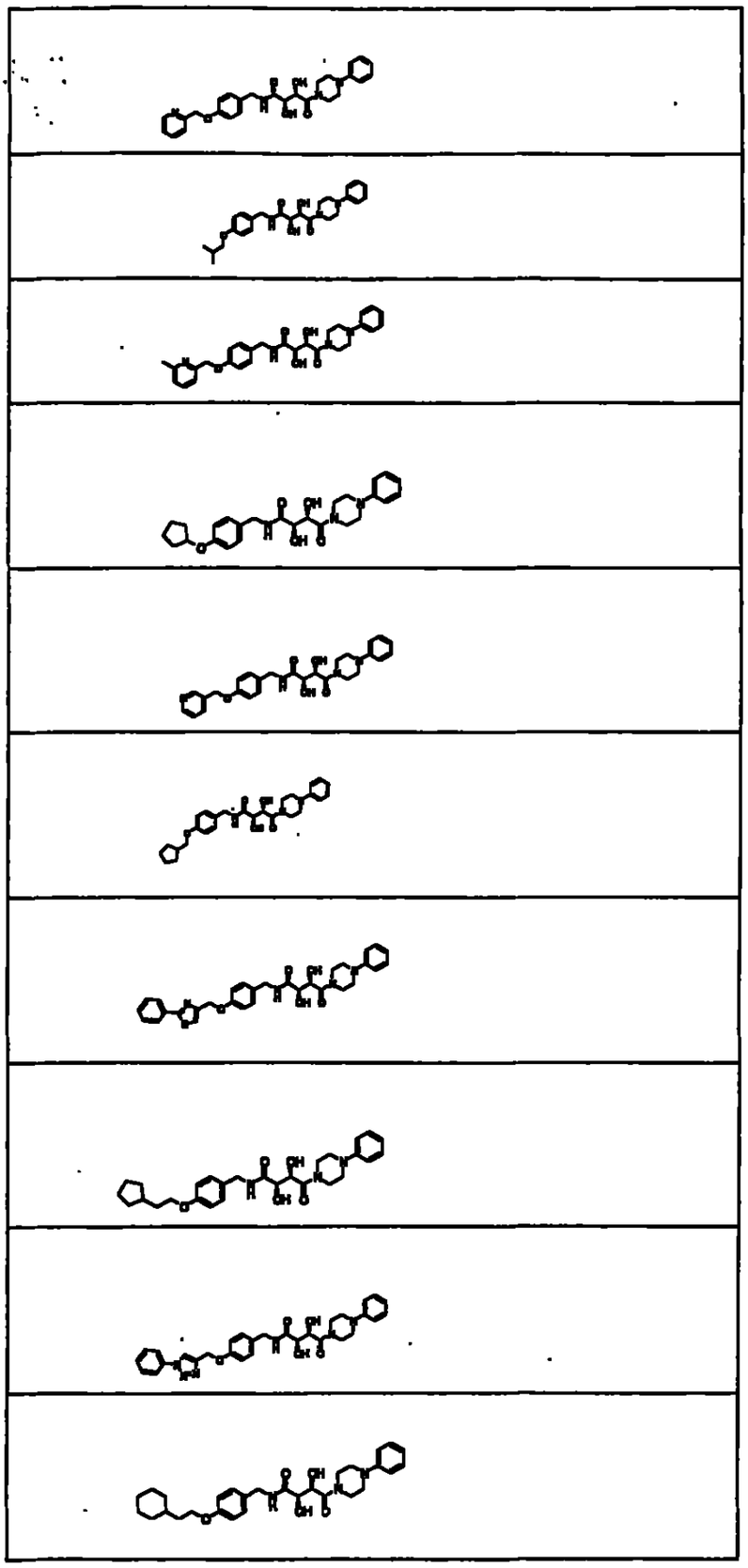


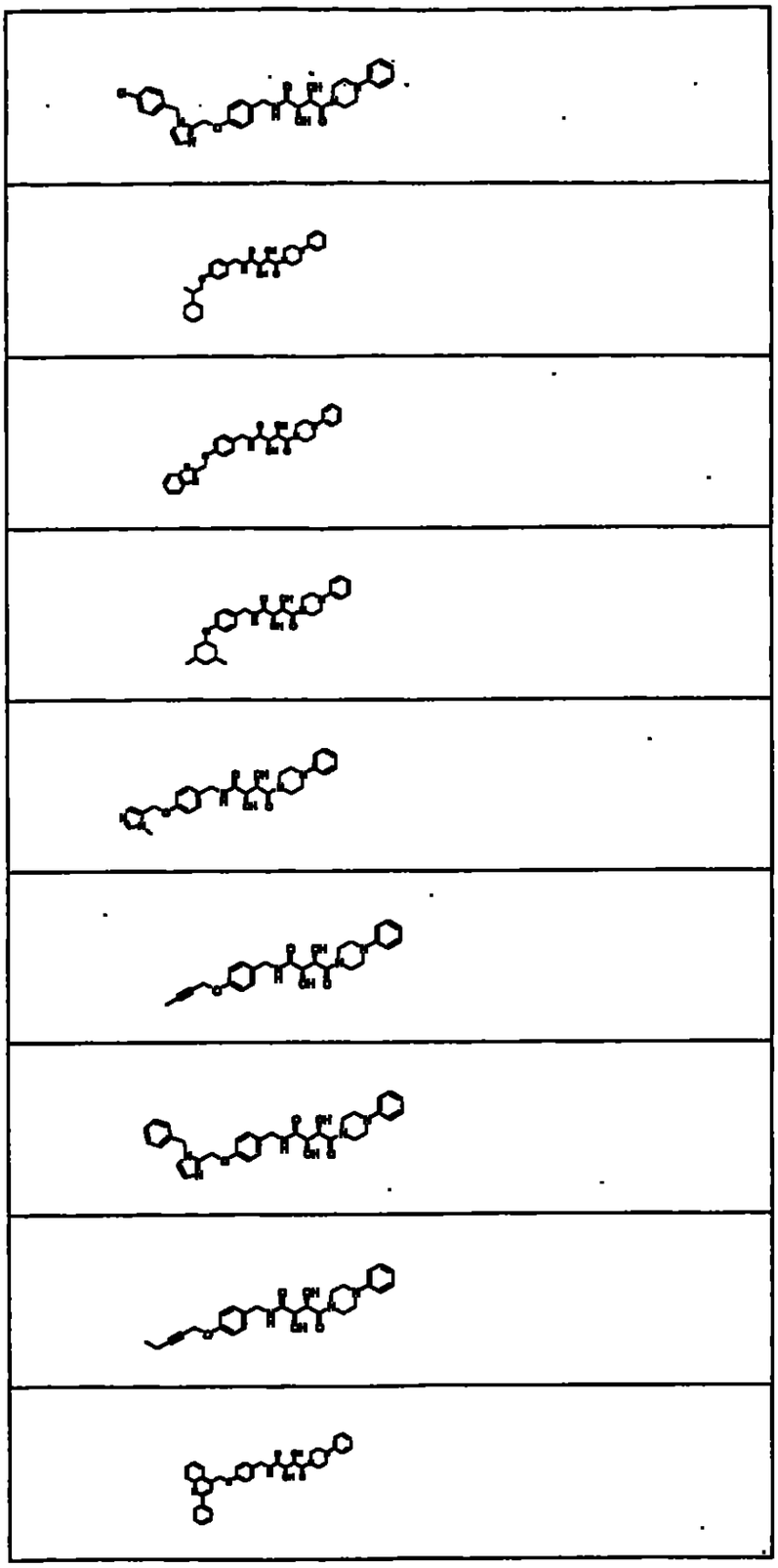


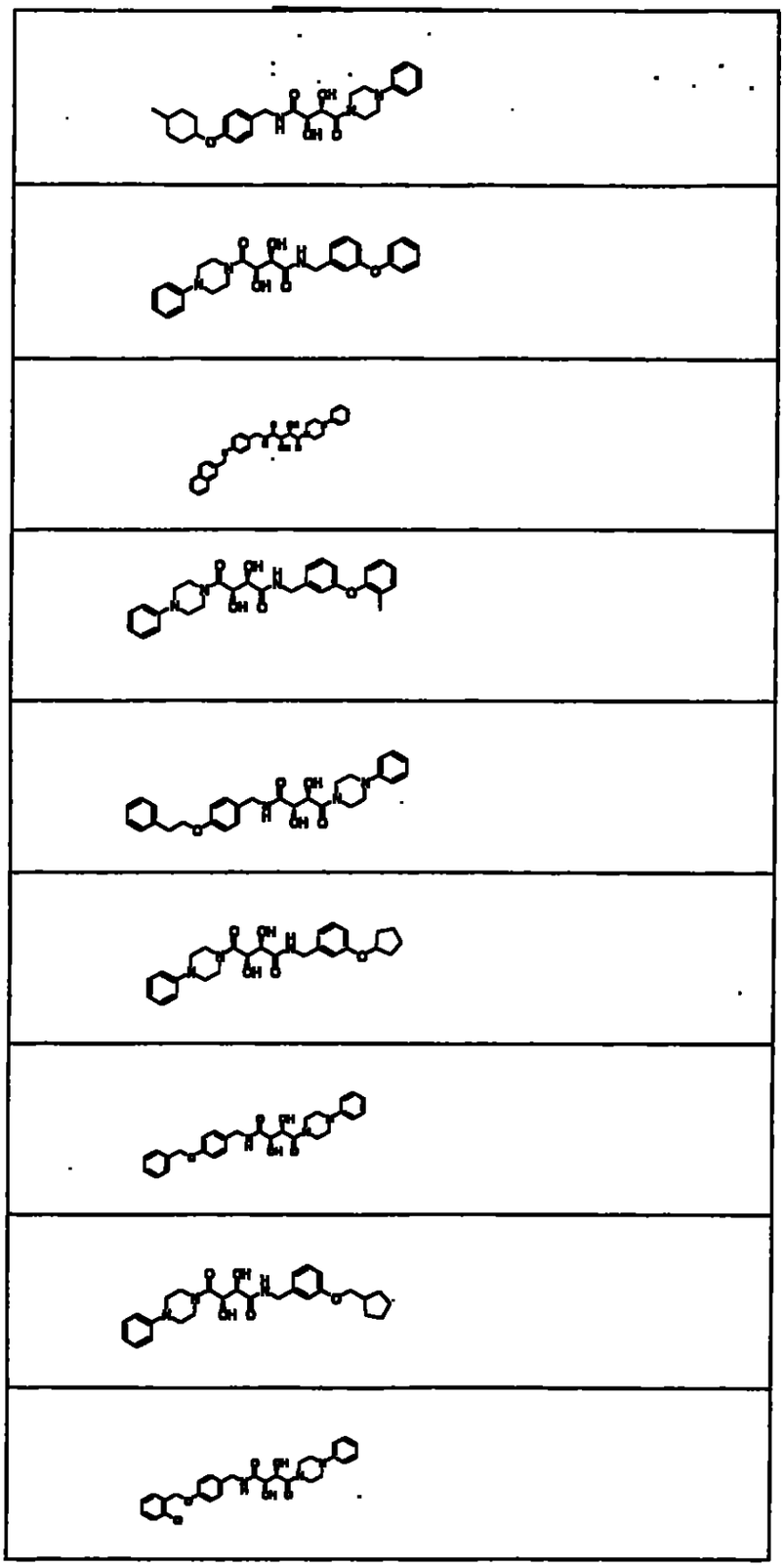


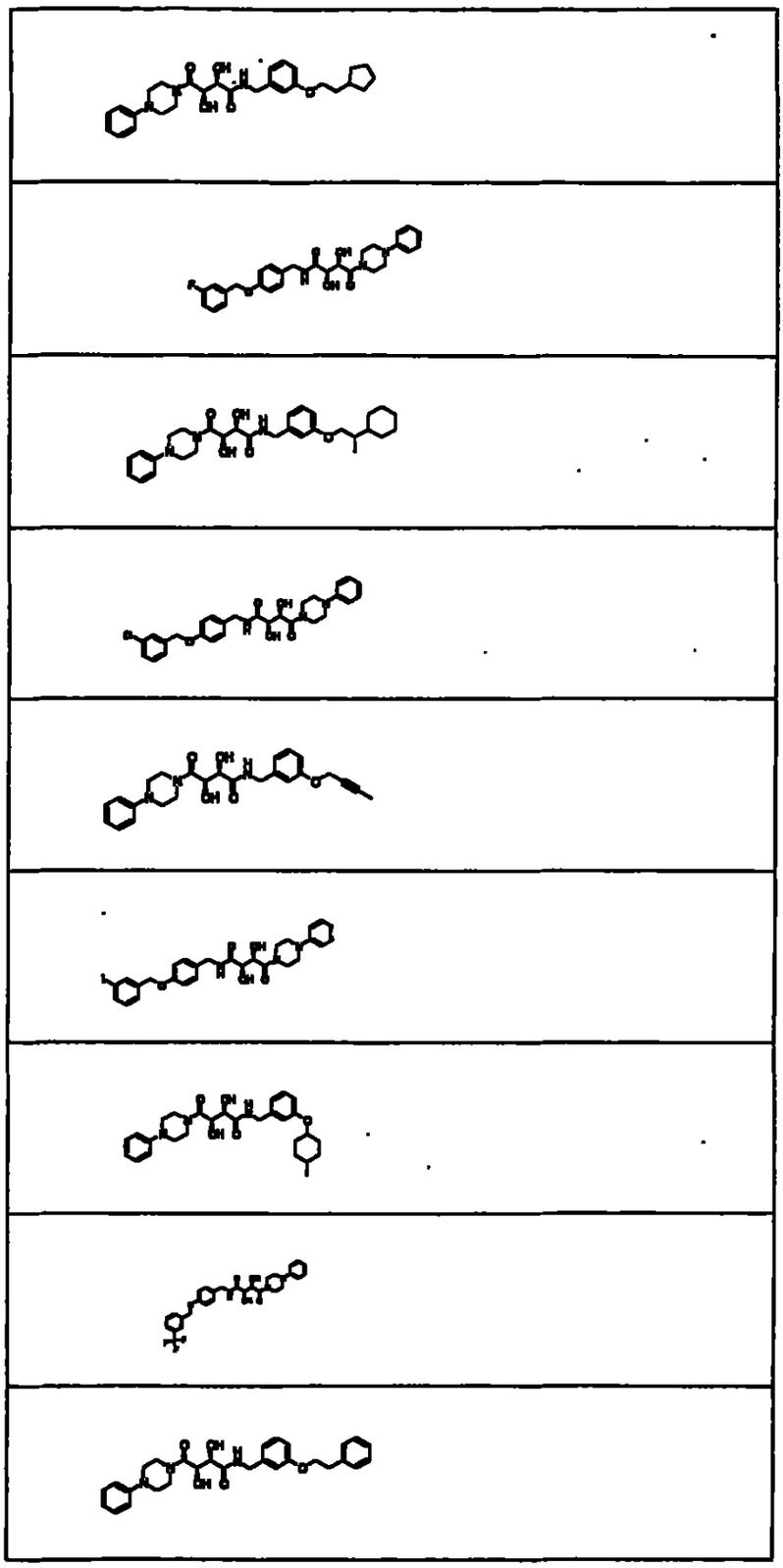


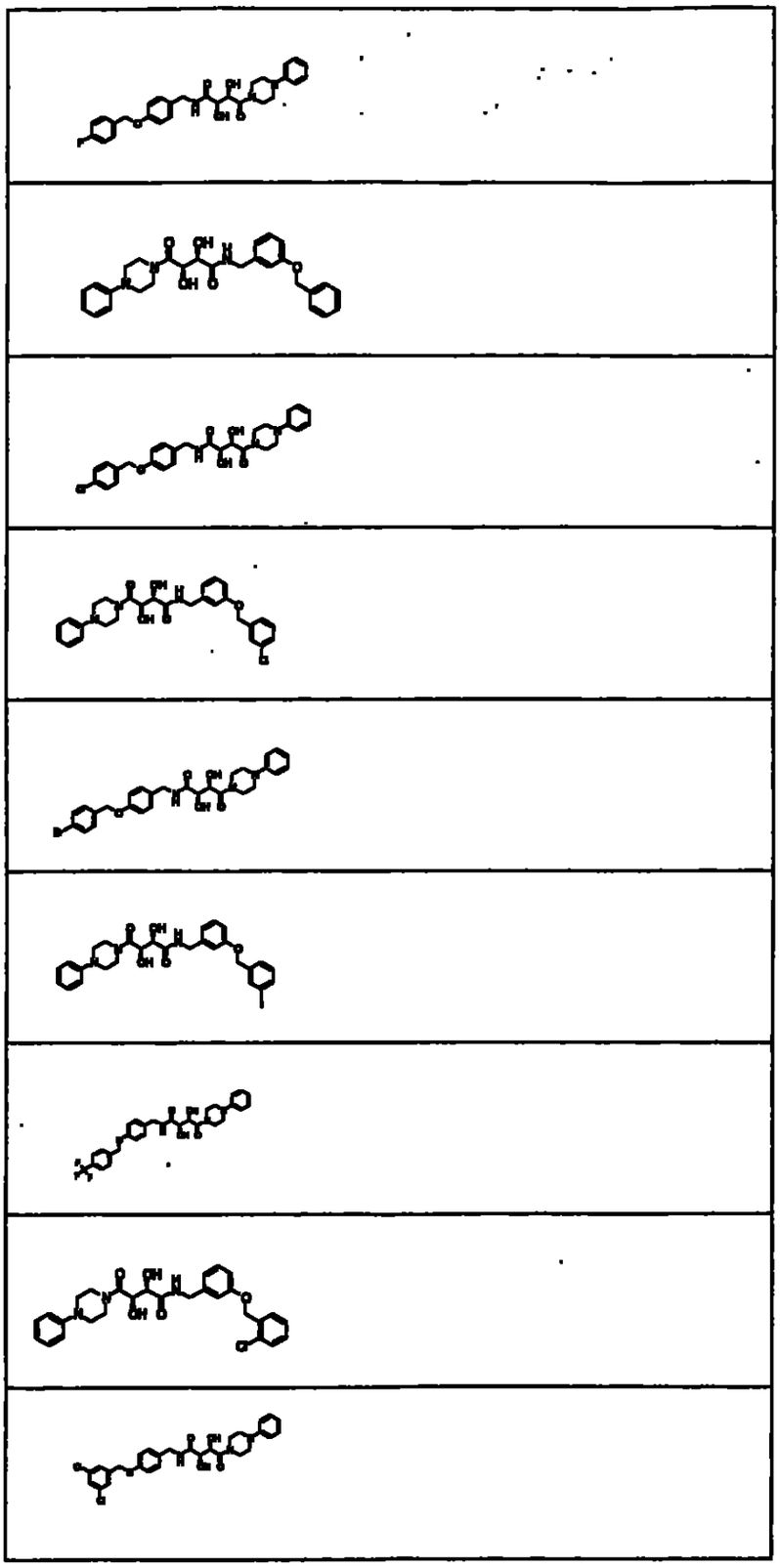


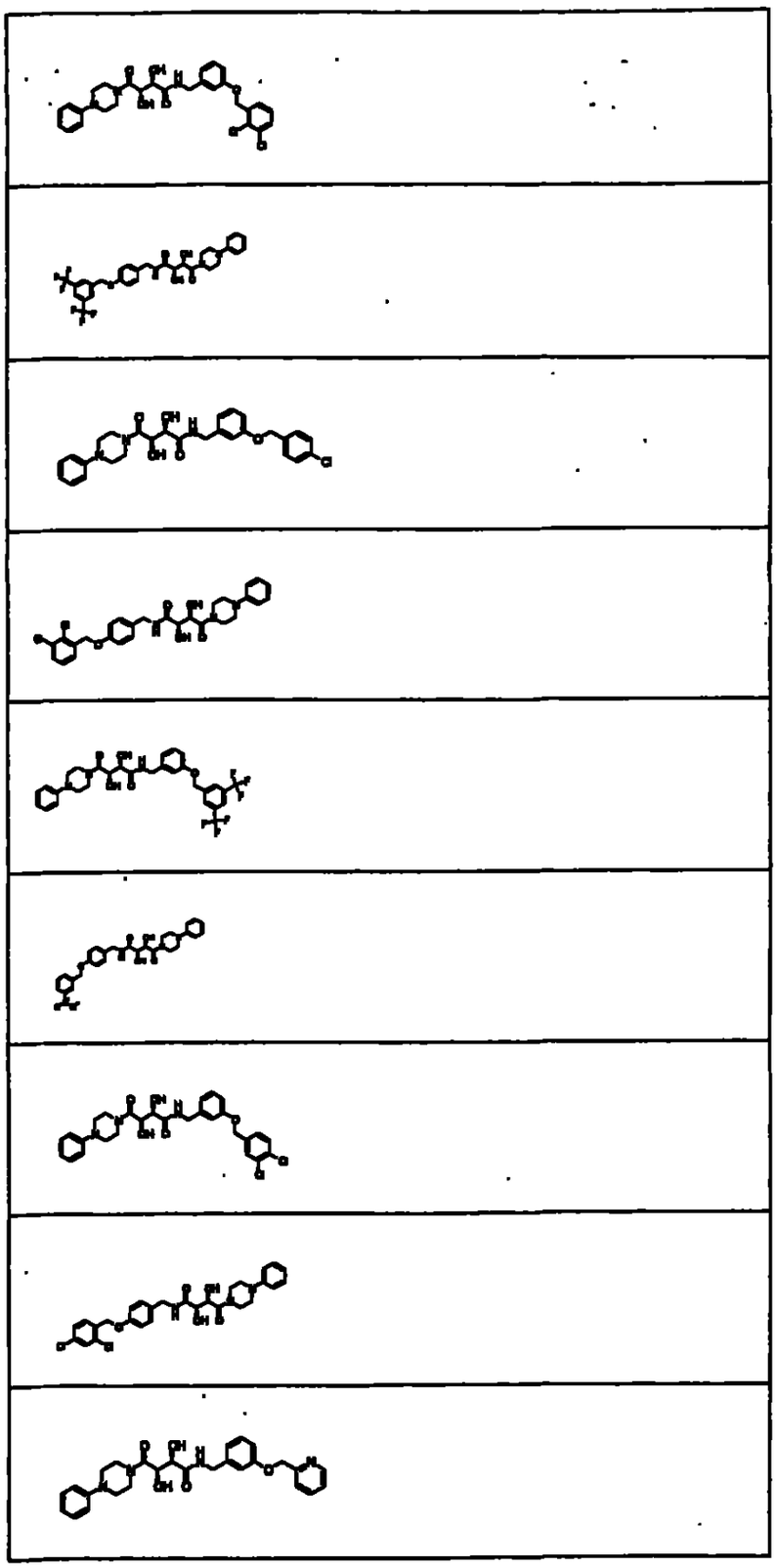


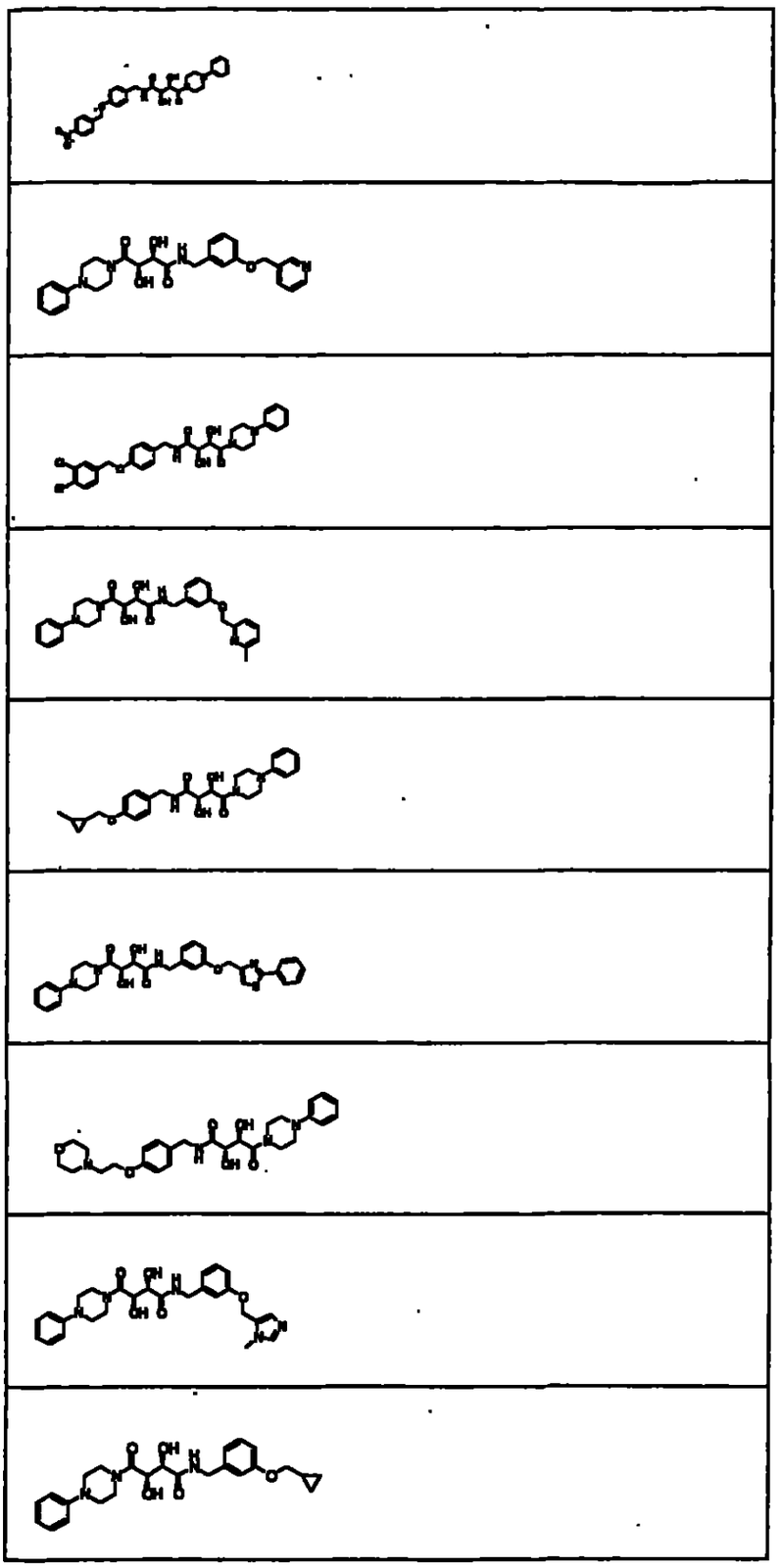


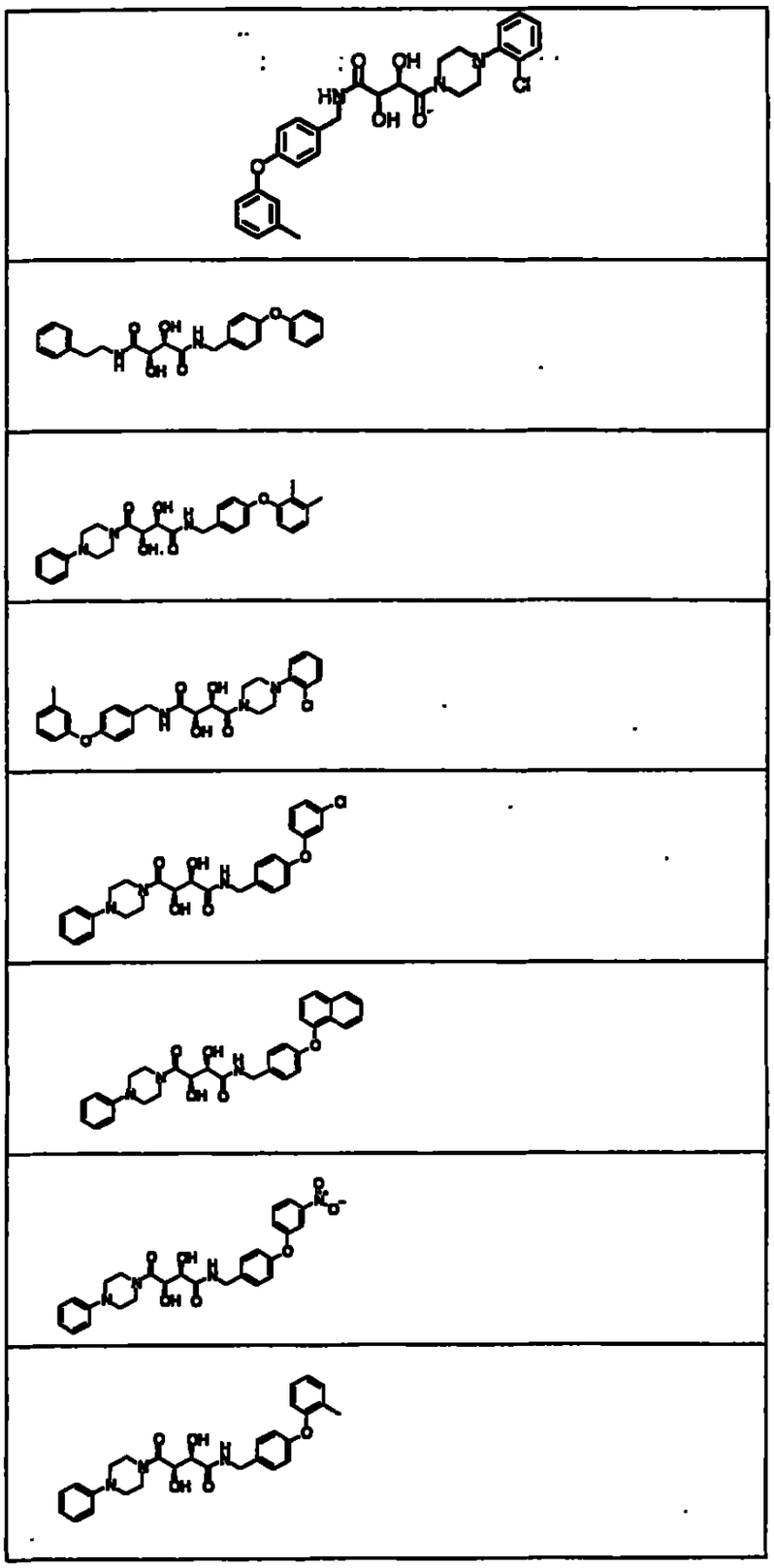


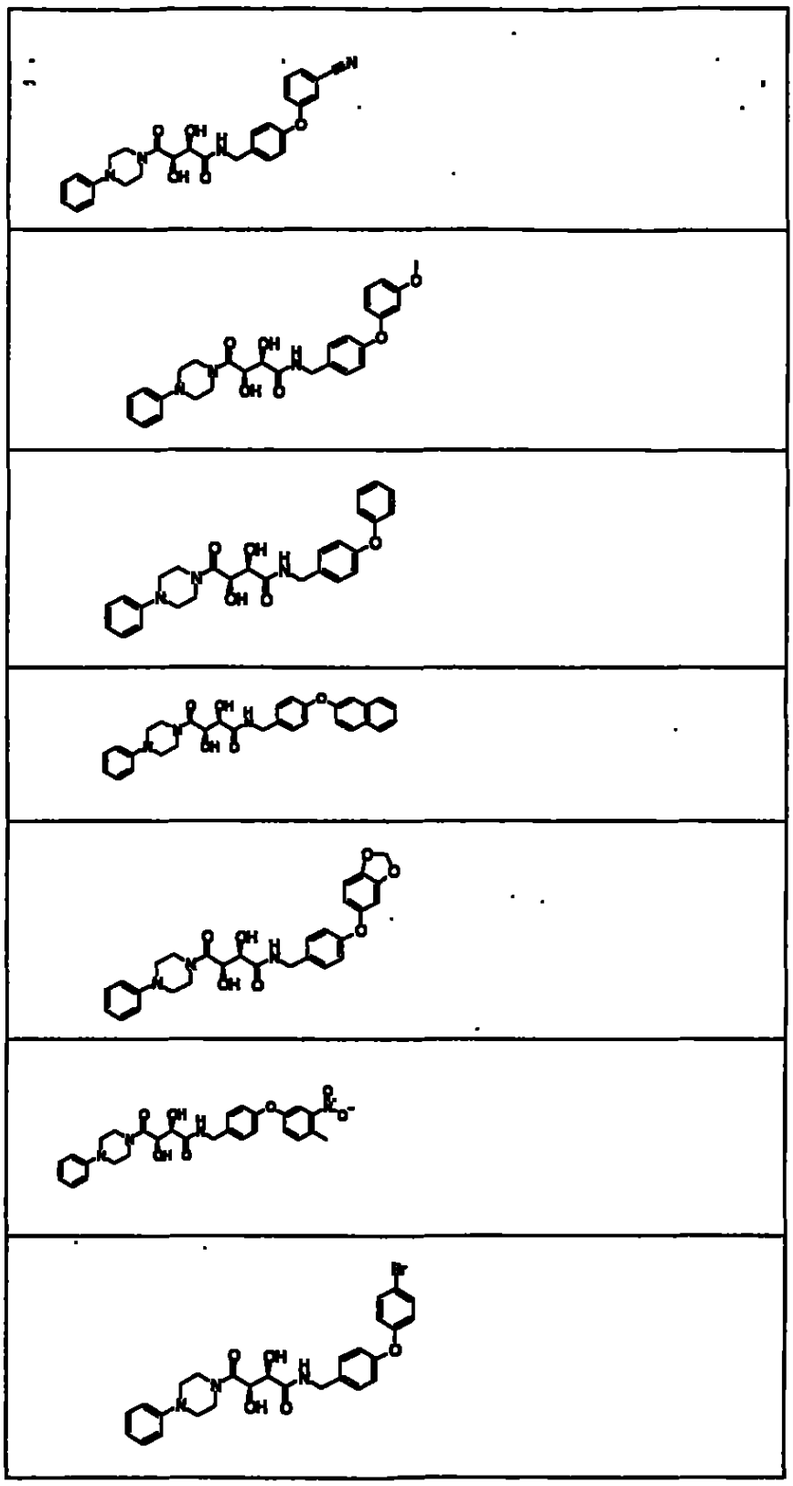


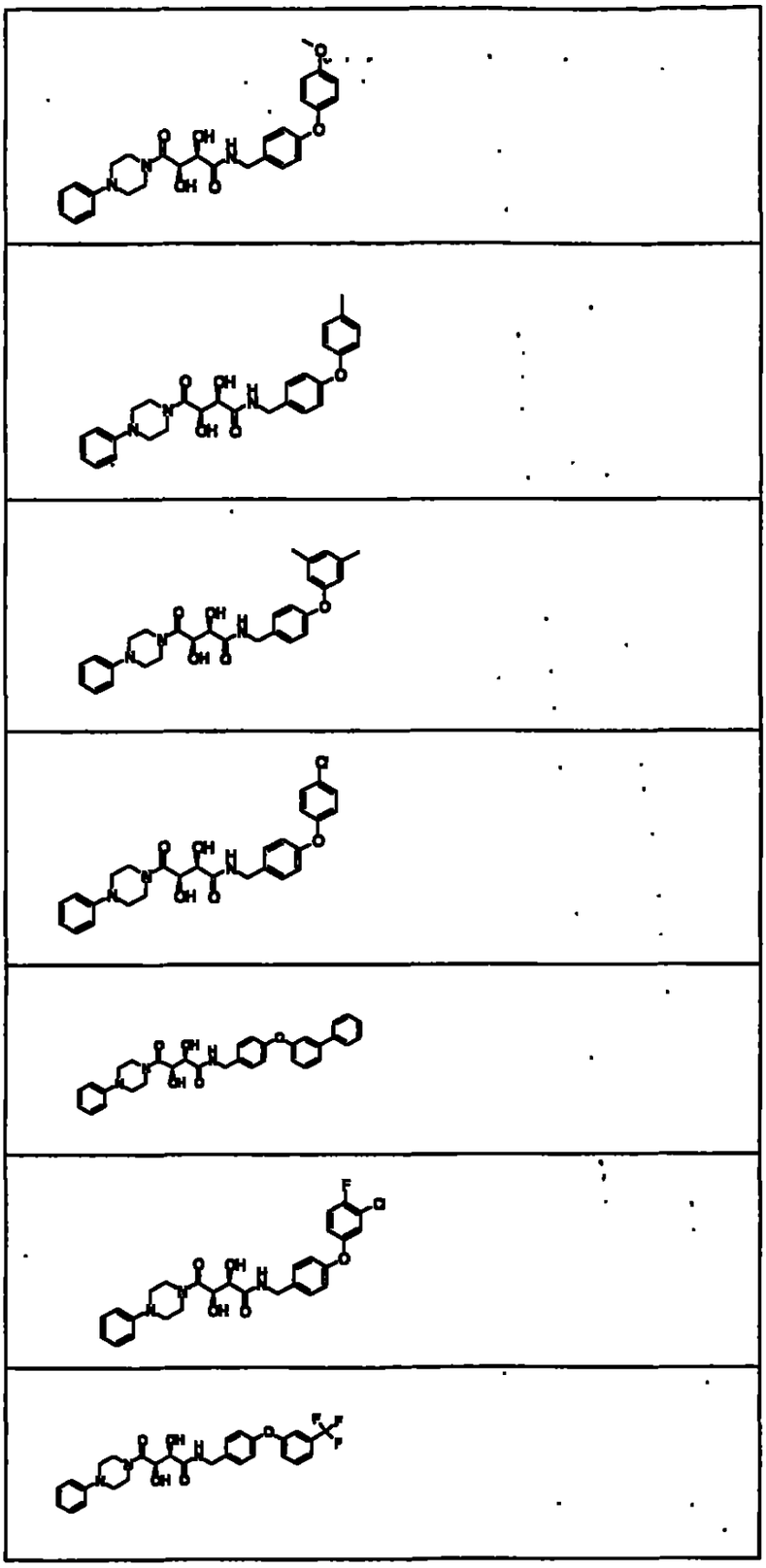


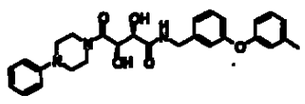


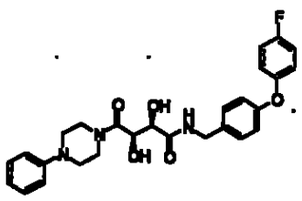


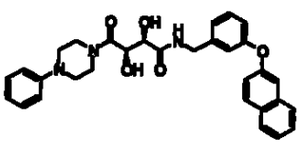


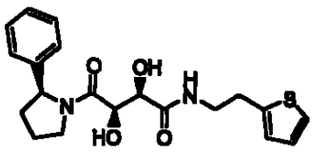


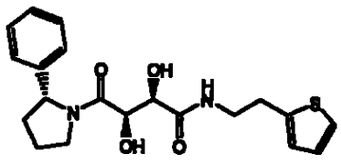


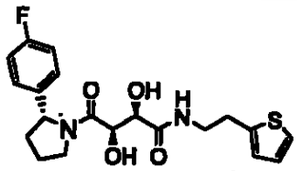


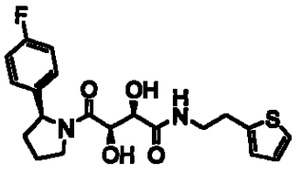


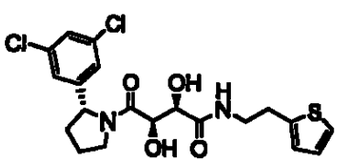


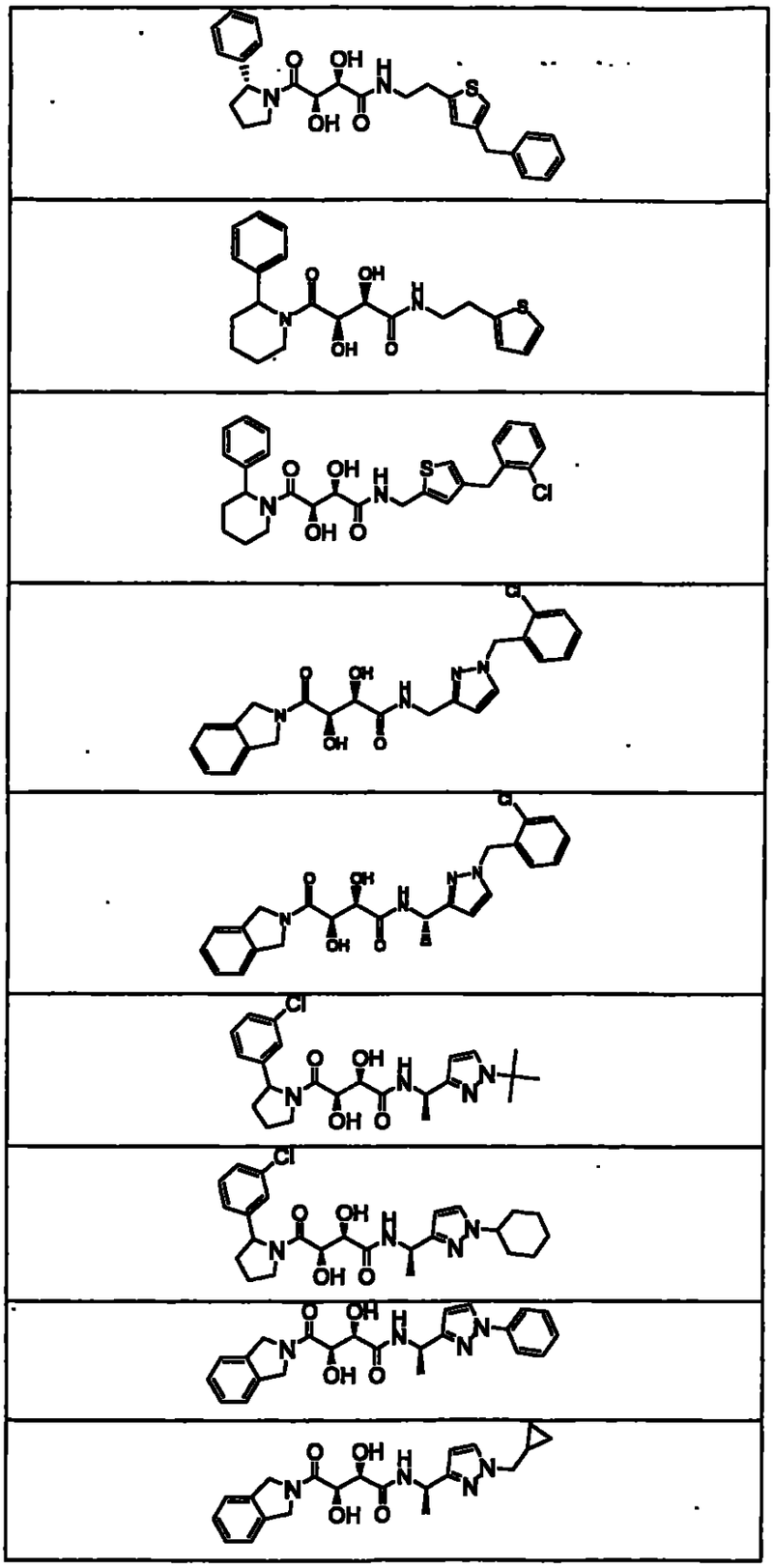


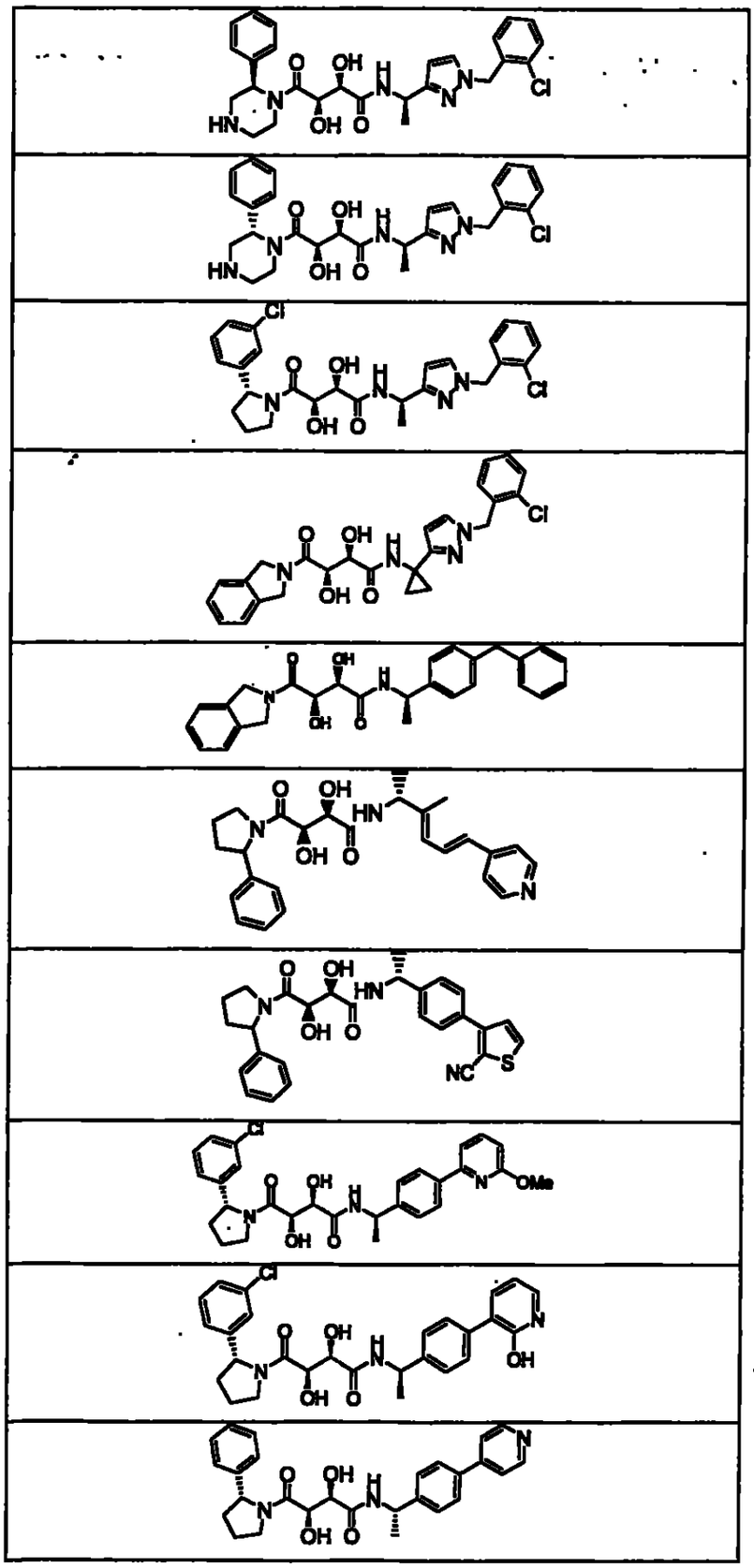


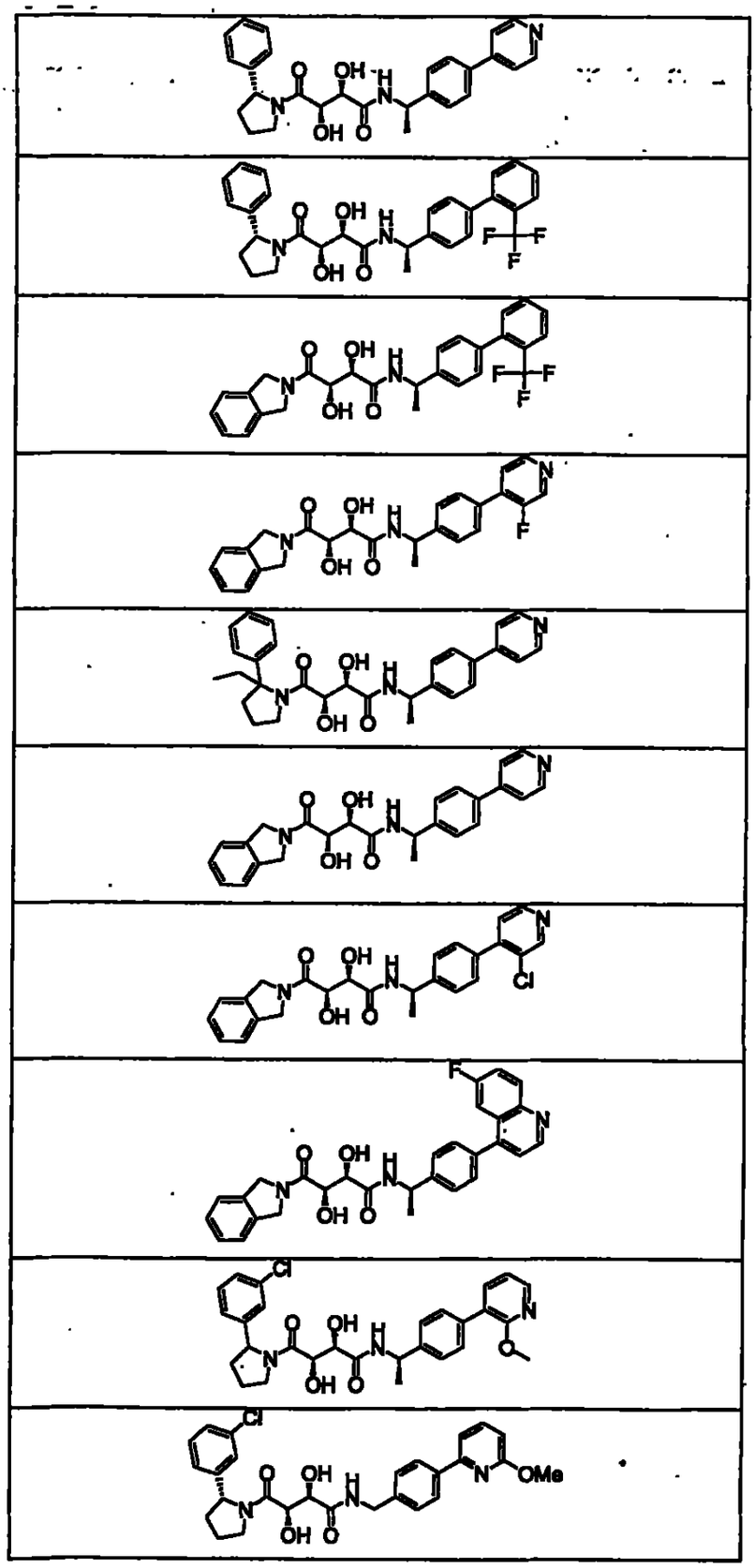


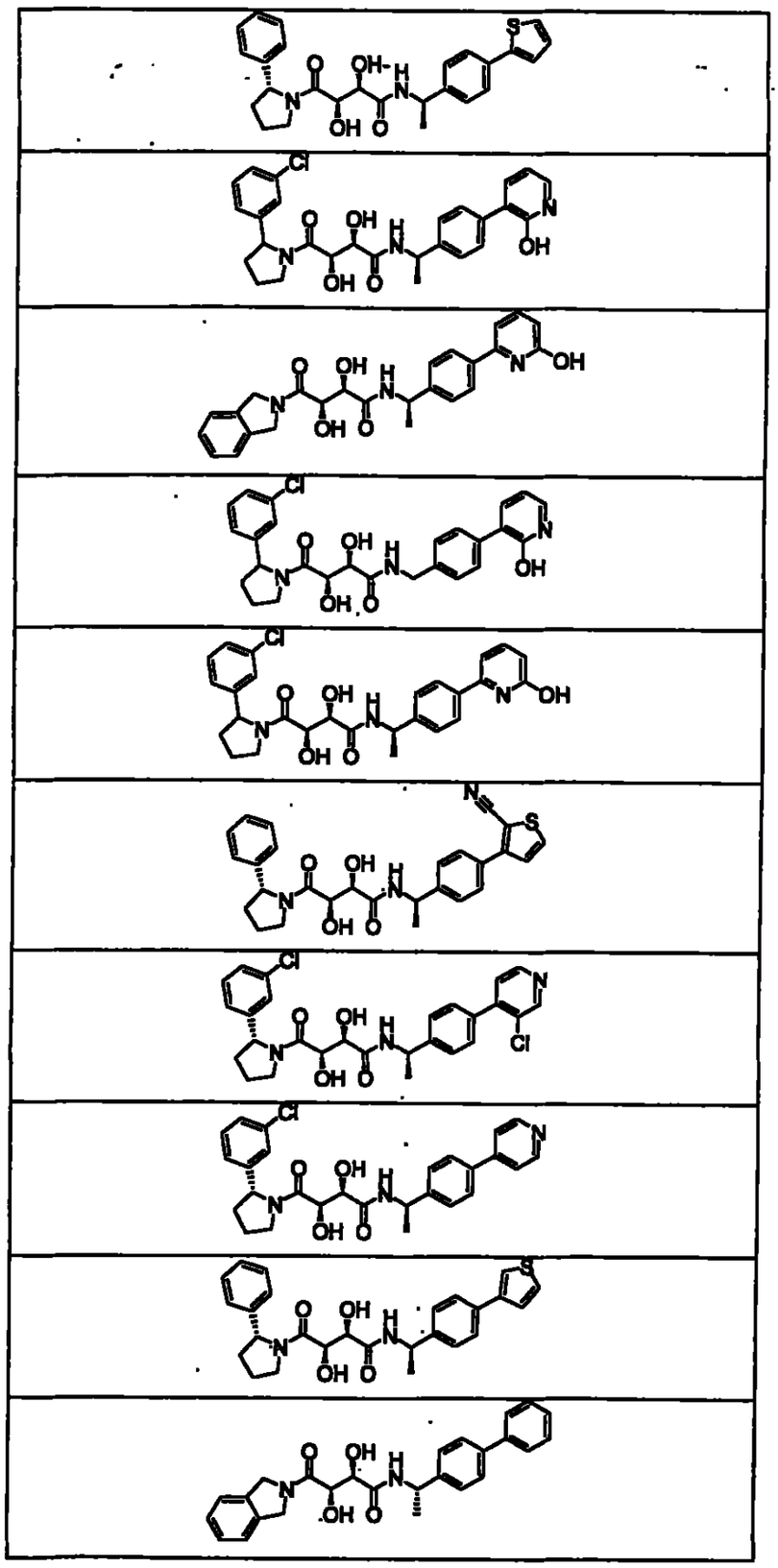


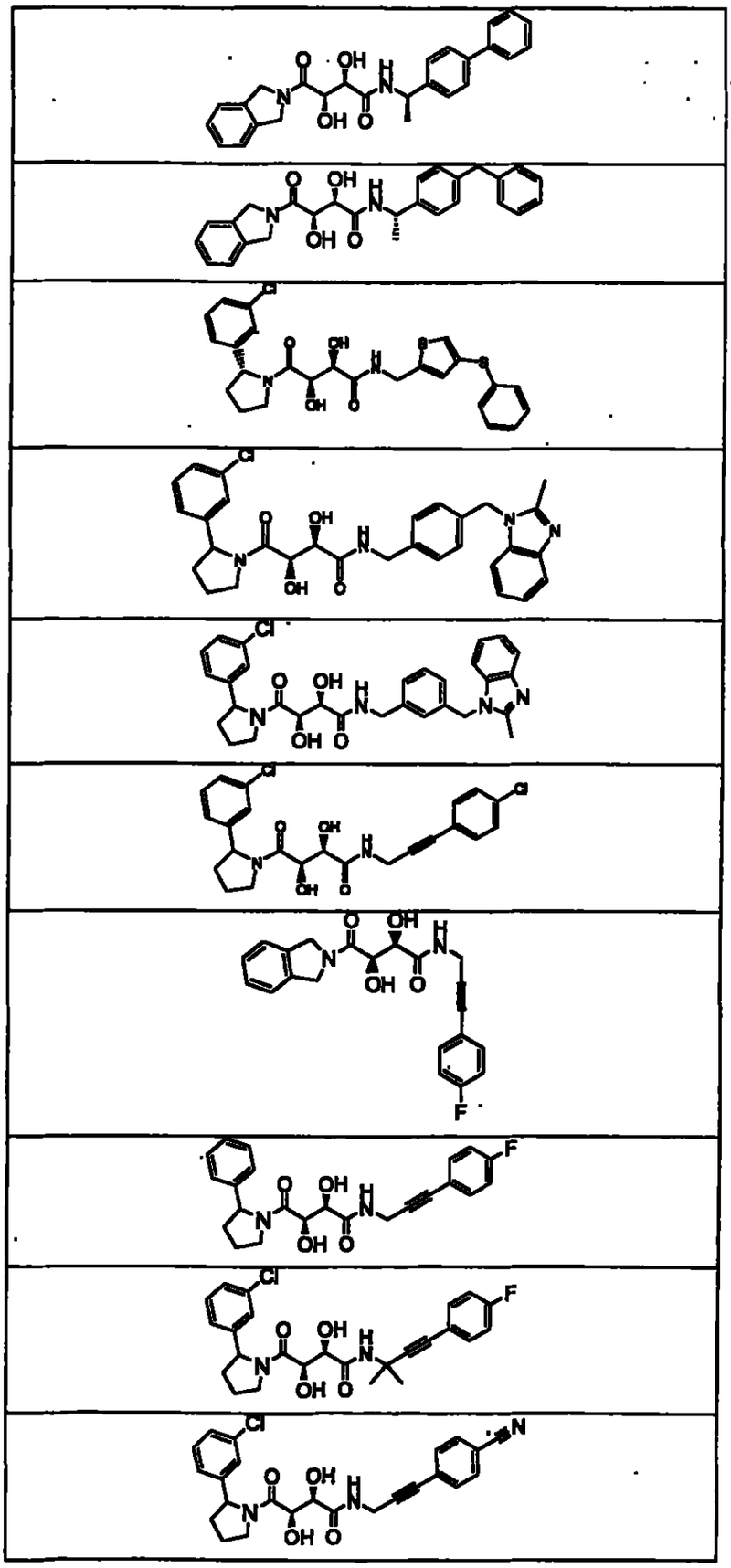


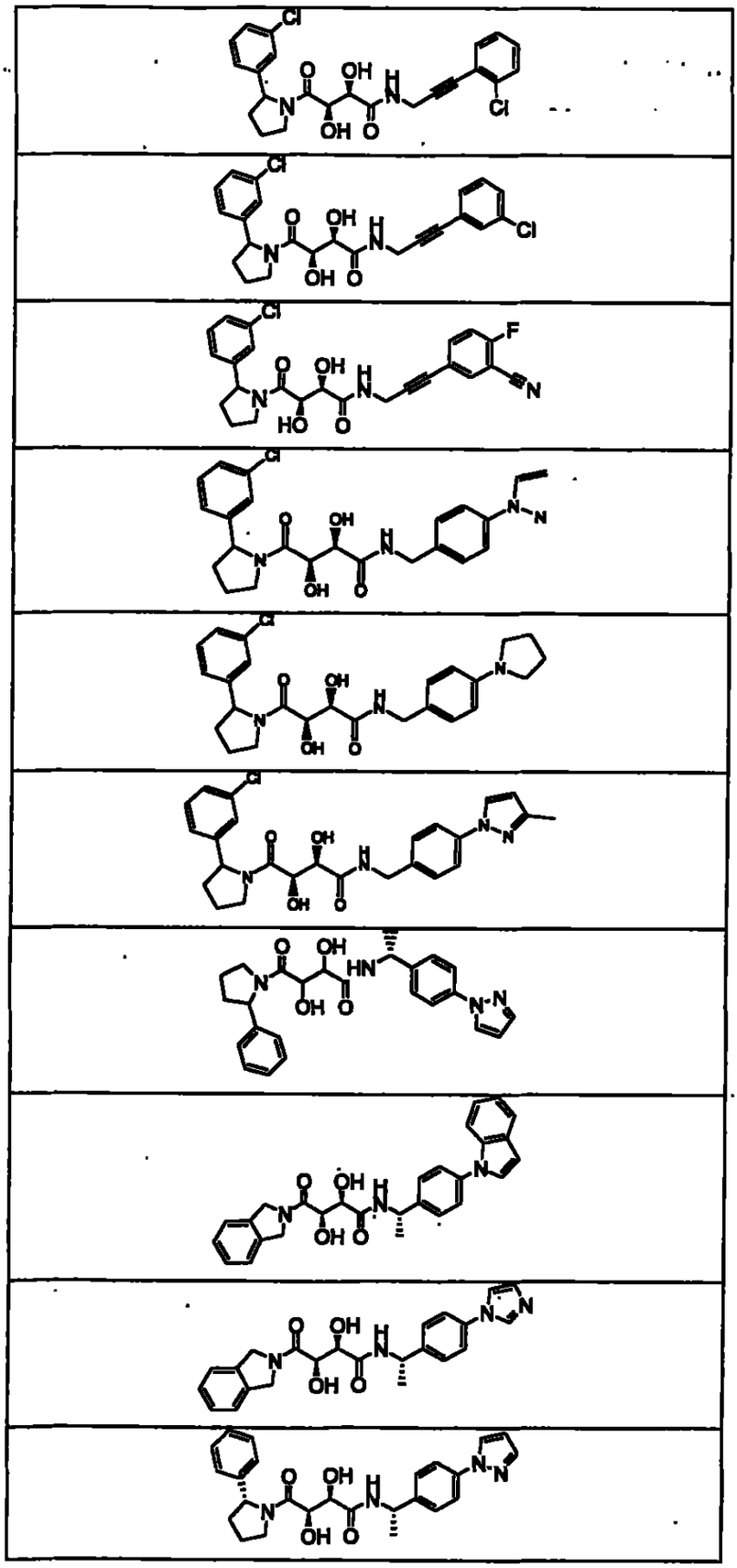


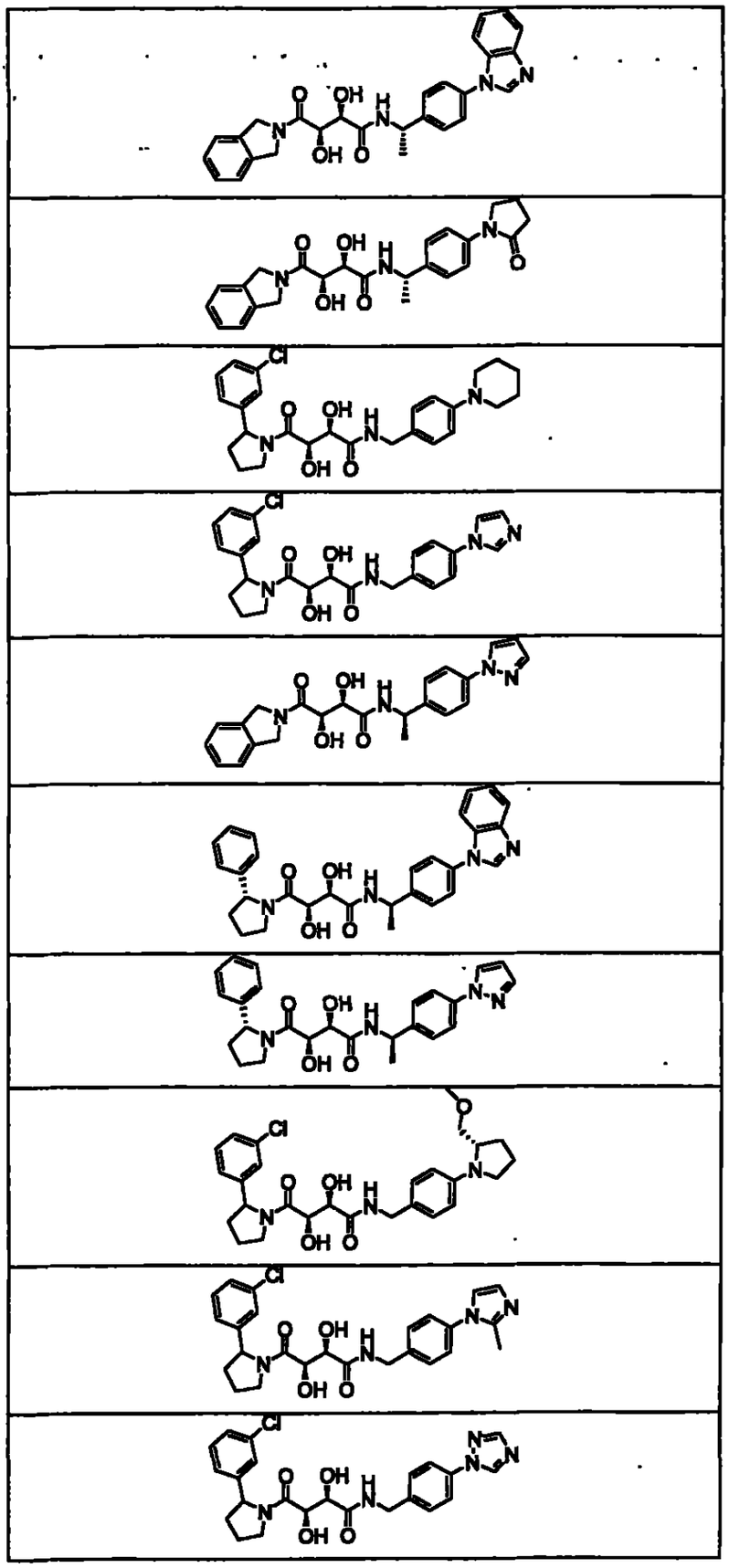


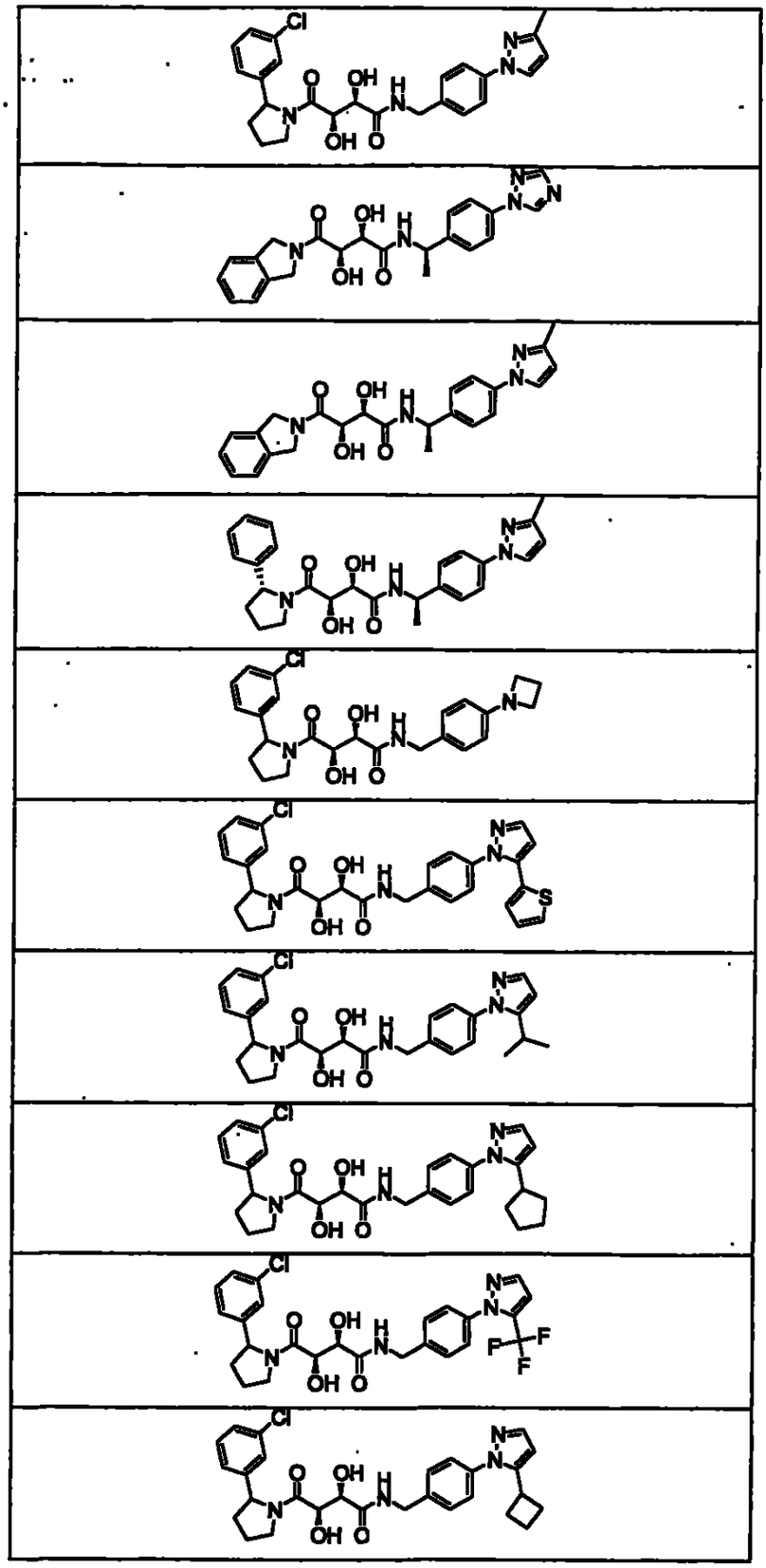


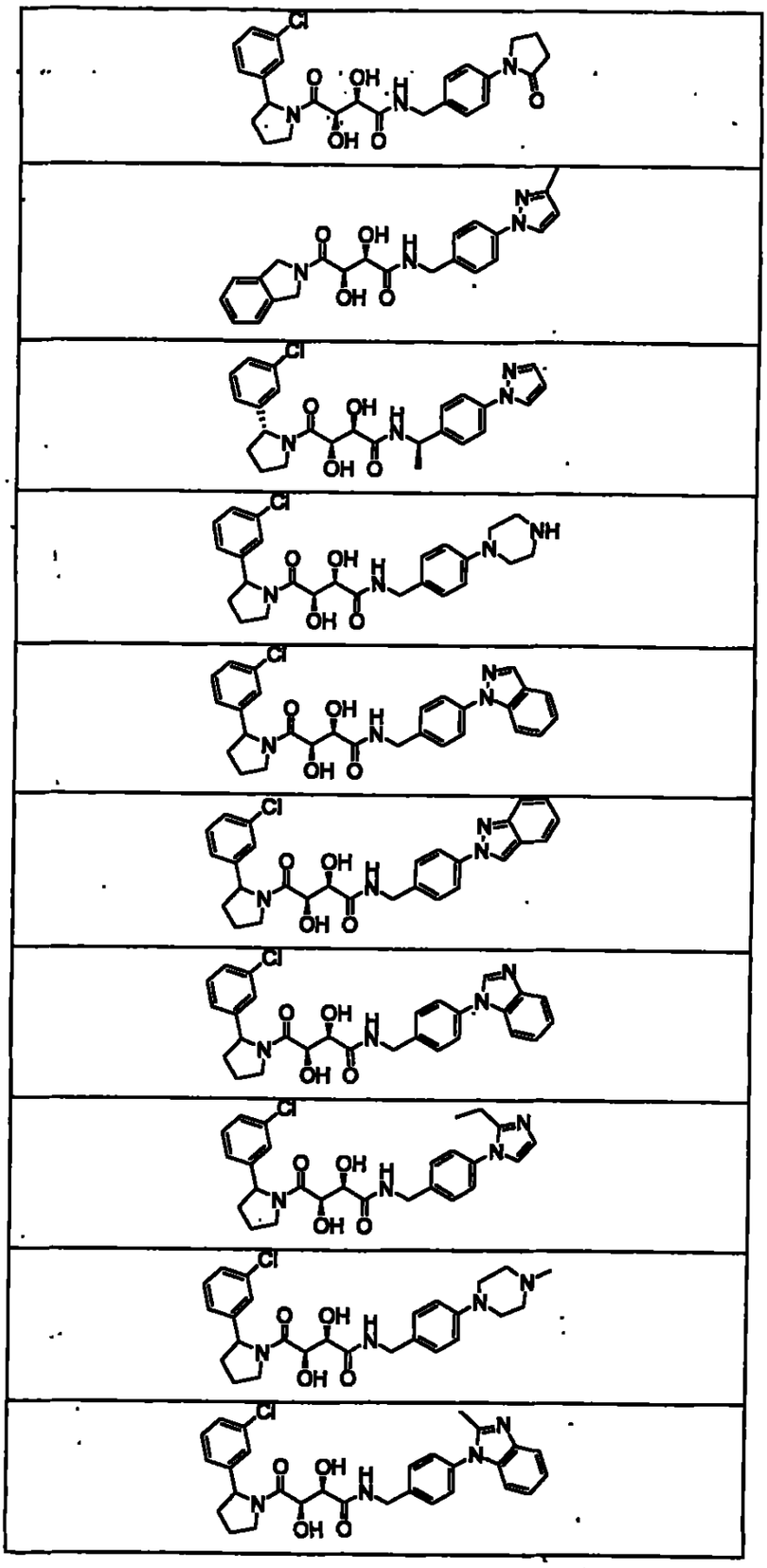


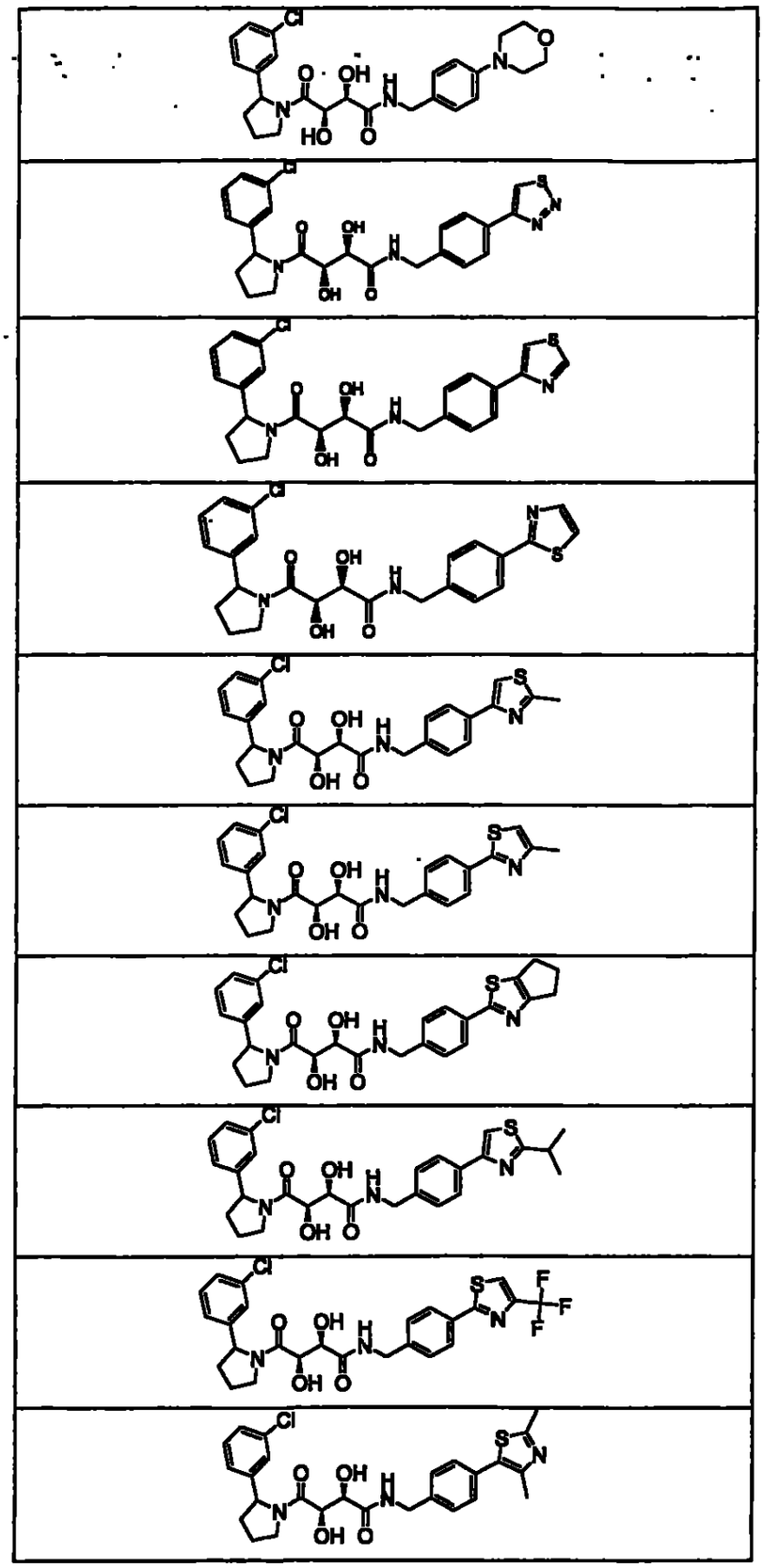


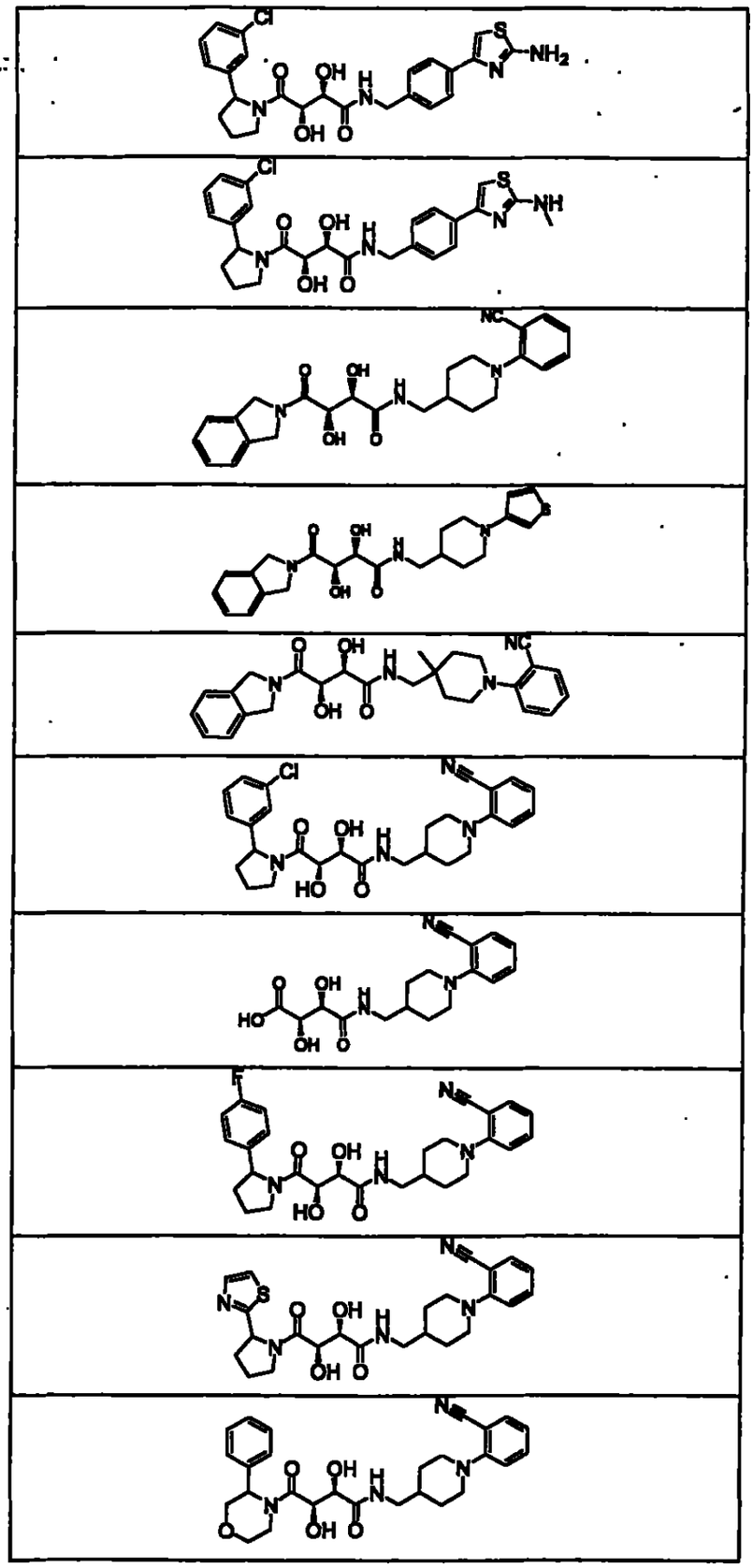


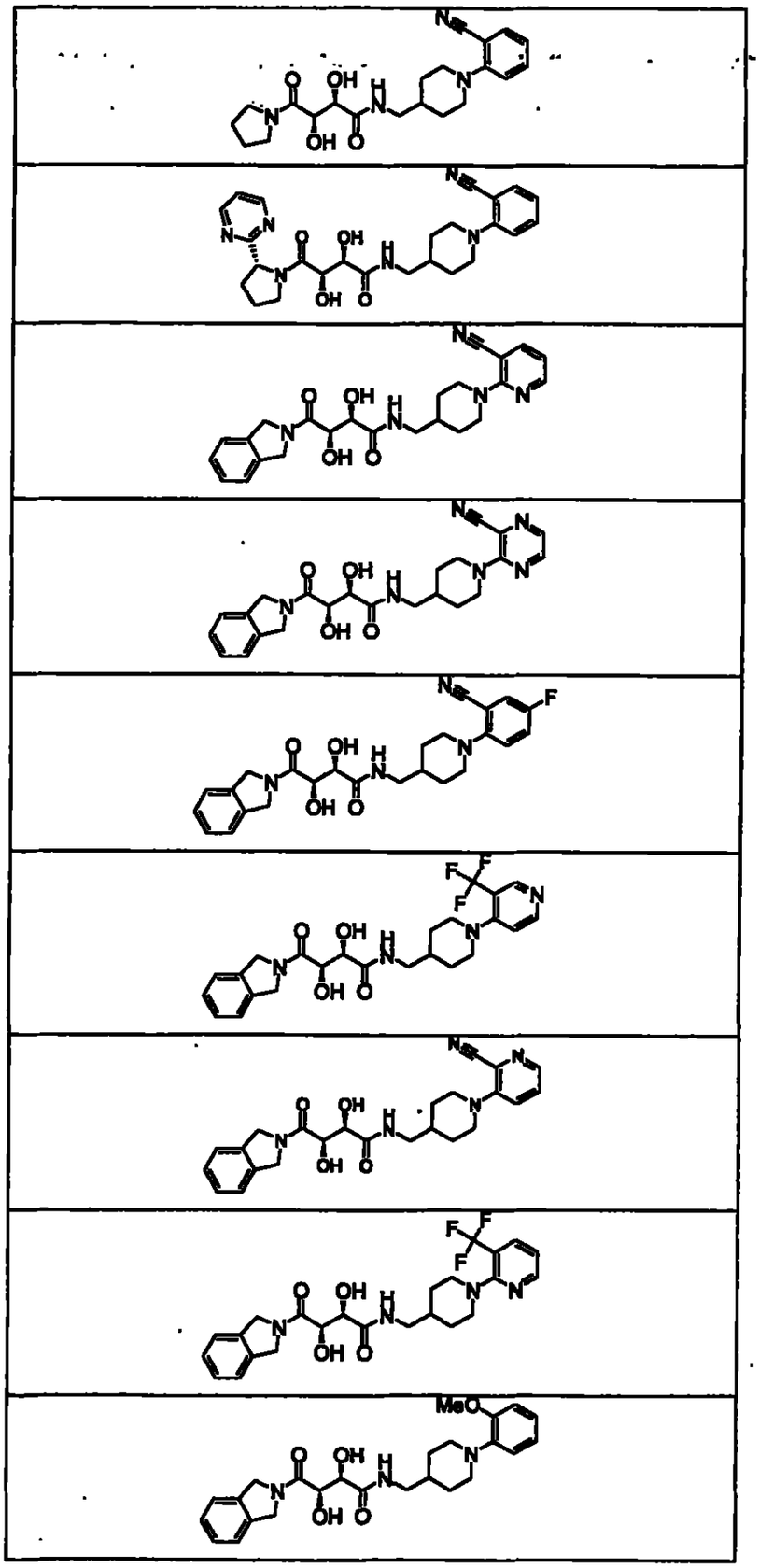


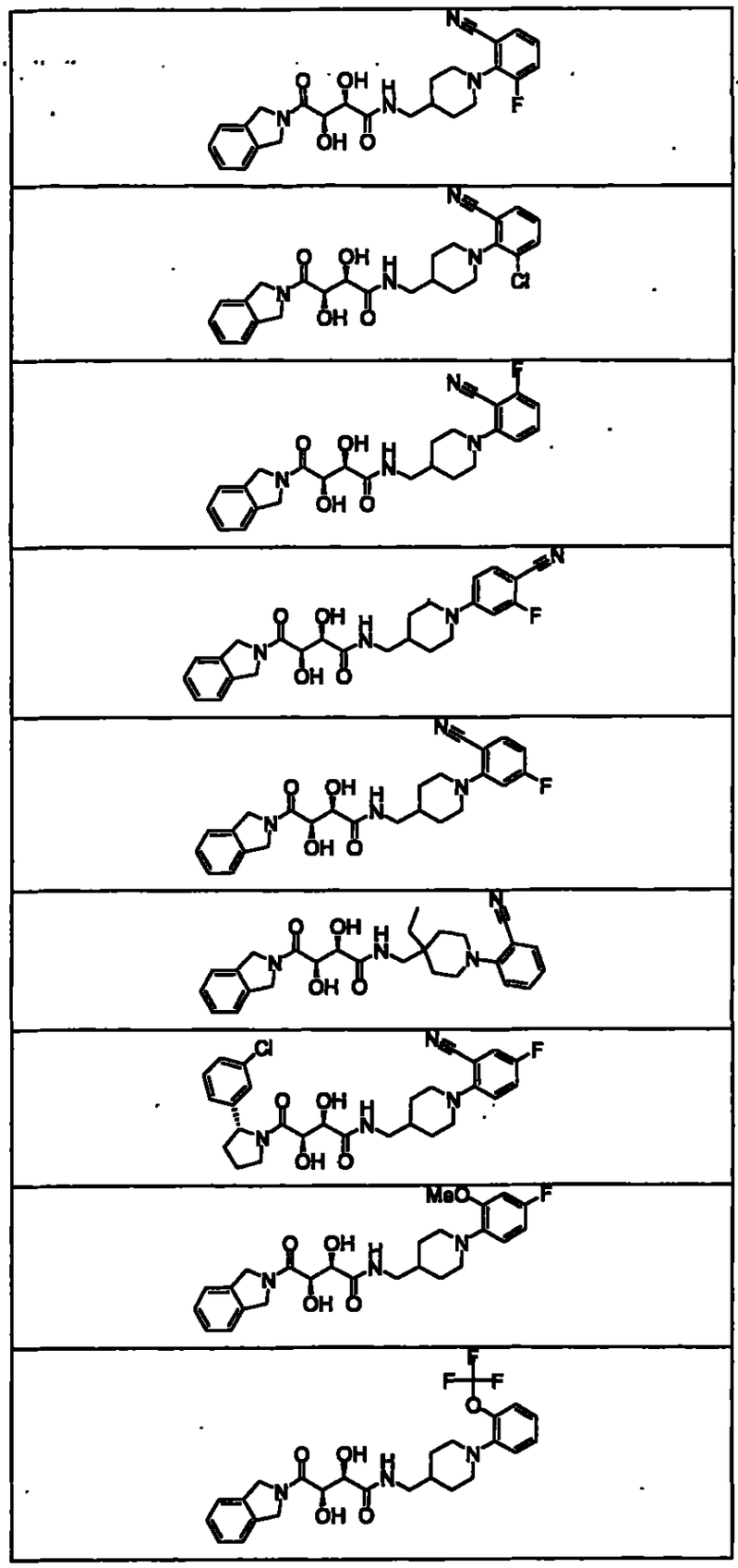


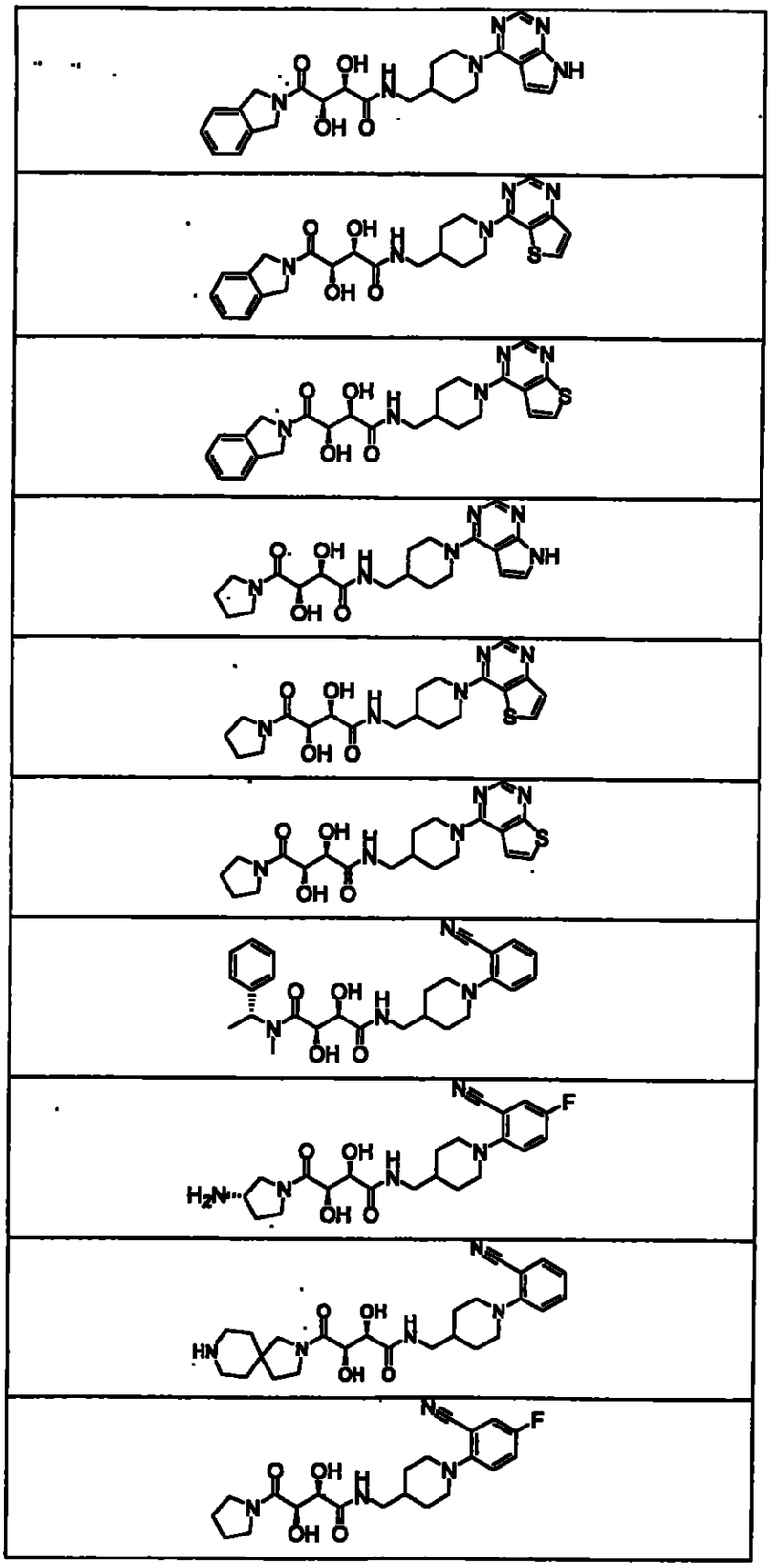


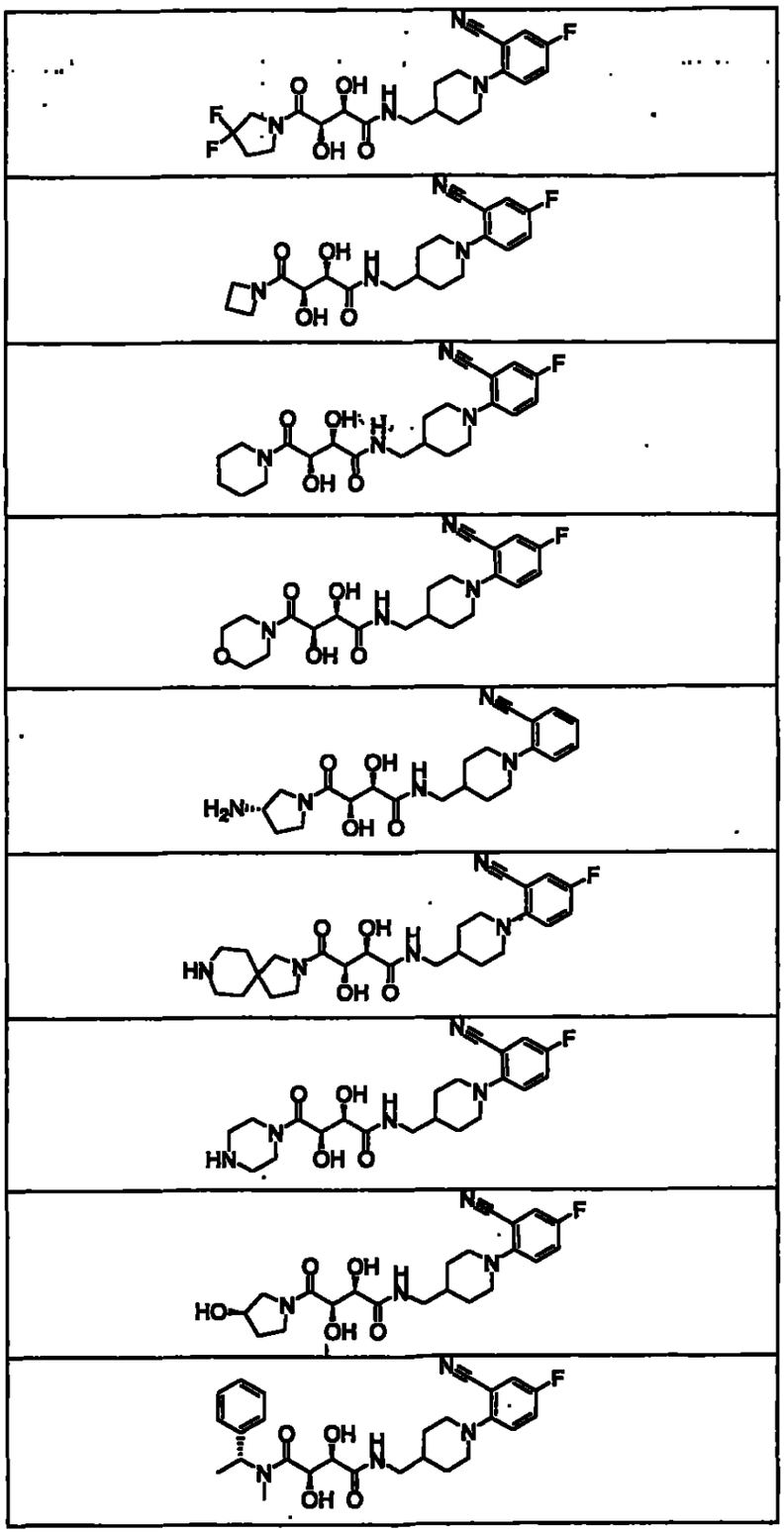


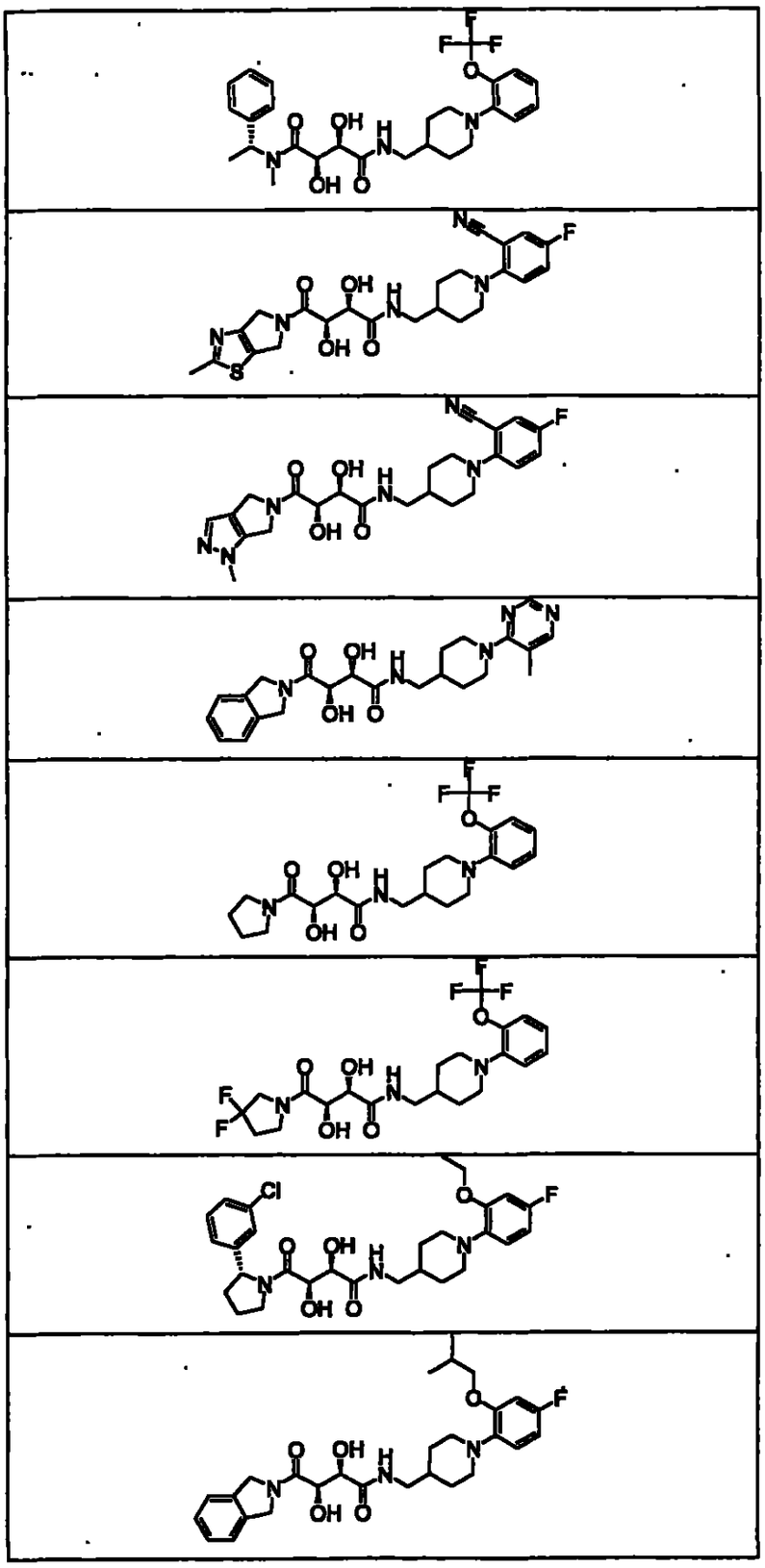


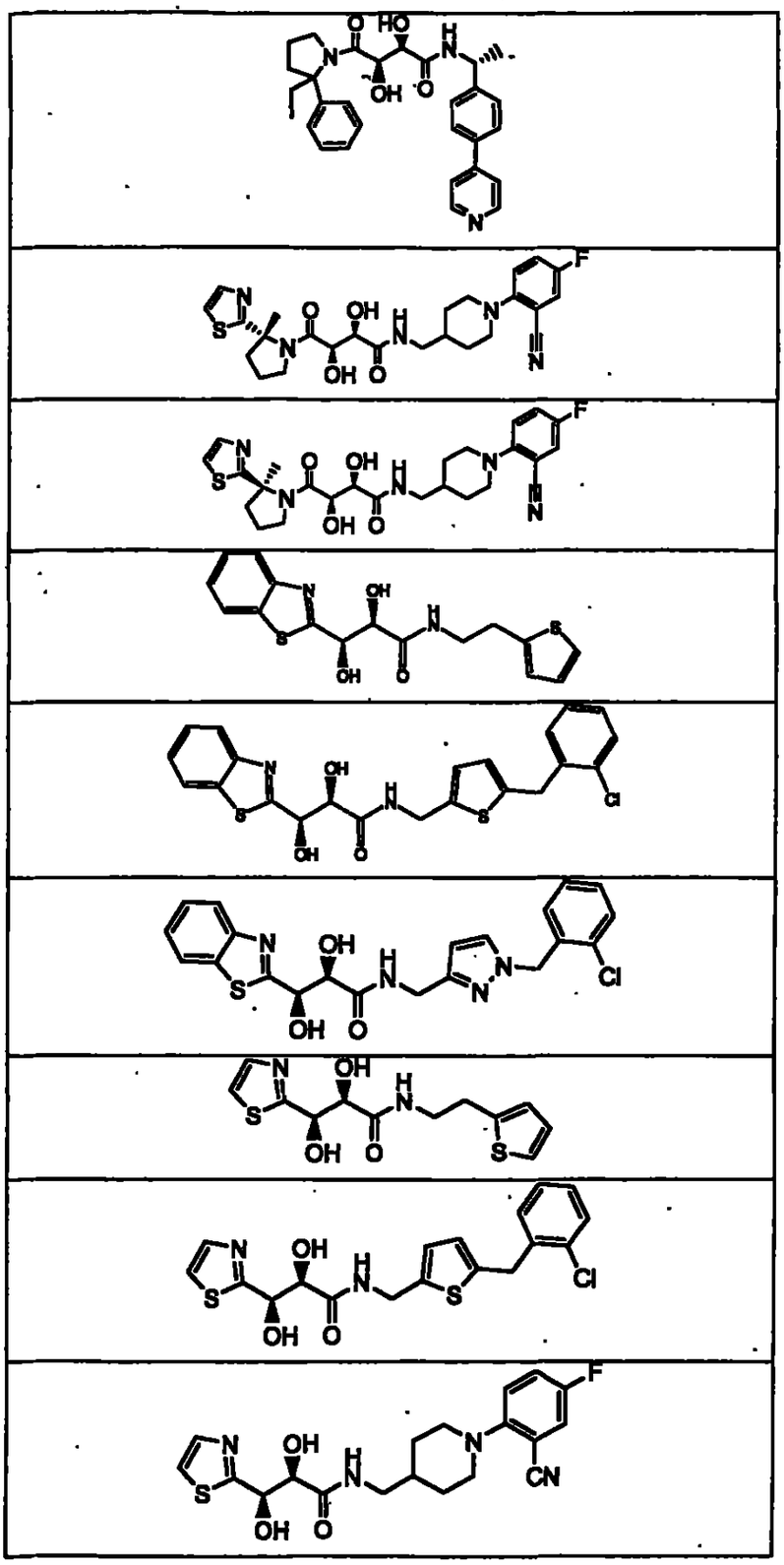


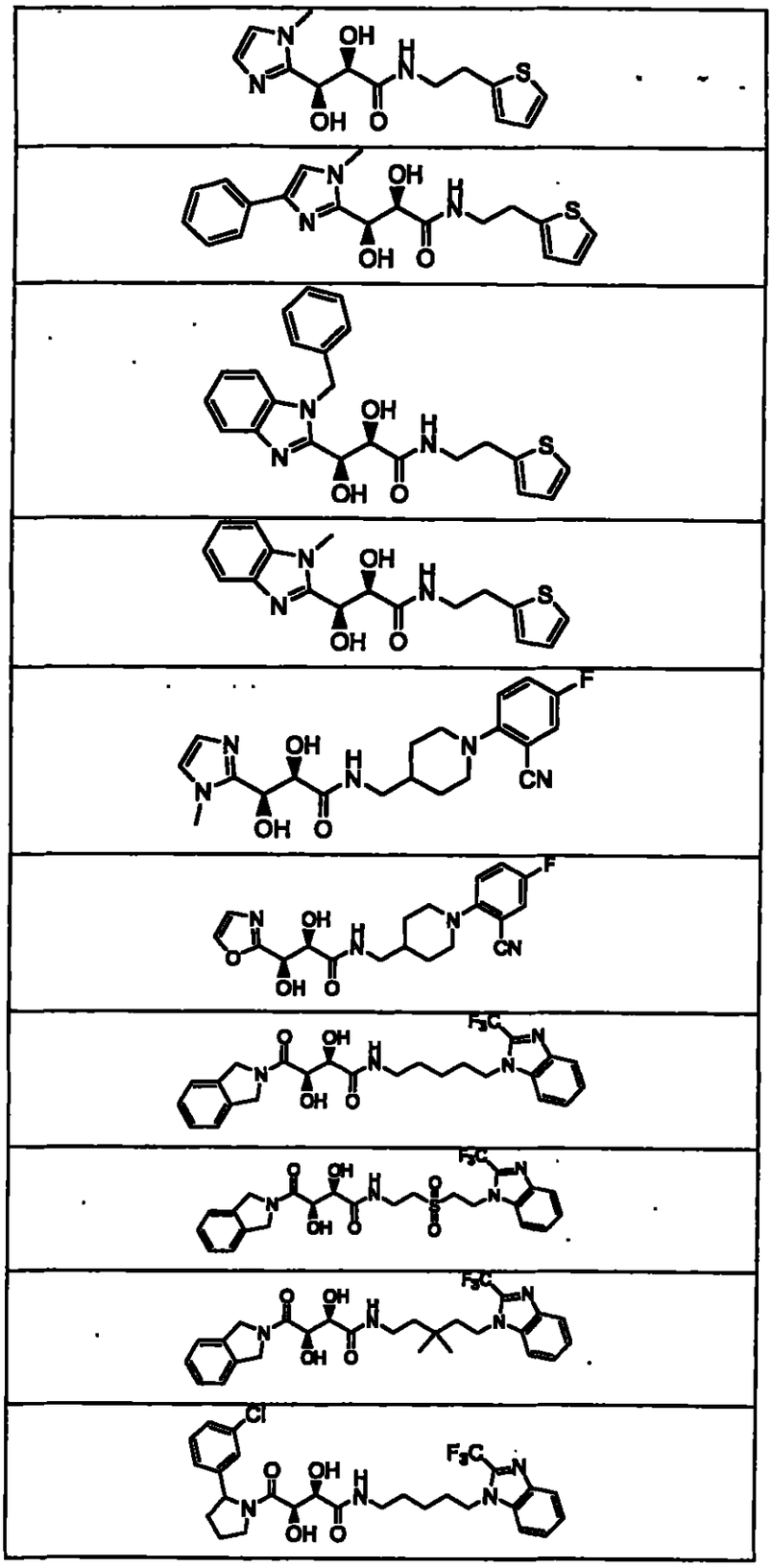


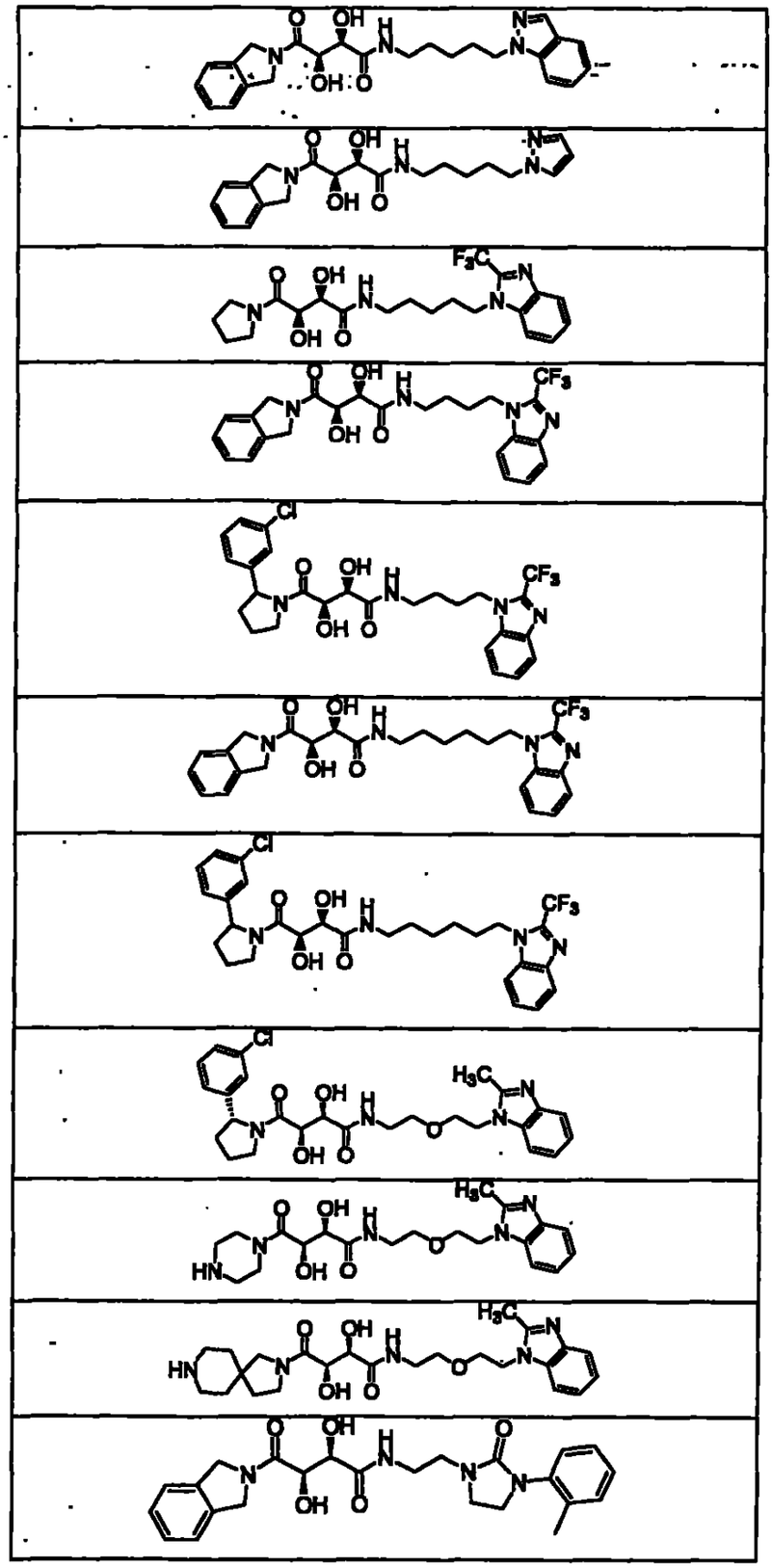


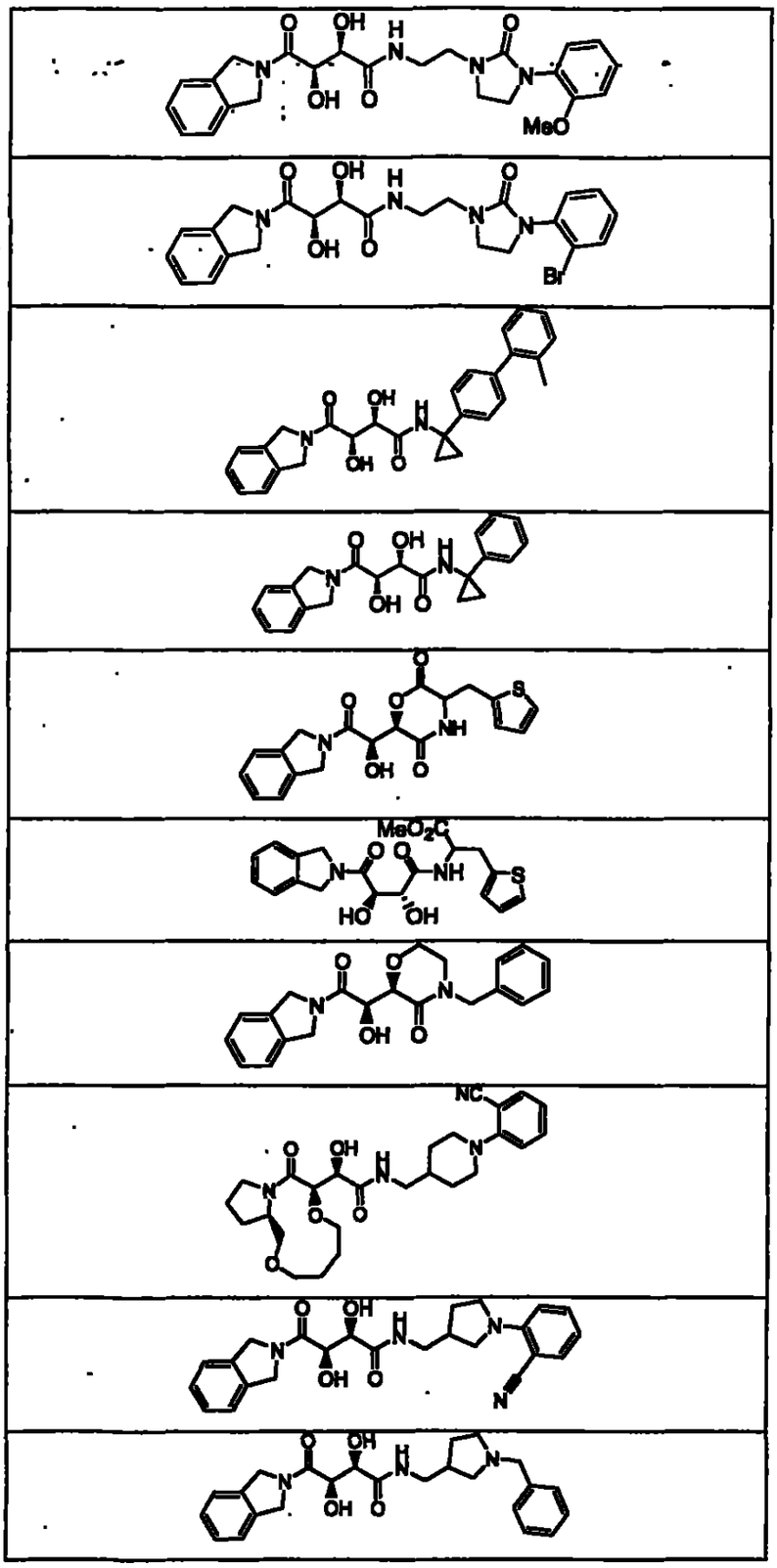


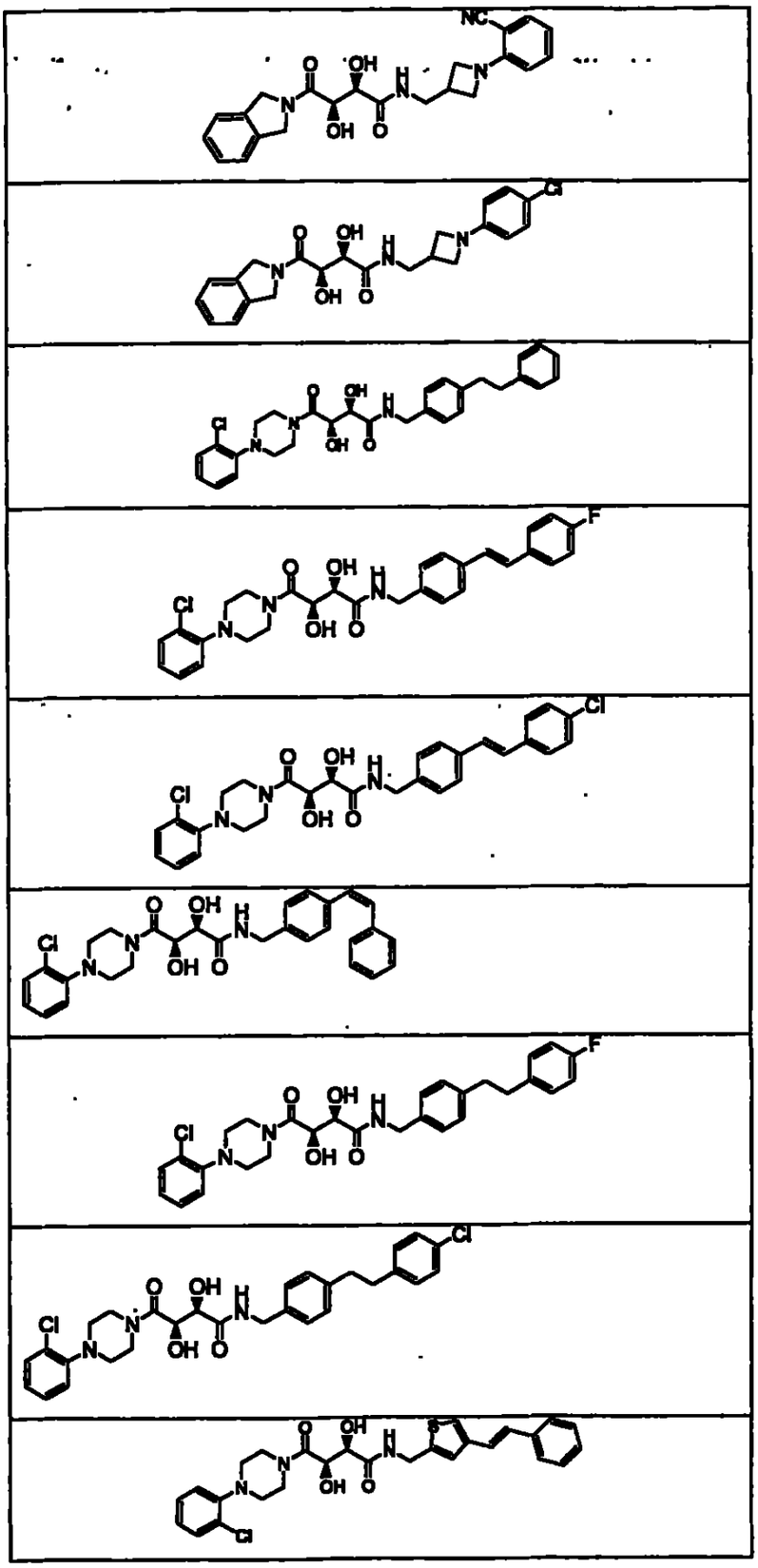


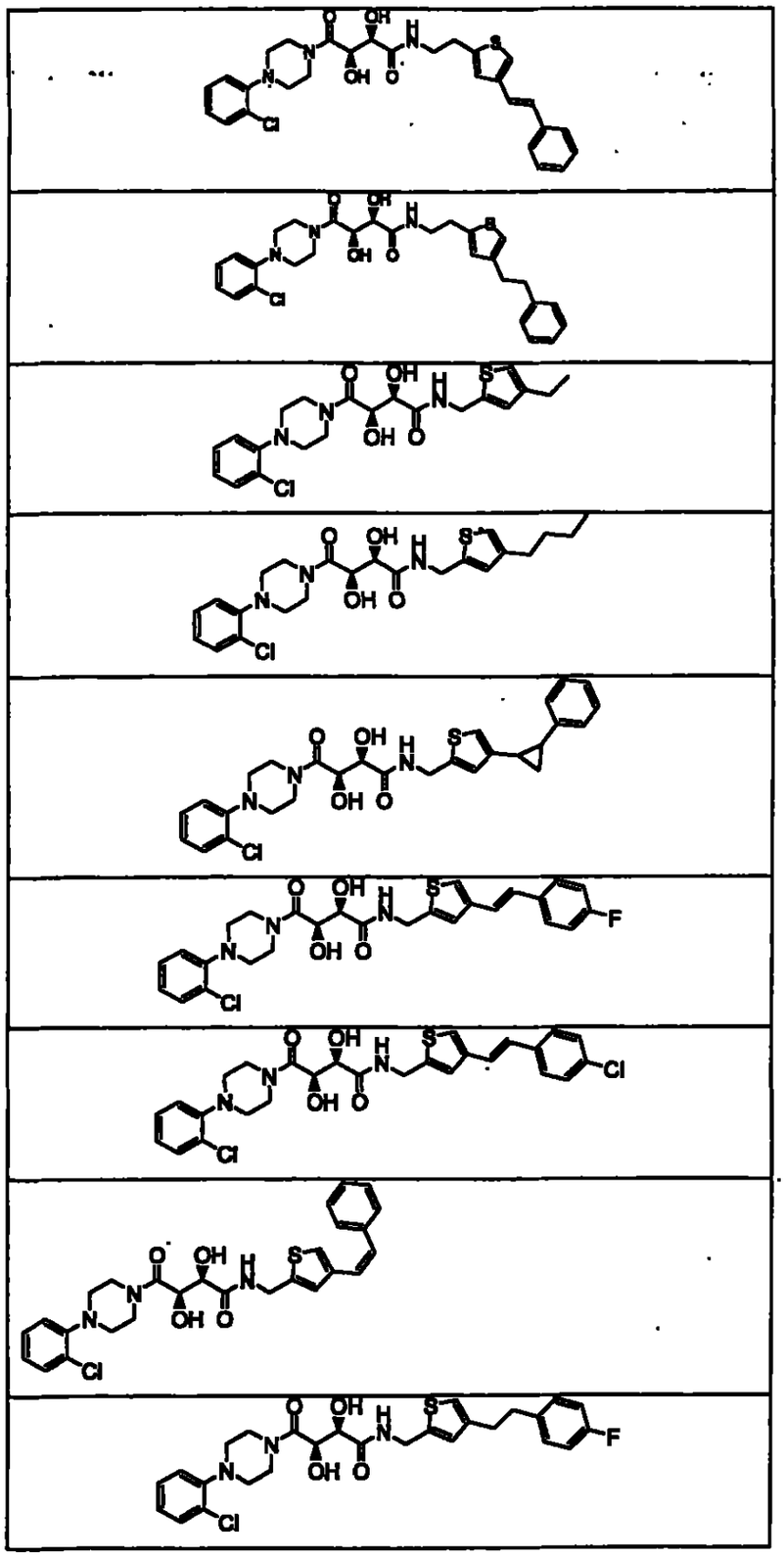


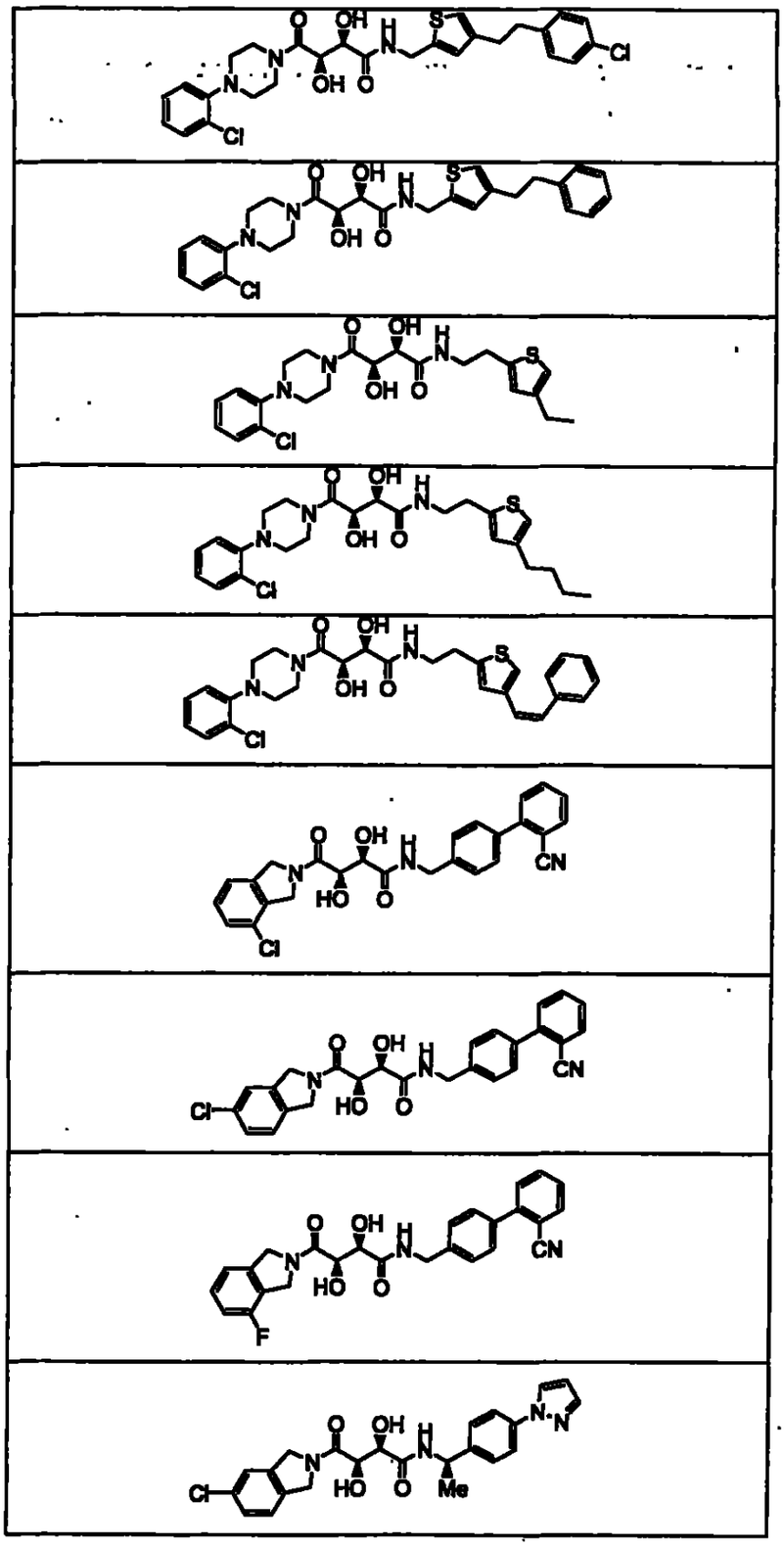


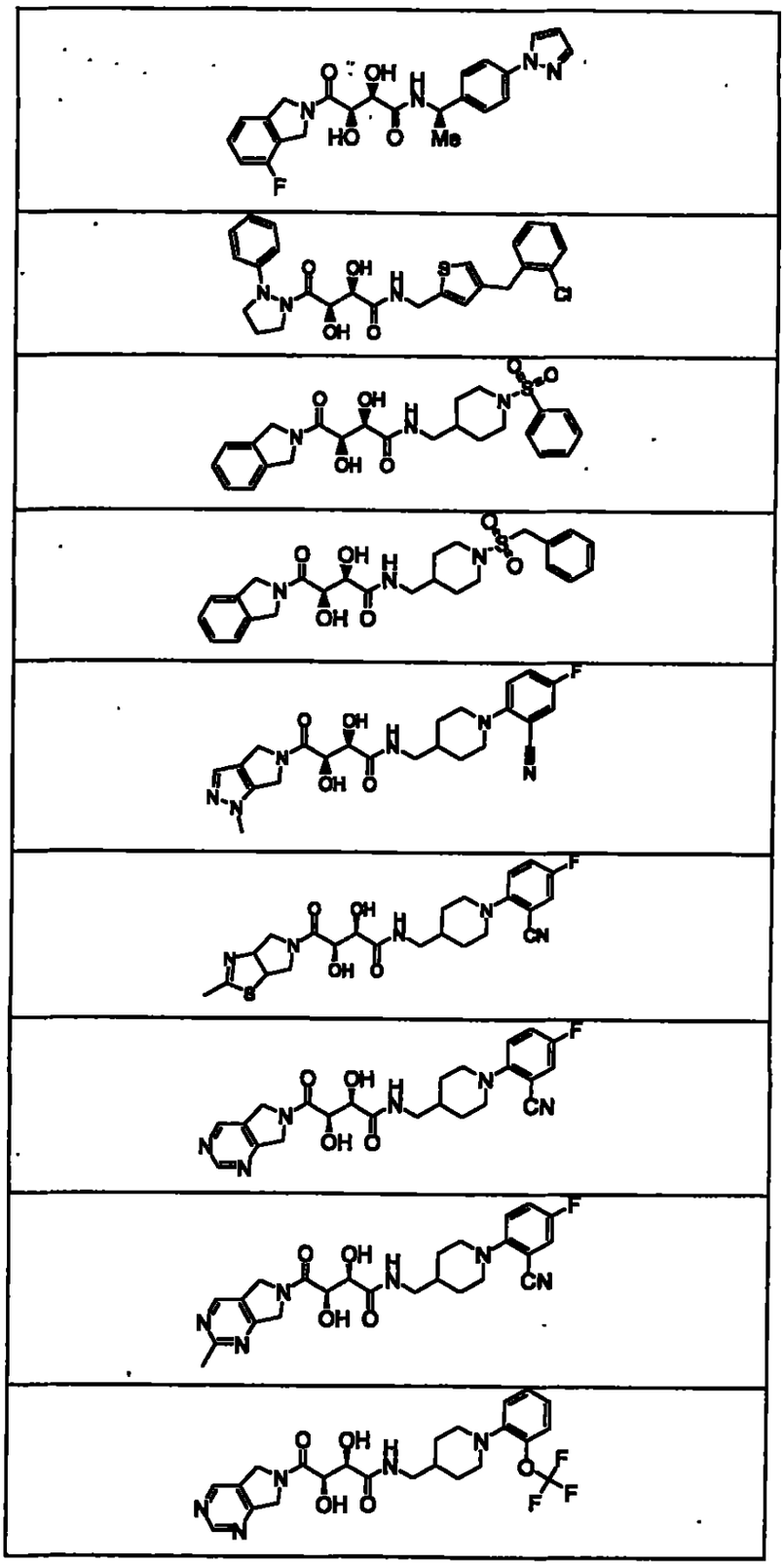


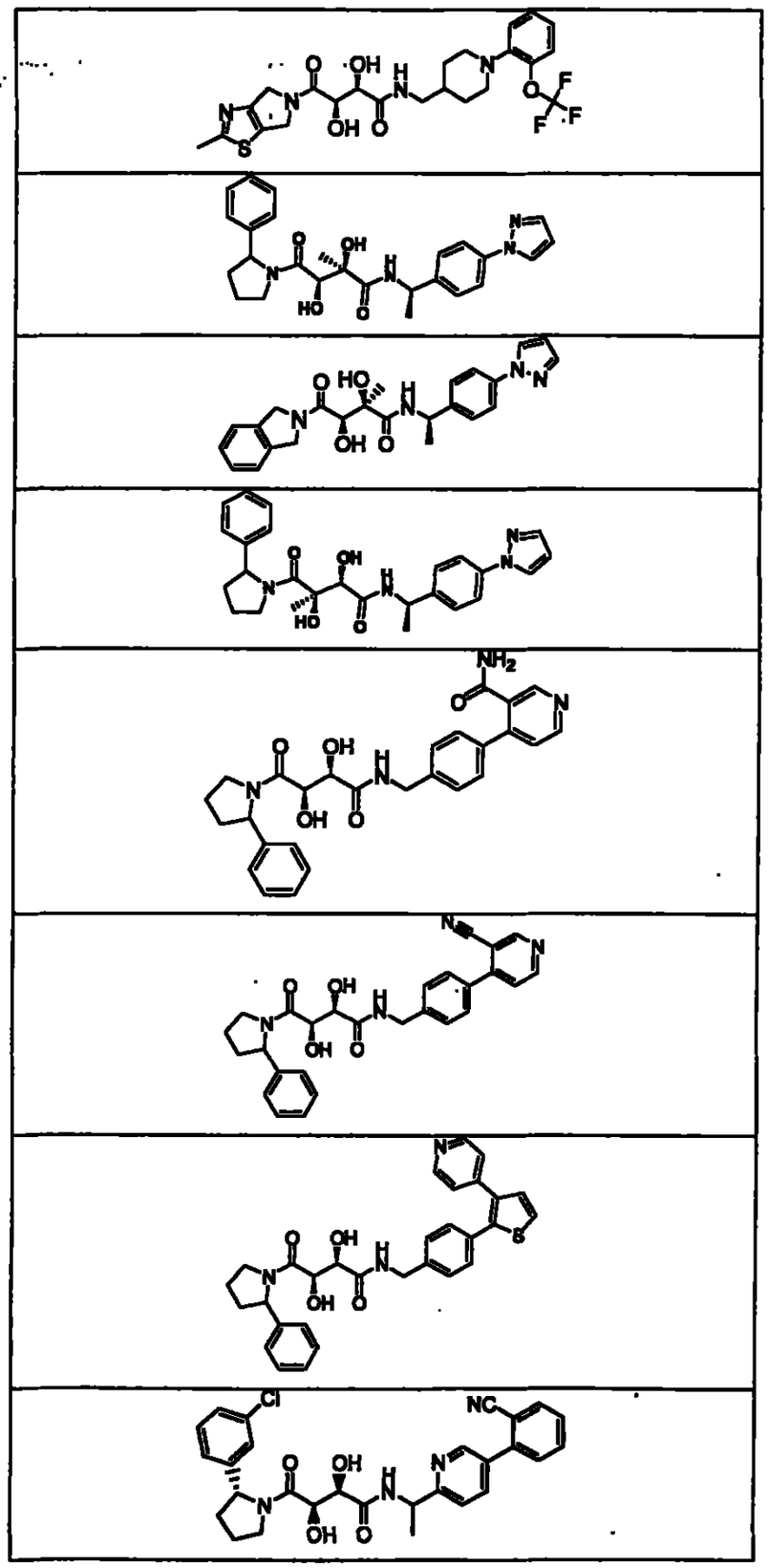

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HO
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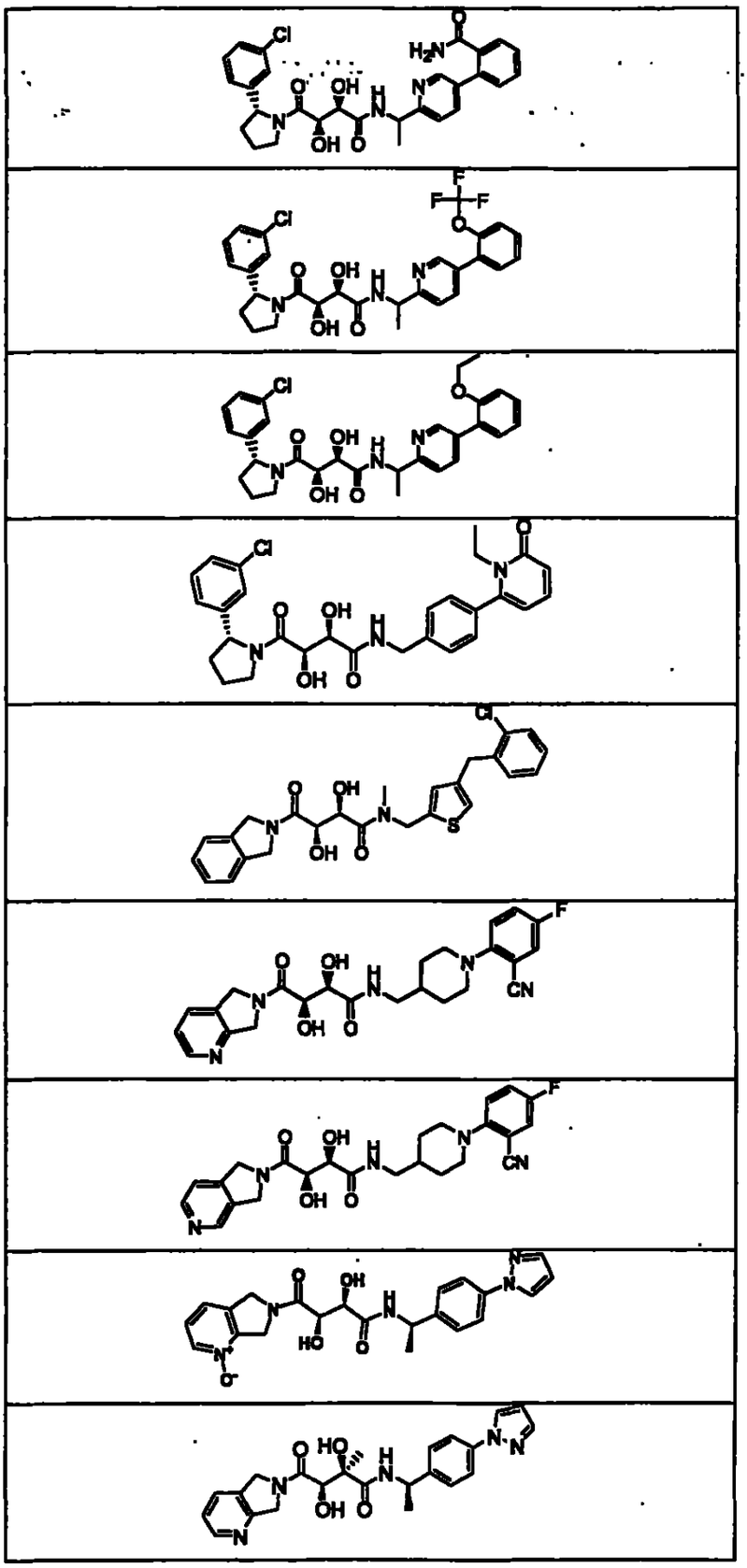


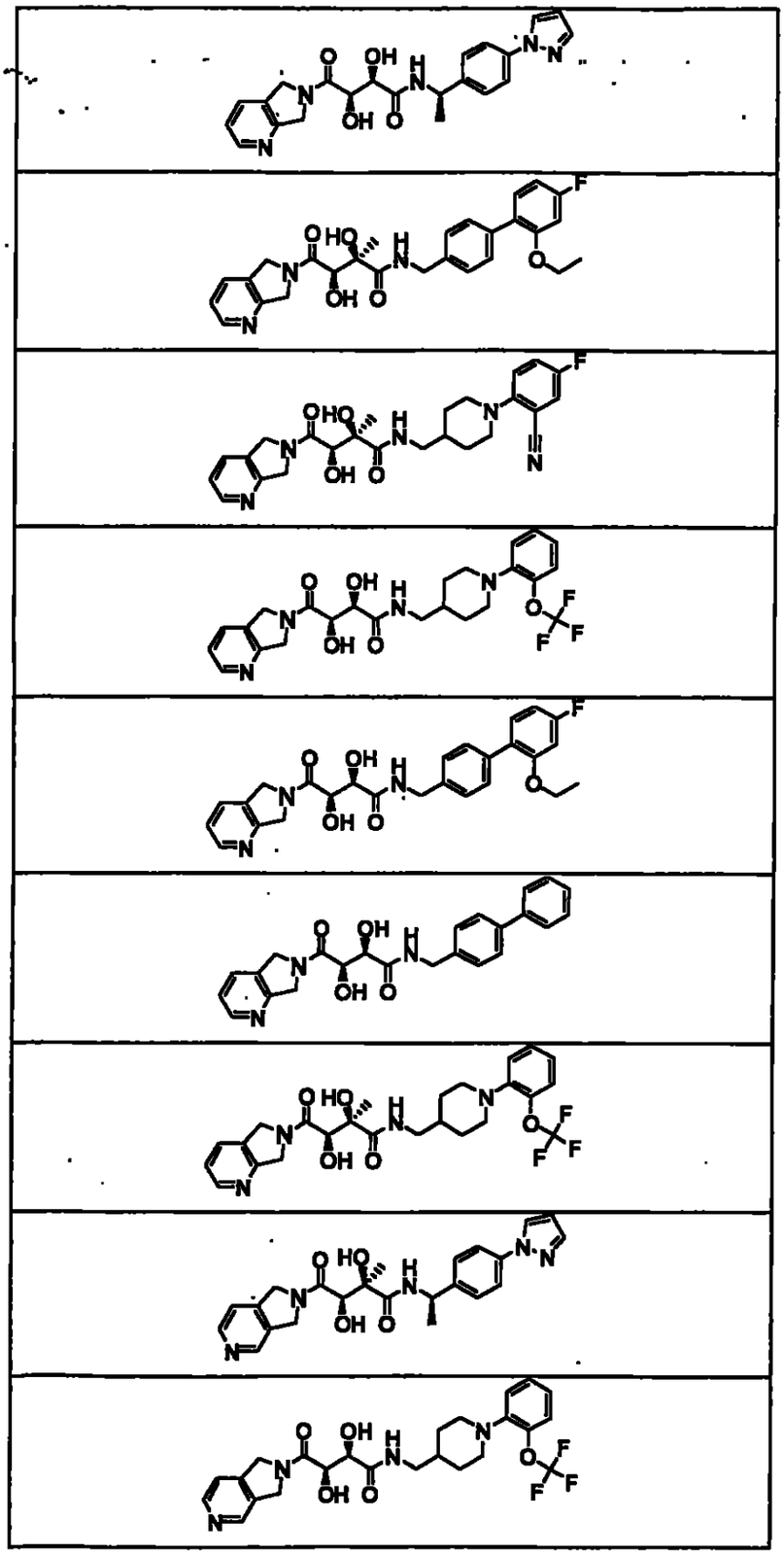


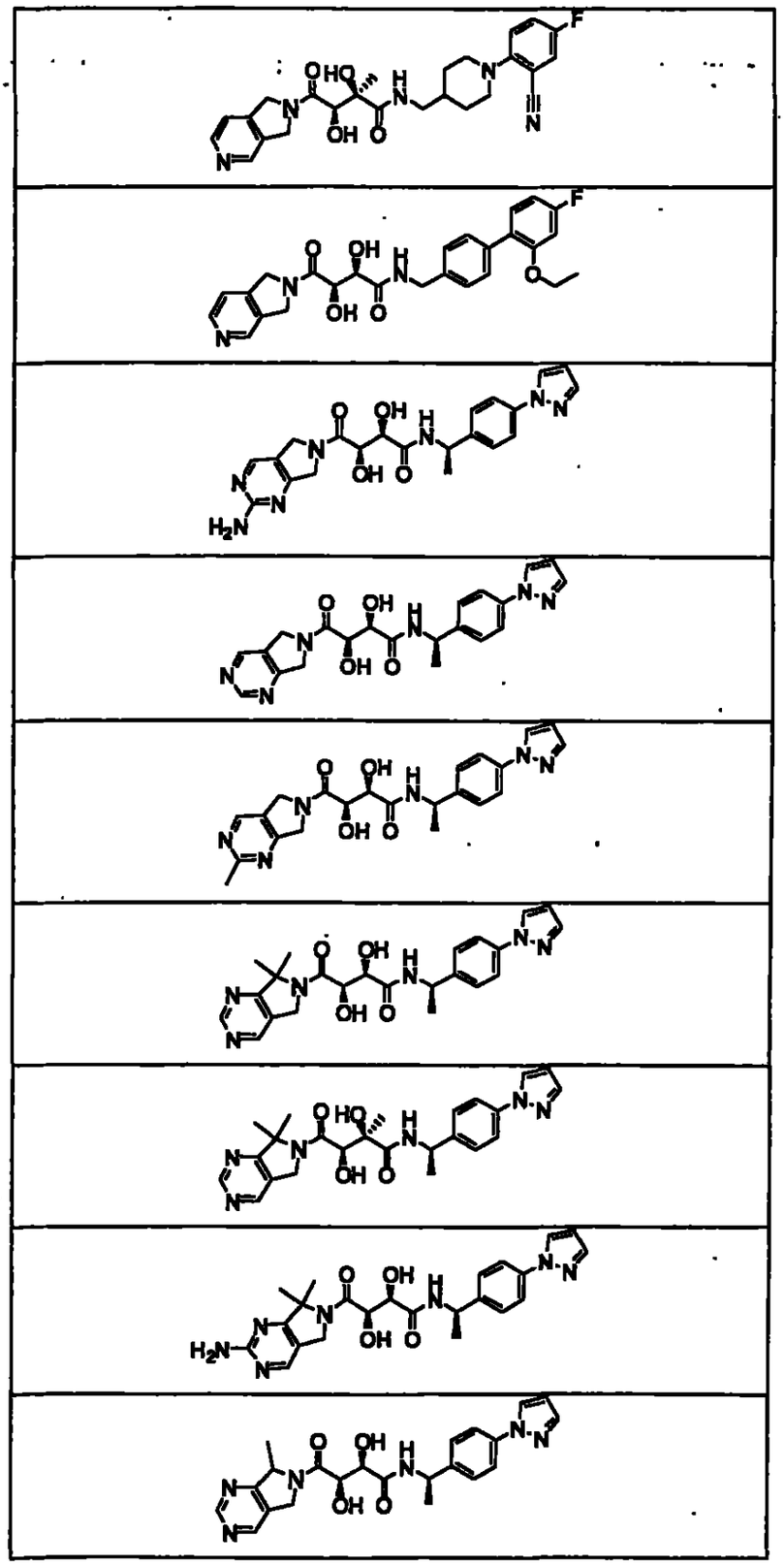


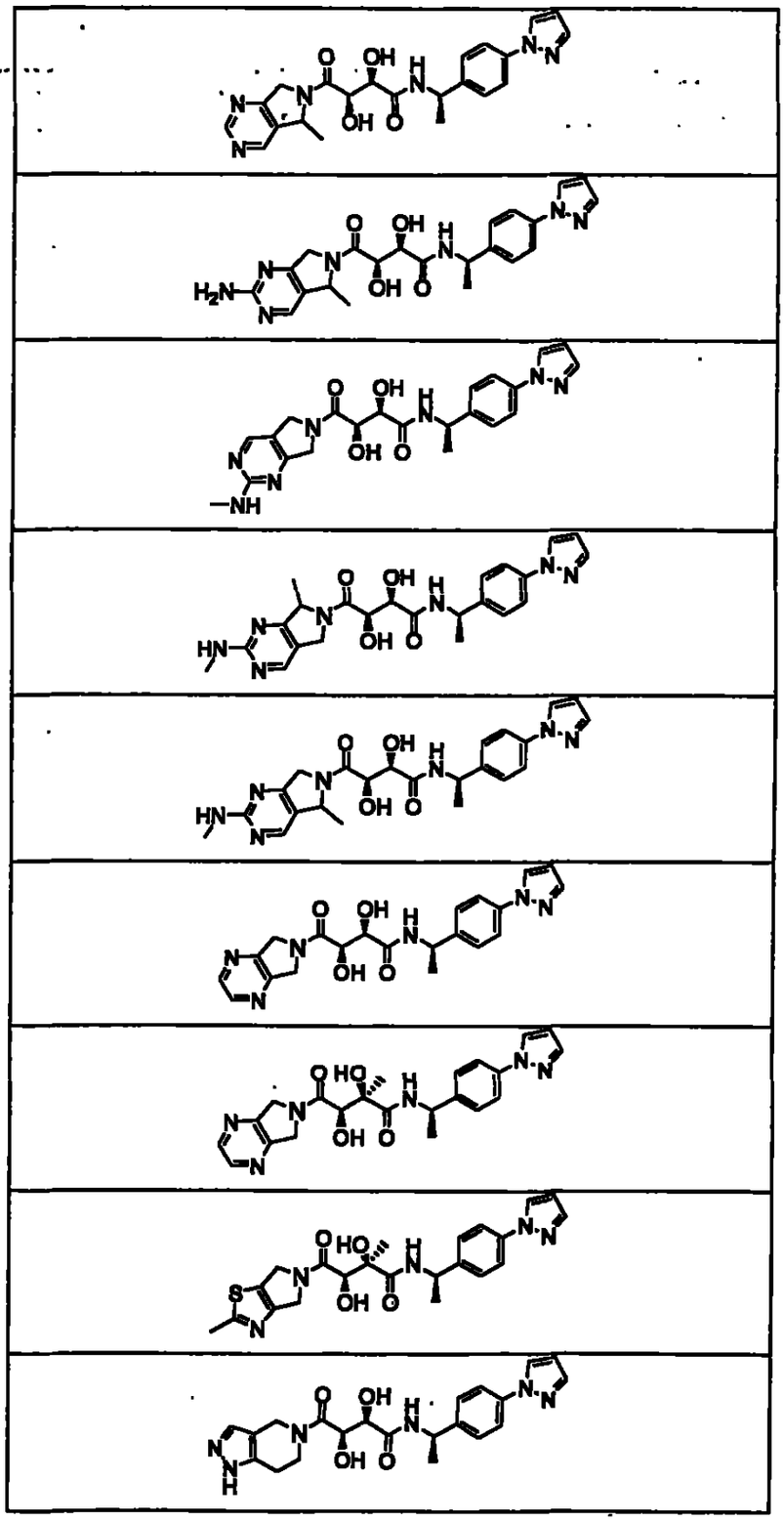


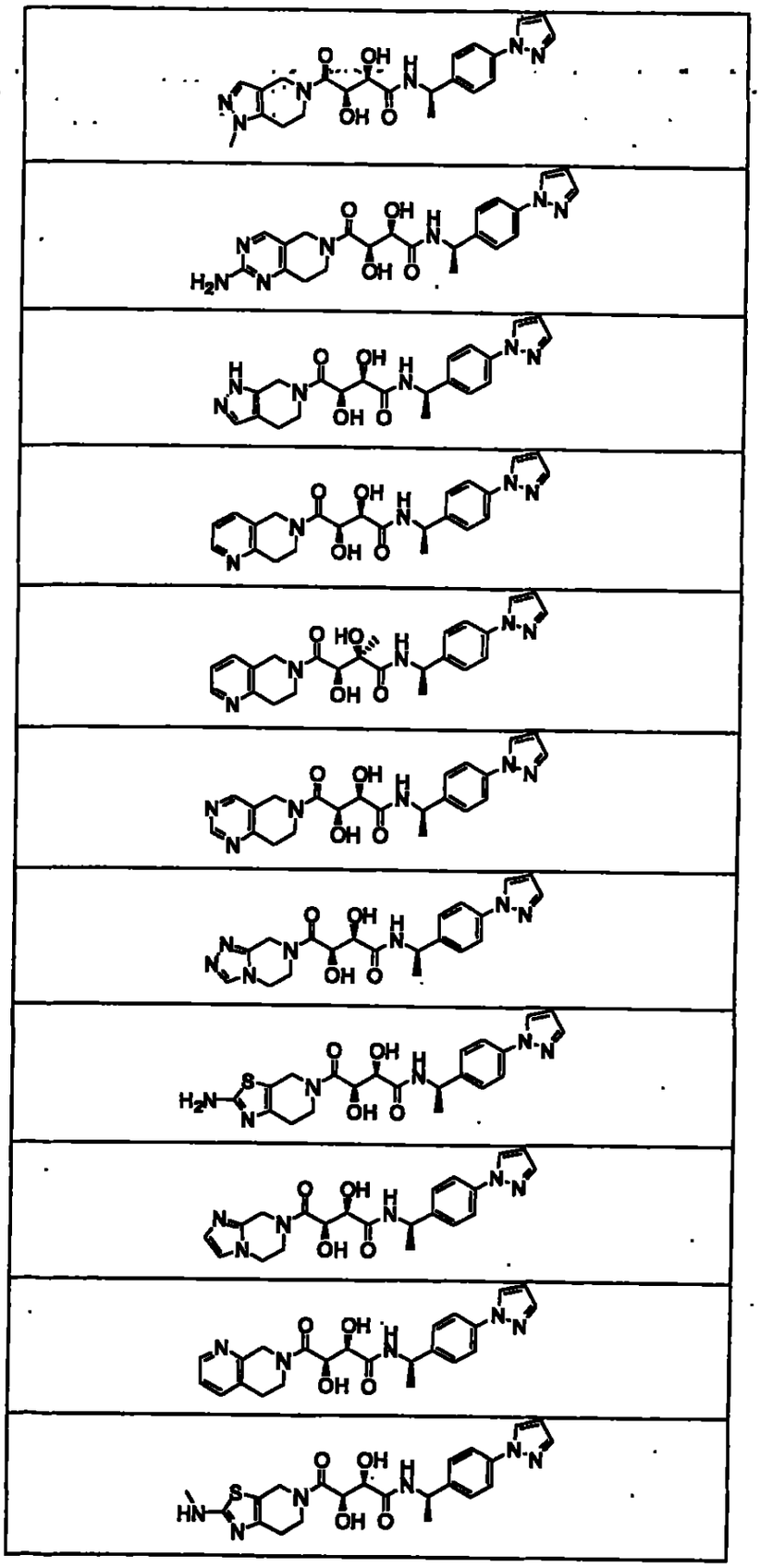


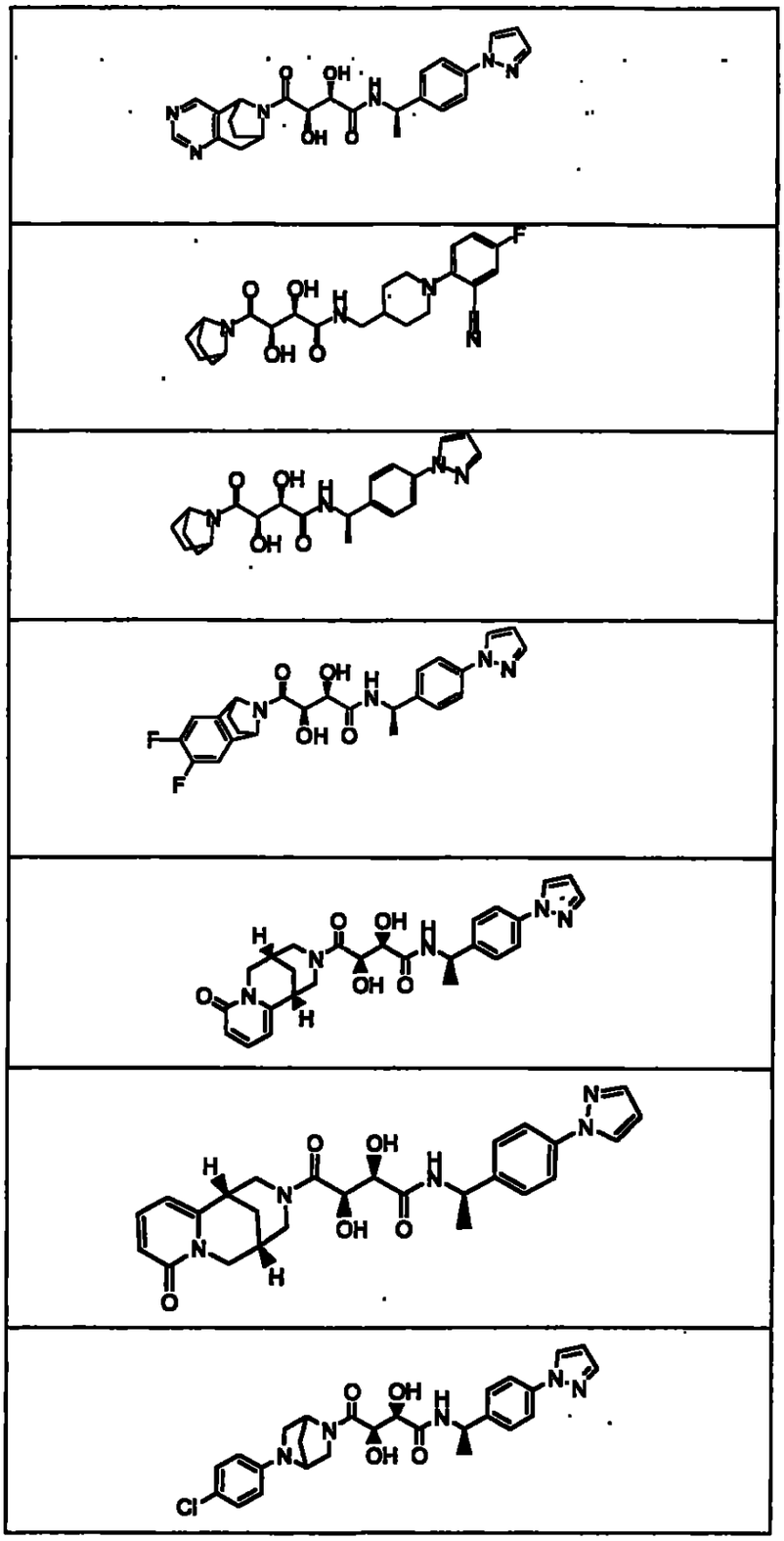


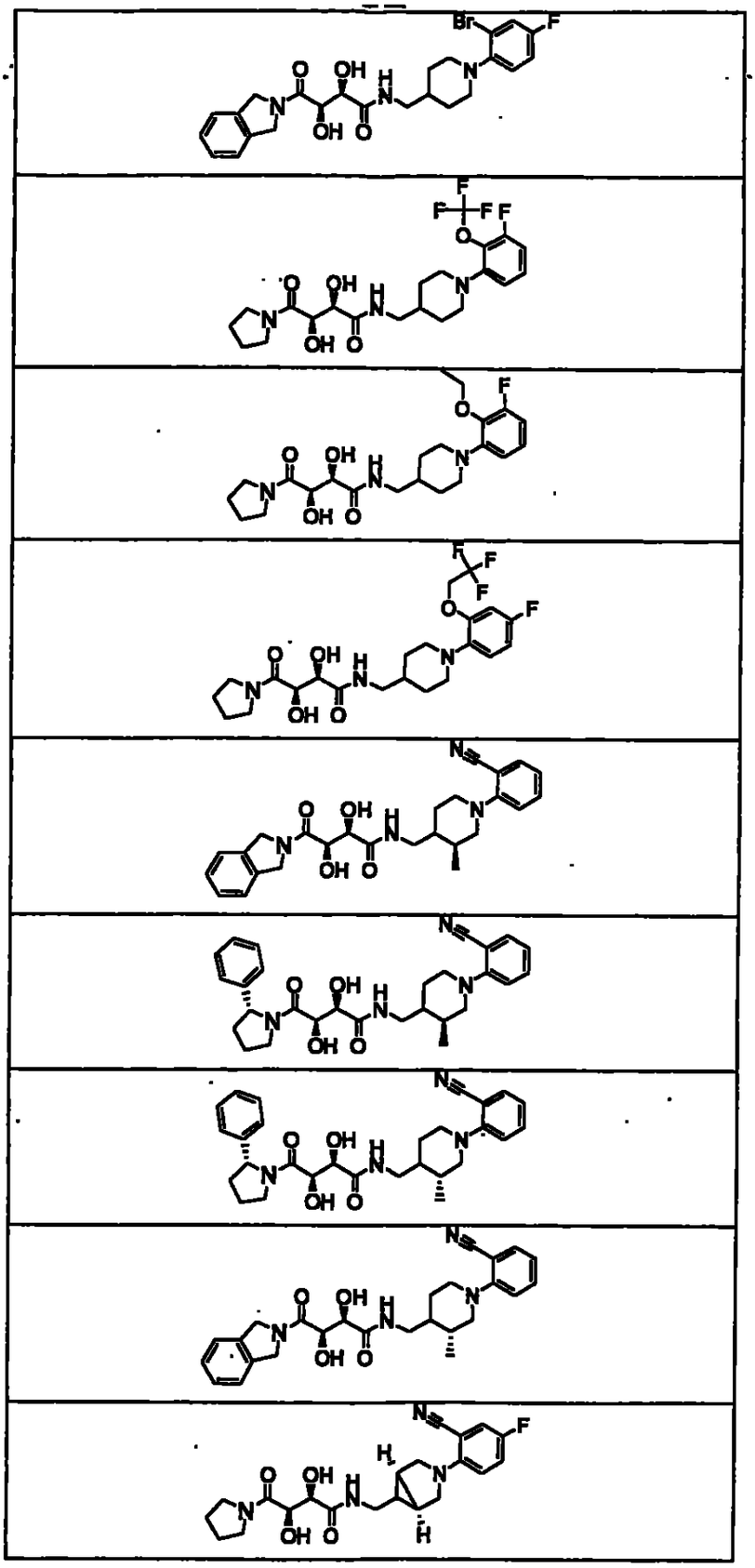


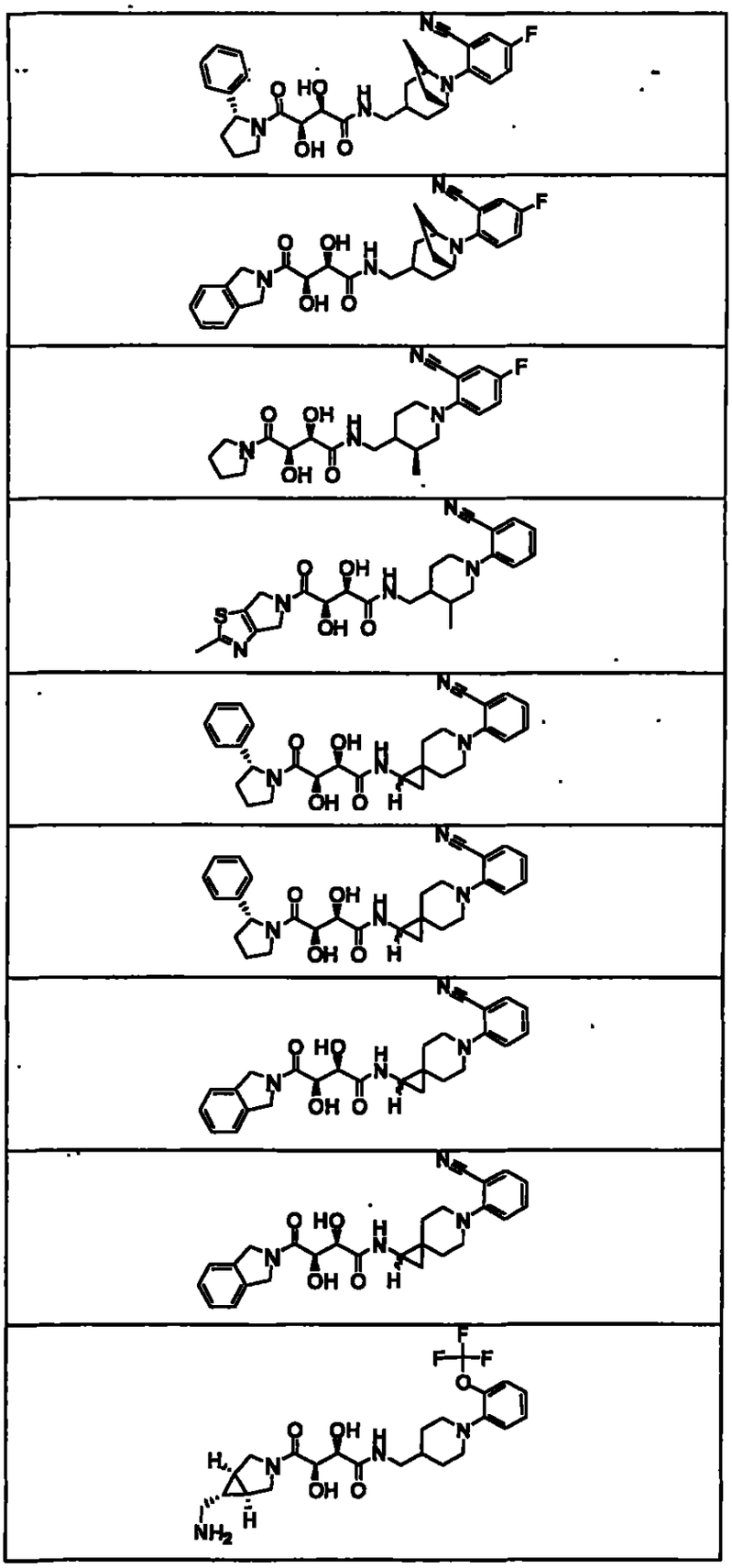


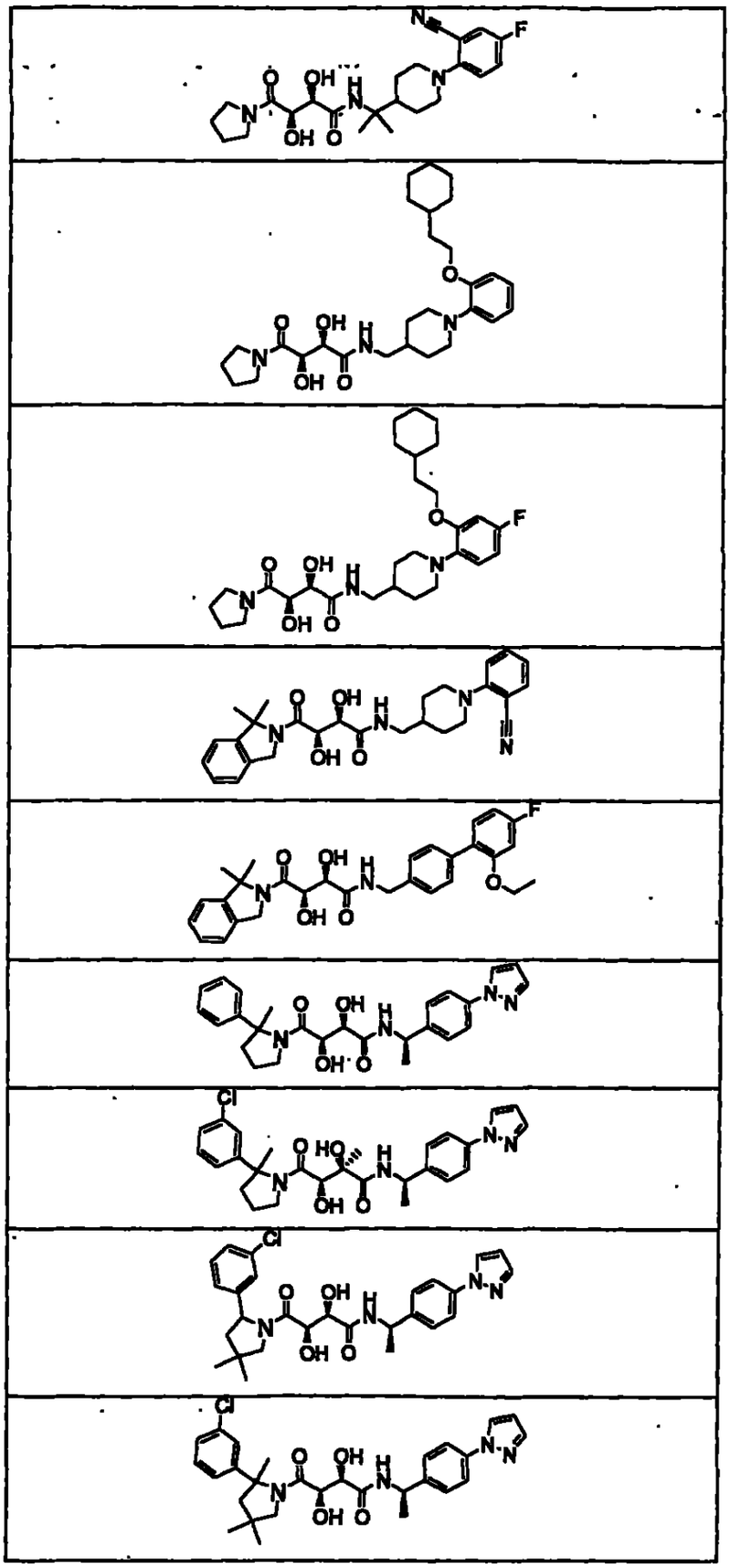


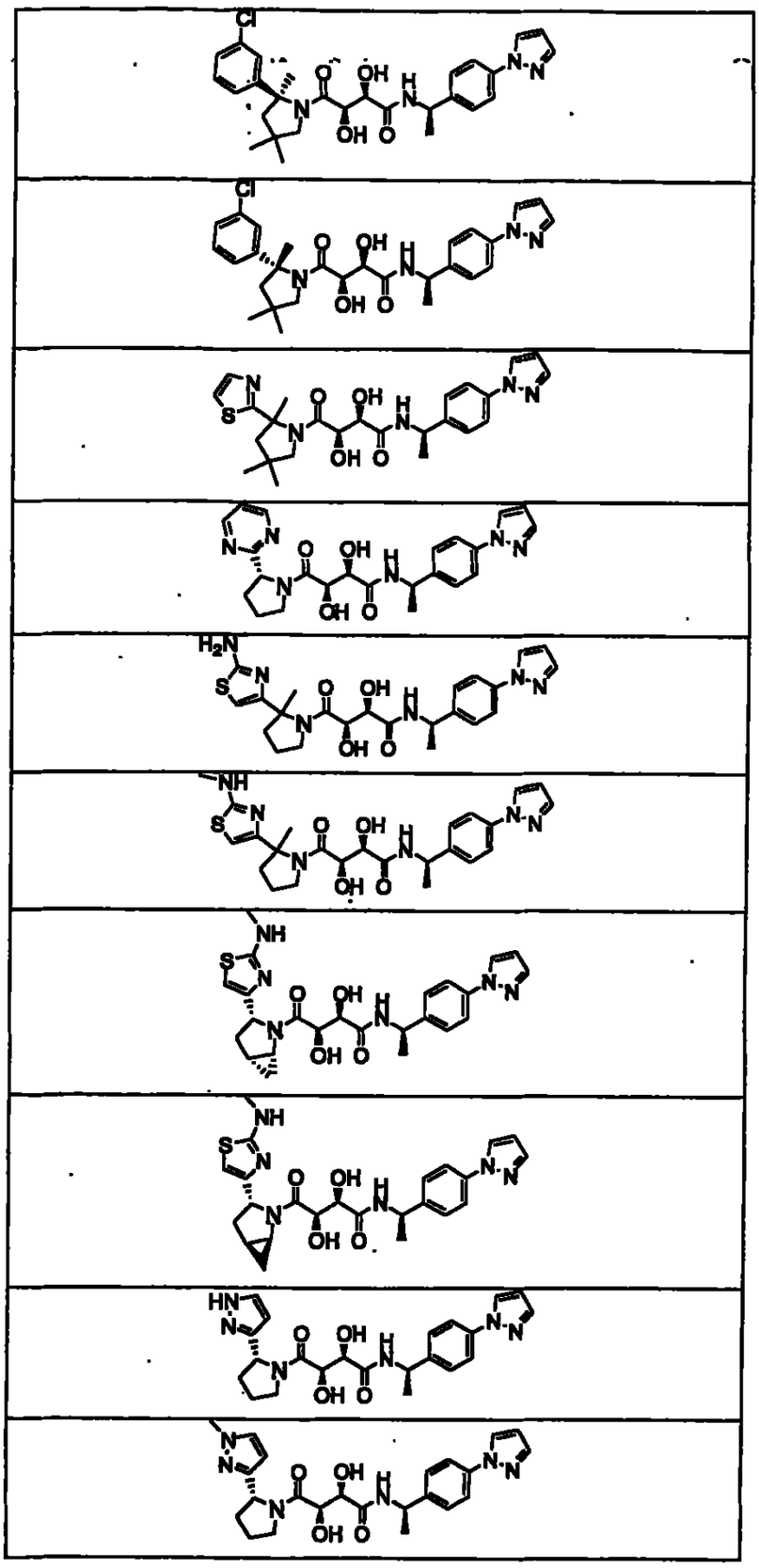


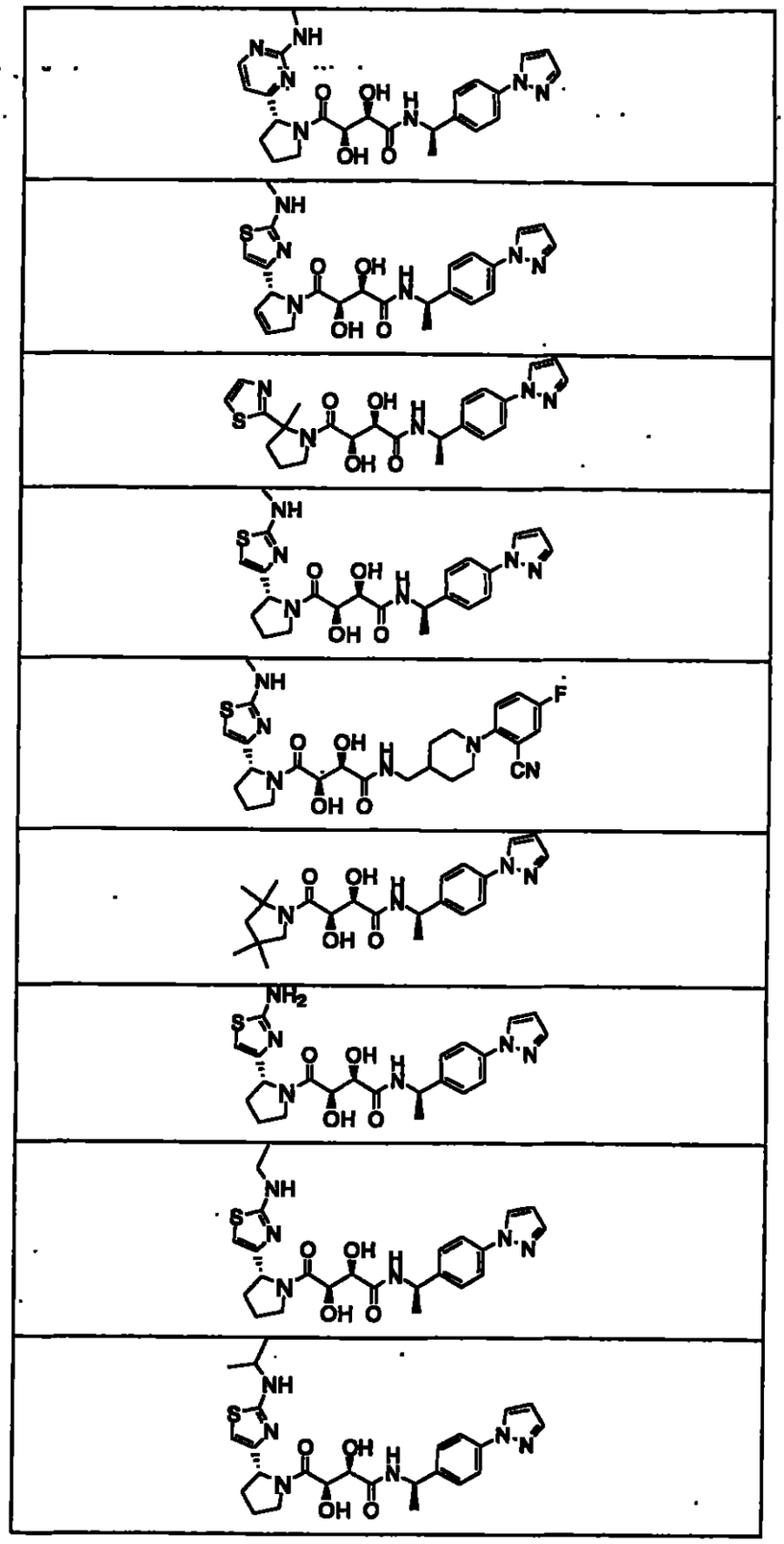


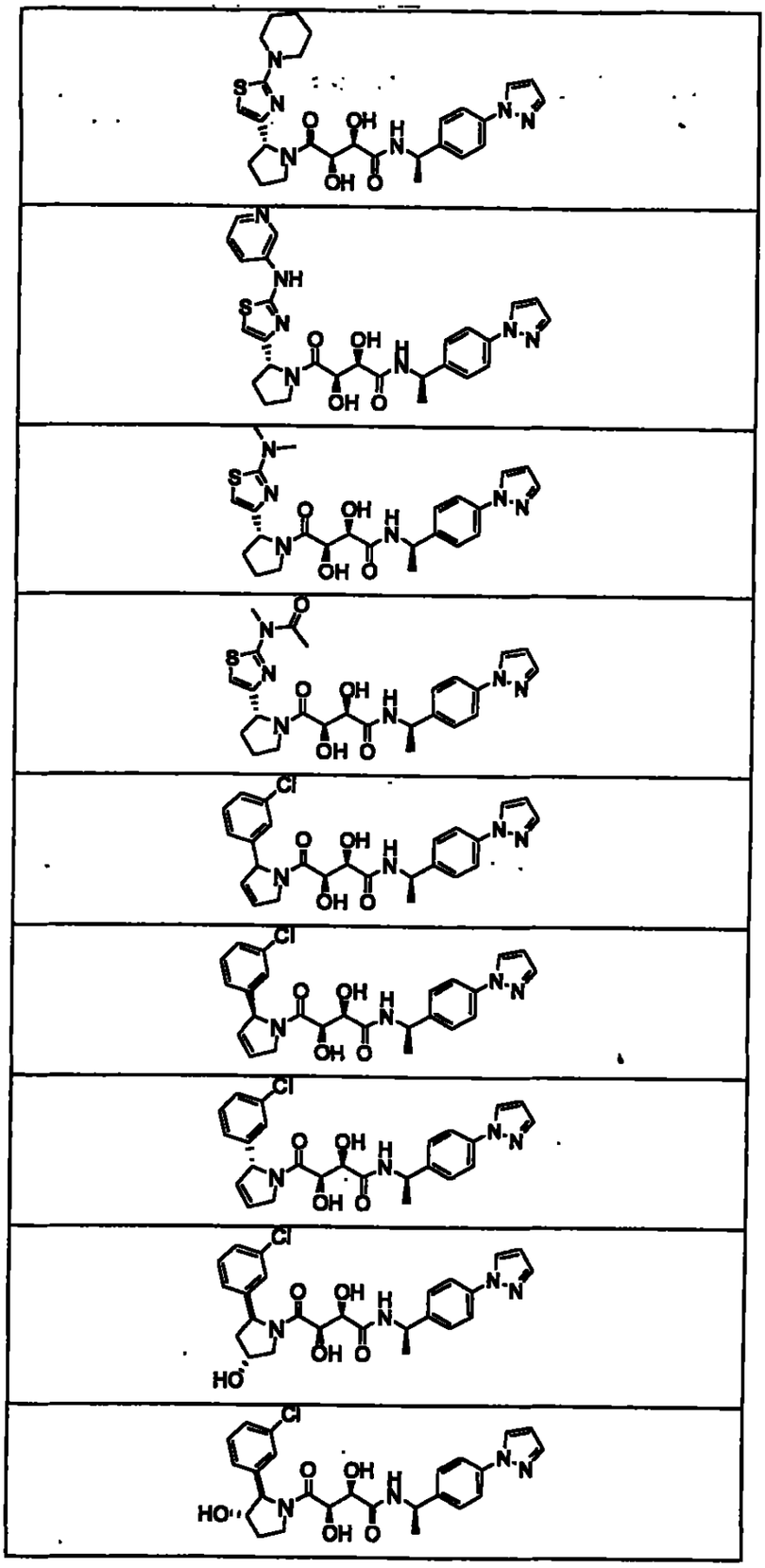


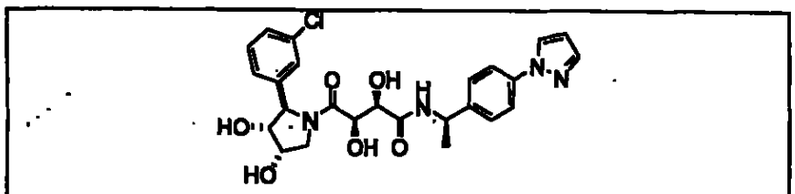


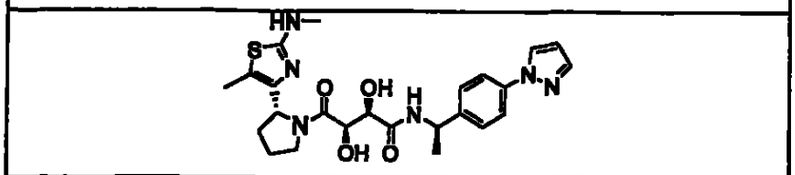


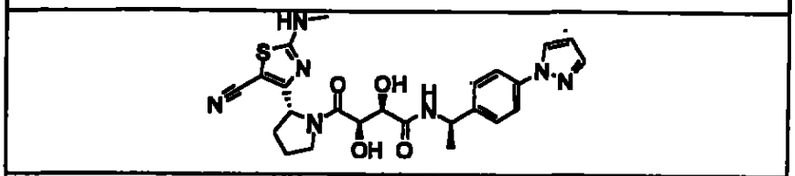


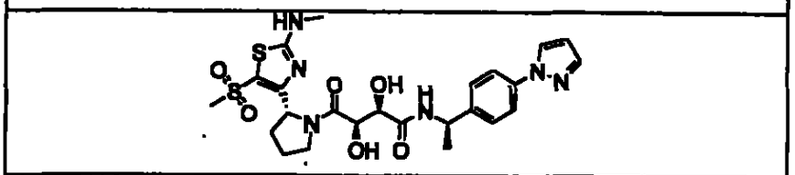


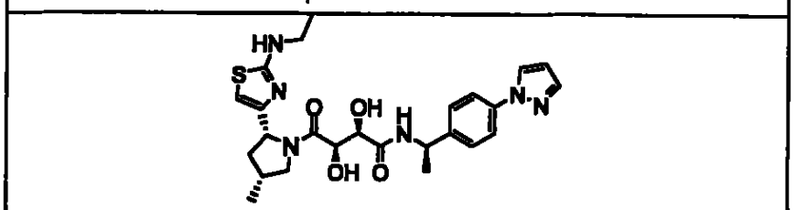


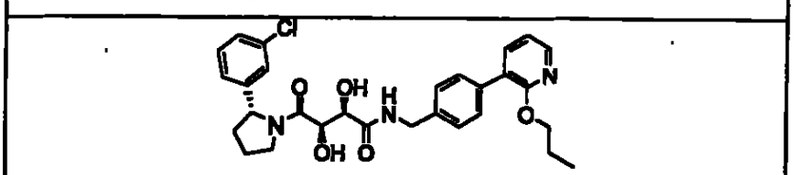


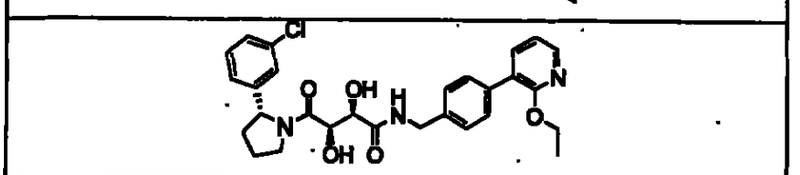


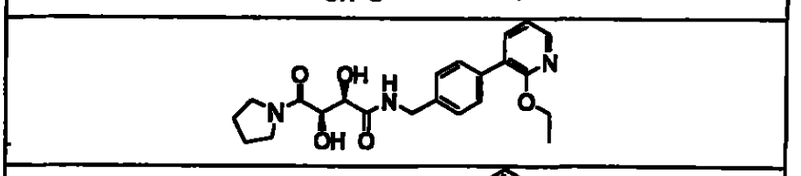


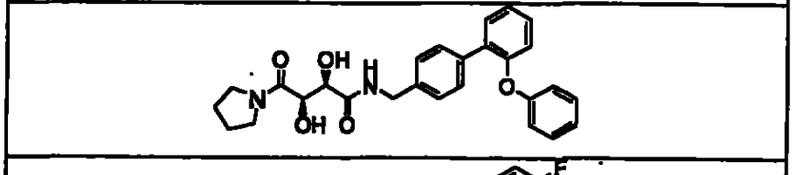


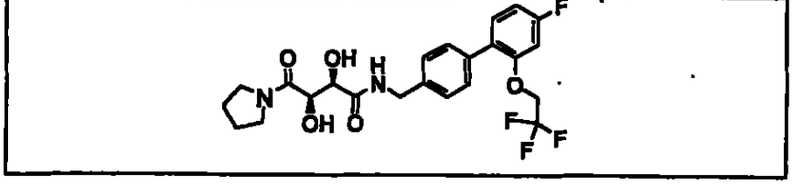


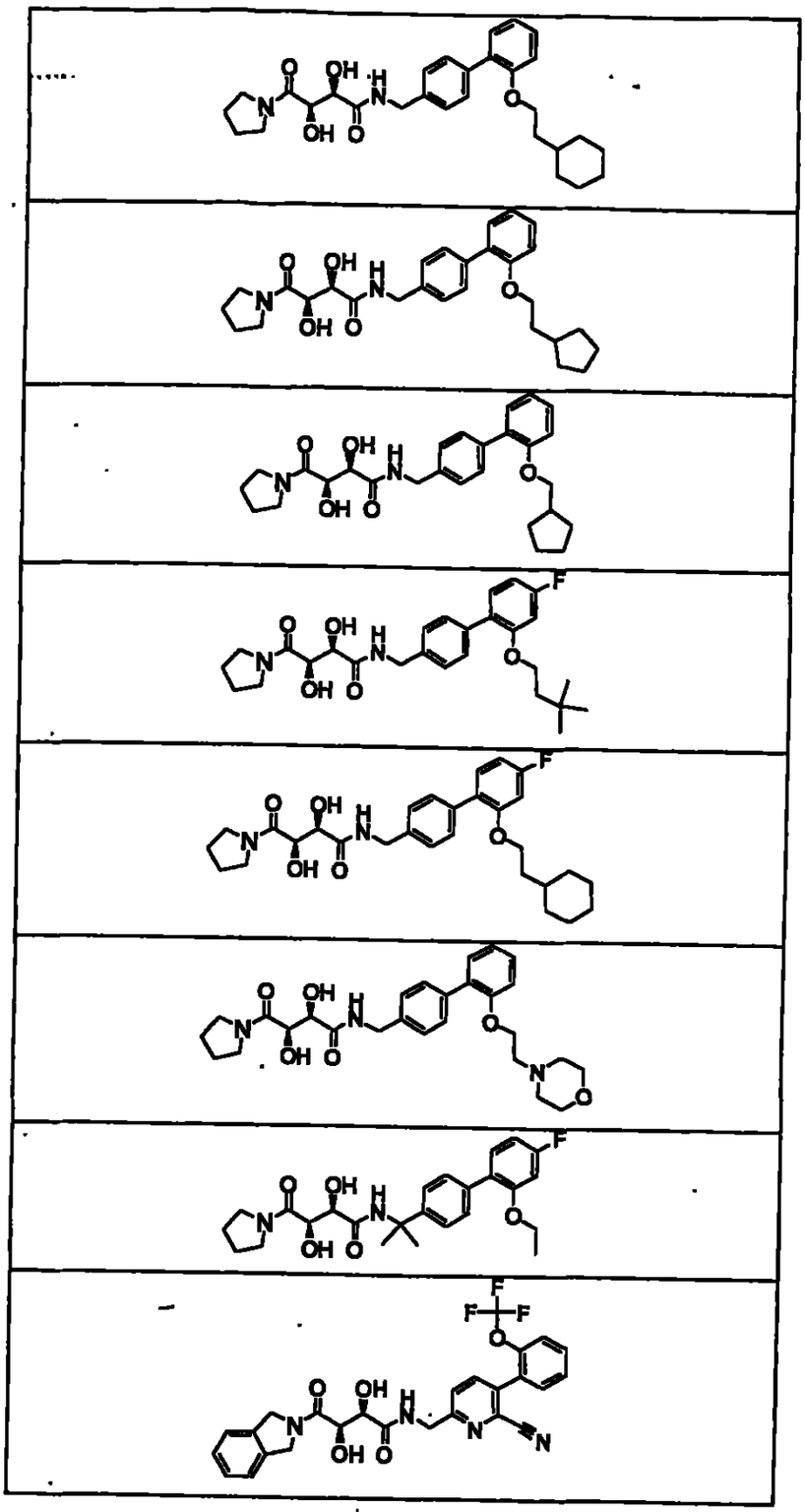


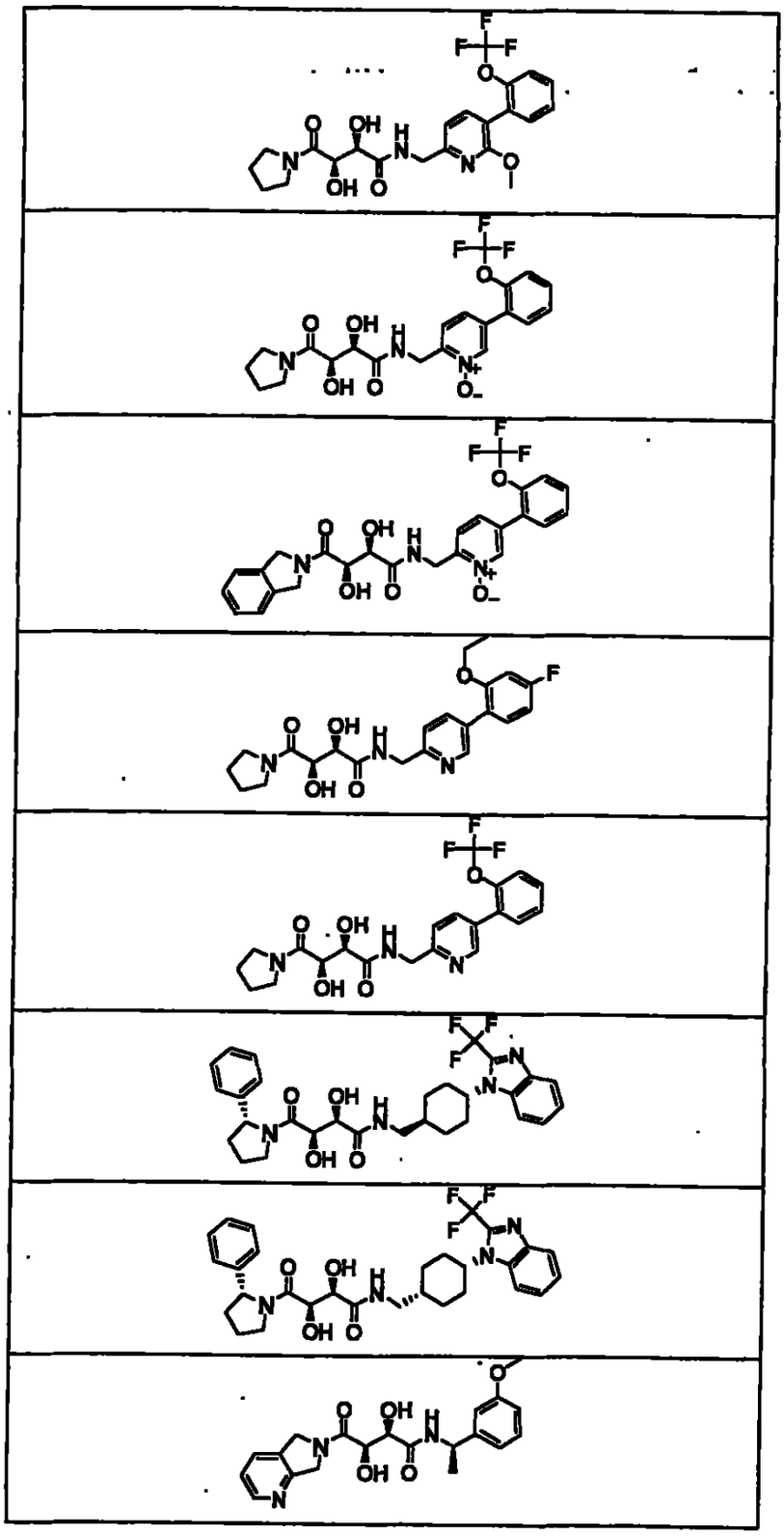


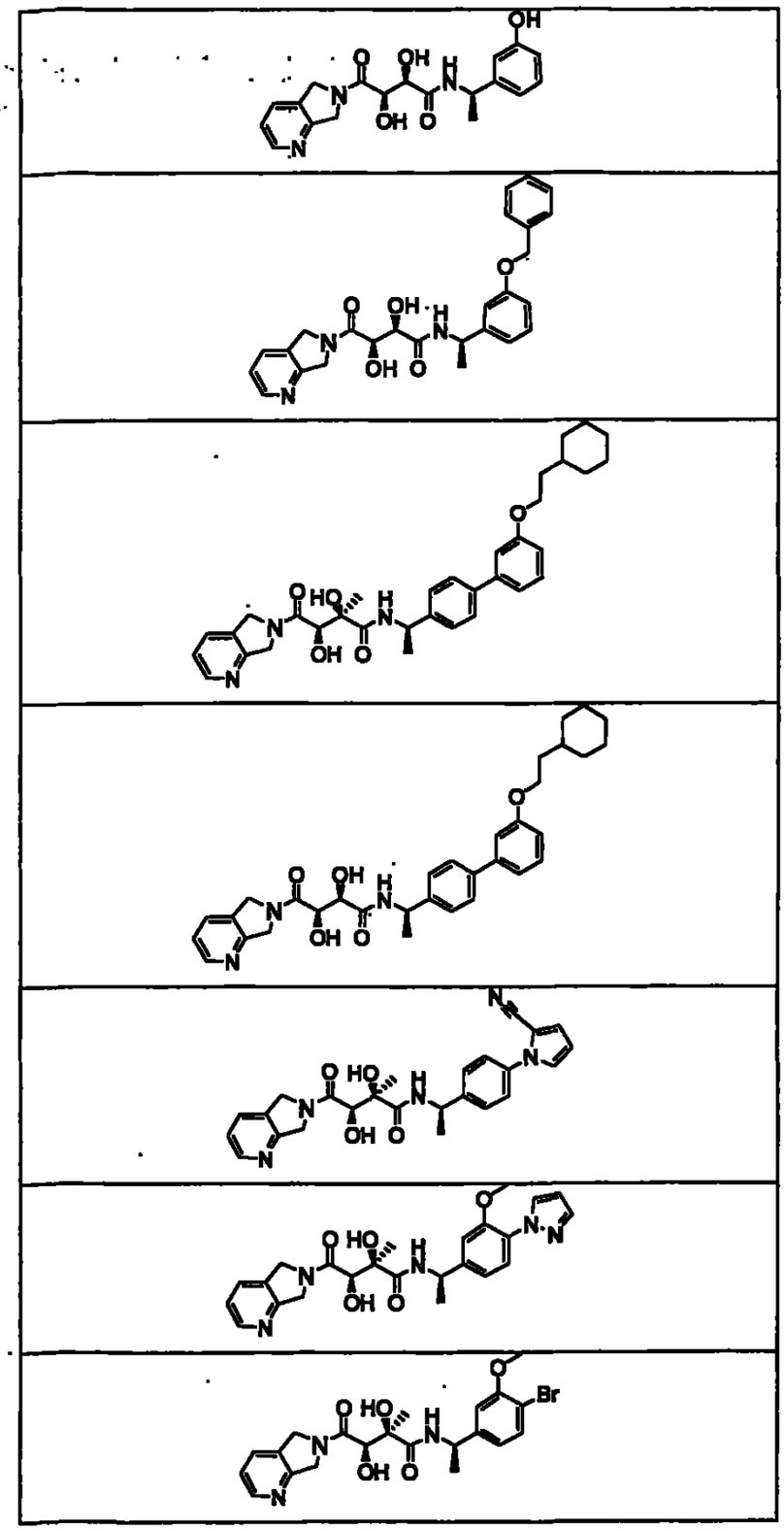


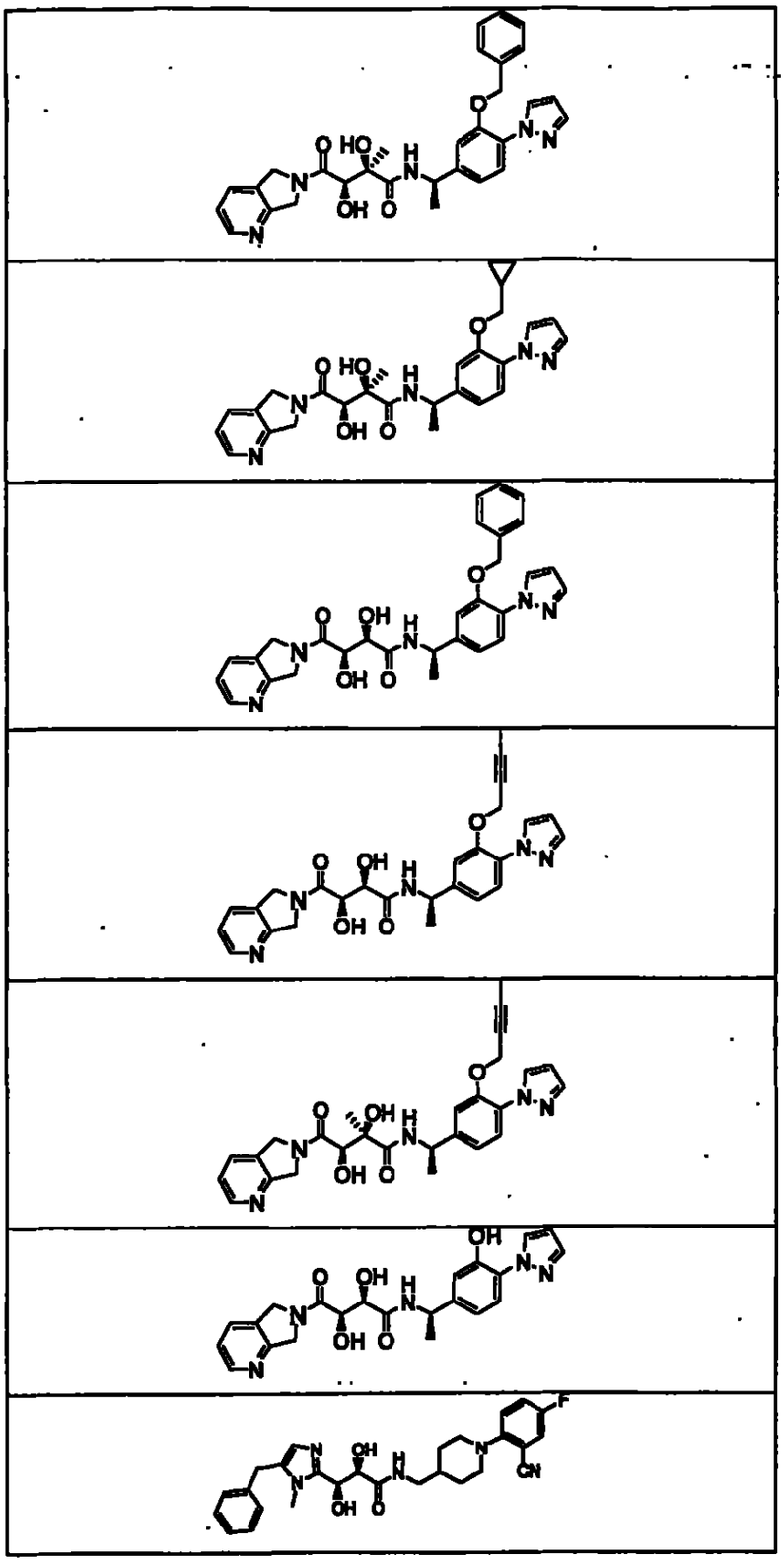


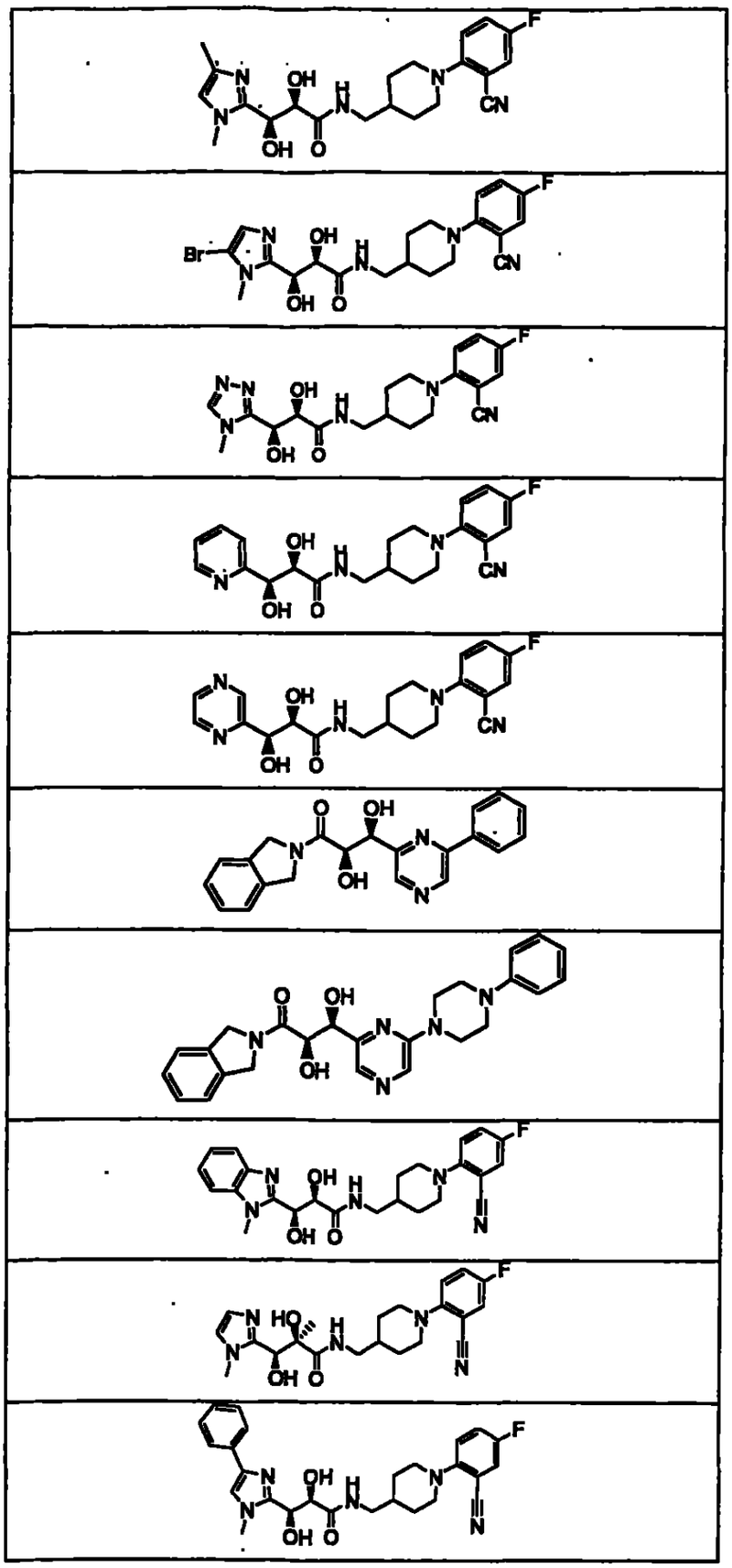


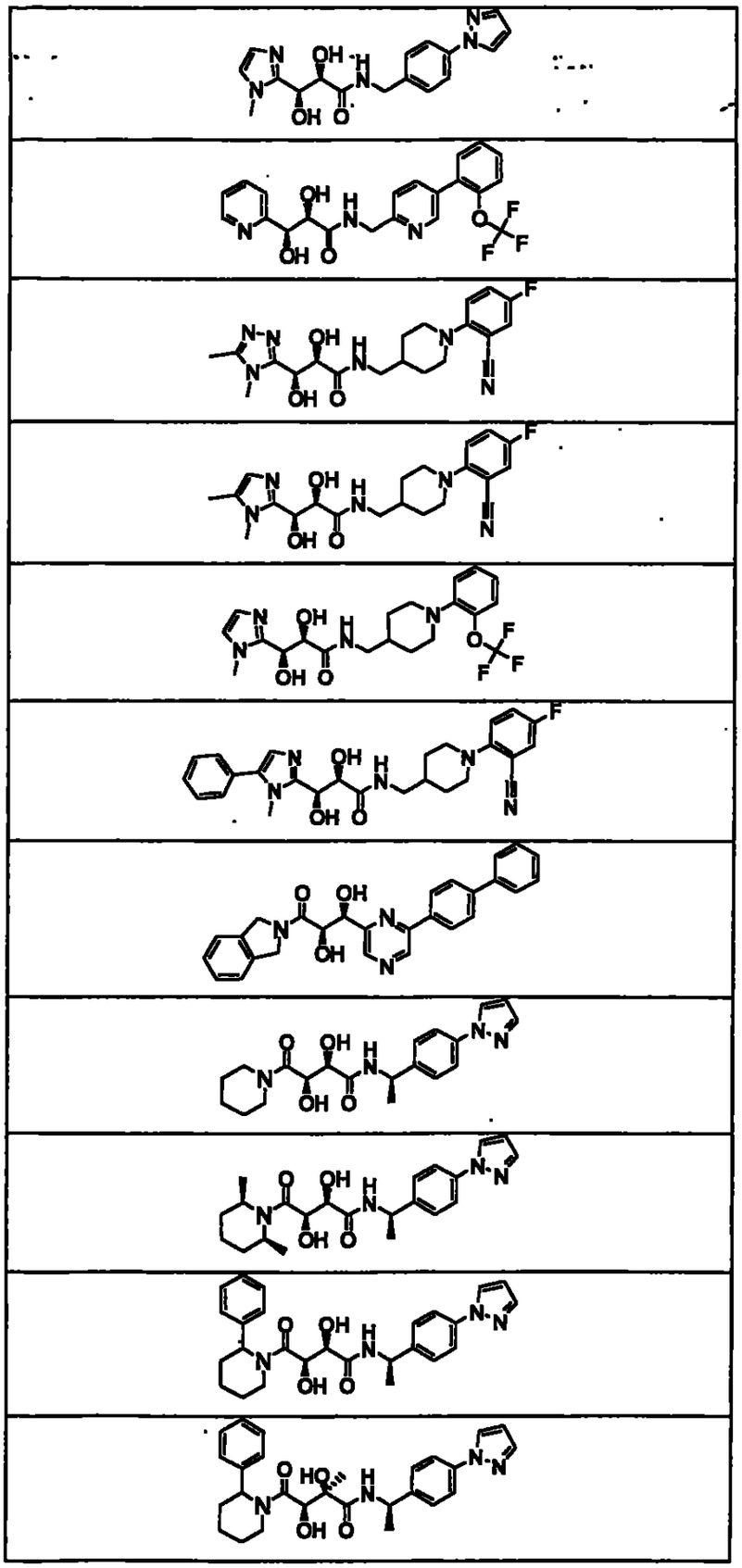


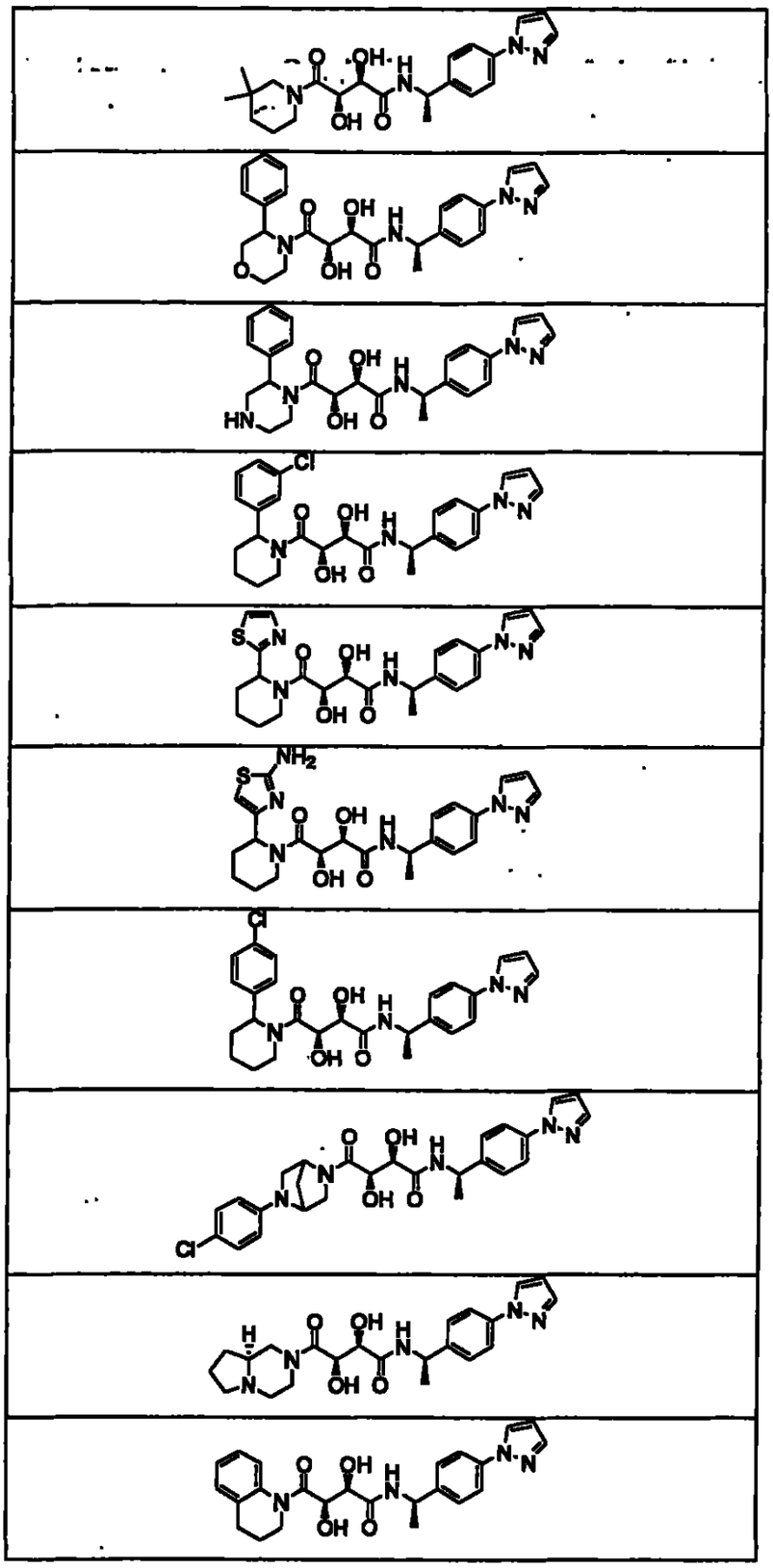


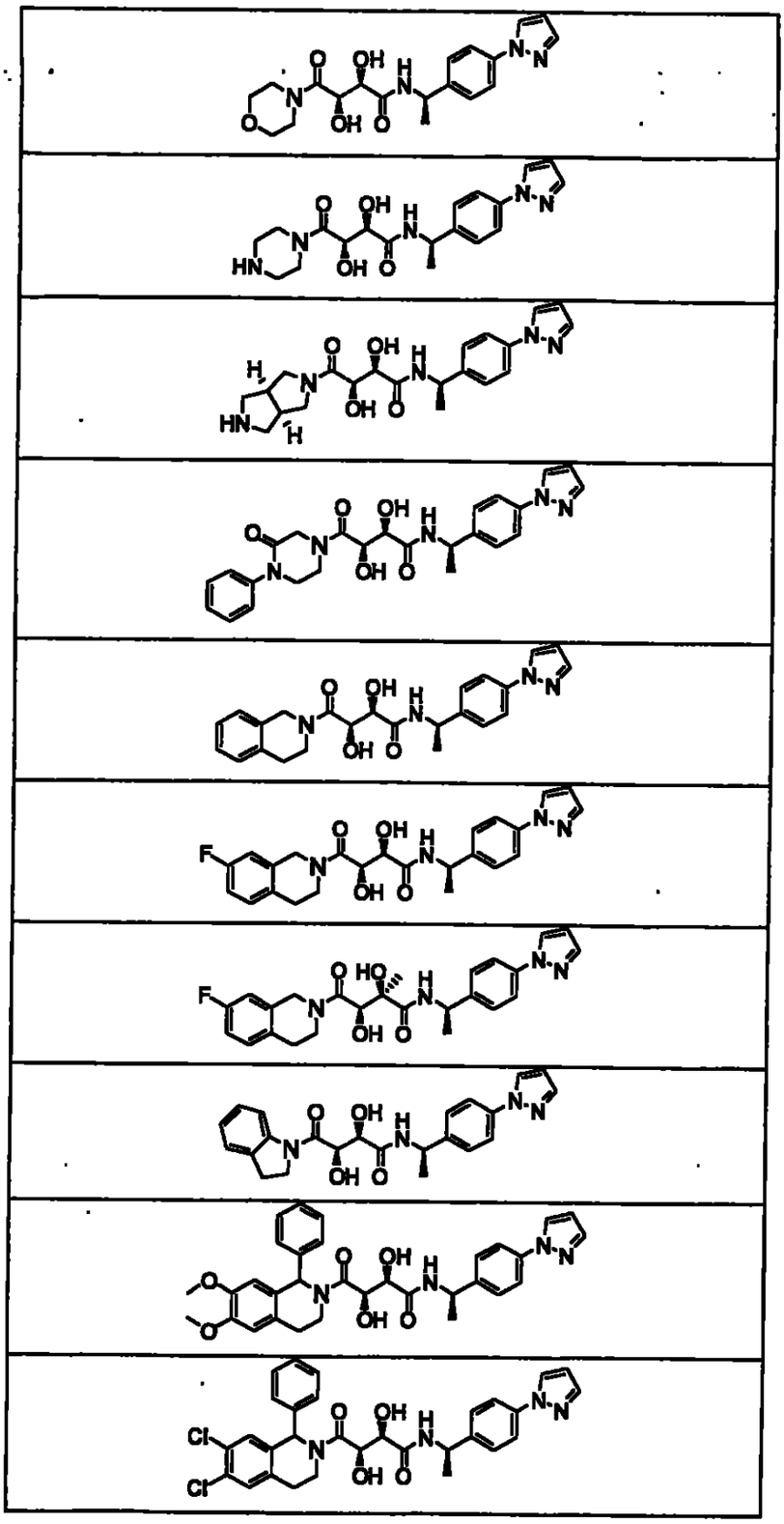


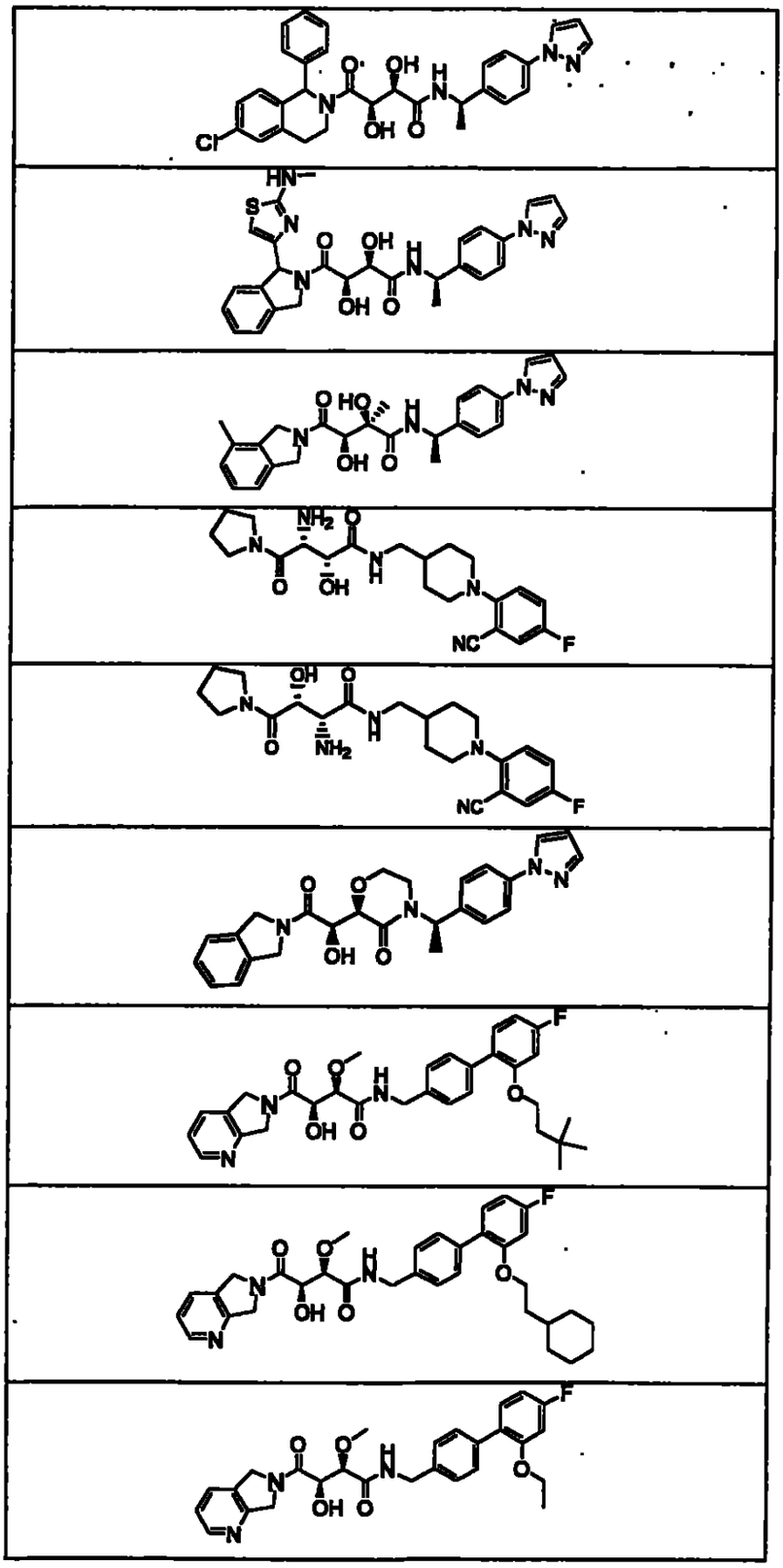


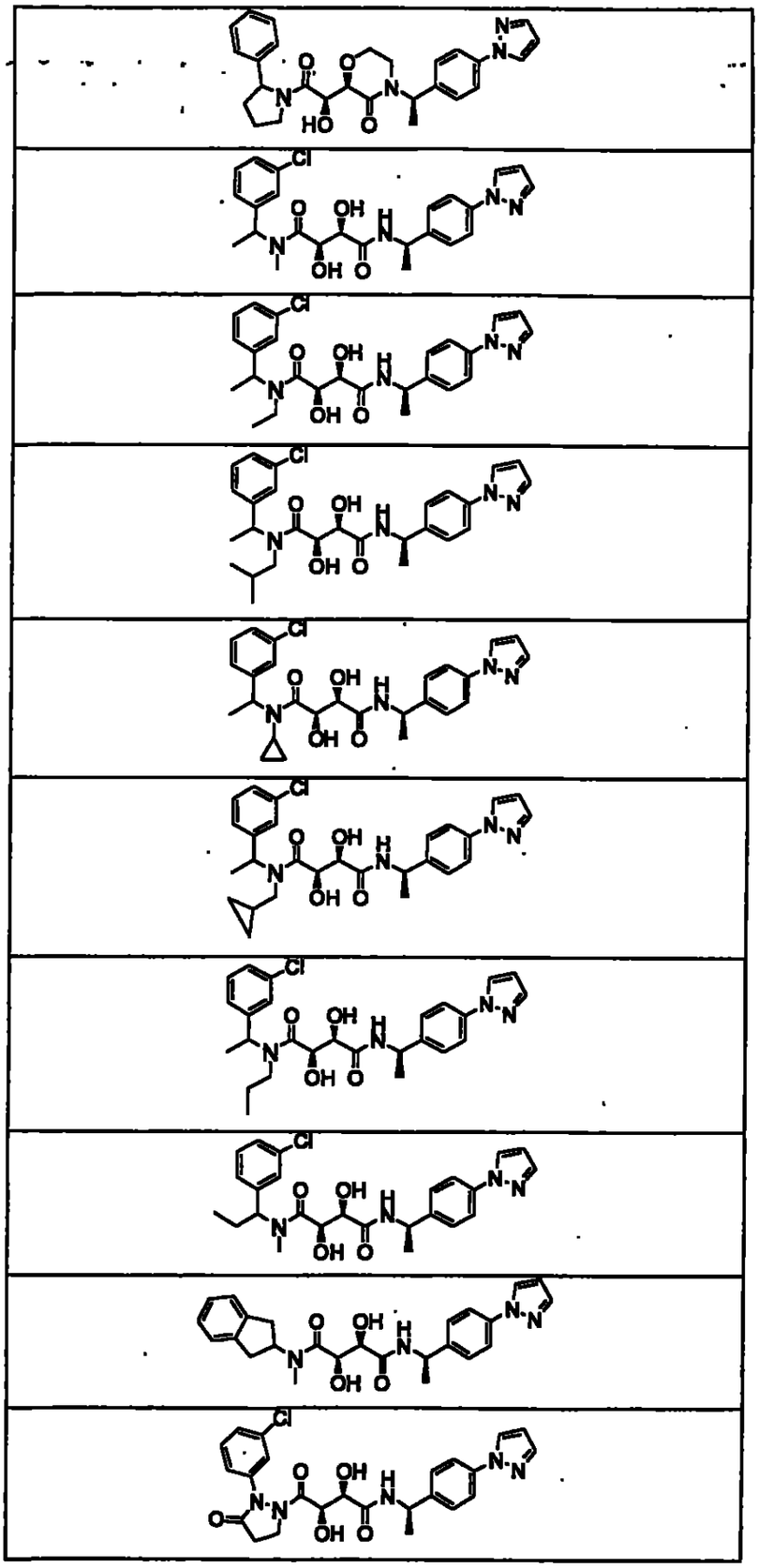


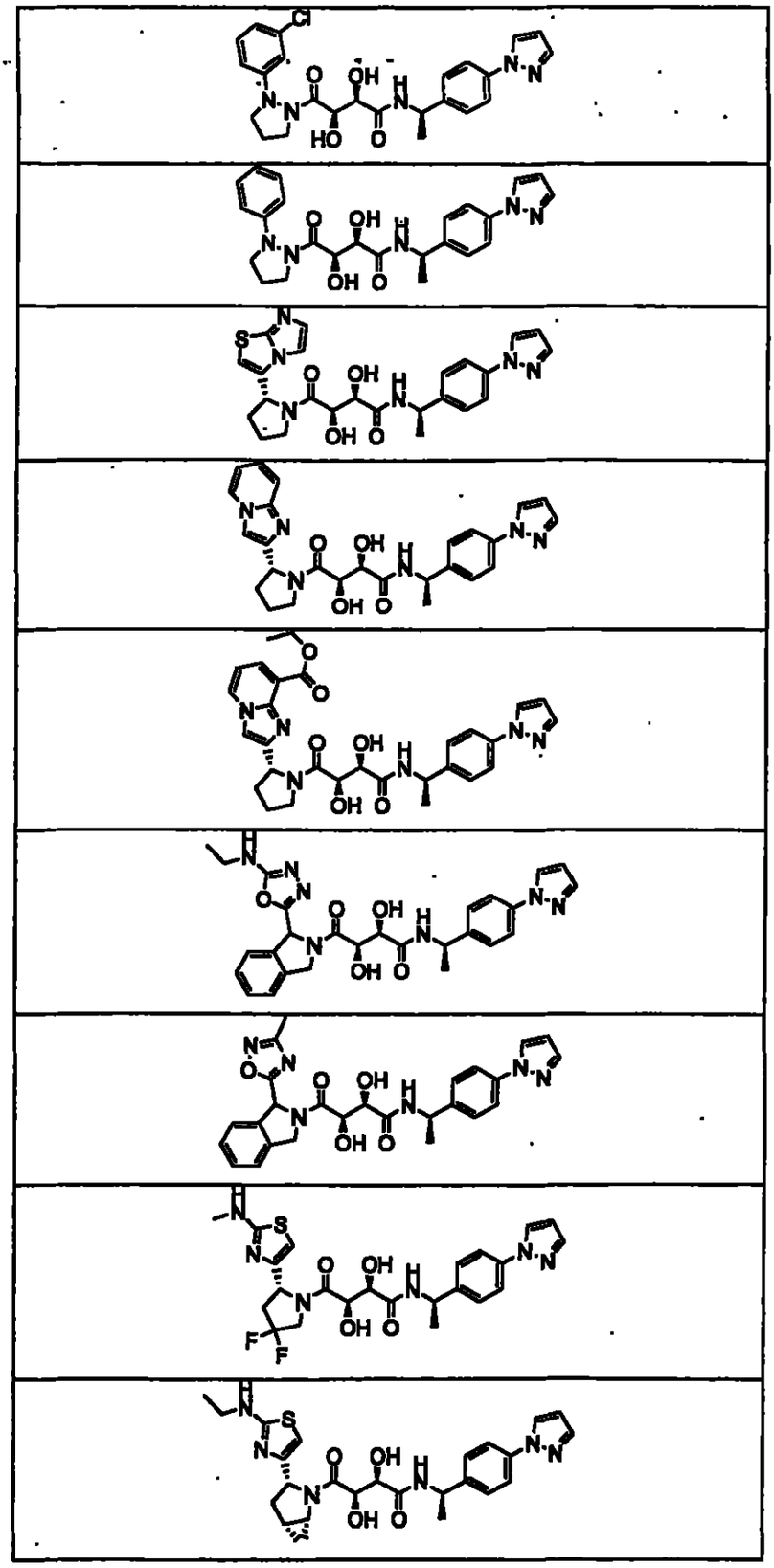


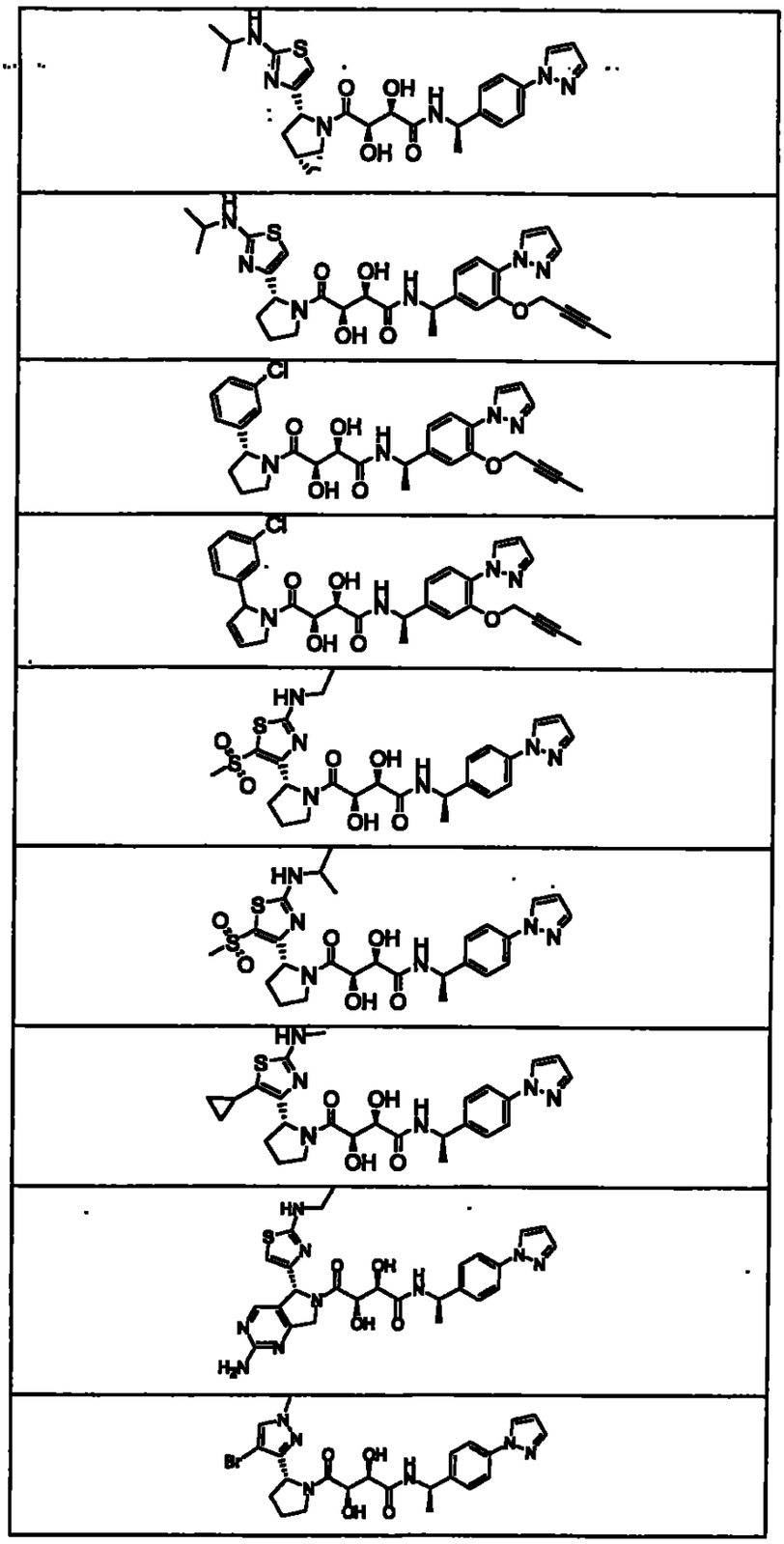


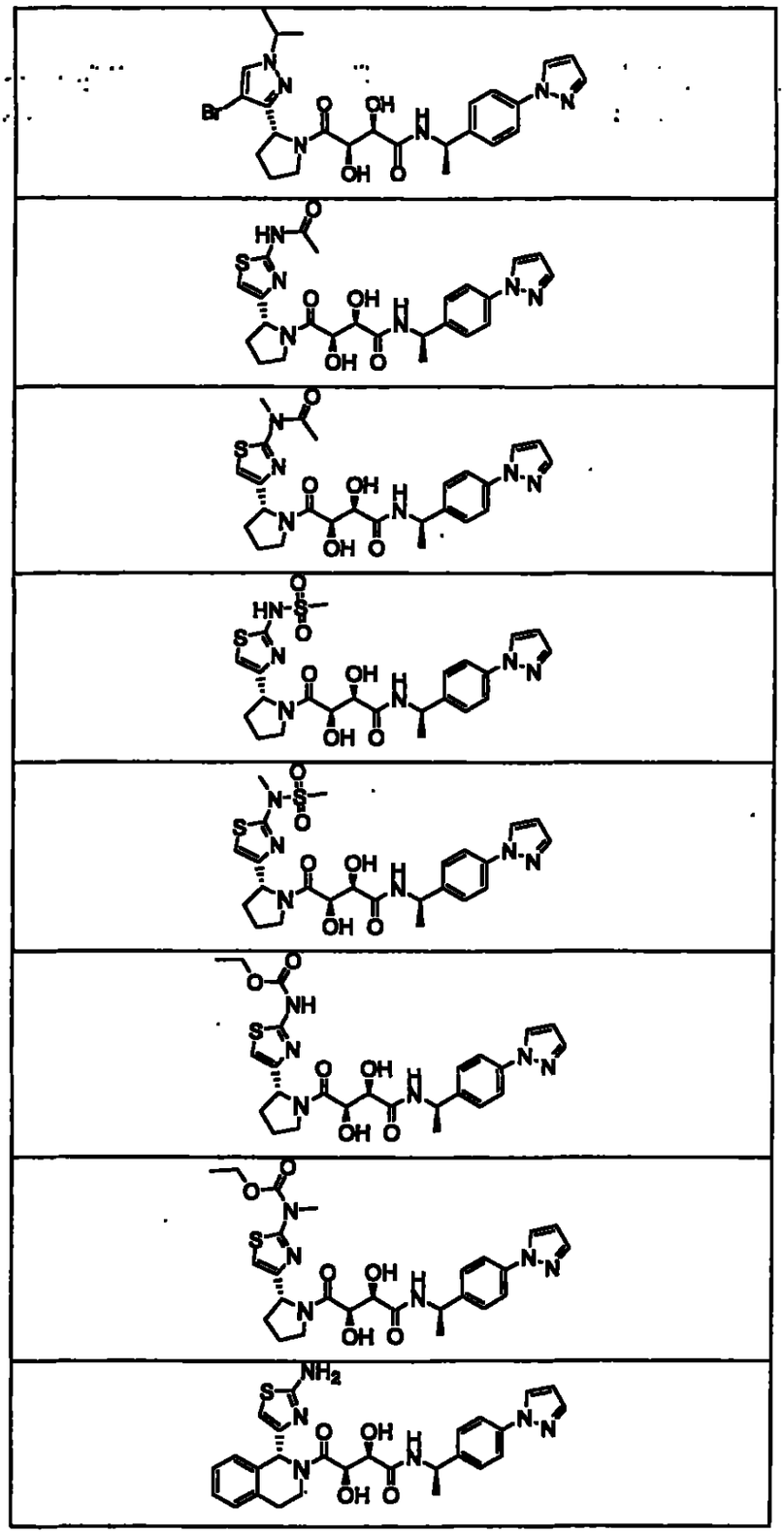


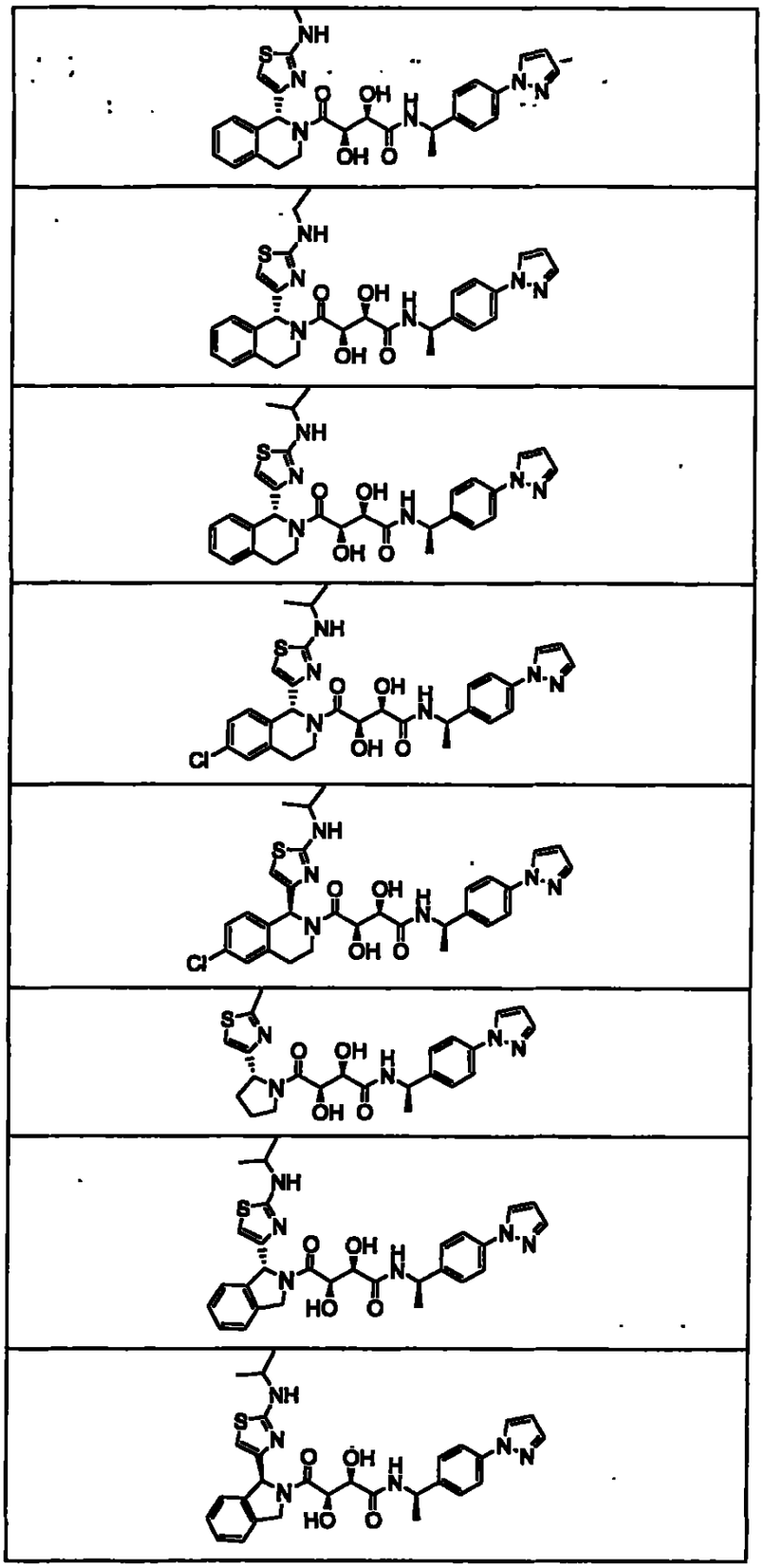


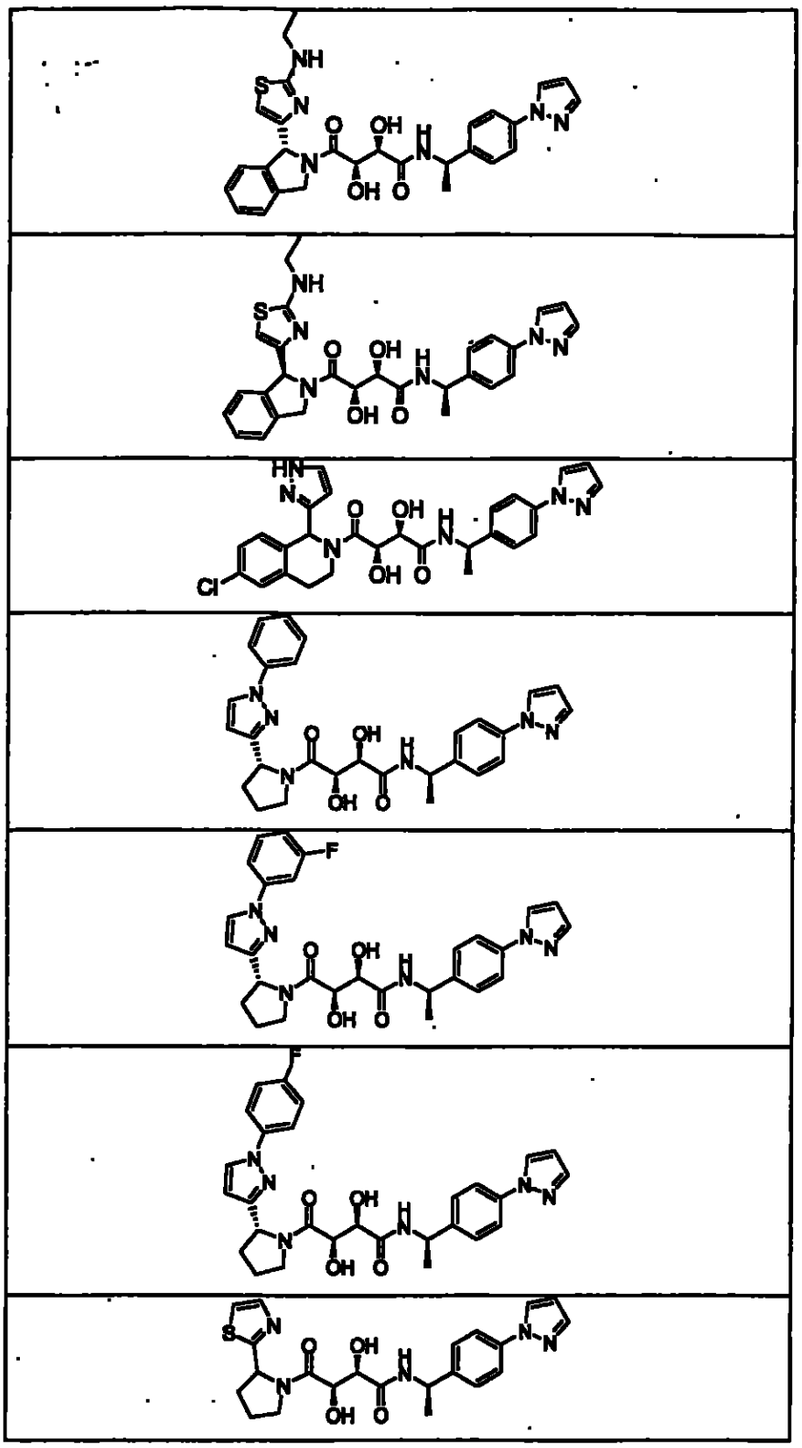




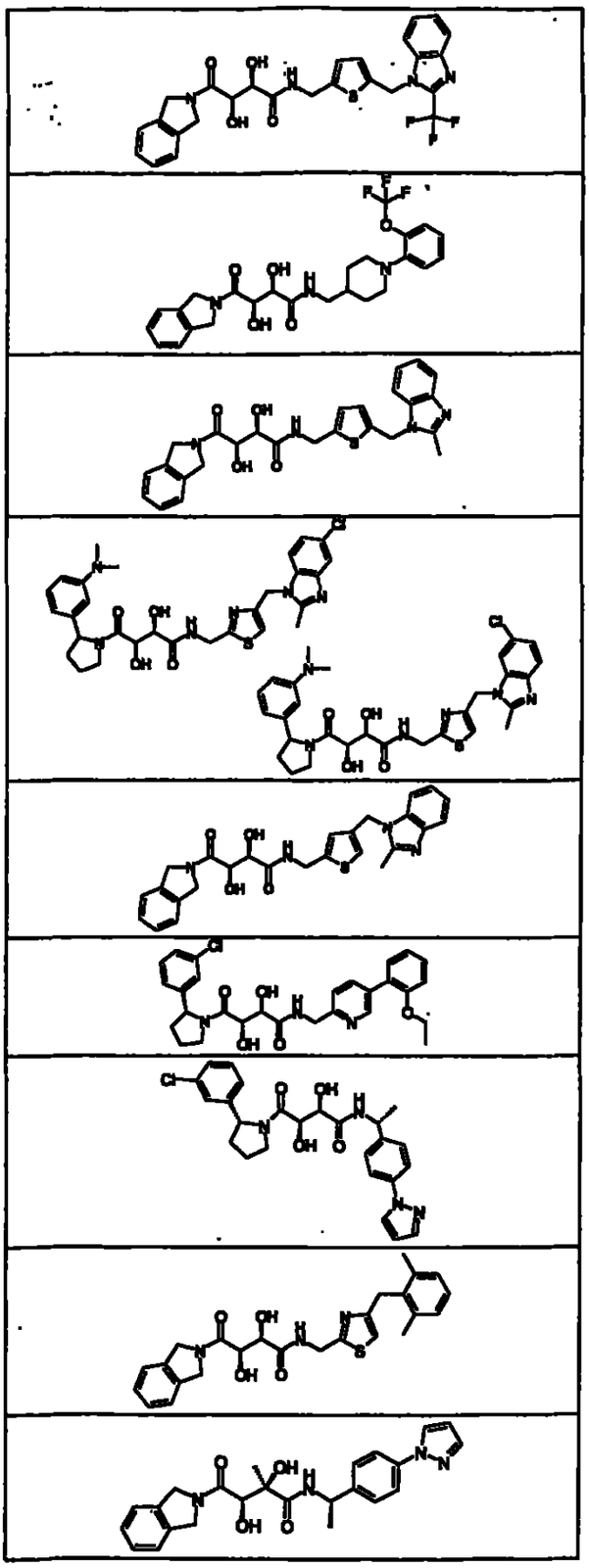


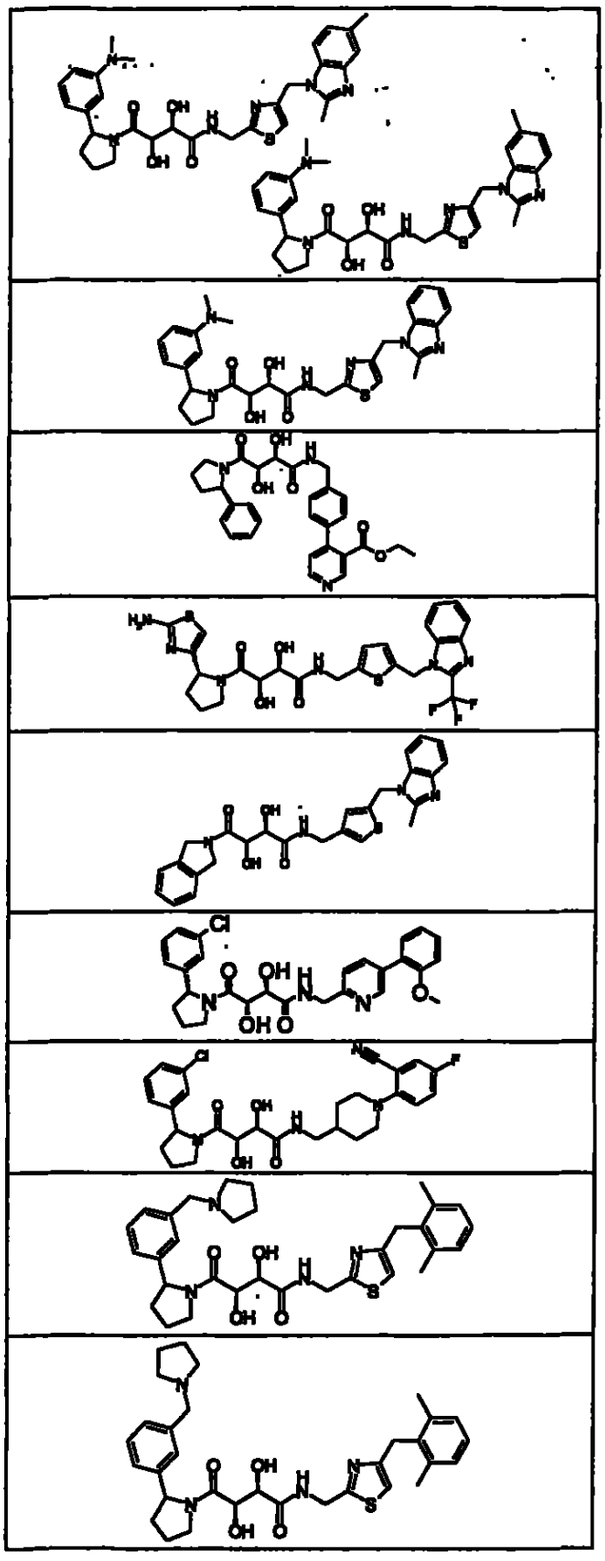


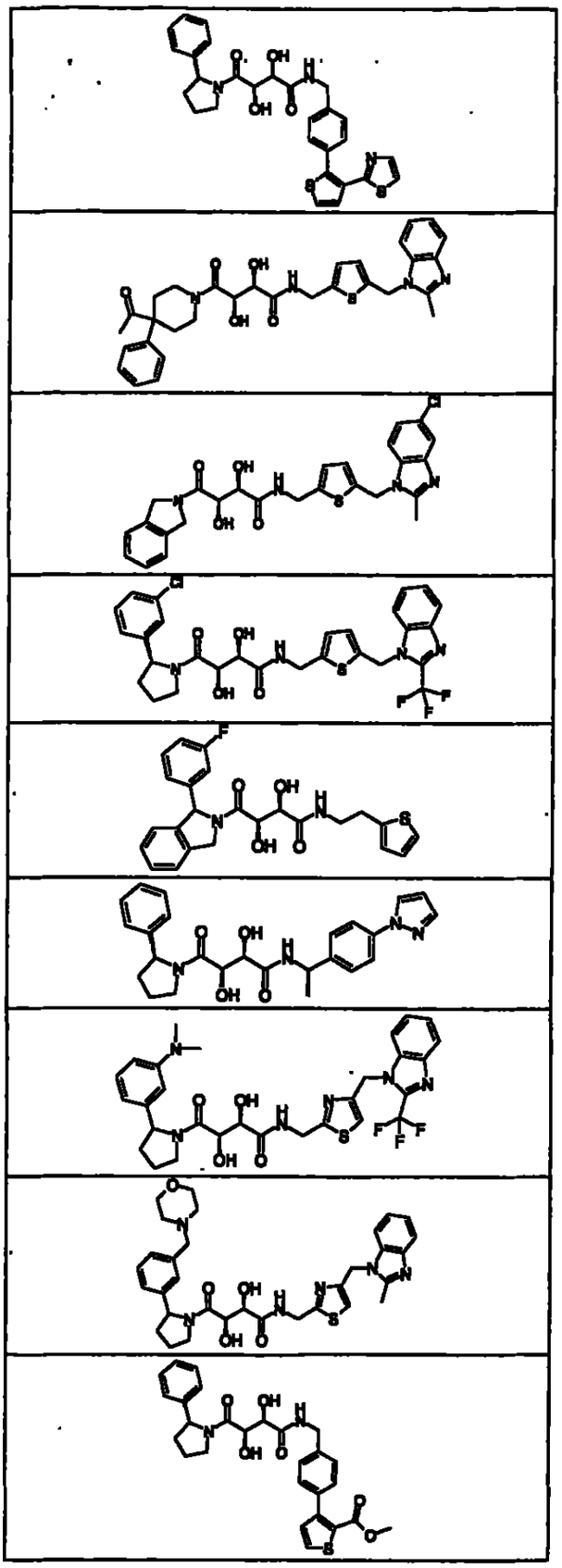


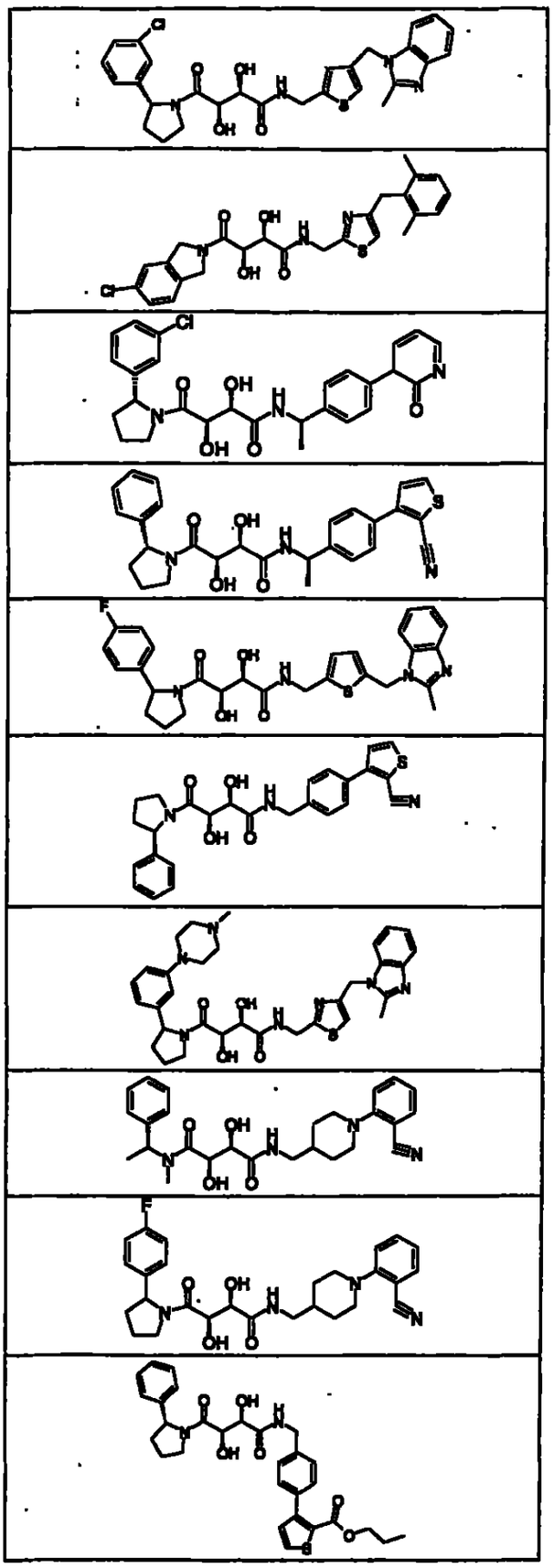


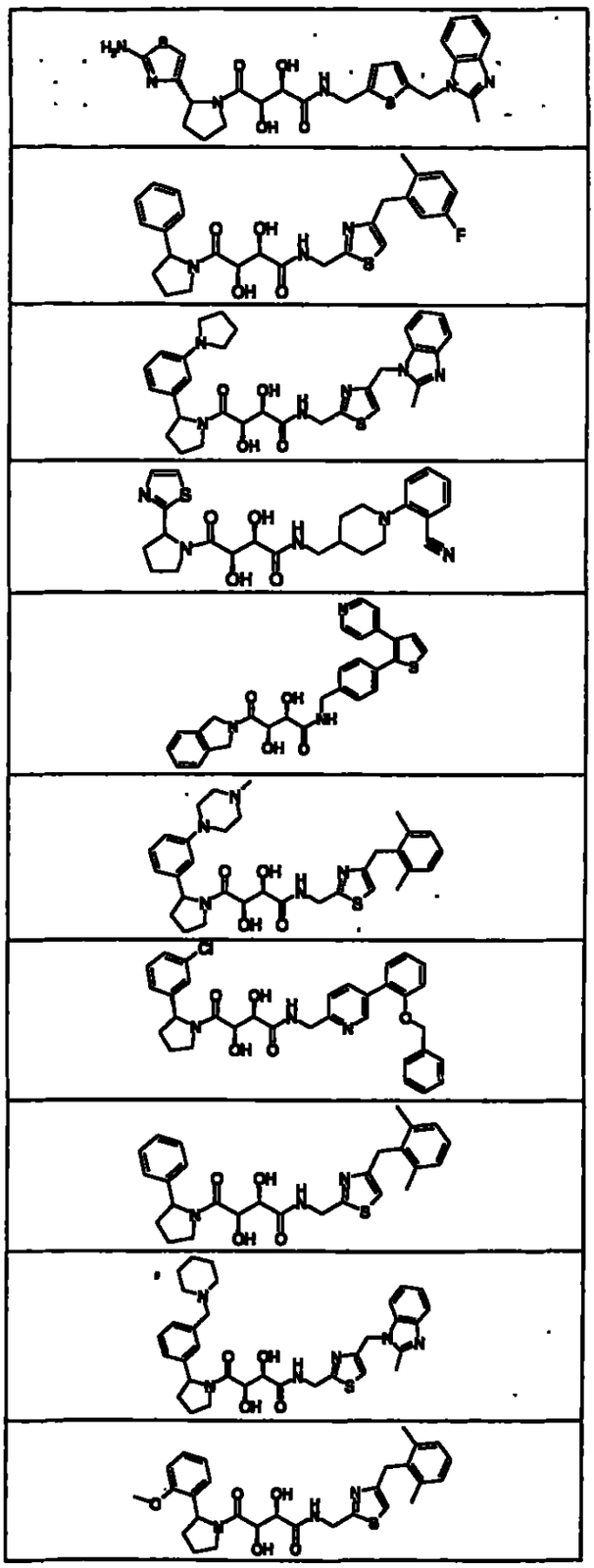
61. The compound of claim 60, said compound being selected from the compounds of structures listed below:

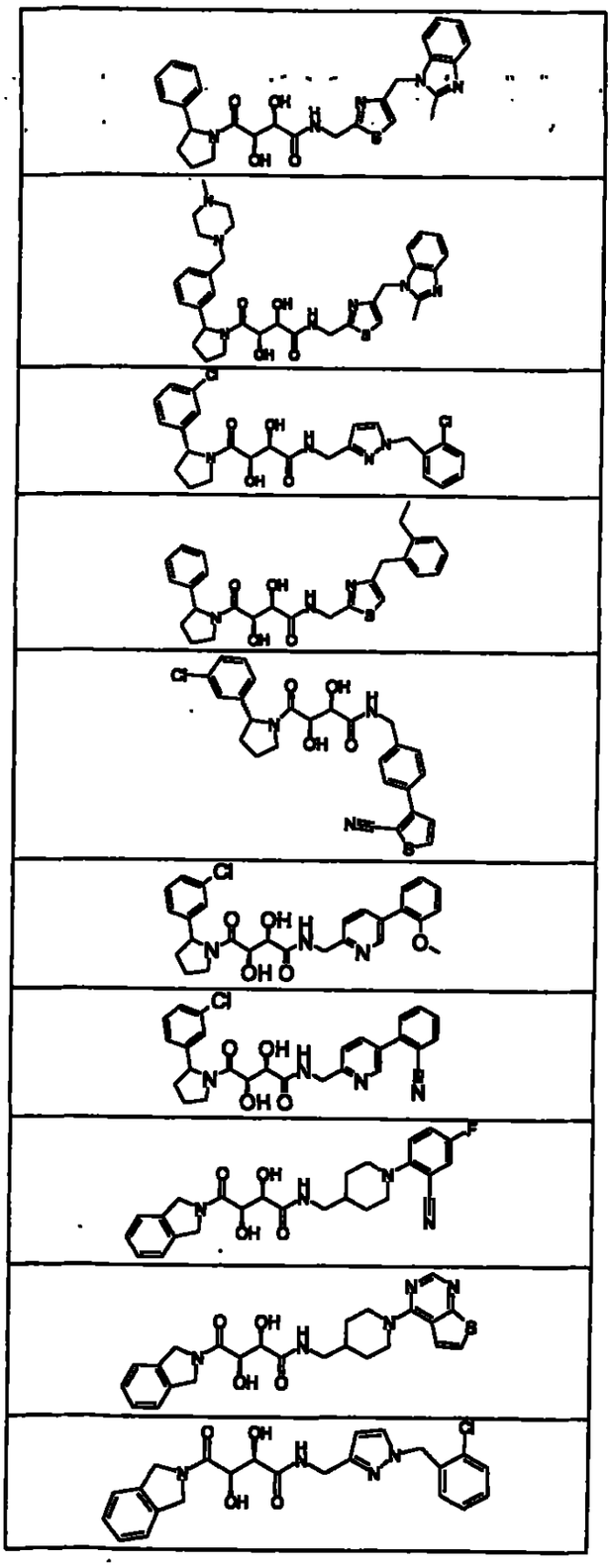


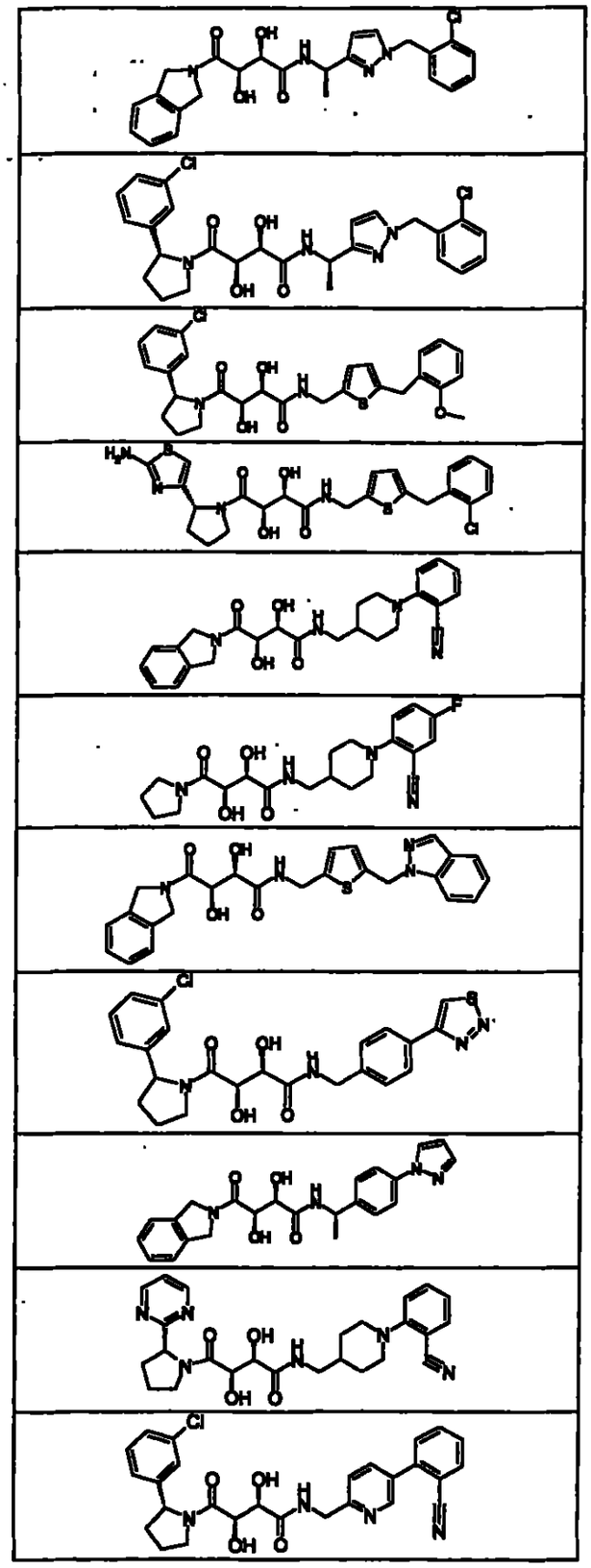


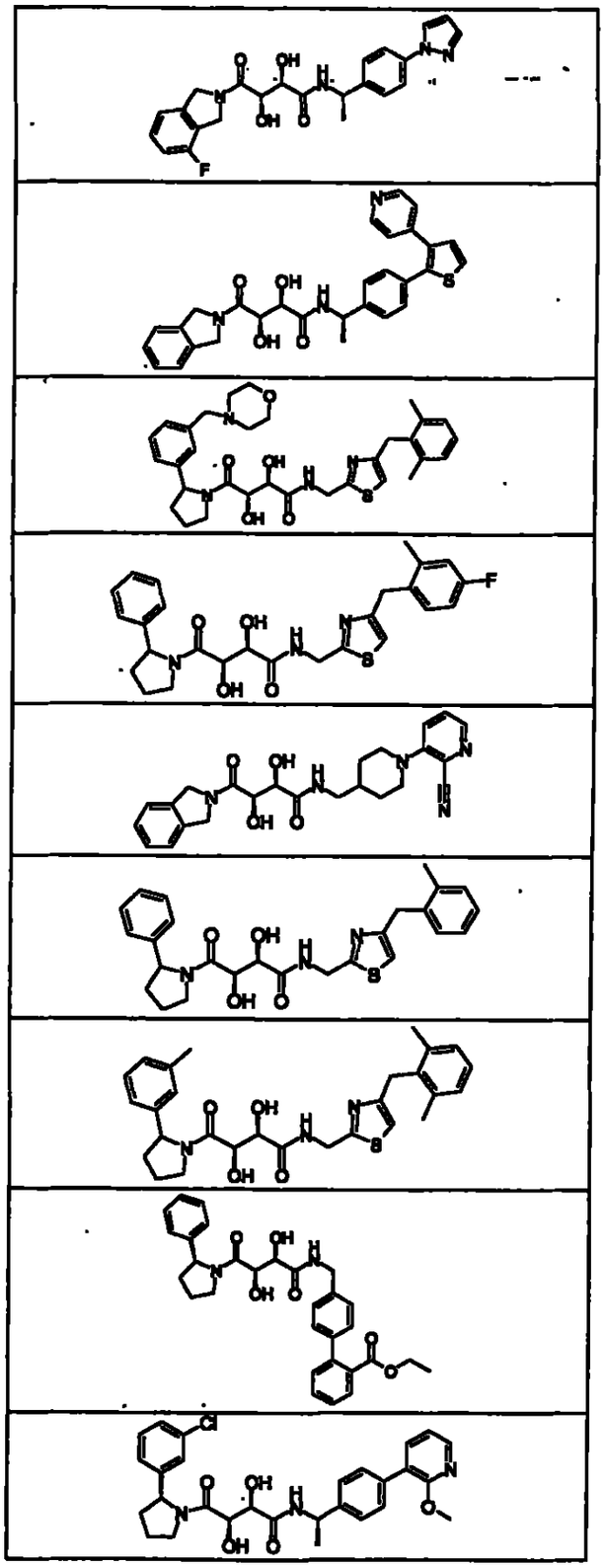


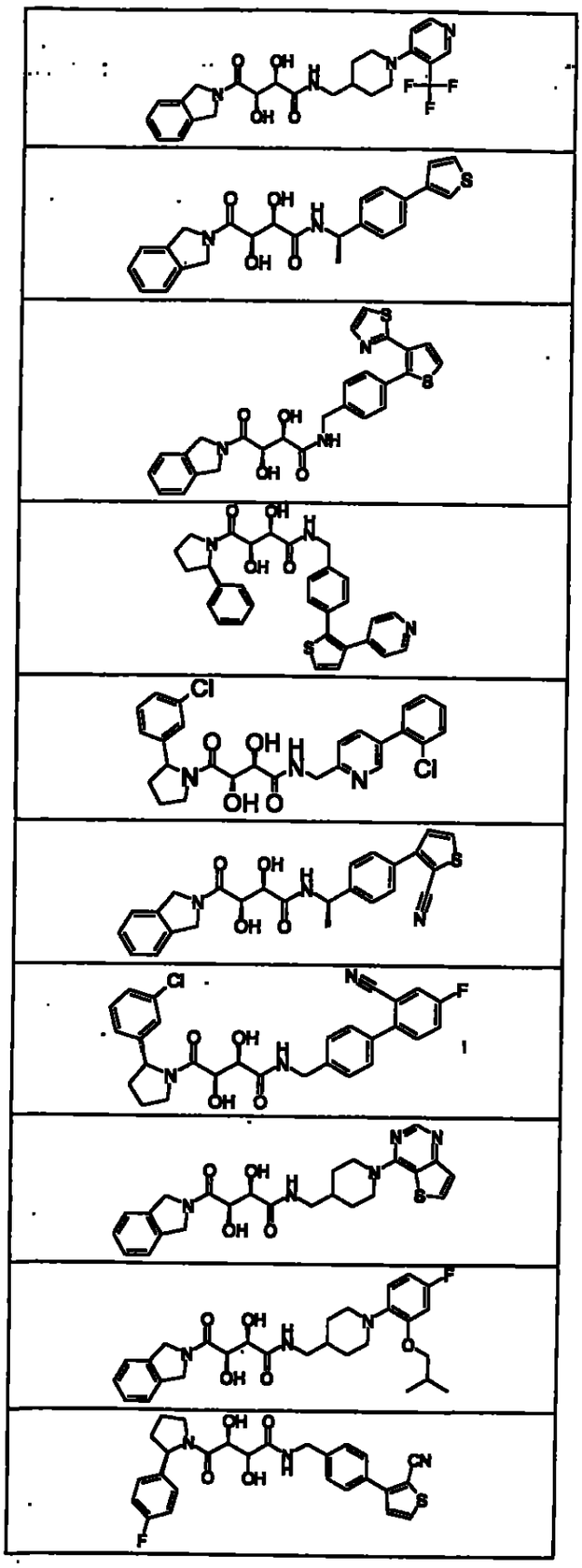


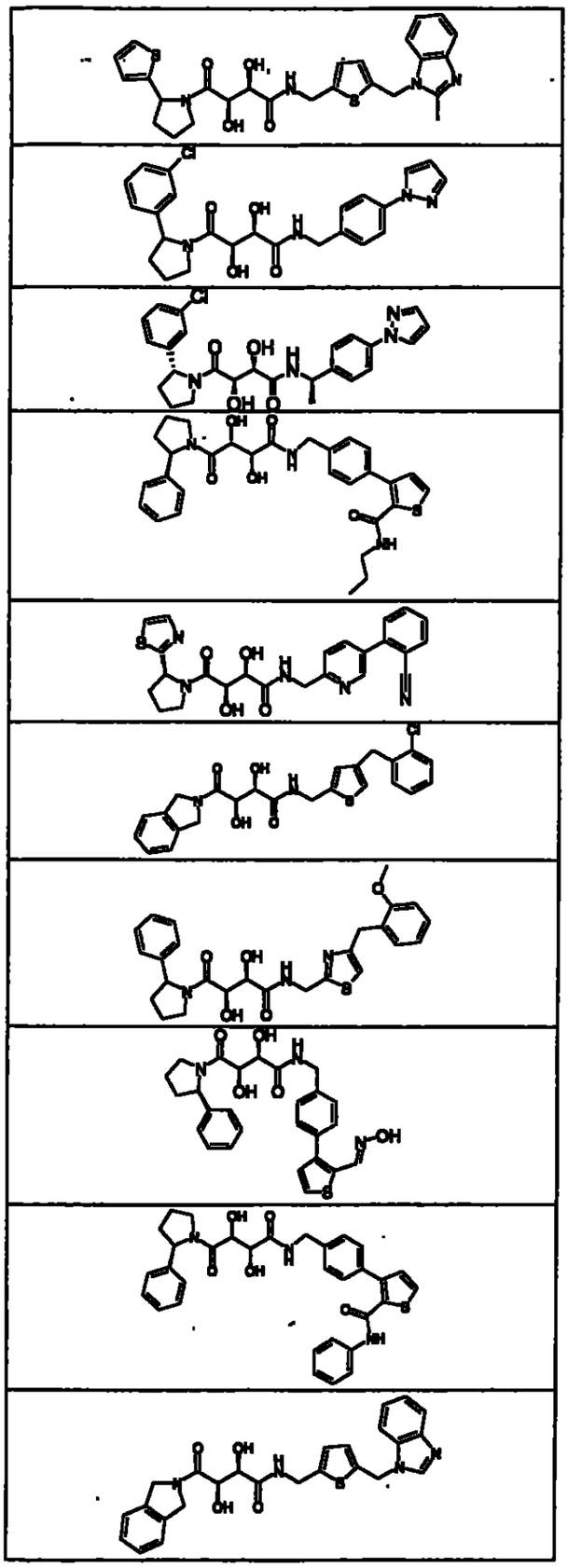


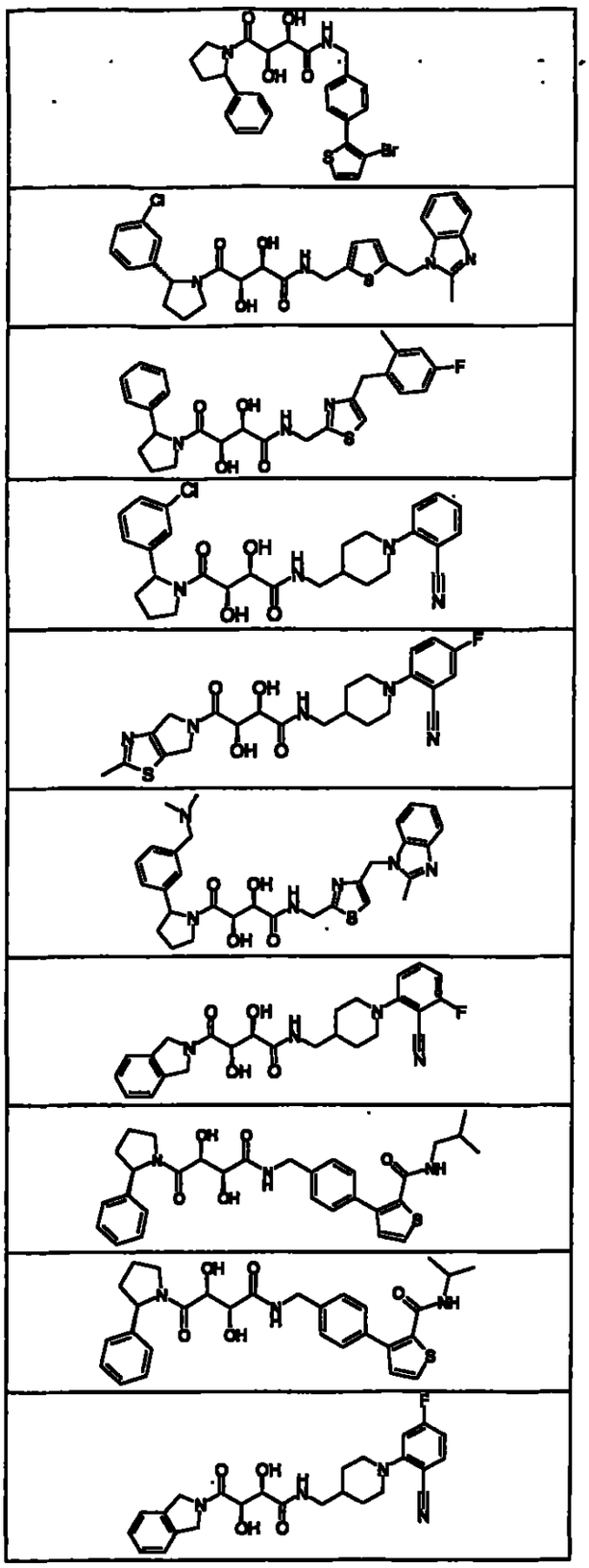


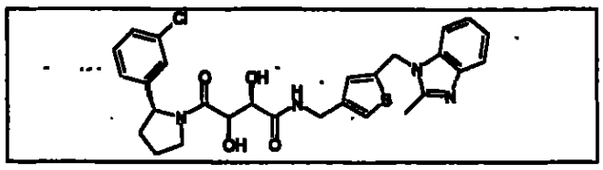


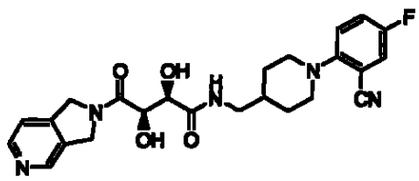


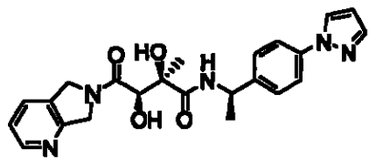


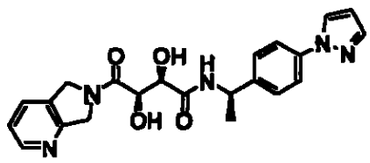


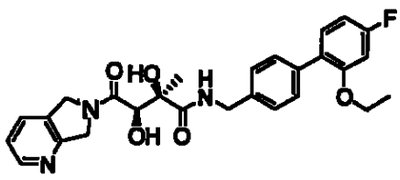


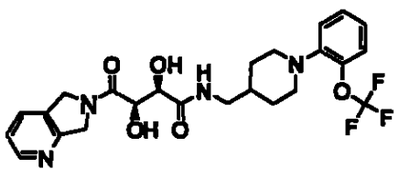


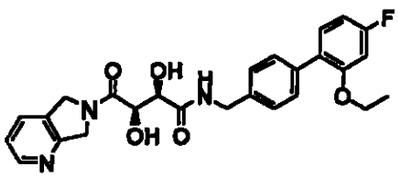


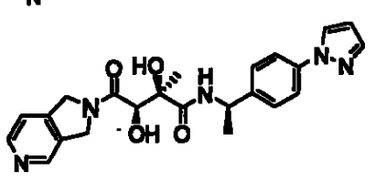


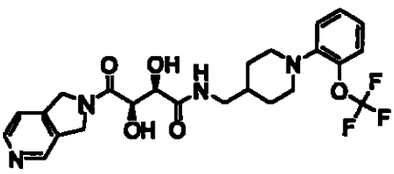


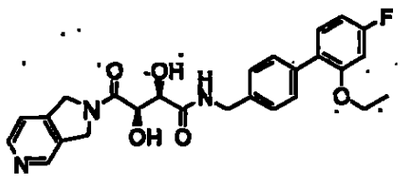


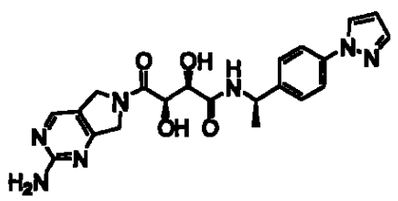


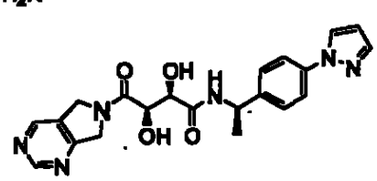


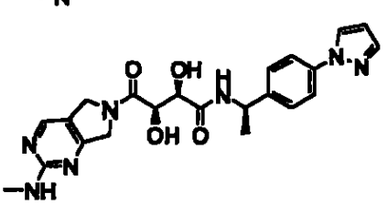


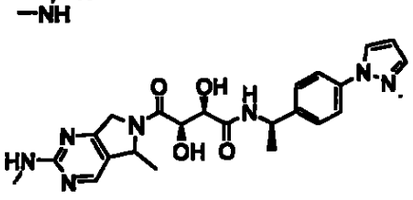


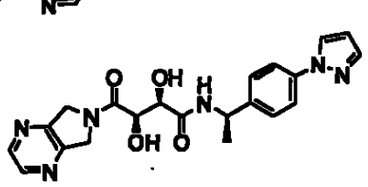


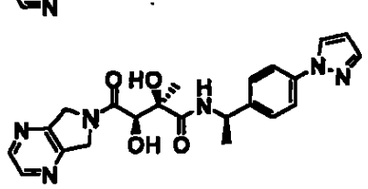


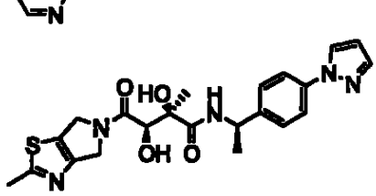


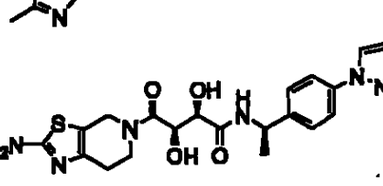




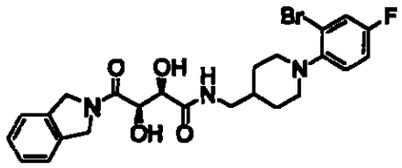


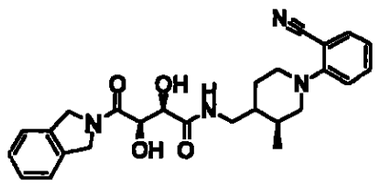


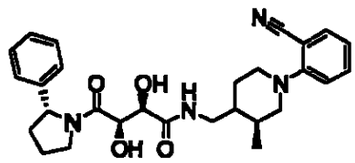


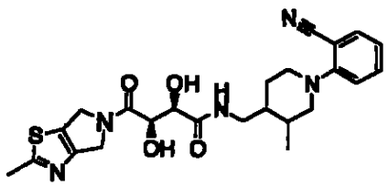


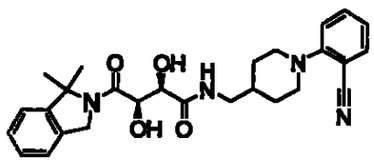


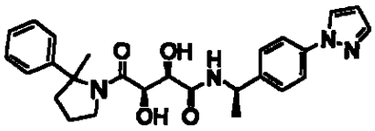


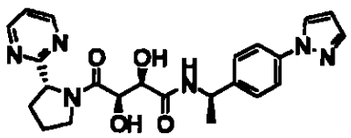


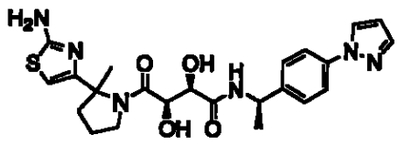


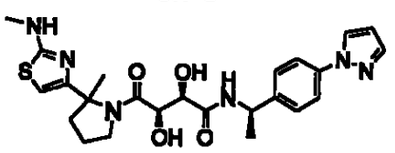


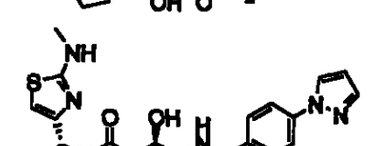


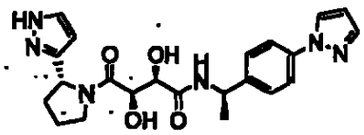


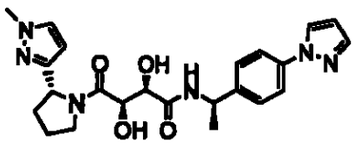


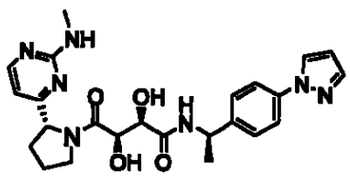


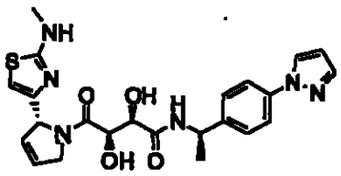


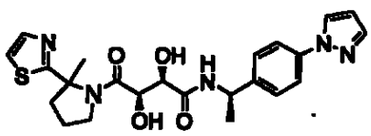


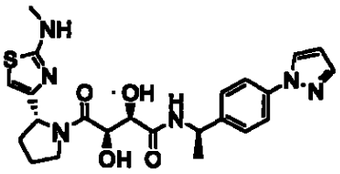


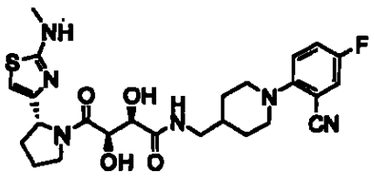


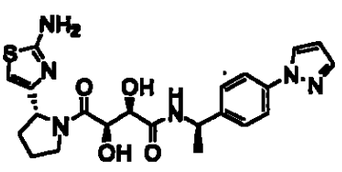


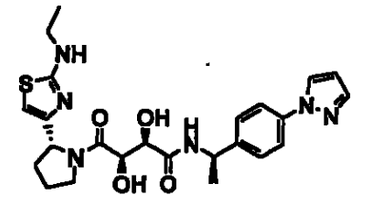


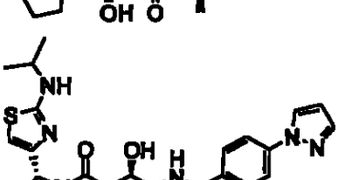


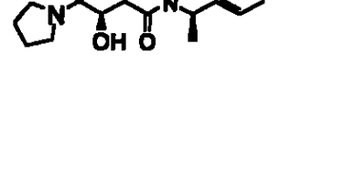


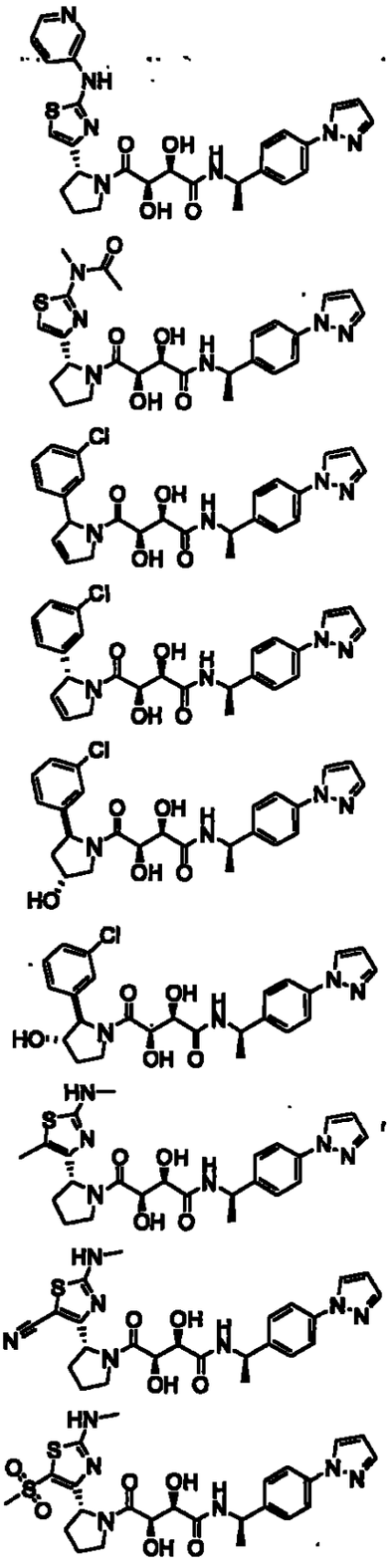


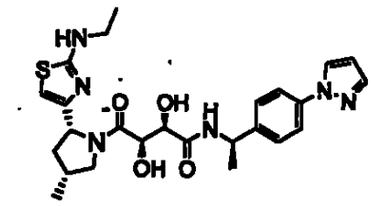


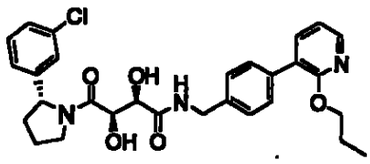


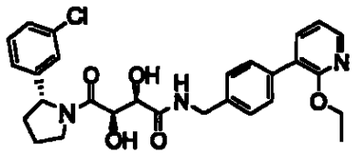


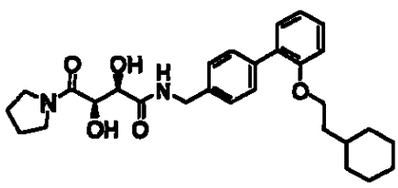


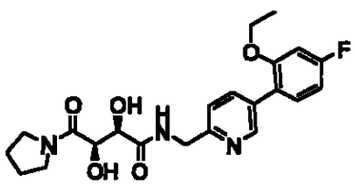


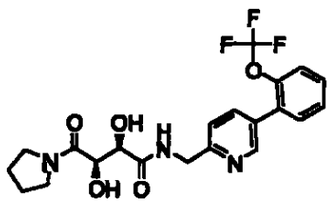


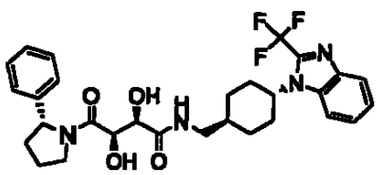


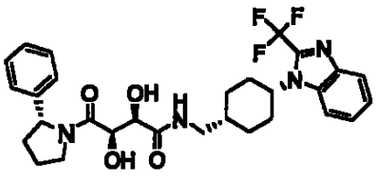


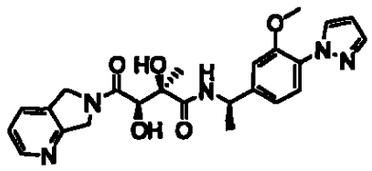


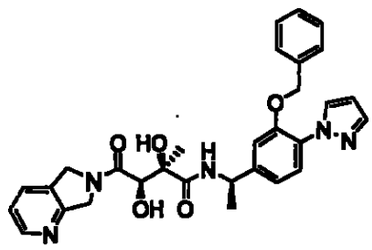


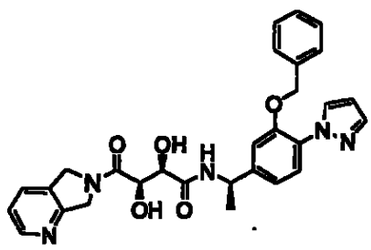


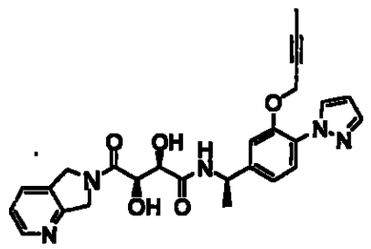


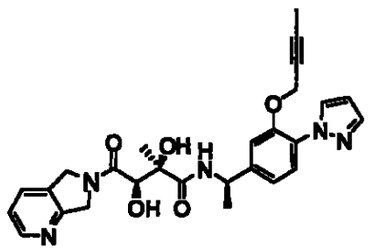


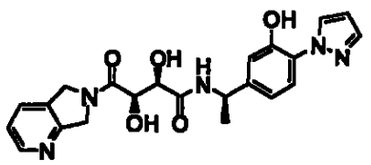


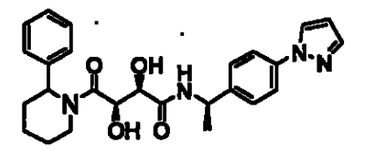


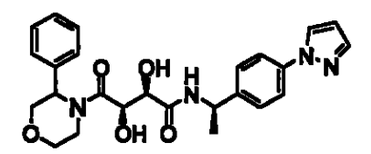


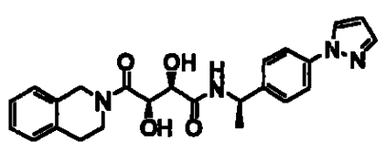


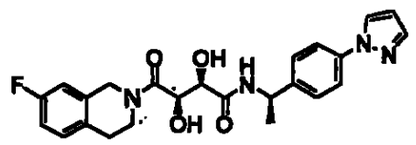


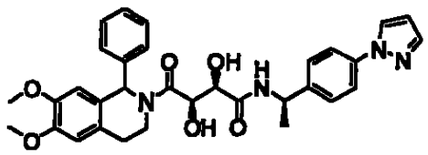


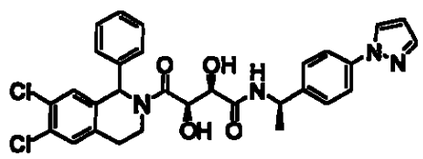


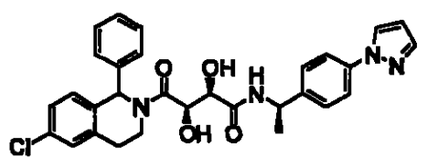


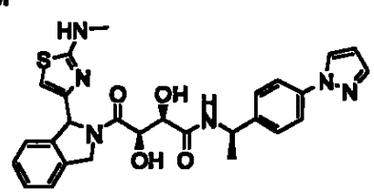


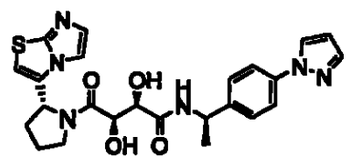


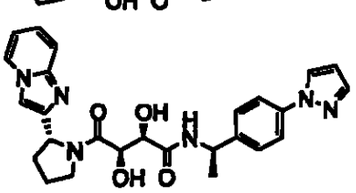


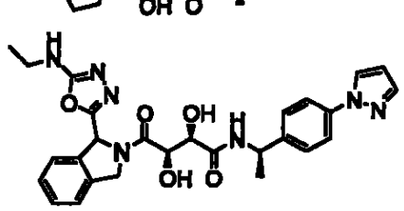


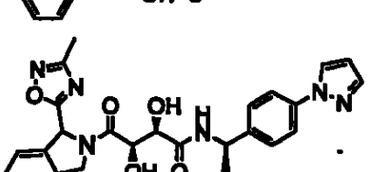


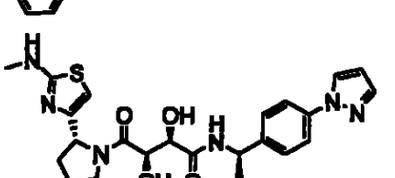


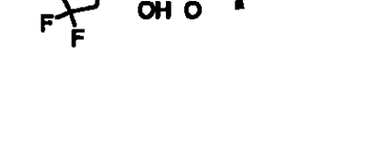


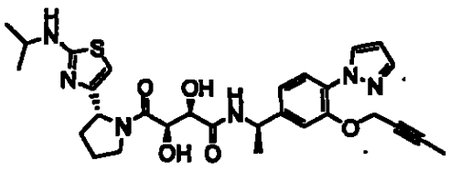


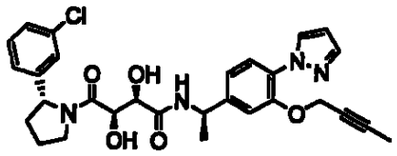


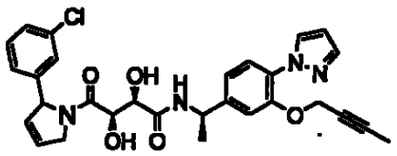


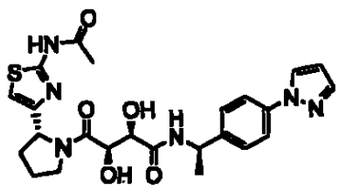


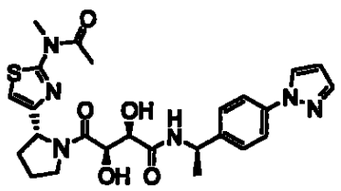


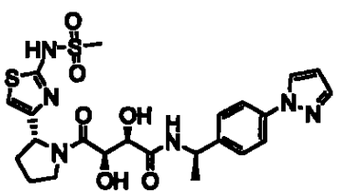


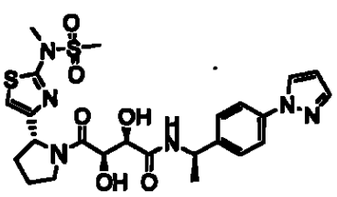


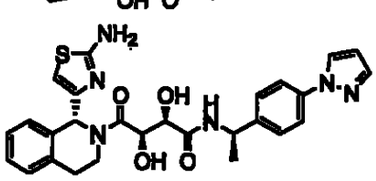


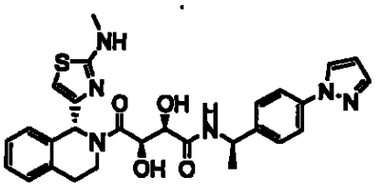


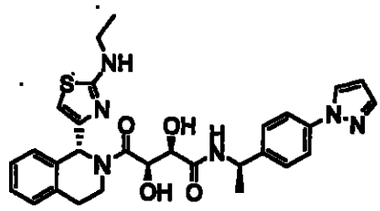


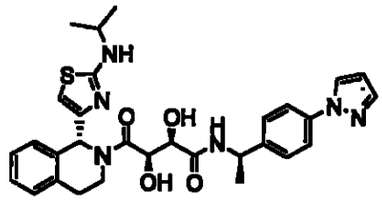


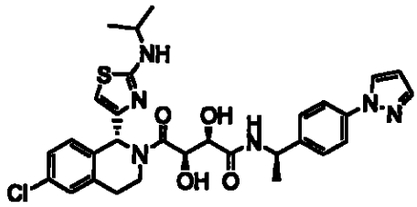


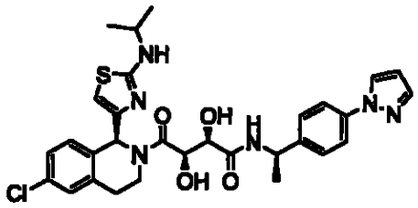


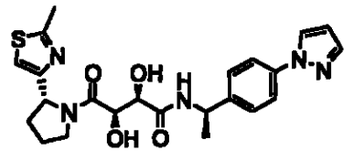


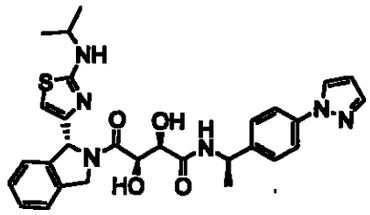


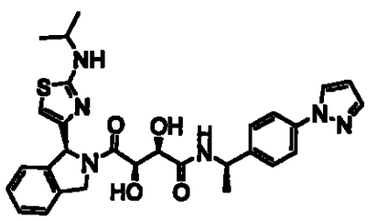


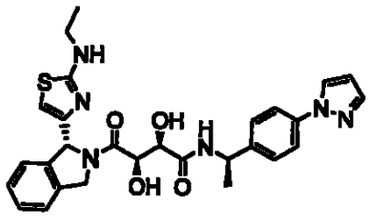


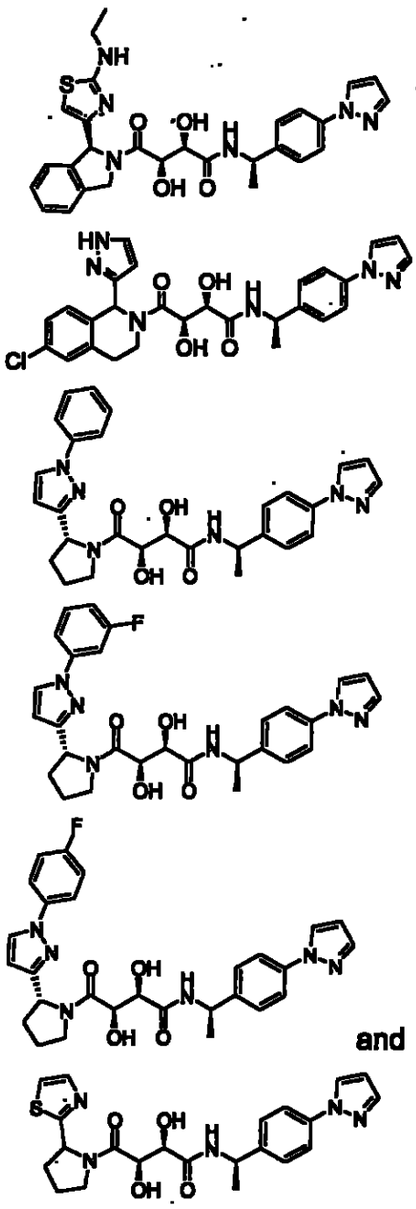






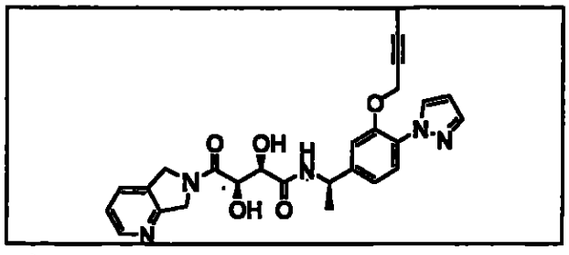


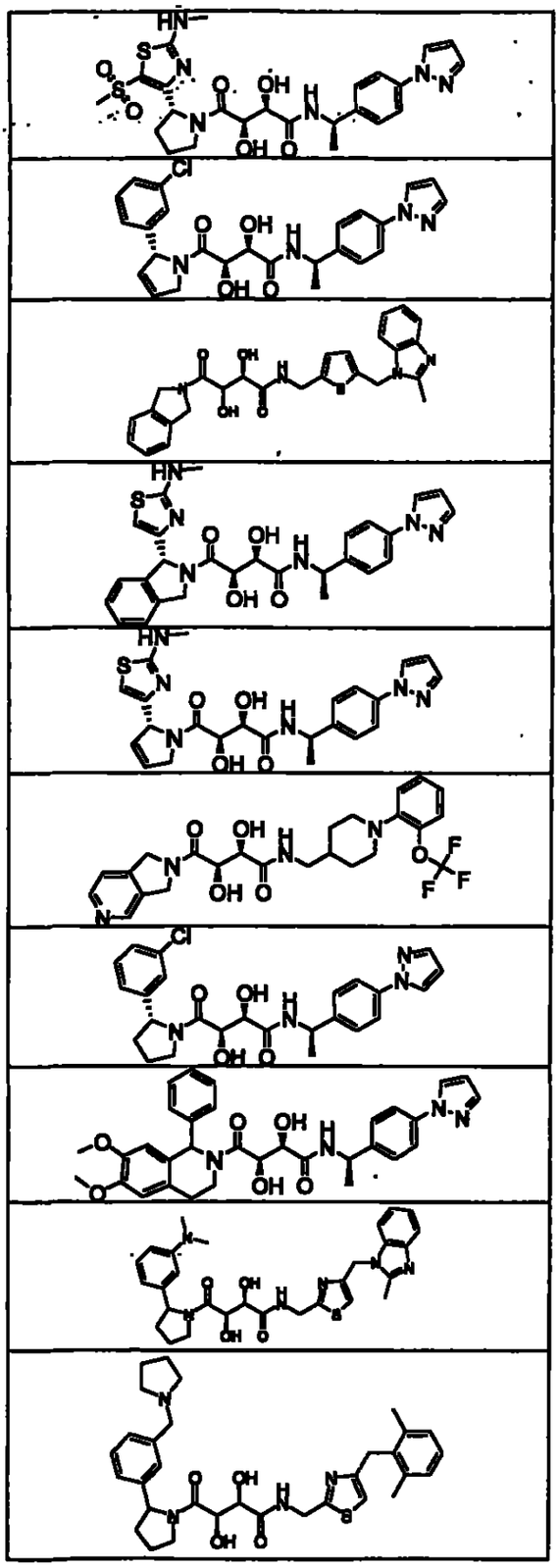


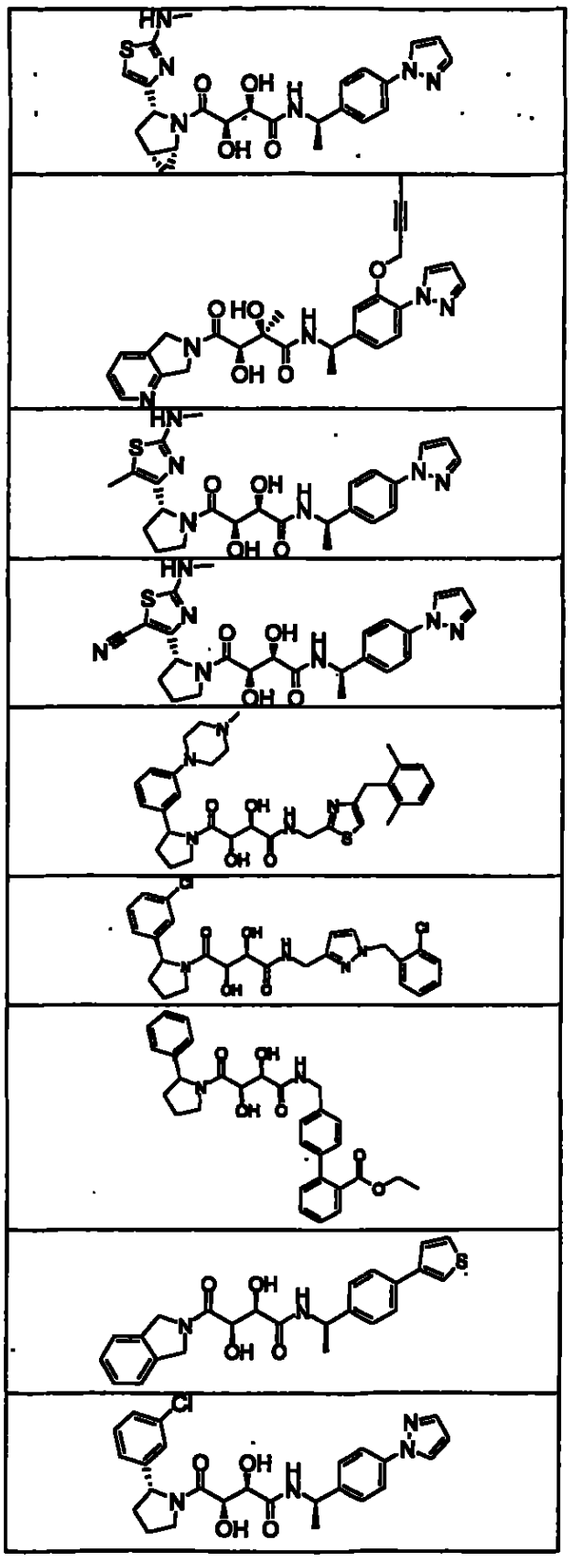


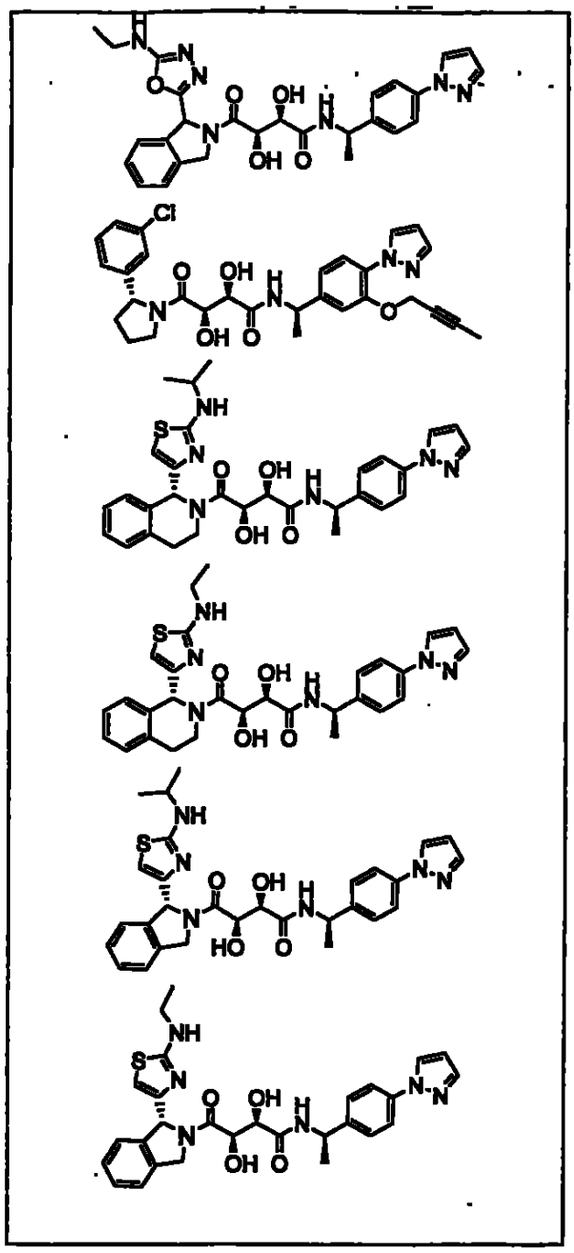
and

62. The compound of claim 61, said compound being selected from the compounds of structures listed below:









63. A pharmaceutical composition comprising as an active ingredient at least one compound of claim 1.

64. The pharmaceutical composition of claim 1 additionally comprising at least one pharmaceutically acceptable carrier.

65. A method of treating disorders associated with tumor necrosis factor-alpha-converting enzyme (TACE), tumor necrosis factor-alpha (TNF-α), matrix metalloproteinases (MMPs), a disintegrin and metalloproteases (ADAMs) or any combination thereof, said method comprising administering

to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound of claim 1.

66. The use of a compound of claim 1 for the manufacture of a medicament to treat disorders associated with TACE, TNF-α, MMPs, ADAMs or any combination thereof.

67. A method of preparing a pharmaceutical composition for treating the disorders associated with TACE, TNF-α, MMPs, ADAMs or any combination thereof, said method comprising bringing into intimate contact at least one compound of claim 1 and at least one pharmaceutically acceptable carrier.

68. A pharmaceutical composition for treating disorders associated with TACE, TNF-α, MMP, ADAM or any combination thereof in a subject comprising, administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

69. A compound of claim 1 in purified form.

70. A method of treating a condition or disease mediated by TACE, MMPs, TNF-α, aggrecanase, or any combination thereof in a subject comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

71. The method of claim 70, wherein said aggrecanase is aggrecanase 1 or aggrecanase 2.

72. A method of treating a condition or disease selected from the group consisting of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, inflammatory bowel disease, multiple sclerosis and psoriasis in a subject, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

73. A method of treating a condition or disease selected from the group consisting of fever, cardiovascular conditions, hemorrhage, coagulation,

cachexia, anorexia, alcoholism, acute phase response, acute infection, shock, graft versus host reaction, autoimmune disease and HIV infection in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

74. A method of treating a condition or disease selected from the group consisting of septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, osteo and rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, uveitis, Wegener's granulomatosis, Behcehe disease, Sjogren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, transplant rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and bronchitis in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

75. A method of treating a condition or disease associated with COPD, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

76. A method of treating a condition or disease associated with rheumatoid arthritis, comprising: administering to the subject in need of such

treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

77. A method of treating a condition or disease associated with Crohn's disease, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

78. A method of treating a condition or disease associated with psoriasis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

79. A method of treating a condition or disease associated with ankylosing spondylitis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

80. A method of treating a condition or disease associated with sciatica, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

81. A method of treating a condition or disease associated with complex regional pain syndrome, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

82. A method of treating a condition or disease associated with psoriatic arthritis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

83. A method of treating a condition or disease associated with multiple sclerosis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof, in combination with a compound selected from the group consisting of Avonex□, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis.

84. The method of claim 71 further comprising administering to said subject a therapeutically effective amount of at least one medicament selected from the group consisting of disease modifying anti-rheumatic drugs (DMARDS), NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, biological response modifiers (BRMs), anti-inflammatory agents and H1 antagonists.

85. A method of claim 73, further comprising administering to said subject a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDS, NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, BRMs, anti-inflammatory agents and H1 antagonists.

86. A method of claim 75, further comprising administering to said subject a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDS, NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, BRMs, anti-inflammatory agents and H1 antagonists.

C MPUESTOS PARA EL TRATAMIENT DE TRAST RN S INFLAMATORIOS

ANTECEDENTES DE LA INVENCÓN

Campo de la Invención

La presente invención se refiere a compuestos funcionales derivados del ácido tartárico que pueden inhibir las maloproteinasas de matriz (MMPS), una desintegrina y metaloproteasas (ADAMs) y/o a la enzima convertidora del factor de necrosis tumoral alfa (TACE), y al hacerlo evitan la liberación del factor de necrosis tumoral alfa (TNF-α), a composiciones farmacéuticas que comprenden dichos compuestos y a métodos de tratamiento que utilizan tales compuestos.

Descripción

La osteoartritis y la artritis reumatoidea (OA y RA, respectivamente) son enfermedades destructivas del cartílago articular caracterizadas por la erosión localizada de la superficie del cartílago. Los descubrimientos han demostrado que el cartílago articular de las cabezas femorales de pacientes con OA, por ejemplo, poseían una incorporación reducida de sulfato radiomarcado respecto de los controles, sugiriendo que debe existir un nivel aumentado de degradación del cartílago en OA (Mankin et al. J. Bone Joint Surg. 52A (1970) 424-434). Existen cuatro clases de enzimas degradantes de proteínas en células de mamíferos: serina-, cisteína-, aspártico- y metaloproteasas. La evidencia disponible sustenta la idea de que son las metaloproteasas las responsables de la degradación de la matriz extracelular del cartílago articular en OA y RA. Se han encontrado actividades aumentadas de colagenasas y estromelisina en el cartílago de OA y la actividad se correlaciona con la gravedad de la lesión (Mankin et al. Arthritis Rheum. 21, 1978, 761-766, Woessner et al. Arthritis Rheum. 26, 1983, 63-68 y Ibid. 27, 1984, 305-312). Además, se identificó la agrecanasa (una metaloproteasa identificada recientemente) que produce el producto de ruptura

específico de los proteoglicanos, que se encuentra en pacientes que padecen RA y OA (Lohmander L. S. et al. Arthritis Rheum. 36, 1993, 1214-22).

Las metaloproteasas (MPs) se han implicado como enzimas clave en la destrucción de cartílagos y huesos de mamíferos. Se puede esperar que la patogénesis de tales enfermedades se pueda modificar de manera beneficiosa mediante la administración de inhibidores de MP (ver Wahl et al. Ann. Rep. Med. Chem. 25, 175-184, AP, San Diego, 1990).

Las MMPs son una familia de más de 20 enzimas diferentes que están involucradas en una variedad de procesos biológicos importantes en la ruptura sin control del tejido conectivo, incluyendo proteoglicanos y colágeno, conduciendo a la resorción de la matriz extracelular. Esta es una característica de muchas condiciones patológicas, tales como AR y AO, úlcera de córnea, epidérmica o gástrica; metástasis o invasión tumoral; enfermedad periodontal y enfermedad ósea. Comúnmente, estas enzimas catabólicas se regulan de manera ajustada a nivel de sus síntesis al igual que a nivel de su actividad extracelular a través de la acción de inhibidores específicos, tales como alfa-2-macroglobulinas y TIMPs (inhibidor tisular de MPs), que forman complejos inactivos con las MMP.

El factor de necrosis tumoral alfa (TNF-α) es una citoquina asociada a la célula que se procesa a partir de una forma precursora de 26 kDa dando una forma activa de 17 kd. *Ver* Black R.A. "Tumor necrosis factor-alpha converting enzyme" Int J Biochem Cell Biol. 2002 Jan;34(1):1-5 y Moss ML, White JM, Lambert MH, Andrews RC. "TACE and other ADAM proteases as targets for drug discovery" Drug Discov Today. 2001 Apr 1;6(8):417-426, cada uno de los cuales se incorpora a la presente a modo de referencia.

Se ha demostrado que el TNF-α desempeña un rol central en respuestas inmunes e inflamatorias. La sobre-expresión o expresión inadecuada de TNF-α es una característica distintiva de una cantidad de enfermedades, incluyendo AR,

enfermedad de Crohn, esclerosis múltiple, psoriasis y sepsis. La inhibición de la producción de TNF-α ha demostrado ser beneficiosa en muchos modelos preclínicos de enfermedad inflamatoria, convirtiendo a la inhibición de la producción o señalización de TNF-α en un blanco atractivo para el desarrollo de fármacos anti-inflamatorios novedosos.

El TNF-α es un mediador primario, en seres humanos y animales, de inflamación, fiebre y respuestas de fase aguda, similares a aquellas observadas durante la infección aguda o shock. Se demostró que el exceso de TNF-α puede ser letal. El bloqueo de los efectos del TNF-α con anticuerpos específicos puede ser beneficioso en una diversidad de afecciones, incluyendo enfermedades autoinmunes tales como AR (Feldman et al, Lancet, (1994) 344, 1105), diabetes mellitus insulino-no dependiente (Lohmander L. S. et al., Arthritis Rheum. 36 (1993) 1214-22) y Enfermedad de Crohn (Macdonald T. et al., Clin. Exp. Immunol. 81 (1990) 301).

Los compuestos que inhiben la producción de TNF-α son, por lo tanto, de importancia terapéutica para el tratamiento de trastornos inflamatorios. Recientemente, se ha demostrado que las metaloproteasas, tales como TACE, son capaces de convertir TNF-α de su forma inactiva a la activa (Gearing et al Nature, 1994, 370, 555). Debido a que se ha observado la producción en exceso de TNF-α en varias enfermedades también caracterizadas por la degradación del tejido mediada por MMP, los compuestos que inhiben la producción de MMPs y TNF-α también pueden tener una ventaja particular en enfermedades en las que están involucrados ambos mecanismos.

Un enfoque para inhibir los efectos perjudiciales del TNF-α es inhibir la enzima TACE antes de que pueda procesar al TNF-α a su forma soluble. TACE es un miembro de la familia ADAM de proteínas de membrana del tipo I y media la difusión de ectodominio de varias proteínas de señalización y adhesión con

anclaje a membrana. TACE se ha tomado cada vez más importante en el estudio de varias enfermedades, incluyendo enfermedades inflamatorias, debido a su papel en la escisión del TNF-α de su secuencia en "tallo" y por lo tanto en la liberación de la forma soluble de la proteína TNF-α (Black R.A. Int J Biochem Cell Biol. 2002 34,1-5).

Existen varias patentes que revelan inhibidores de MMP basados en hidroxamatos, carboxilatos y/o lactamas.

US 6.677.355 y US 6.534.491(B2) describen compuestos que son derivados del ácido hidroxámico e inhibidores de MMP.

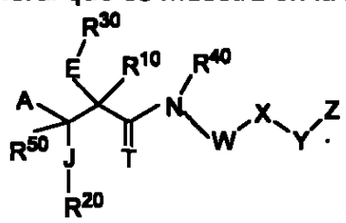
US 6.495.565 revela derivados de lactamas que son potenciales inhibidores de maloproteasas de matriz y/o TNF-α.

Existe la necesidad en la técnica de inhibidores de MMPs, ADAMs, TACE y TNF-α, que pueden ser útiles como compuestos anti-inflamatorios y terapias protectoras del cartílago. La inhibición de TNF-α, TACE y/u otras MMPs puede evitar la degradación del cartílago mediante estas enzimas, aliviando de esa manera los estados patológicos de OA y RA al igual que muchas otras enfermedades autoinmunes.

SÍNTESIS DE LA INVENCIÓN

En sus muchas realizaciones, la presente invención provee una clase novedosa de compuestos inhibidores de TACE, de la producción de TNF-α, MMPs, ADAMs o cualquier combinación de las mismas, métodos para preparar tales compuestos, composiciones farmacéuticas que comprenden uno o más de tales compuestos y métodos de tratamiento, prevención, inhibición o alivio de una o más enfermedades relacionadas con TACE, TNF-α, MMPs, ADAMs o cualquier combinación de las mismas usando tales compuestos o composiciones farmacéuticas.

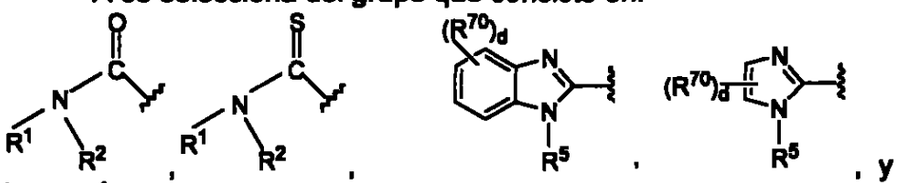
En una realización, la presente solicitud revela un compuesto, o sales aceptables para uso farmacéutico o solvatos de dicho compuesto, teniendo dicho compuesto la estructura general que se muestra en la fórmula (I):



fórmula (I)

o una sal aceptable para uso farmacéutico o solvato de la misma, donde:

A se selecciona del grupo que consiste en:



$-CO_2R^1$;

d es 0 a 4;

J se selecciona del grupo que consiste en: O, S, y NR^5;

E se selecciona del grupo que consiste en: O, S y NR^5;

T es O o S;

R^1 y R^2 son iguales o diferentes, seleccionándose cada uno independientemente del grupo que consiste en H, alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroaralquilo y heteroarilo; o de manera alternativa R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 4-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde cada uno de dichos alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroaralquilo, heteroarilo y anillo heterocíclico de 4-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o

diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70} que se indican más adelante;

R^{10} se selecciona del grupo que consiste en H, alquilo, y fluoroalquilo;

R^{20} se selecciona del grupo que consiste en H, alquilo, y fluoroalquilo;

R^{30} es H o alquilo, o de manera alternativa R^{30} y R^{40} tomados junto con el N al cual R^{40} se muestra unido en la Fórmula I, se unen para formar un anillo heterocíclico de 4-7 miembros, donde dicho anillo heterocíclico es no sustituido o sustituido de manera independiente opcionalmente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70} que se indican más adelante;

R^{40} es H o alquilo;

R^{50} es H o alquilo;

W es $-(CR^{13}{}_2)_n-$, donde n es 0 a 5 o un enlace covalente, o de manera alternativa dos grupos R^{13} se pueden fusionar para formar un cicloalquilo de 3-8 miembros, donde dicho cicloalquilo de 3-8 miembros puede ser no sustituido u sustituido opcionalmente de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^6 siguiente;

X está ausente o presente, y si se encuentra presente X se selecciona del grupo que consiste en un enlace covalente, alquilo, alquenilo, alquinilo, cicloalquilo, heterociclilo, arilo, y heteroarilo, donde dicho alquilo, alquenilo, alquinilo, cicloalquilo, heterociclilo, arilo, y heteroarilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70} que se indican más adelante;

Y está ausente o presente, y si se encuentra presente Y se selecciona del grupo que consiste en un enlace covalente, $-[C(R^6)_2]_n-$ donde n es 1 a 2, -O-, -S-,

$-NR^1-$, $-SO_v-$ donde v es 1 a 2, $-SO_n(CR^6_2)_p-$ donde n es 1 o 2 y p es 1 a 4, $-O(CR^6_2)_q-$ o $-(CR^6_2)_qO-$ donde q es 1 a 4, $-N(R^7)S(O)_n-$ o $-S(O)_nN(R^7)-$ donde n es 1 o 2, y $-N(R^7)C(O)-$ o $-C(O)N(R^7)-$;

Z se selecciona del grupo que consiste en H, alquilo, alquenilo, alquinilo, cicloalquilo, heterociclilo, arilo, y heteroarilo, dicho cicloalquilo, heterociclilo, arilo, y heteroarilo duendo fusionados opcionalmente con arilo, heterociclilo, heteroarilo o cicloalquilo; donde cada uno de dicho alquilo, alquenilo, alquinilo, cicloalquilo, heterociclilo, arilo, y heteroarilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70} que se indican más adelante;

R^5 se selecciona del grupo que consiste en hidrógeno, alquilo, y alquilarilo;

cada R^6 es igual o diferente y se selecciona independientemente del grupo que consiste en hidrógeno, halógeno, $-SR^{15}$, $-S(O)_qR^{15}$ donde q es 1 a 2, alquilo, cicloalquilo, heterociclilo, alcoxilo, hidroxi, nitro, ciano, amino, alquenilo, alquinilo, arilalquilo, aminocarbonilo, alquilcarbonilo, y alcoxicarbonilo;

cada R^7 es igual o diferente y se selecciona independientemente del grupo que consiste en hidrógeno, alquilo, arilo, cicloalquilo, heteroarilo, heterociclilo, alquenilo, alquinilo, arilalquilo, alquilcarbonilo, y alcoxicarbonilo, donde cada uno de arilo, heteroarilo y heterociclilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70} abajo;

R^{13} es igual o diferente y se selecciona independientemente del grupo que consiste en hidrógeno, halógeno, -OH, $-OR^{14}$, alquilo, cicloalquilo, heterociclilo, alquenilo, alquinilo, alquilarilo, alquilamino, y alquilcarbonilo;

R^{14} es alquilo;

cada R^{70} es un sustituyente para H donde se indicó y es igual o diferente y se selecciona independientemente del grupo que consiste en alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, halo, -CN, $-CF_3$, $-OCF_3$, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)_qN(R^{15})(R^{16})$ donde q es 1 a 2, $-C(=NOR^{15})R^{16}$, $-N(R^{15})(R^{16})$, -alquil-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{17})S(O)_2N(R^{16})(R^{15})$, $-N(R^{17})S(O)N(R^{16})(R^{15})$, $-N(R^{17})C(O)N(R^{16})(R^{15})$, $-CH_2-N(R^{17})C(O)N(R^{16})(R^{15})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, y $-S(O)_qR^{15}$ donde q es 1 a 2; y donde cada uno de alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, alquenilo y alquinilo son no sustituidos o sustituidos de manera independiente por 1 a 5 grupos seleccionados de manera independiente del grupo que consiste en alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, halo, $-CF_3$, -CN, $-OR^{15}$, $-N(R^{15})(R^{16})$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$ y $-N(R^{15})S(O)R^{16}$;

cada R^{15}, R^{16} y R^{17} se seleccionan de manera independiente del grupo que consiste en H, alquilo, cicloalquilo, heterociclilo, arilo, y heteroarilo, o de manera alternativa R^{15} y R^{16} tomados juntos con el N al cual estos se muestran unidos, se unen para formar un anillo heterocíclico de 4-8 miembros, donde dicho cicloalquilo de 4-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de abajo restos R^{75};

cada R^{75} se selecciona independientemente del grupo que consiste en alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, alquenilo y alquinilo, y donde cada uno del alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, alquenilo y alquinilo son no sustituidos o sustituidos de manera independiente por 1 a 5 grupos seleccionados de manera

independiente del grupo que consiste en alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, halo, $-CF_3$, $-CN$, $-OR^{19}$, $-N(R^{19})_2$, $-C(O)OR^{19}$, $-C(O)N(R^{19})_2$, y $-N(R^{19})S(O)R^{19}$; y

cada R^{19} se selecciona independientemente del grupo que consiste en H, alquilo, cicloalquilo, heterociclilo, arilo y heteroarilo.

Los compuestos de Fórmula I pueden ser útiles como inhibidores y pueden ser útiles para el tratamiento y prevención de enfermedades relacionadas con TACE, TNF-α, MMPs, ADAMs o cualquier combinación de las mismas.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

En sus varias realizaciones, la presente invención provee una clase novedosa de inhibidores de TACE, de la producción de TNF-α, MMPs, ADAMs o cualquier combinación de las mismos, composiciones farmacéuticas que contienen uno o más de los compuestos, métodos para preparar formulaciones farmacéuticas que comprenden uno o más de tales compuestos y métodos para el tratamiento, prevención o alivio de uno o más de los síntomas de la inflamación.

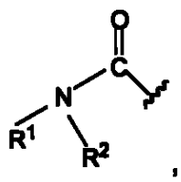
En una realización, la presente invención proporciona compuestos que se representan mediante la Fórmula estructural (I) anterior o una sal aceptable para uso farmacéutico, solvato o isómero de los mismos, donde los diversos restos son según se describió anteriormente.

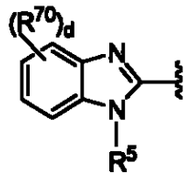
En una realización, R^1 y R^2 son iguales o diferentes, seleccionándose cada uno independientemente del grupo que consiste en alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroaralquilo, y heteroarilo; o de manera alternativa R^1 y R^2, tomados juntos con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 4-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde cada uno de dicho alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroaralquilo, heteroarilo y anillo

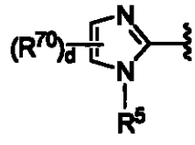
heterocíclico de 4-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de R^{70}.

En una realización, R^1 y R^2 son iguales o diferentes, seleccionándose cada uno independientemente del grupo que consiste en H, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroaralquilo, y heteroarilo; o de manera alternativa R^1 y R^2, tomados juntos con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 4-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, tal anillo heterocíclico siento fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde cada uno de dicho alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroaralquilo, heteroarilo y anillo heterocíclico de 4-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de R^{70}.

En una realización, A se selecciona del grupo que consiste en:

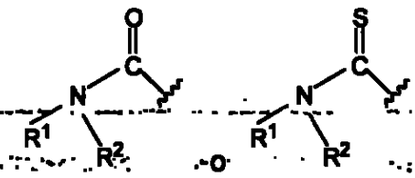


,


y


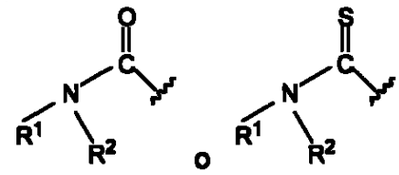
donde R^1 y R^2, tomados juntos con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 4-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente por R^{70}, o fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 4-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70}.

En otra realización, A es



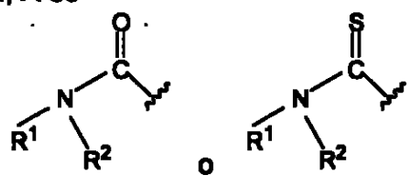
donde R^1 y R^2 son iguales o diferentes, seleccionándose cada uno independientemente del grupo que consiste en H, alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroaralquilo, y heteroarilo; donde dicho alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroaralalquilo y heteroarilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70}.

En otra realización, A es



donde R^1 y R^2 son iguales o diferentes, seleccionándose cada uno independientemente del grupo que consiste en alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroaralquilo, y heteroarilo; donde dicho alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroaralalquilo y heteroarilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70}.

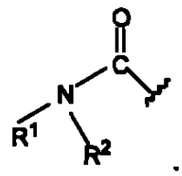
En otra realización, A es



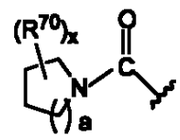
donde R^1 y R^2 son iguales o diferentes, seleccionándose cada uno independientemente del grupo que consiste en H, cicloalquilo, heterociclilo, arilo,

arilalquilo, heteroaralquilo y heteroarilo; donde dicho alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroaralalquilo y heteroarilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70}.

En otra realización, A es

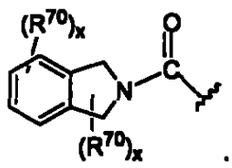


En otra realización, A es



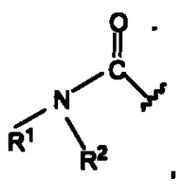
donde a es de 0 a 4 y x es de 0 a 4,

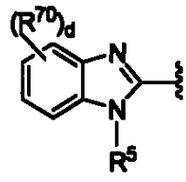
En otra realización, A es



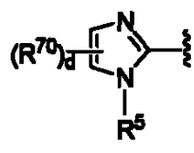
donde cada x es de manera independiente 0 a 4,

En otra realización, A se selecciona del grupo que consiste en:





y

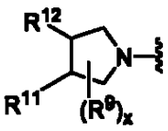


donde R^1 y R^2,

tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 3-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente con R^{70}, o fusionado

opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 3-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70};

donde se forma un anillo a partir de $-NR^1R^2$ y dicho anillo es



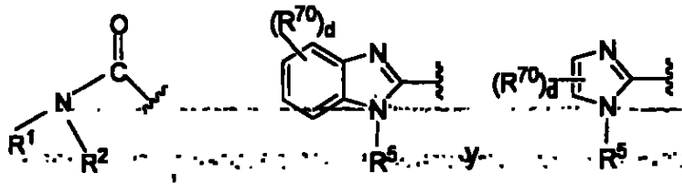
donde

cada R^9 es un sustituyente para H donde se indicó y puede ser igual o diferente, seleccionándose cada uno independientemente del grupo que consiste en -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alquilo, arilo, heteroarilo, alquenilo, alquinilo, cicloalquilo y heterociclilo, donde dicho alquilo, arilo, heteroarilo, alquenilo, alquinilo, cicloalquilo y heterociclilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70};

R^{11} y R^{12} tomados junto con el carbono al cual cada R^{11} y R^{12} se muestran unidos son heteroarilo fusionado o cicloalquilo fusionado, donde cada heteroarilo fusionado y cicloalquilo fusionado puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70}; y

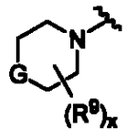
x es de 0 a 4, y cuando x es mayor que 1, cada resto R^9 puede ser igual o diferente, seleccionándose cada resto independientemente del grupo de restos R^9.

En otra realización, A se selecciona del grupo que consiste en:



donde R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 3-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente por R^{70}, o fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 3-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto *independientemente del grupo* de restos R^{70};

donde se forma un anillo a partir de $-NR^1R^2$ y dicho anillo es

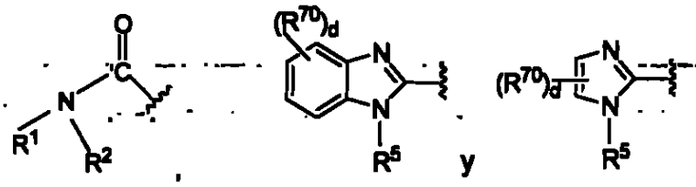


donde cada R^9 es un sustituyente para H donde se indicó y puede ser igual o diferente, seleccionándose cada uno independientemente del grupo que consiste en -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alquilo, arilo, heteroarilo, alquenilo, alquinilo, cicloalquilo y heterociclilo, donde dicho alquilo, arilo, heteroarilo, alquenilo, alquinilo, cicloalquilo y heterociclilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70};

x es de 0 a 4, y cuando x es mayor que 1, cada resto R^9 puede ser igual o diferente, seleccionándose cada resto independientemente del grupo de restos R^9; y

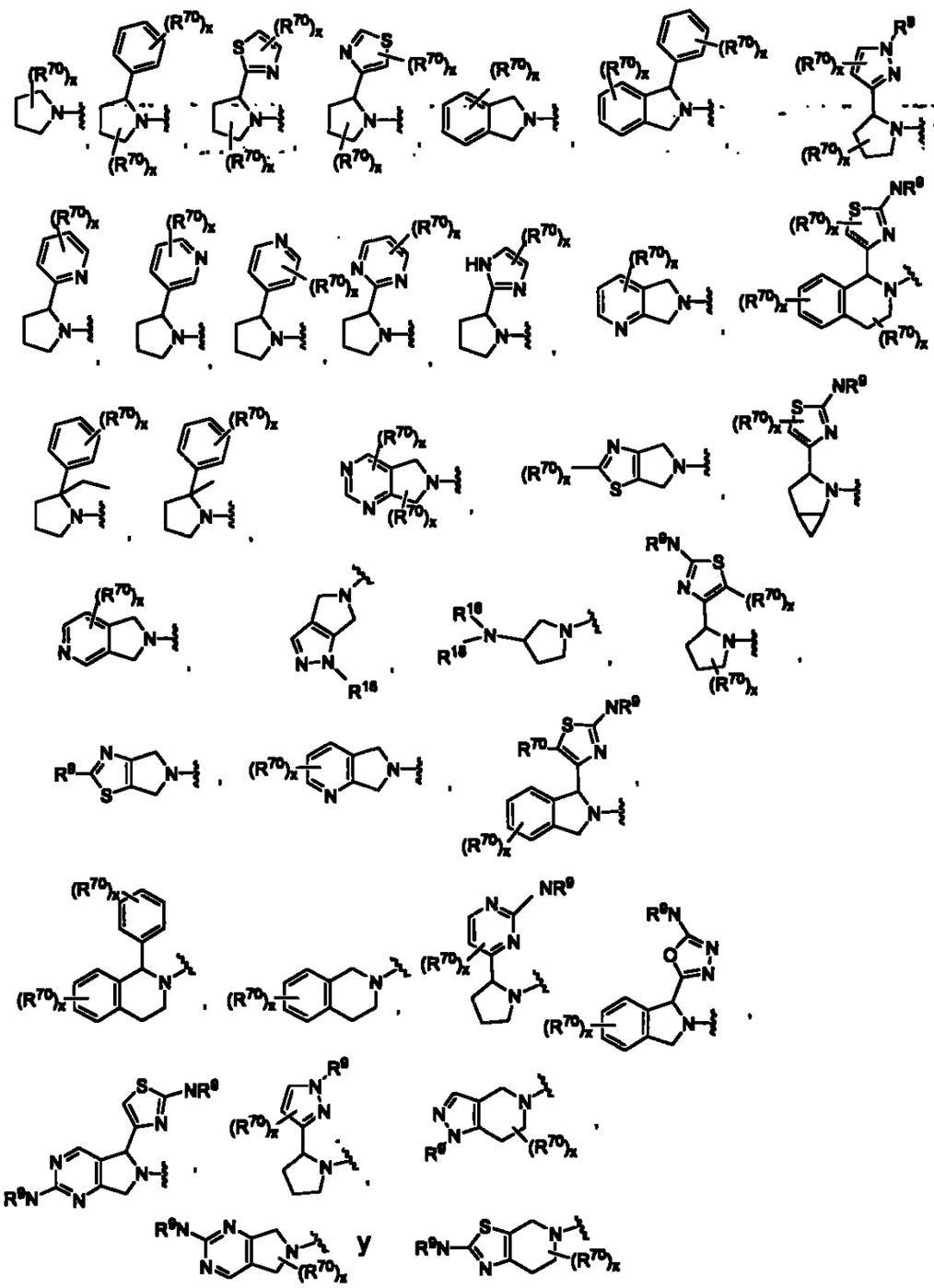
G se selecciona del grupo que consiste en CH_2, NR^7, O, S, o SO_2.

En otra realización, A se selecciona del grupo que consiste en:



donde R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 3-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente con R^{70}, o fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 3-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70};

un anillo se forma de $-NR^1R^2$ y dicho anillo se selecciona del grupo que consiste en



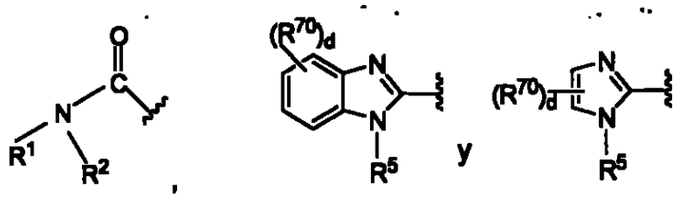
y

donde

x es de 0 a 4, y cuando x es mayor que 1, cada resto R^{70} puede ser igual o diferente, seleccionándose cada resto independientemente del grupo de restos R^{70}; y

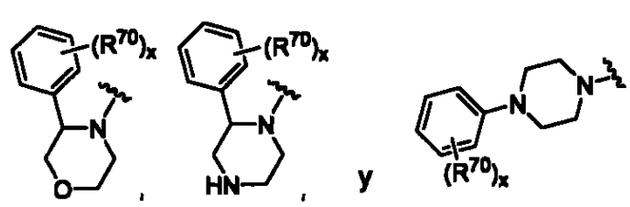
cada R^{18} es igual o diferente y es independientemente H o alquilo.

En otra realización, A se selecciona del grupo que consiste en:



donde R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 3-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente por R^{70}, o fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 3-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70};

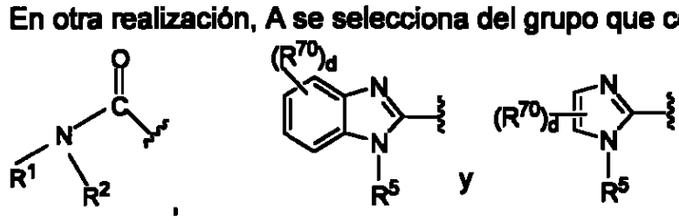
un anillo se forma a partir de $-NR^1R^2$ y dicho anillo se selecciona del grupo que consiste en



donde

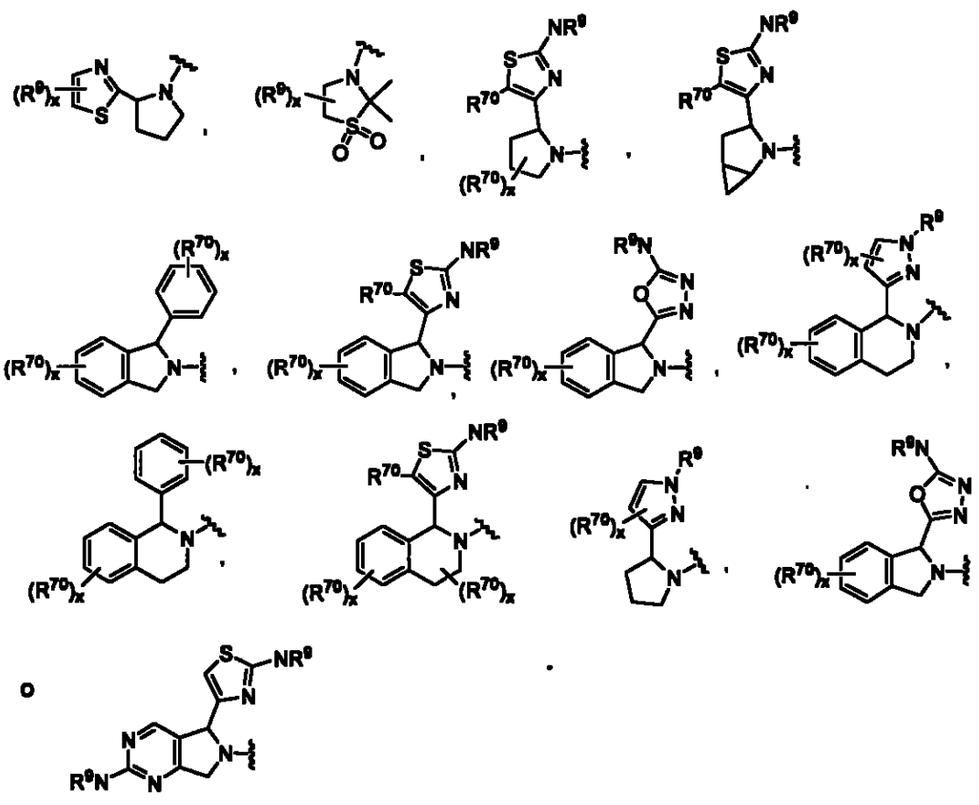
x es de 0 a 4, y cuando x es mayor que 1, cada resto R^{70} puede ser igual o diferente, seleccionándose cada resto independientemente del grupo de restos R^{70}.

En otra realización, A se selecciona del grupo que consiste en:



donde R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 3-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente por R^{70}, o fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 3-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70};

un anillo se forma a partir de $-NR^1R^2$ y dicho anillo es



donde

cada R^9 es un sustituyente para H donde se indicó y puede ser igual o diferente, seleccionándose cada uno independientemente del grupo que consiste en -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alquilo, arilo, heteroarilo,

alquenilo, alquinilo, cicloalquilo y heterociclilo, donde dicho alquilo, arilo, heteroarilo, alquenilo, alquinilo, cicloalquilo y heterociclilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70}; y

x es de 0 a 4, y cuando x es mayor que 1, cada resto R^9 puede ser igual o diferente, seleccionándose cada resto independientemente del grupo de restos R^9.

En otra realización, J es O.

En otra realización, E es O.

En otra realización, R^{10} es H o alquilo.

En otra realización, R^{20}, R^{30}, R^{40}, y R^{50} son todos iguales y son H.

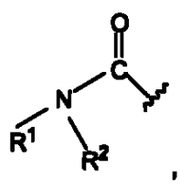
En otra realización, R^6 es H o alquilo.

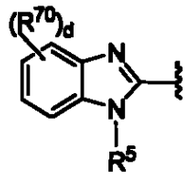
En otra realización, R^6 es H.

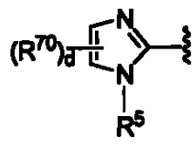
En otra realización, R^{13} es H o alquilo.

En otra realización, R^{13} es H o $-CH_3$.

En otra realización, A se selecciona del grupo que consiste en



,


y


donde R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 4-6 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente por R^{70}, donde R^{70} es arilo.

En otra realización, Y es un enlace covalente o $-[C(R^6)_2]_n-$ donde n es de 1 a 2, $-CH_2-$.

En otra realización, Y se selecciona del grupo que consiste en un enlace covalente, $-CH_2-$, $-C(H)(OH)-$, $-C(O)-$ y $-O-$.

En otra realización, Y es un enlace covalente o $-CH_2-$.

En otra realización, Y es un enlace covalente.

En otra realización, W es $-(CR^{13}{}_2)_n-$, donde n es 0-5,

En otra realización, W es $-(CR^{13}{}_2)_n-$, donde n es 1-5 y cada R^{13} es H o alquilo.

En otra realización, W se selecciona del grupo que consiste en $-CH_2-$, $-C(H)(CH_3)-$, $-C(CH_3)_2-$ y $-CH_2CH_2-$.

En otra realización, W es $-CH_2-$.

En otra realización, W es $-C(H)(CH_3)-$.

En otra realización, X se selecciona del grupo que consiste en alquilo, arilo, heterociclilo y heteroarilo.

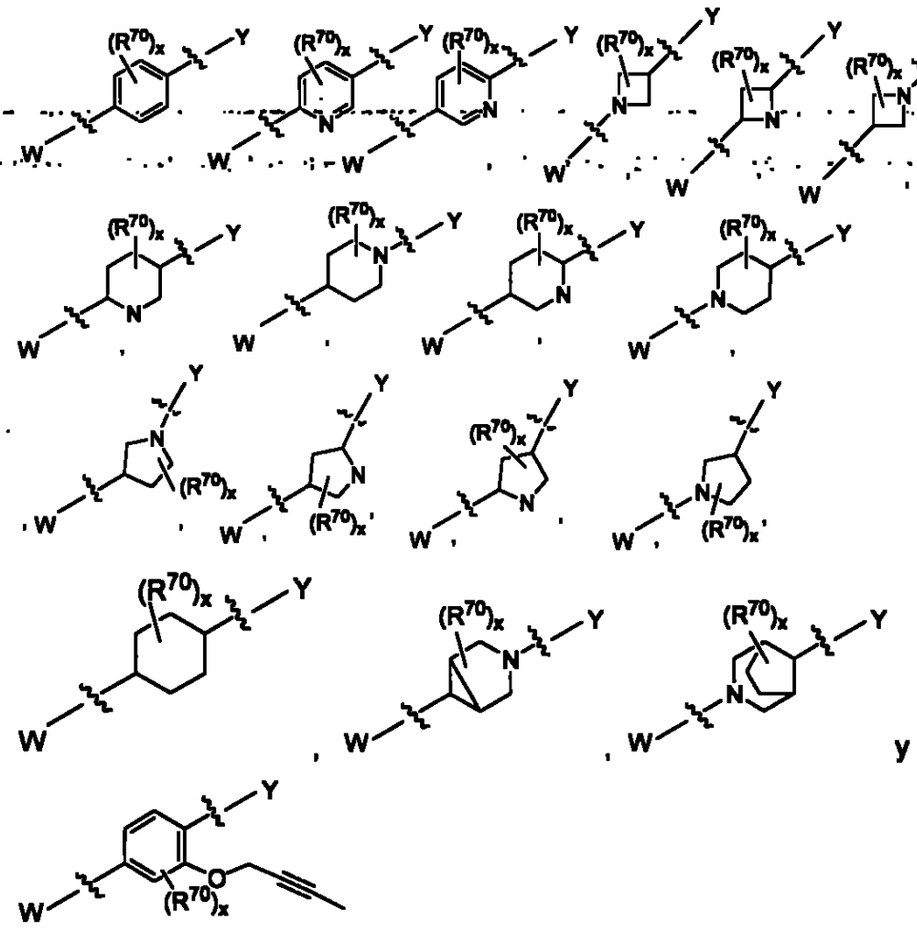
En otra realización, X es arilo.

En otra realización, X es heteroarilo.

En otra realización, X se selecciona del grupo que consiste en fenilo, azetidinilo, pirrolidinilo, piperidinilo, piridinilo, tienilo, tiazolilo, oxazolilo, imidazolilo y pirazolilo.

En otra realización, X se selecciona del grupo que consiste en fenilo, piridinilo y piperidinilo.

En otra realización, X se selecciona del grupo que consiste en

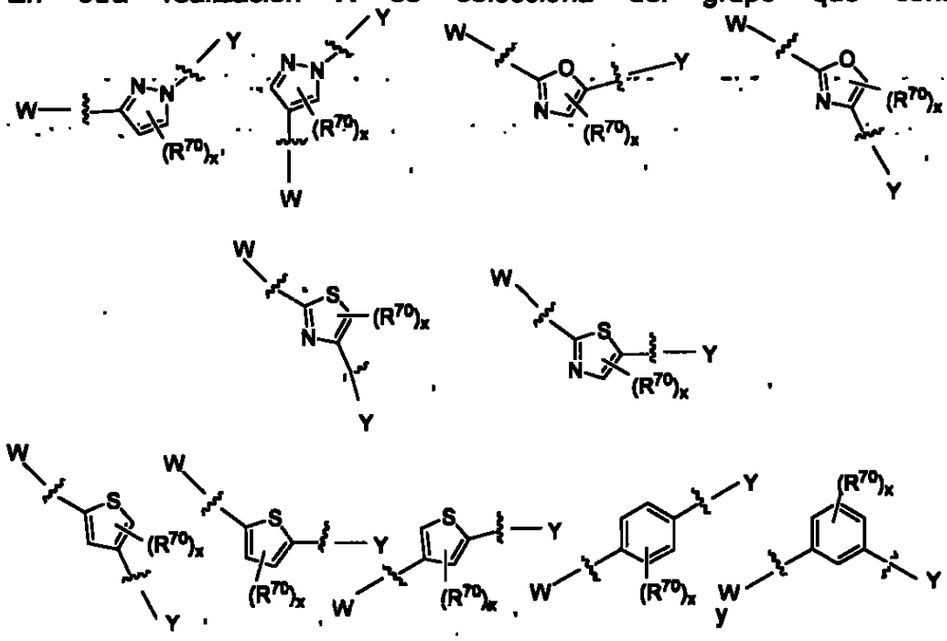


donde

x es de 0 a 4, y donde x es mayor que 1, cada resto R^{70} puede ser igual o diferente, seleccionándose cada resto independientemente del grupo de restos R^{70}.

En los restos que se muestran arriba para X, X es el resto comprendido por ~~—~~ y W e Y se muestran solamente para indicar cuál es el extremo de X que está unido a W y cuál a Y. Se producen descripciones similares a lo largo de esta solicitud con connotaciones similares.

En otra realización X se selecciona del grupo que consiste en

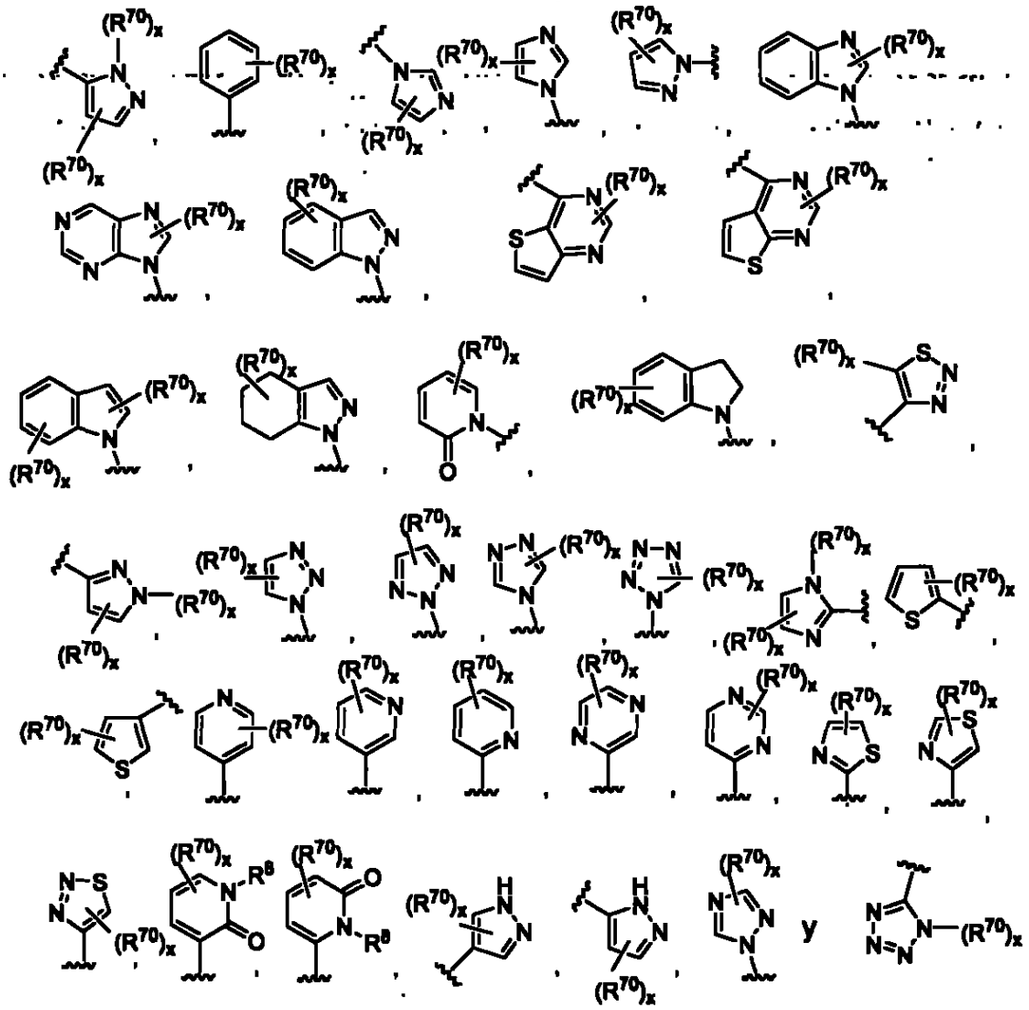


donde x es de 0 a 4, y cuando x es mayor que 1, cada resto R^{70} puede ser igual o diferente, seleccionándose cada resto independientemente del grupo de restos R^{70}.

En otra realización, Z se selecciona del grupo que consiste en H, arilo y heteroarilo.

En otra realización, Z se selecciona del grupo que consiste en H, fenilo, indolilo, benzoimidazolilo, pirazolilo, tienilo, piridinilo, tiazolilo, tiadiazolilo, imidazolilo, pirrolidinilo, pirazinilo, triazolilo, tetrazolilo y tetrazinilo, donde dicho fenilo, indolilo, benzimidazolilo, pirazolilo, tienilo, piridinilo, tiazolilo, tiadiazolilo, imidazolilo, pirrolidinilo, pirazinilo, triazolilo, tetrazolilo y tetrazinilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto de manera independiente del grupo que consiste en restos R^{70}.

En otra realización, Z se selecciona del grupo que consiste en



donde x es de 0 a 4, y cuando x es mayor que 1, cada resto R^{70} puede ser igual o diferente, seleccionándose cada resto independientemente del grupo de restos R^{70}.

En otra realización, Z es fenilo.

En otra realización, Z es un fenilo sustituido por al menos un sustituyente seleccionado del grupo que consiste en ciano, alcoxi, halógeno, alquilo, haloalquilo, hidroxi, arilo, heteroarilo, ariloxi, amino y tetrazol.

En otra realización, Z es tienilo.

En otra realización, Z es un tienilo sustituido por al menos un sustituyente seleccionado del grupo que consiste en ciano, alcoxi, halógeno, alquilo, haloalquilo, hidroxi, arilo, heteroarilo, ariloxi, amino y tetrazol.

En otra realización, Z es pirazolilo.

En otra realización, Z es un pirazolilo sustituido por al menos un sustituyente seleccionado del grupo que consiste en ciano, alcoxi, halógeno, alquilo, haloalquilo, hidroxi, arilo, heteroarilo, ariloxi, amino y tetrazol.

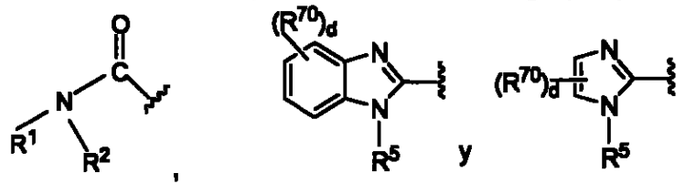
En otra realización, Z es piridinilo.

En otra realización, Z es a piridinilo sustituido por al menos un sustituyente seleccionado del grupo que consiste en ciano, alcoxi, halógeno, alquilo, haloalquilo, hidroxi, arilo, heteroarilo, ariloxi, amino y tetrazol.

En otra realización, Z es imidazolilo.

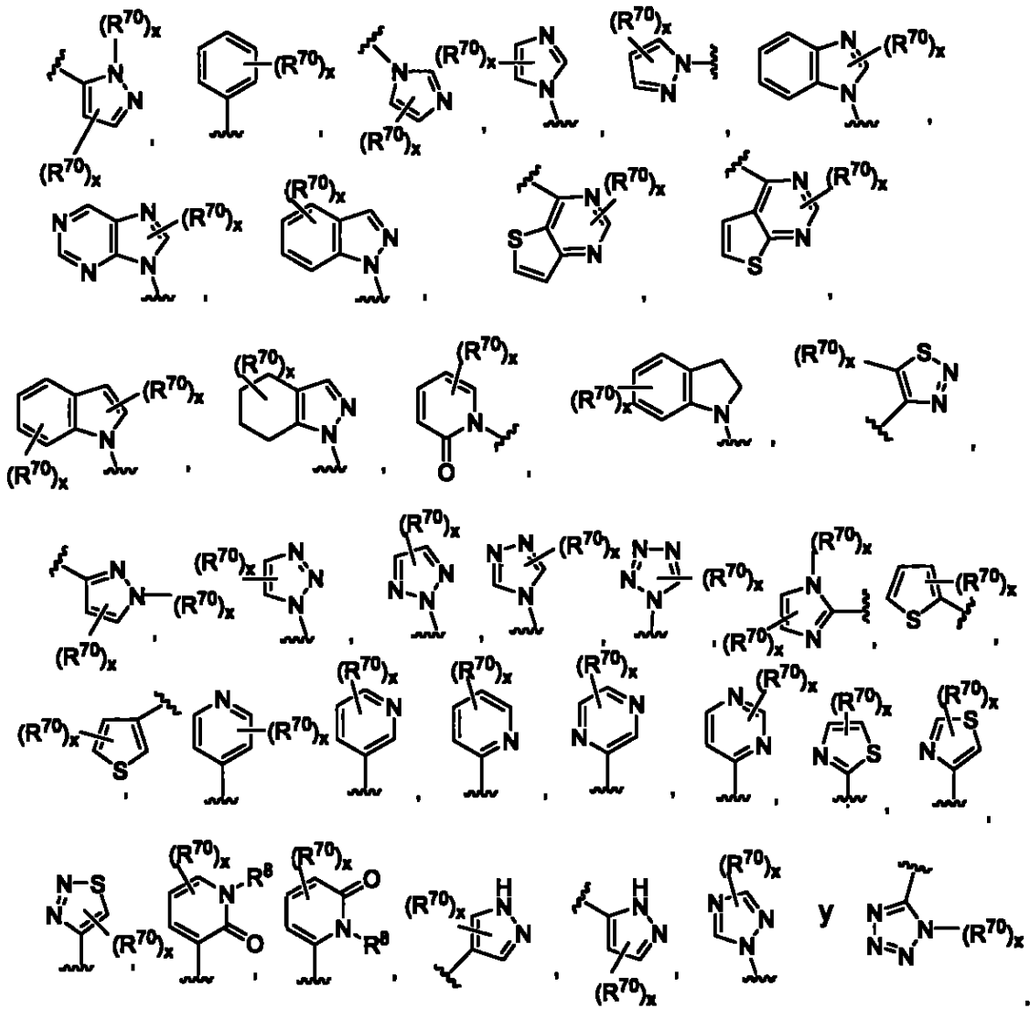
En otra realización, Z es un imidazolilo sustituido por al menos un sustituyente seleccionado del grupo que consiste en ciano, alcoxi, halógeno, alquilo, haloalquilo, hidroxi, arilo, heteroarilo, ariloxi, amino y tetrazol.

En otra realización, A se selecciona del grupo que consiste en:

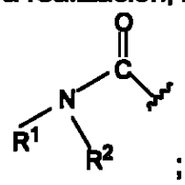


donde R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 4-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente por uno o más R^{70}, o fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 4-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70}; E, J y T son iguales y son O; R^{10} es

h o alquilo; R^{20}, R^{30}, R^{40}, y R^{50} son iguales y son H; W es $-(CR^{13}{}_2)_n-$, donde n es 0 a 5; X se selecciona del grupo que consiste en arilo, heteroarilo y heterociclilo; Y se selecciona del grupo que consiste en un enlace covalente, $-[C(R^6)_2]_n-$ donde n es 1 a 2, -O-, -S-, y $-NR^1-$; y Z se selecciona del grupo que consiste en

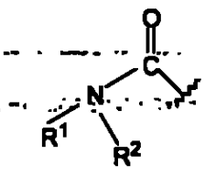


En otra realización, A es:

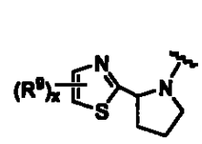
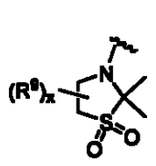
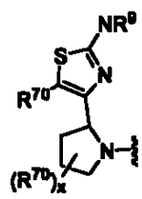
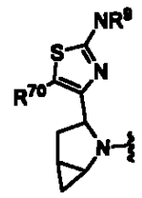
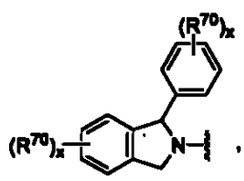
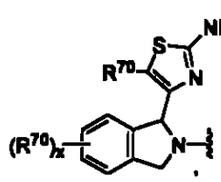
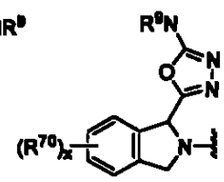
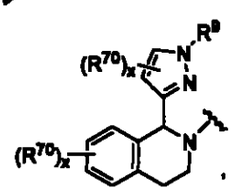
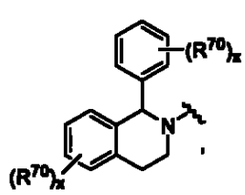
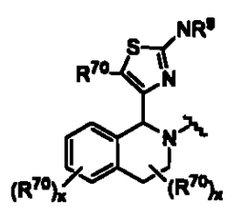
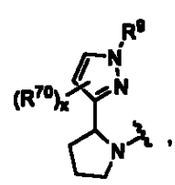


donde

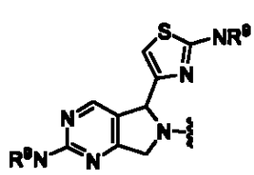
el $-NR^1R^2$ de



es

o

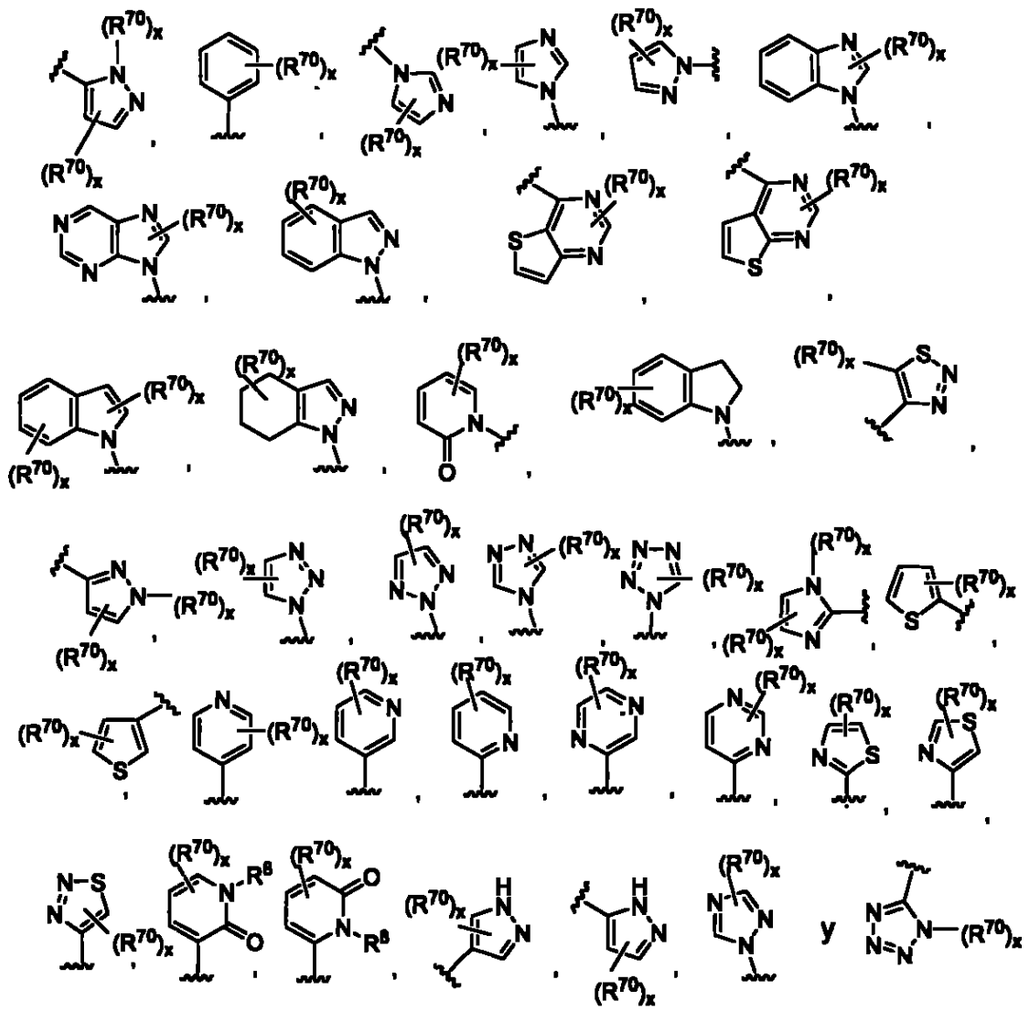


donde

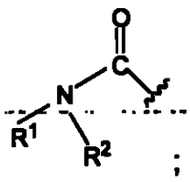
cada R^9 es un sustituyente para H donde se indicó y puede ser igual o diferente, seleccionándose cada uno independientemente del grupo que consiste en -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alquilo, arilo, heteroarilo, alquenilo, alquinilo, cicloalquilo y heterociclilo, donde dicho alquilo, arilo, heteroarilo, alquenilo, alquinilo, cicloalquilo y heterociclilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70}; y

x es de 0 a 4, y cuando x es mayor que 1, cada resto R^9 puede ser igual o diferente, seleccionándose cada resto independientemente del grupo de restos R^9;

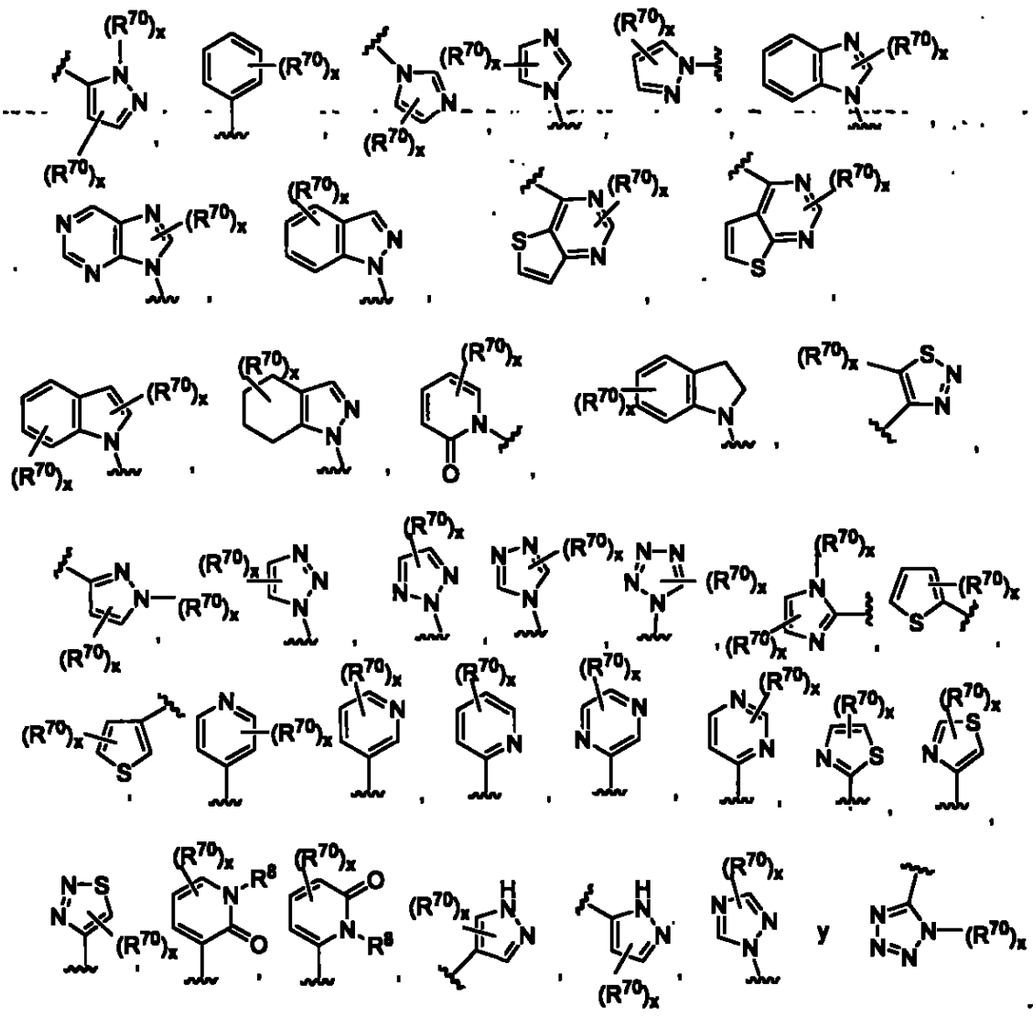
E, J y T son iguales y son O; R^{10} es h o alquilo; R^{20}, R^{30}, R^{40}, y R^{50} son iguales y son H; W es $-(CR^{13}_2)_n-$, donde n es 0 a 5; X se selecciona del grupo que consiste en arilo, heteroarilo y heterociclilo; Y se selecciona del grupo que consiste en un enlace covalente, $-[C(R^6)_2]_n-$ donde n es 1 a 2, -O-, -S-, y $-NR^1-$; y Z se selecciona del grupo que consiste en



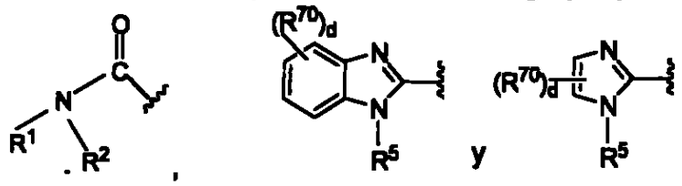
En otra realización, A es:



donde R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 4-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente por uno o más R^{70}, o fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 4-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70}; E, J y T son iguales y son O; R^{10} es h o alquilo; R^{20}, R^{30}, R^{40}, y R^{50} son iguales y son H; W es $-(CR^{13}_2)_n-$,donde n es 0 a 5; X se selecciona del grupo que consiste en arilo, heteroarilo y heterociclilo; Y se selecciona del grupo que consiste en un enlace covalente, $-[C(R^6)_2]_n-$ donde n es 1 a 2, -O-, -S-, y $-NR^1-$; y Z se selecciona del grupo que consiste en



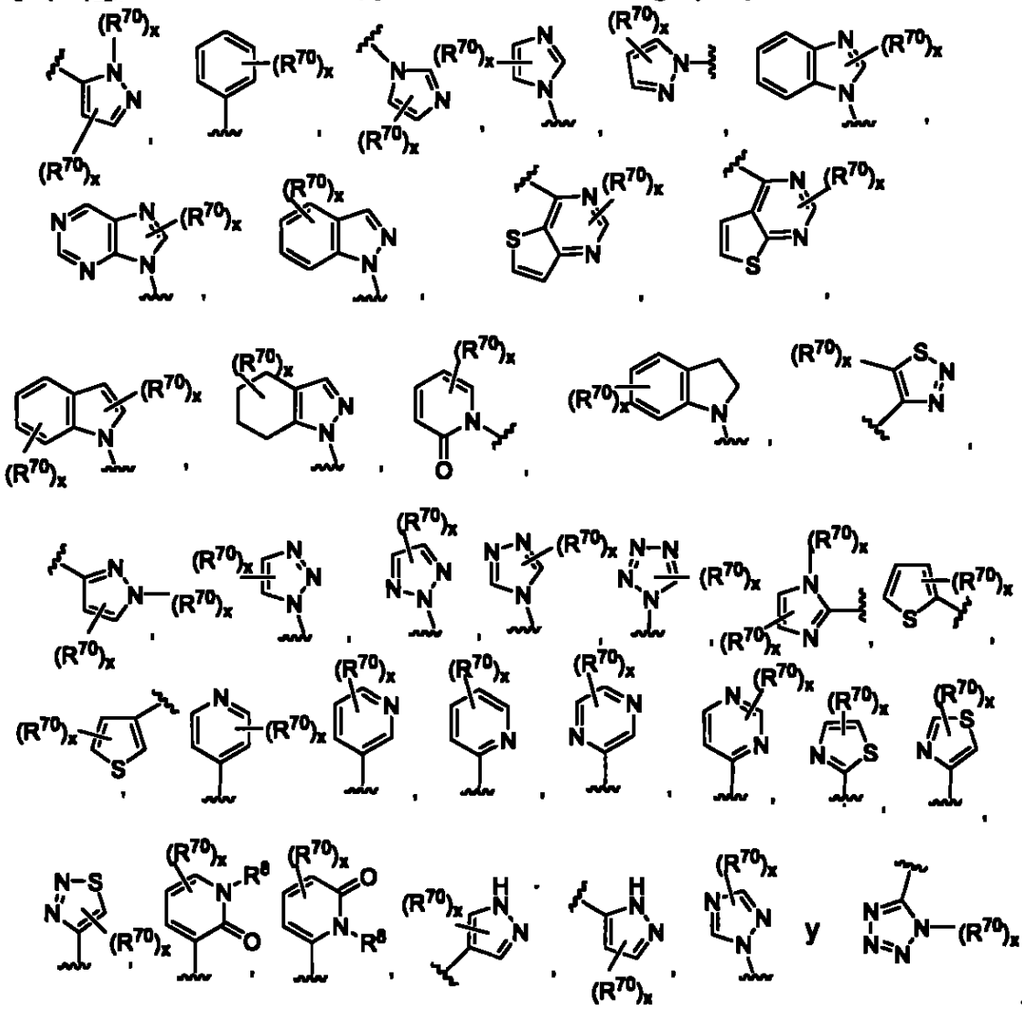
En otra realización, A se selecciona del grupo que consiste en:



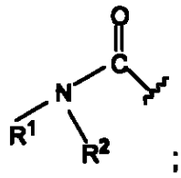
donde R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 3-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente por uno o más R^{70}, o fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 3-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más

restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70};

donde E, J y T son iguales y son O; R^{10} es h o alquilo; R^{20}, R^{30}, R^{40}, y R^{50} son iguales y son H; W es $-(CR^{6}{}_{2})_{n}-$, donde n es 0 a 5; X se selecciona del grupo que consiste en fenilo, piperidinilo, piridinilo, tienilo, tiazolilo, oxazolilo y pirazolilo; Y es $-[C(R^{6})_{2}]_{n}-$ donde n es 1 a 2; y Z se selecciona del grupo que consiste en



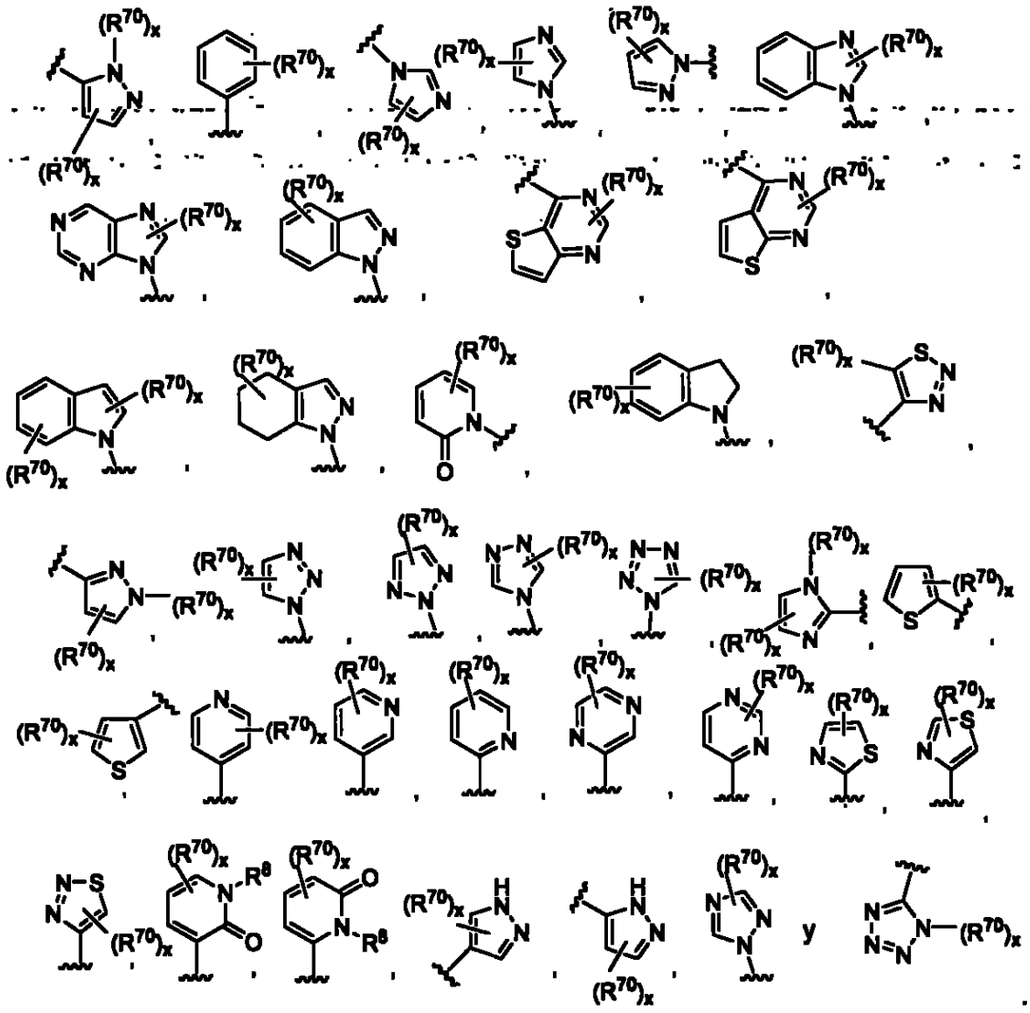
En otra realización, A es:



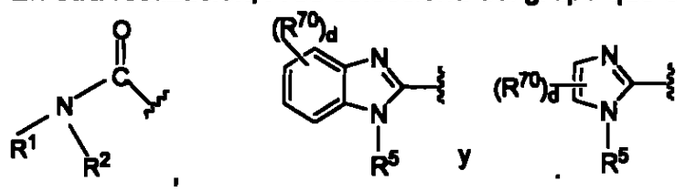
;

donde R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 3-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente por uno o más R^{70}, o fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 3-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70};

donde E, J y T son iguales y son O; R^{10} es h o alquilo; R^{20}, R^{30}, R^{40}, y R^{50} son iguales y son H; W es $-(CR^6{}_2)_n-$, donde n es 0 a 5; X se selecciona del grupo que consiste en fenilo, piperidinilo, piridinilo, tienilo, tiazolilo, oxazolilo y pirazolilo; Y es $-[C(R^6)_2]_n-$ donde n es 1 a 2; y Z se selecciona del grupo que consiste en



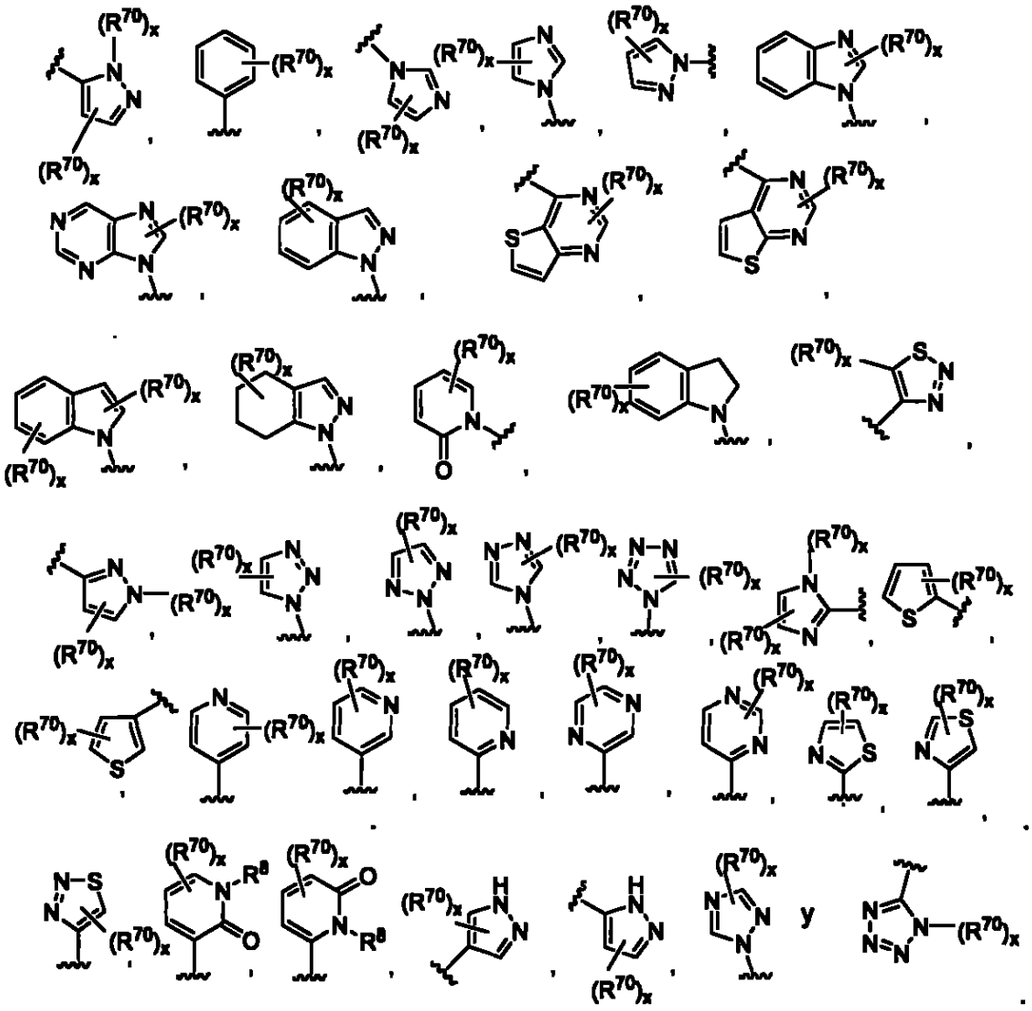
En otra realización, A se selecciona del grupo que consiste en:



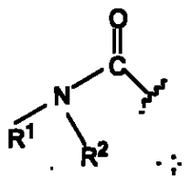
donde R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 3-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente por uno o más R^{70}, o fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 3-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más

restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70};

E, J y T son iguales y son O; R^{10} es h o alquilo; R^{20}, R^{30}, R^{40}, y R^{50} son iguales y son H; W es $-(CR^{6}_{2})_{n}-$, donde n s 0 a 5; X se selecciona del grupo que consiste en fenilo, piperidinilo, piridinilo, tienilo, tiazolilo, oxazolilo y pirazolilo; Y se selecciona del grupo que consiste en O-, -S-, y $-NR^{1}-$; y Z se selecciona del grupo que consiste en

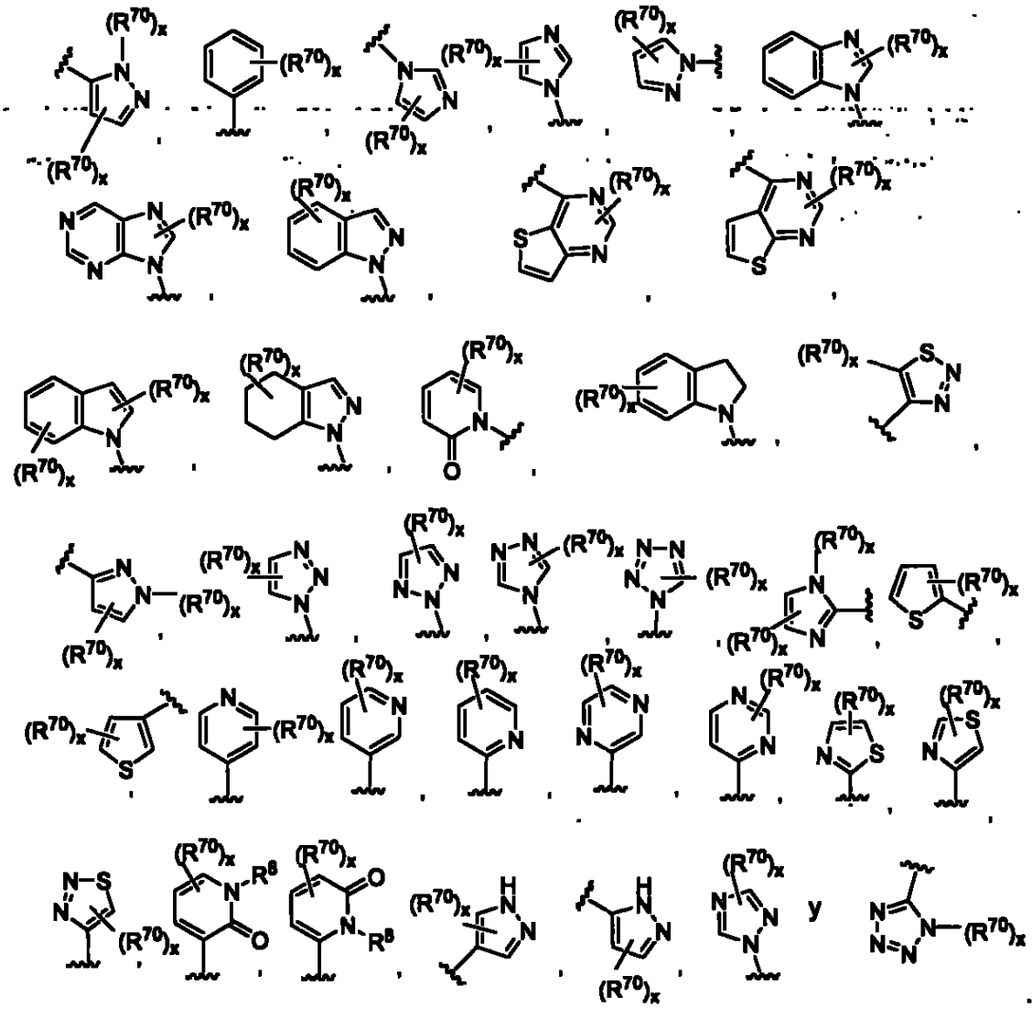


En otra realización, A es

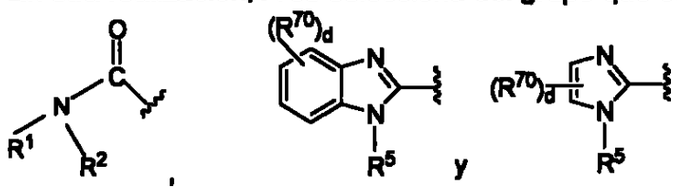


donde R^1 y R^2, tomados juntos con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 3 -8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente por uno o más R^{70}, o fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 3-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70};

donde E, J y T son iguales y son O; R^{10} es h o alquilo; R^{20}, R^{30}, R^{40}, y R^{50} son iguales y son H; W es $-(CR^6_2)_n-$, donde n es 0 a 5; X se selecciona del grupo que consiste en fenilo, piperidinilo, piridinilo, tienilo, tiazolilo, oxazolilo y pirazolilo; Y se selecciona del grupo que consiste en O-, -S-, y $-NR^1-$; y Z se selecciona del grupo que consiste en



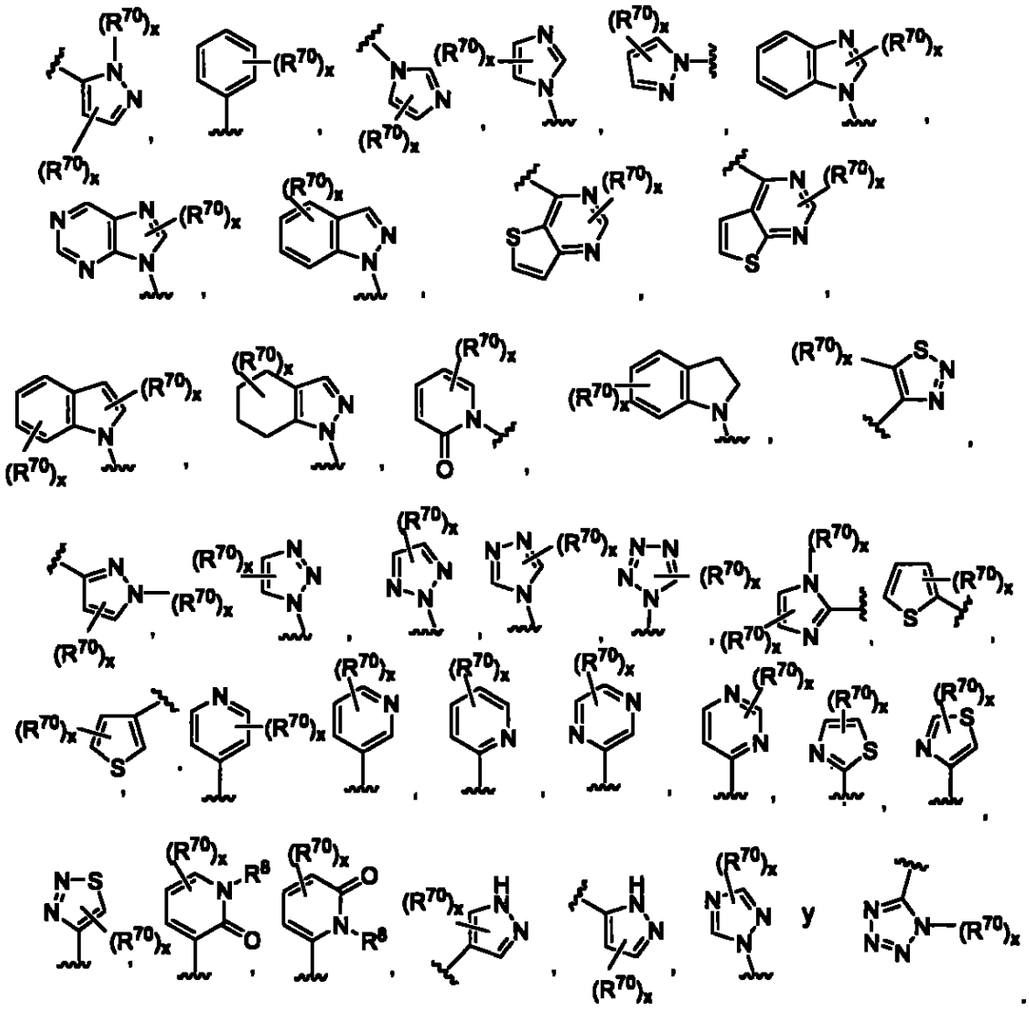
En otra realización, A se selecciona del grupo que consiste en:



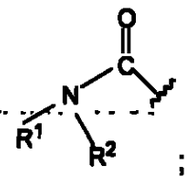
donde R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 3-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente por uno o más R^{70}, o fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 3-8 miembros puede ser no

sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70};

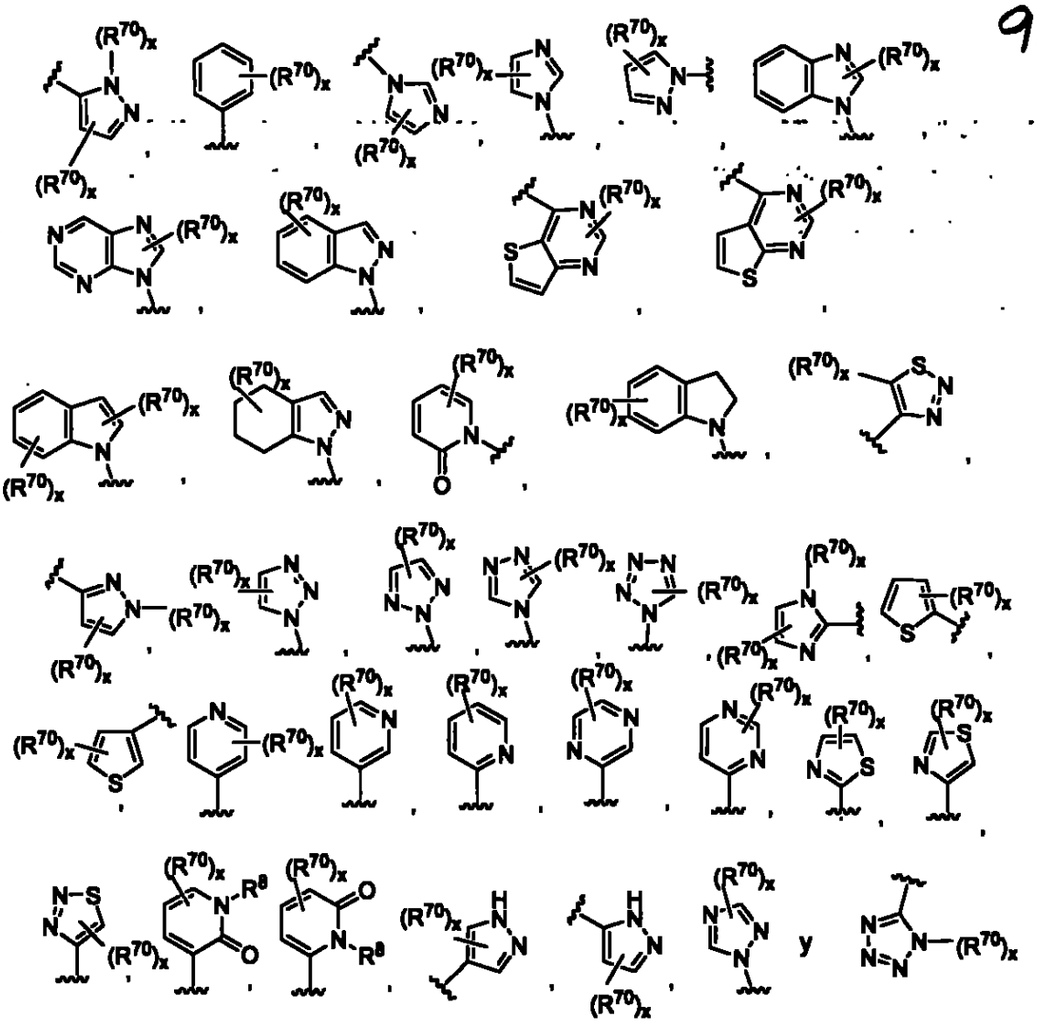
donde E, J y T son iguales y son O; R^{10} es h o alquilo; R^{20}, R^{30}, R^{40}, y R^{50} son iguales y son H; W es $-(CR^{13}{}_2)_n-$ donde n es 1 o 2; X se selecciona del grupo que consiste en fenilo, piperidinilo, piridinilo, tienilo, tiazolilo, oxazolilo y pirazolilo; Y es un enlace covalente y Z se selecciona del grupo que consiste en



En otra realización, A es



donde R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 3-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente por uno o más R^{70}, o fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 3-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70}; donde E, J y T son iguales y son O; R^{10} es H o alquilo; R^{20}, R^{30}, R^{40}, y R^{50} son iguales y son H; W es $-(CR^{13}_2)_n-$ donde n es 1 o 2; X se selecciona del grupo que consiste en fenilo, piperidinilo, piridinilo, tienilo, tiazolilo, oxazolilo y pirazolilo; Y es un enlace covalente y Z se selecciona del grupo que consiste en



En otra realización, X se selecciona del grupo que consiste en fenilo, piperidinilo, piridinilo, tienilo, tiazolilo, oxazolilo, y pirazolilo.

En otra realización, X se selecciona del grupo que consiste en fenilo, piperidinilo, tienilo, y piridinilo e Y se selecciona del grupo que consiste en un enlace covalente, $-[C(R^6)_2]_n-$ donde n es 1 a 2 y -O-.

En otra realización, X es fenilo e Y se selecciona del grupo que consiste en un enlace covalente, $-CH_2-$ y -O-.

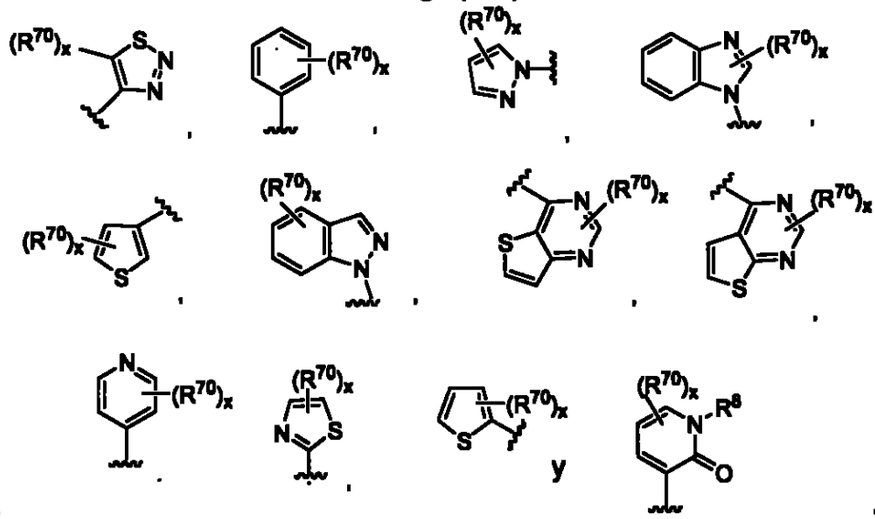
En otra realización, X es piperidinilo, Y es un enlace covalente, y Z es arilo o heteroarilo que posee dos sustituyentes que pueden ser iguales o diferentes, seleccionándose cada resto de manera independiente del grupo que consiste en

ciano, alcoxi, halógeno, alquilo, haloalquilo, hidroxi, arilo, heteroarilo, ariloxi y amino.

En otra realización, W se selecciona del grupo que consiste en $-CH_2-$, $-C(H)CH_3-$, $-C(CH_3)_2-$ e Y es un enlace covalente.

En otra realización, W es $-CH_2-$ e Y es $-CH_2-$.

En otra realización, Z se selecciona del grupo que consiste en



y

Otra realización de la invención revela los compuestos que se muestran en la Tabla 1 más adelante.

Según se emplean anteriormente, y a lo largo de la presente revelación, se entenderá que los siguientes términos, salvo que se indique lo contrario, poseen los siguientes significados:

"Paciente" incluye tanto seres humanos como animales.

"Mamíferos" significa seres humanos y otros animales mamíferos.

"Alquilo" significa un grupo hidrocarbonado alifático que puede ser recto o ramificado y que comprende alrededor de 1 a alrededor de 20 átomos de carbono en la cadena. Los grupos alquilo preferidos contienen alrededor de 1 a alrededor de 12 átomos de carbono en la cadena. Grupos alquilo de mayor preferencia contienen alrededor de 1 a alrededor de 6 átomos de carbono en la cadena.

Ramificado significa que uno o más grupos alquilo inferiores tales como metilo, etilo o propilo, se encuentran unidos a una cadena lineal de alquilo. "Alquilo inferior" significa un grupo que posee alrededor de 1 a alrededor de 6 átomos de carbono en la cadena que pueden ser rectos o ramificados. El término "alquilo sustituido" significa que el grupo alquilo puede estar sustituido con uno o más sustituyentes que pueden ser iguales o diferentes, cada sustituyente siendo seleccionado de manera independiente del grupo que consiste en halo, alquilo, arilo, cicloalquilo, ciano, hidroxi, alcoxi, alquiltio, amino, -NH(alquilo), -NH(cicloalquilo), -N(alquilo)$_2$, carboxi y –C(O)O-alquilo. Ejemplos no limitativos de grupos alquilo incluyen metilo, etilo, n-propilo, isopropilo y t-butilo. El término "fluoroalquilo" significa un grupo alquilo en el cual alquilo es según se describió anteriormente donde uno o más hidrógenos se reemplazan con átomos de fluoruro.

"Alquenilo" significa un grupo hidrocarbonado alifático que contiene al menos un doble enlace carbono-carbono y que puede ser recto o ramificado y comprende alrededor de 2 a alrededor de 15 átomos de carbono en la cadena. Los grupos alquenilo preferidos poseen alrededor de 2 a alrededor de 12 átomos de carbono en la cadena; y más preferiblemente alrededor de 2 a alrededor de 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior tal como metilo, etilo o propilo, se encuentran unidos a una cadena lineal de alquenilo. "Alquenilo inferior" significa alrededor de 2 a alrededor de 6 átomos de carbono en la cadena que puede ser recta o ramificada. Ejemplos no limitativos de grupos alquenilo adecuados incluyen etenilo, propenilo, n-butenilo, 3-metilbut-2-enilo, n-pentenilo, octenilo y decenilo.

"Alquinilo" significa un grupo alifático hidrocarbonado que contiene al menos un triple enlace carbono-carbono que puede ser recto o ramificado y que comrpende alrededor de 2 a alrededor de 15 átomos de carbono en la cadena.

Los grupos alquinilo preferidos poseen alrededor de 2 a alrededor de 12 átomos de carbono en la cadena; y más preferiblemente alrededor de 2 a alrededor de 4 átomos de carbono en la cadena. Ramificado significa que uno o más grupos de alquilo inferior, tales como metilo, etilo o propilo, se encuentran unidos a una cadena alquinilo lineal. "Alquinilo inferior" significa alrededor de 2 a alrededor de 6 átomos de carbono en la cadena que puede ser recta o ramificada. Ejemplos no limitativos de grupos alquinilo adecuados incluyen etinilo, propinilo, 2-butinilo y 3-metilbutinilo. El término "alquinilo sustituido " significa que el grupo alquinilo puede estar sustituido por uno o más sustituyentes que pueden ser iguales o diferentes, cada sustituyente siendo seleccionado de manera independiente del grupo que consiste en alquilo, arilo y cicloalquilo.

"Arilo" significa un sistema anular monocíclico o multicíclico aromático que comprende alrededor de 6 a alrededor de 14 átomos de carbono, preferentemente alrededor de 6 a alrededor de 10 átomos de carbono. El grupo arilo puede estar sustituido opcionalmente con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son según se definió en la presente. Ejemplos no limitativos de grupos arilo adecuados incluyen fenilo y naftilo.

"Heteroarilo" significa un sistema anular monocíclico o multicíclico aromático que comprende alrededor de 5 a alrededor de 14 átomos anulares, preferentemente alrededor de 5 a alrededor de 10 átomos anulares, en los cuales uno o más de los átomos anulares es un elemento que no es el carbono, por ejemplo, nitrógeno, oxígeno o azufre, solos o en combinación. Los heteroarilos preferidos contienen de alrededor de 5 a alrededor de 6 átomos anulares. El "heteroarilo" se puede sustituir opcionalmente por uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son según se definió en la presente. El prefijo aza, oxa o tia antes del nombre de la raíz significa que al menos un átomo de nitrógeno, oxígeno o azufre respectivamente, se encuentra

presente como un átomo anular. Un átomo de nitrógeno de un heteroarilo se puede oxidar opcionalmente para el N-óxido correspondiente. Ejemplos no limitativos de heteroarilos adecuados incluyen piridilo, pirazinilo, furanilo, tienilo, pyrimidinilo, piridone (including N-substituted piridones), isoxazolilo, isotiazolilo, oxazolilo, tiazolilo, pirazolilo, furazanilo, pirrolilo, pirazolilo, triazolilo, 1,2,4-tiadiazolilo, pirazinilo, piridazinilo, quinoxalinilo, ftalazinilo, oxindolilo, imidazo[1,2-a]piridinilo, imidazo[2,1-b]tiazolilo, benzofurazanilo, indolilo, azaindolilo, benzoimidazolilo, benzotienilo, quinolinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidilo, pirrolopiridilo, imidazopiridilo, isoquinolinilo, benzoazaindolilo, 1,2,4-triazinilo, benzotiazolilo y similares. El término "heteroarilo" También se refiere a restos heteroarilo parcialmente saturados tales como, por ejemplo, tetrahidroisoquinolilo, tetrahidroquinolilo y similares.

"Aralquilo" o "arilalquilo" significa un grupo aril-alquilo- en el cual el arilo y alquilo son según se describió anteriormente. Los aralquilos preferidos comprenden un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilo adecuados incluyen bencilo, 2-fenetilo y naftalenilmetilo. El enlace al resto progenitor es a través del alquilo.

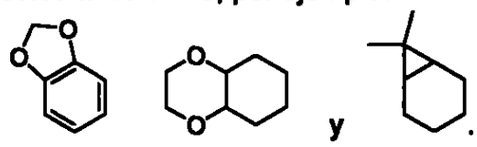
"Alquilarilo" significa un grupo alquil-arilo- en el cual el alquilo y arilo son según se describió anteriormente. Alquilarilos preferidos comprenden un grupo alquilo inferior preferido. Un ejemplo no limitativo de un grupo alquilarilo adecuado es tolilo. El enlace al resto progenitor es a través del arilo.

"Cicloalquilo" significa un sistema anular mono cíclico o multicíclico no aromático que comprende alrededor de 3 a alrededor de 10 átomos de carbono, preferentemente alrededor de 5 a alrededor de 10 átomos de carbono. Los anillos cicloalquilo preferidos contienen alrededor de 5 a alrededor de 7 átomos anulares. El cicloalquilo se puede sustituir opcionalmente por uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son según se definió

anteriormente. Ejemplos no limitativos de cicloalquilos monocíclicos incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares. Ejemplos no limitativos de cicloalquilos multicíclicos adecuados incluyen 1-decalinilo, norbornilo, adamantilo y similares, al igual que especies parcialmente saturadas tales como, por ejemplo, indanilo, tetrahidronaftilo y similares.

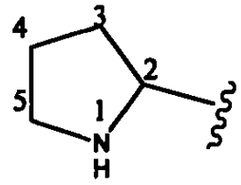
"Halógeno" significa flúor, cloro, bromo, o yodo. Se prefieren flúor, cloro y bromo.

"Sustituyente del sistema anular" significa un sustituyente unido a un sistema anular aromático o no aromático que, por ejemplo, reemplaza un hidrógeno disponible en el sistema anular. Sustituyentes del sistema anular pueden ser iguales o diferentes, seleccionándose cada uno independientemente del grupo que consiste en alquilo, alquenilo, alquinilo, arilo, heteroarilo, aralquilo, alquilarilo, heteroaralquilo, heteroarilalquenilo, heteroarilalquinilo, alquilheteroarilo, hidroxi, hidroxialquilo, alcoxi, ariloxi, aralcoxi, acilo, aroilo, halo, nitro, ciano, carboxi, alcoxicarbonilo, ariloxicarbonilo, aralcoxicarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquiltio, ariltio, heteroariltio, aralquiltio, heteroaralquiltio, cicloalquilo, heterociclilo, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, $-C(=NH)-NH(alquilo)$, Y_1Y_2N-, $Y_1Y_2N-alquil-$, $Y_1Y_2NC(O)-$, $Y_1Y_2NSO_2-$ y $-SO_2NY_1Y_2$, donde Y_1 e Y_2 pueden ser iguales o diferentes y se seleccionan de manera independiente del grupo que consiste en hidrógeno, alquilo, arilo, cicloalquilo, y aralquilo. "Sustituyente del sistema anular" también puede significar un resto simple que reemplaza simultáneamente dos hidrógenos disponibles sobre dos átomos de carbono adyacentes (un H sobre cada carbono) en un sistema anular. Ejemplos de dicho resto son metilendioxi, etilendioxi, $-C(CH_3)_2-$ y similares que forman restos tales como, por ejemplo:



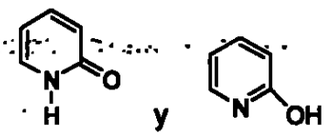
"Heterociclilo" significa un sistema anular monocíclico o multicíclico no aromático que comprende alrededor de 3 a alrededor de 10 átomos anulares, preferentemente alrededor de 5 a alrededor de 10 átomos anulares, en los cuales uno o más de los átomos en el sistema anular es un elemento que no es carbono, por ejemplo nitrógeno, oxígeno o azufre, solos o en combinación. No se encuentran átomos adyacentes de oxígeno y/o azufre en el sistema anular. Heterociclillos preferidos contienen alrededor de 5 a alrededor de 6 átomos anulares. El prefijo aza, oxa o tia antes del nombre de la raíz del heterociclilo significa que al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente se encuentra presente como un átomo anular. Cualquier –NH en un anillo heterociclilo puede existir protegido, tales como por ejemplo, un grupo -N(Boc), -N(CBz), -N(Tos) y similares; tales protecciones también son consideradas parte de la presente invención. El heterociclilo se puede sustituir opcionalmente por uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son según se definió en la presente. El átomo de nitrógeno o azufre del heterociclilo se puede oxidar opcionalmente al N-óxido correspondiente, S-óxido o S,S-dióxido. Ejemplos no limitativos de anillos monocíclicos heterociclilos incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, lactama, lactona y similares.

Se debe observar que en sistemas anulares que contienen heteroátomos de la presente invención, no se encuentran grupos hidroxilo sobre átomos de carbono adyacentes a un N, O o S, al igual que no hay grupos N o S sobre el carbono adyacente a otro heteroátomo. Por lo tanto, por ejemplo, en el anillo:



no hay -OH unidos directamente a los carbonos marcados 2 y 5,

También se debe observar que formas tautoméricas tales como, por ejemplo, los restos:



son considerados equivalentes en ciertas realizaciones de la presente invención.

"Alquinilalquilo" significa un grupo alquinil-alquil- en el cual el alquinilo y el alquilo son según se describió anteriormente. Alquinilalquilos preferidos contienen un alquinilo inferior y un grupo alquilo inferior. El enlace al resto progenitor es a través del alquilo. Ejemplos no limitativos de grupos alquinilalquilo adecuados incluyen propargilmetilo.

"Heteroaralquilo" significa un grupo heteroaril-alquil- en el cual el heteroarilo y alquilo son según se describió anteriormente. Los heteroaralquilos preferidos contienen un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilo adecuados incluyen piridilmetilo y quinolin-3-ilmetilo. El enlace al resto progenitor es a través del alquilo.

"Hidroxialquilo" significa un grupo HO-alquil-en el cual el alquilo es según se definió anteriormente. Los hidroxialquilos preferidos contienen alquilo inferior. Ejemplos no limitativos de grupos hidroxialquilo adecuados incluyen hidroximetilo y 2-hidroxietilo.

"Acilo" significa un grupo H-C(O)-, alquil-C(O)- o cicloalquil-C(O)-, en el cual los diversos grupos son según se describió anteriormente. El enlace al reto progenitor es a través del carbonilo. Los acilos preferidos contienen un alquilo inferior. Ejemplos no limitativos de grupos acilo adecuados incluyen formilo, acetilo y propanoílo.

"Aroílo" significa un grupo aril-C(O)- en el cual el grupo arilo es según se describió previamente. El enlace al resto progenitor es a través del carbonilo. Ejemplos no limitativos de grupos adecuados incluyen benzoílo y 1- naftoílo.

"Alcoxi" significa un grupo alquil-O- n el cual el grupo alquilo es según se describió previamente. Ejemplos no limitativos de grupos alcoxi adecuados incluyen metoxi, etoxi, n-propoxi, isopropoxi y n-butoxi. El enlace al resto progenitor es a través del oxígeno de éter.

"Ariloxi" significa un grupo aril-O- en el cual el grupo arilo es según se describió previamente. Ejemplos no limitativos de grupos ariloxi adecuados incluyen fenoxi y naftoxi. El enlace al resto progenitor es a través del oxígeno de éter.

"Aralquiloxi" significa un grupo aralquil-O- en el cual el grupo aralquilo es según se describió previamente. Ejemplos no limitativos de grupos aralquiloxi adecuados incluyen benciloxi y 1- o 2-naftalenmetoxi. El enlace al resto progenitor es a través del oxígeno de éter.

"Alquiltio" significa un grupo alquil-S- en el cual el grupo alquilo es según se describió previamente. Ejemplos no limitativos de gruidos alquiltio adecuados incluyen metiltio y etiltio. El enlace al resto progenitor es a través del azufre.

"Ariltio" significa un grupo aril-S- en el cual el grupo arilo es según se describió previamente. Ejemplos no limitativos de grupos ariltio adecuados incluyen feniltio y naftilotio. El enlace al resto progenitor es a través del azufre.

"Aralquiltio" significa un grupo aralquil-S- en el cual el grupo aralquilo es según se describió previamente. Un ejemplo no limitativo de un grupo aralquiltio adecuado es benciltio. El enlace al resto progenitor es a través del azufre.

"Alcoxicarbonilo" significa un grupo alquil-O-CO-. Ejemplos no limitativos de grupos alcoxicarbonilo adecuados incluyen metoxicarbonilo y etoxicarbonilo. El enlace al resto progenitor es a través del carbonilo.

"Ariloxicarbonilo" significa un grupo aril-O-C(O)-. Ejemplos no limitativos de de grupos ariloxicarbonilo adecuados incluyen fenoxicarbonilo y naftoxicarbonilo. El enlace al resto progenitor es a través del carbonilo.

"Aralcoxicarbonilo" significa un grupo aralquil-O-C(O)-. Un ejemplo no limitativo de un grupo aralcoxicarbonilo adecuado es benciloxicarbonilo. El enlace al resto progenitor es a través del carbonilo.

"Alquilsulfonilo" significa un grupo alquil-$S(O_2)$-. Los grupos preferidos son aquellos en los cuales el grupo alquilo es alquilo inferior. El enlace al resto progenitor es a través del sulfonilo.

"Arilsulfonilo" significa un grupo aril-$S(O_2)$-. El enlace al resto progenitor es a través del sulfonilo.

El término "sustituido" significa que uno o más hidrógenos sobre el átomo designado se reemplaza con una selección del grupo indicado, siempre que no se exceda la valencia normal del átomo designado en circunstancias existentes, y que la sustitución produzca un compuesto estable. Las combinaciones de los sustituyentes y/o variables se permiten solamente si tales combinaciones producen compuestos estables. Mediante "compuesto estable" o "estructura estable" se significa un compuesto que es lo suficientemente robusto para sobrevivir el aislamiento en un nivel útil de pureza de una mezcla de reacción y la formulación en un agente terapéutico eficaz.

El término "opcionalmente sustituido" significa la sustitución opcional con los grupos, radicales o restos especificados.

El término "aislado" o "en forma aislada" para un compuesto se refiere al estado físico de dicho compuesto después de que se aísla de un proceso sintético o fuente natural o combinación de los mismos. El término "purificado" o "en forma purificada" para un compuesto se refiere al estado físico de dicho compuesto después de que se obtuvo de un proceso de purificación o procesos descriptos en la presente o conocidos para un experto en la técnica, en pureza suficiente para que se pueda caracterizar mediante las técnicas analíticas estándar que se describen en la presente o conocidas para el experto en la técnica.

Se debe observar también que se asume que cualquier carbono, al igual que heteroátomo, con valencias no completas en el texto, esquemas, ejemplos y Tablas en la presente, posee la cantidad suficiente de átomos(s) de hidrógeno para cubrir dichas valencias.

Cuando un grupo funcional en un compuesto se denomina "protegido", esto significa que el grupo se encuentra en forma modificada para producir las reacciones secundarias deseadas en el lugar protegido cuando el compuesto se somete a la reacción. Aquellas personas con experiencia en la técnica reconocerán los grupos protectores adecuados, al igual que mediante referencia a libros de texto estándar, tales como, por ejemplo, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

Cuando cualquier variable (por ej., arilo, heterociclo, R^2, etc.) aparece más de una vez en cualquier constituyente o en la Fórmula I, su definición en cada caso es independiente de su definición en cualquier otro caso.

Según se emplea en la presente, el término "composición" pretende comprender un producto que comprende los componentes especificados en las cantidades especificadas, al igual que cualquier producto que resulta, directa o indirectamente, de la combinación de los componentes especificados en las cantidades especificadas.

Los pro-fármacos y solvatos de los compuestos de la invención también se contemplan en la presente. El término pro-fármaco, según se emplea en la presente, denota un compuesto que es un precursor del fármaco, al administrarlo a un sujeto, sufre una conversión química mediante procesos metabólicos o químicos para producir un compuesto de fórmula I o una sal o solvato de los mismos. Se provee una discusión de pro-fármacos en T. Higuchi y V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 de la Serie del A.C.S. Symposium Series, y en *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed.,

American Pharmaceutical Association y Pergamon Press, ambas se incorporan a la presente a modo de referencia a los mismos.

"Solvato" significa una asociación física de un compuesto de la presente invención con una o más moléculas del solvente. Esta asociación física comprende diversos grados de enlaces iónicos y covalentes, incluyendo uniones puente de hidrógeno. En ciertas instancias, el solvato será capaz de aislamiento, por ejemplo cuando uno o más moléculas del solvente se incorporan en la marca de cristal del sólido cristalino. "Solvato" abarca tanto fase de solvatos de fase de la solución e aislables. Ejemplos no limitativos de solvatos adecuados incluyen etanolatos, metanolatos y similares. "Hidrato" es un solvato donde la molécula del solvente es H_2O.

"Cantidad efectiva " o "cantidad terapéuticamente efectiva" se usa para describir una cantidad de compuesto o una composición de la presente invención efectiva para la inhibición de las CDK y, de esa manera, produce el efecto terapéutico, de alivio, inhibidor o preventivo deseado.

Los compuestos de Fórmula I pueden formar sales que también se encuentran dentro del alcance de la presente invención. Se entiende que la referencia a un compuesto de fórmula I en la presente incluye las sales del mismo, salvo que se especifique lo contrario. El término "sal(es)", según se emplea en la presente, denota sales de ácidos que se forman con ácidos inorgánicos y/u orgánicos, al igual que sales de bases formadas con bases inorgánicas y/u orgánicas. Además, cuando un compuesto de fórmula I contiene tanto un resto básico, tal como, pero sin limitación,, una piridina o imidazol, como un resto ácido, tal como, pero sin limitación, un ácido carboxílico, se pueden formar zwitteriones ("sales internas") y se incluyen dentro del término "sal(es)" según se emplea en la presente. Se prefieren las sales aceptables para uso farmacéutico (es decir, no tóxicas, aceptables para uso fisiológico), aunque

también son útiles otras sales. Las sales de los compuestos de Fórmula I se pueden formar, por ejemplo, mediante hacer reaccionar un compuesto de fórmula I con una cantidad de ácido o base, tal como una cantidad equivalente, en un medio tal como uno en el cual la sal precipita o en un medio acuoso seguido de liofilización.

Sales ácidas de adición incluyen, acetatos, ascorbatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, alcanforatos, alcanforsulfonatos, fumaratos, clorhidratos, bromhidratos, yodhidratos, lactatos, maleatos, metansulfonatos, naftalensulfonatos, nitratos, oxalatos, fosfatos, propionatos, salicilatos, succinatos, sulfatos, tartratos, tiocianatos, toluensulfonatos (también conocidos como tosilatos) y similares. De manera adicional, se discuten ácidos que en general se consideran adecuados para la formación de sales útiles para uso farmacéutico a partir de compuestos farmacéuticos básicos, por ejemplo, por P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection aand Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; y in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). Estas revelaciones se incorporan a la presente a modo de referencia a los mismos.

Las sales de bases que sirven de ejemplo incluyen sales de amonio, sales de metales alcalinos, tales como sodio, litio, y sales de potasio, sales de metales alcalino-térreos tal como sales de calcio y magnesio, sales con bases orgánicas, (por ejemplo, aminas orgánicas) tales como diciclohexilaminas, t-butil aminas, y sales con aminoácidos tales como arginina, lisina y similares.

Se pueden cuaternizar grupos básicos que contienen nitrógeno con agentes tales como haluros de alquilo inferior (por ejemplo, cloruros, bromuros y yoduros de metilo, etilo y butilo); sulfatos de dialquilo (por ej. sulfatos de dimetilo, dietilo y dibutilo), haluros de cadena larga (por ej. cloruros, bromuros y yoduros de decilo, laurilo y estearilo,), haluros de aralquilo (por ej. bromuros de bencilo y fenetilo), y otros.

Se pretende que la totalidad de dichas sales ácidos y sales de base sean sales aceptables para uso farmacéutico dentro del alcance de la invención y todas las sales de ácidos y de bases son consideradas equivalentes a las formas libres de los compuestos correspondientes para los fines de la presente invención.

Los compuestos de Fórmula I, sales solvatos y pro-fármacos de los mismos, pueden existir en su forma tautomérica (por ejemplo, como una amida o imino éter). La totalidad de tales formas tautoméricas se consideran en la presente como parte de la presente invención.

Todos los estereoisómeros (por ejemplo, isómeros geométricos, isómeros ópticos y similares) de los presentes compuestos (incluyendo los de las sales, solvatos y pro-fármacos de los compuestos tal igual que las sales y solvatos de los pro-fármacos), tales como aquellos que pueden existir debido a carbonos asimétricos en varios sustituyentes, incluyendo formas enantioméricas (que pueden existir aún en ausencia de carbonos asimétricos), formas rotaméticas, atropoisómeros y formas diastereoméricas, se consideran dentro del alcance de la presente invención, al igual que los isómeros de posición (tales como, por ejemplo, 4-piridilo y 3-piridilo). Los estereoisómeros individuales de los compuestos de la invención pueden encontrarse, por ejemplo, sustancialmente libres de otros isómeros, o se pueden mezclar, por ejemplo, como racematos o con todos los demás, u otros estereoisómeros seleccionados. Los centros quirales de la presente invención pueden poseer la configuración S o R, según lo definido

por las Recomendaciones de *IUPAC* 1974. Se pretende que el uso de los términos "sal", "solvato", "pro-fármaco" y similares, se aplique igualmente a la sal, solvato y pro-fármaco de enantiómeros, estereoisómeros, rotámeros, tautómeros, isómeros posiciónales, racematos o pro-fármacos de los compuestos de la invención.

Se pretende que las formas polimórficas de los compuestos de Fórmula I y de las sales, solvatos y pro-fármacos de los compuestos de Fórmula I, se incluyan en la presente invención.

Los compuestos de acuerdo con la invención poseen propiedades farmacológicas; en especial, los compuestos de Fórmula I pueden ser inhibidores de la actividad de TACE, TNF-α, ADAM y/o MMP.

En un aspecto, la invención proveé una composición farmacéutica que comprende como un componente activo al menos un compuesto de fórmula 1.

En otro aspecto, la invención provee una composición farmacéutica de fórmula 1 que adicionalmente comprende al menos un vehículo aceptable para uso farmacéutico.

En otro aspecto, la invención provee un método para el tratamiento de trastornos asociados con TACE, TNF-α, MMPs, ADAMs o cualquier combinación de las mismas, comprendiendo tal tratamiento administrar a un paciente que necesita dicho tratamiento una composición farmacéutica que comprende cantidades terapéuticamente efectivas de al menos un compuesto de fórmula 1.

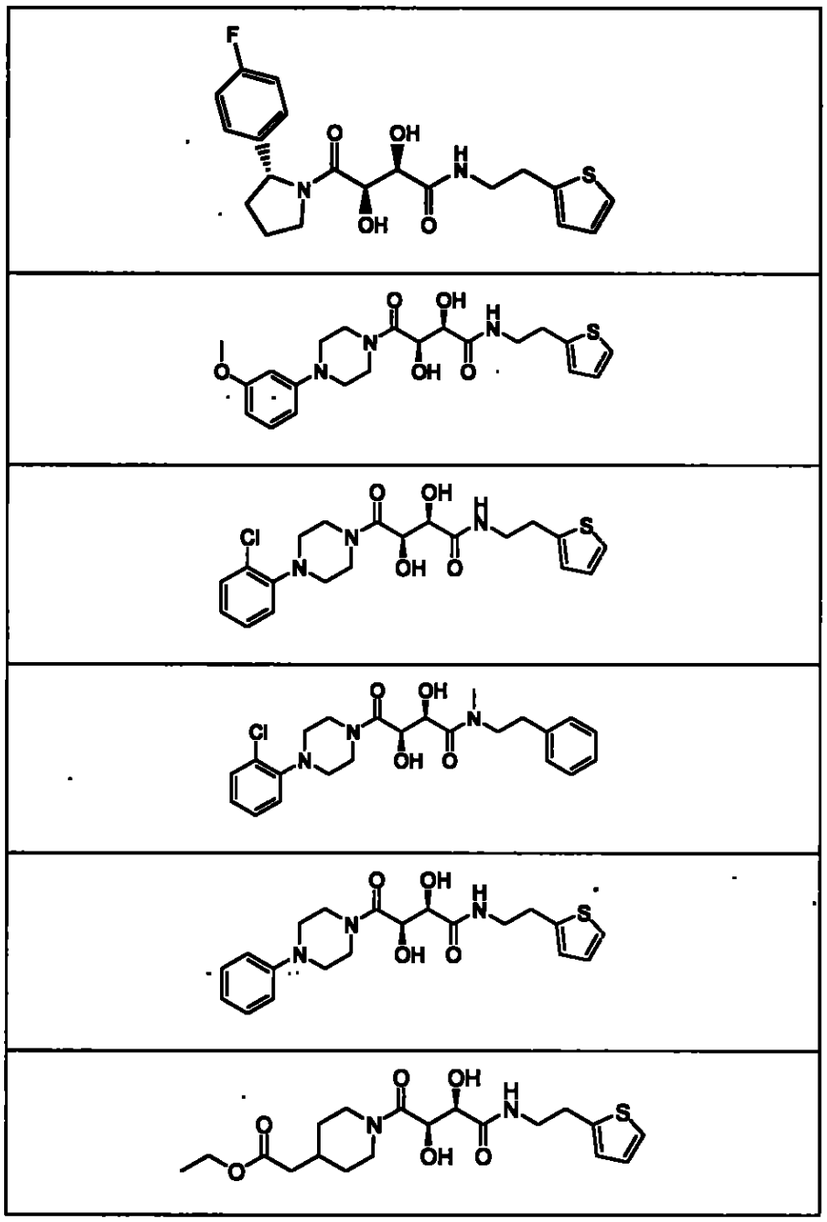
En otro aspecto, la invención provee un uso de un compuesto de fórmula 1 para la fabricación de un medicamento para el tratamiento de trastornos asociados con TACE, TNF-α, MMPs, ADAMs o cualquier combinación de las mismas.

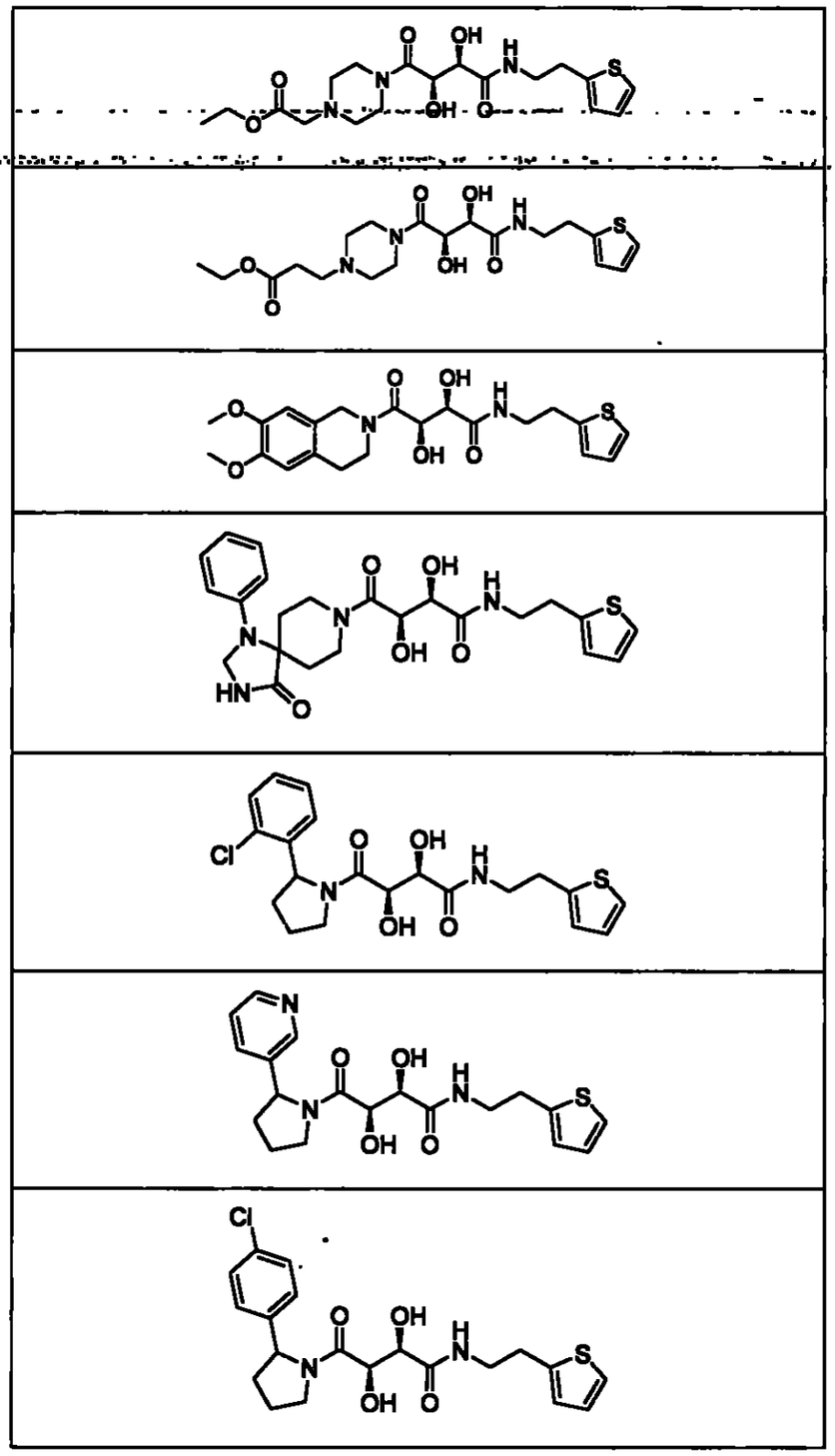
Los compuestos de Fórmula I pueden poseer actividad anti-inflamatoria y/o actividad inmunomoduladora y pueden ser útiles en el tratamiento de

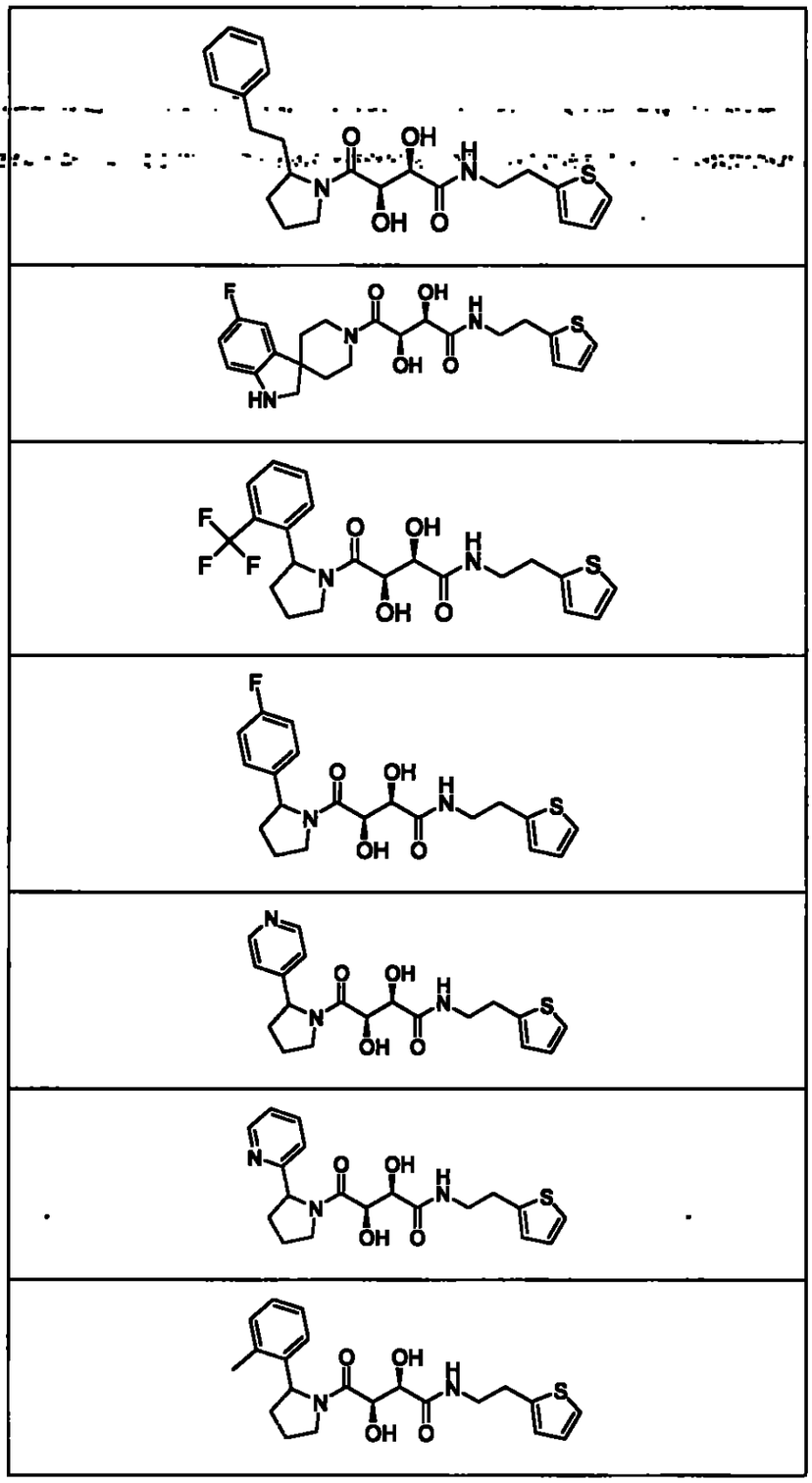
enfermedades que incluyen pero sin limitarse a las mismas, shock séptico, shock hemodinámico, síndrome séptico, lesión de reperfusión pos isquémica, malaria, infección micobacteriana, meningitis, psoriasis, insuficiencia cardíaca congestiva, enfermedades fibróticas, caquexia, rechazo a injerto, cánceres tales como linfoma de células T cutáneo, enfermedades relacionadas con angiogénesis, enfermedades autoinmunes, enfermedades inflamatorias de la piel, enfermedades inflamatorias del intestino, tales como enfermedad de Crohn y colitis, OA y RA, espondilitis anquilosante, artritis psoriásica, enfermedad de Still en adultos, ureítis, granulomatosis de Wegener, enfermedad de Behcehe, síndrome de Sjogren, sarcoidosis, polimiositis, dermatomiositis, esclerosis múltiple, ciática, síndrome de dolor regional complejo, lesión por radiación, lesión alveolar hiperóxica, enfermedad periodontal, VIH, diabetes mellitus no-insulino dependiente, lupus eritematoso sistémico, glaucoma, sarcoidosis, fibrosis pulmonar idiopática, displasia broncopulmonar, enfermedad retinal, esclerodema, osteoporosis, isquemia renal, infarto de miocardio, accidente cerebrovascular, isquemia cerebral, nefritis, hepatitis, glomerulonefritis, aveolitis fibrosa criptogénica, psoriasis, rechazo a transplante, dermatitis atópica, vasculitis, alergia, rinitis alérgica estacional, obstrucción reversible de las vías aéreas, síndrome de insuficiencia respiratoria de adultos, asma, enfermedad obstructiva pulmonar crónica (COPD) y/o bronquitis. Se considera que un compuesto de la presente invención puede ser útil en el tratamiento de una o más de las enfermedades enumeradas.

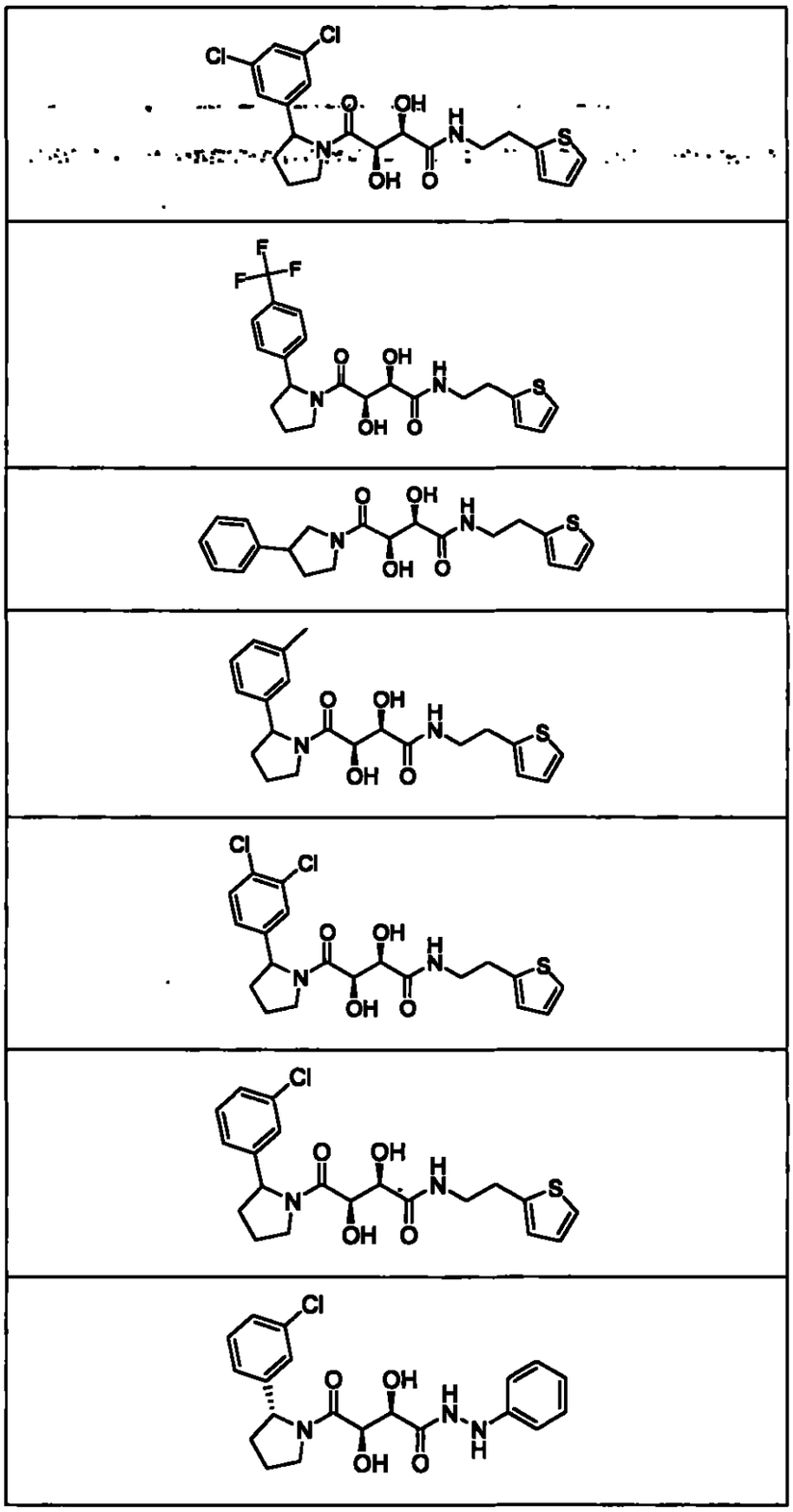
En otro aspecto, la invención provee un método para preparar una composición farmacéutica para el tratamiento de trastornos asociados con TACE, TNF-α, MMPs, ADAMs o cualquier combinación de las mismas, comprendiendo tal método poner en contacto íntimo al menos un compuesto de fórmula 1 y al menos un vehículo aceptable para uso farmacéutico.

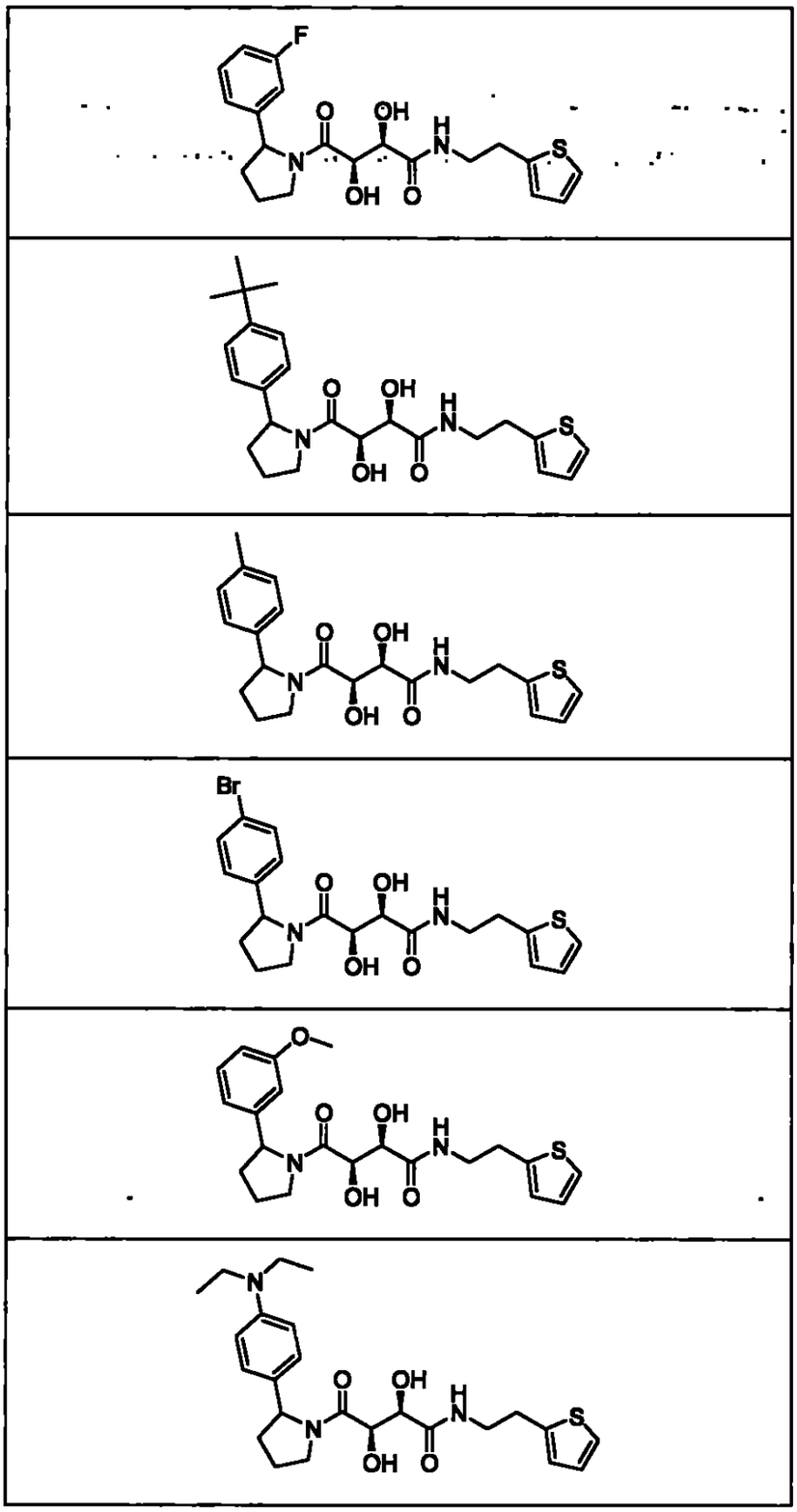
En otro aspecto, la invención provee un compuesto de fórmula (I) que exhibe la actividad inhibidora de TACE, TNF-α, MMPs, ADAMs o cualquier combinación de las mismas; incluyendo enantiómeros, estereoisómeros y tautómeros de dicho compuesto y sales aceptables para uso farmacéutico o solvatos de dicho compuesto, seleccionándose tal compuesto de los compuestos de las estructuras enumeradas a continuación:

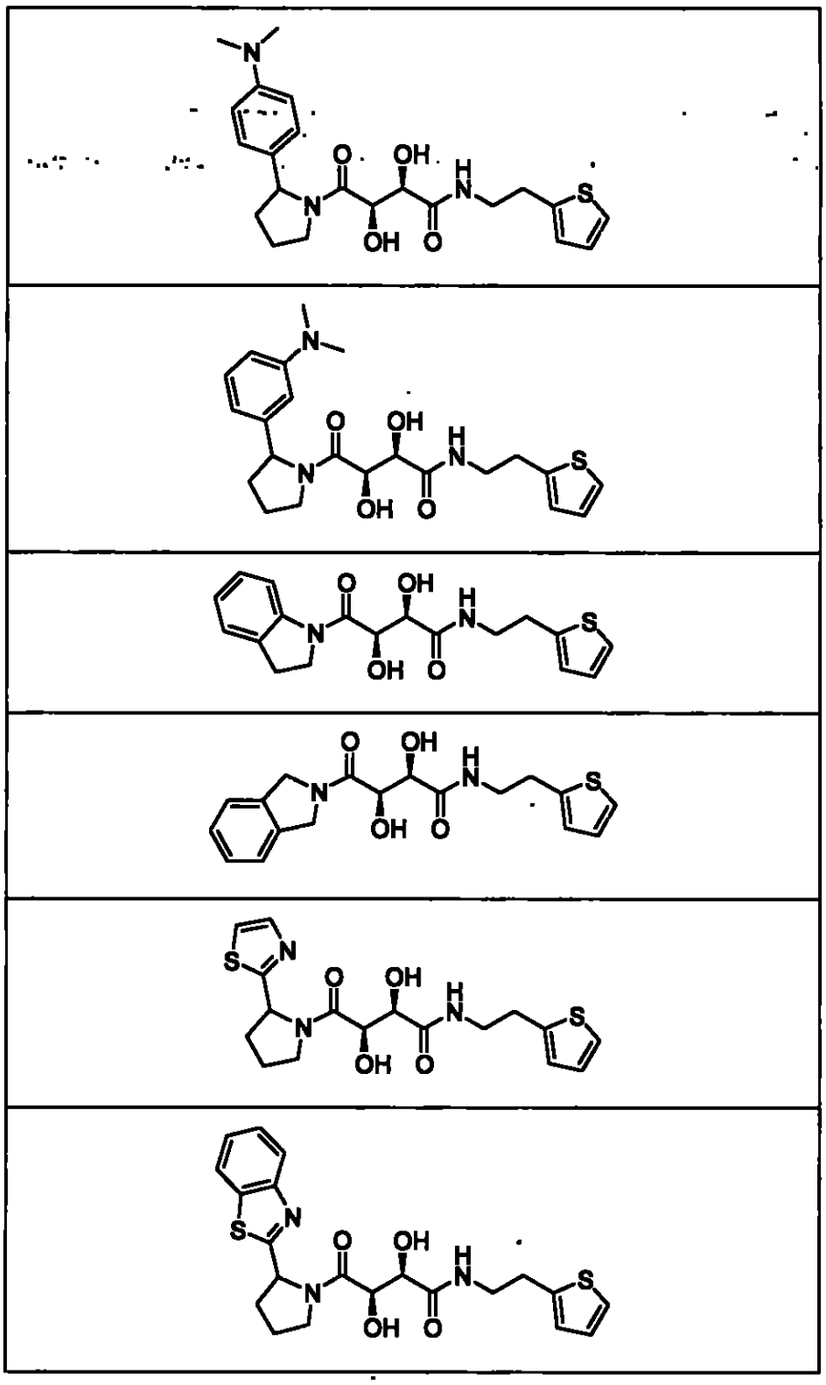


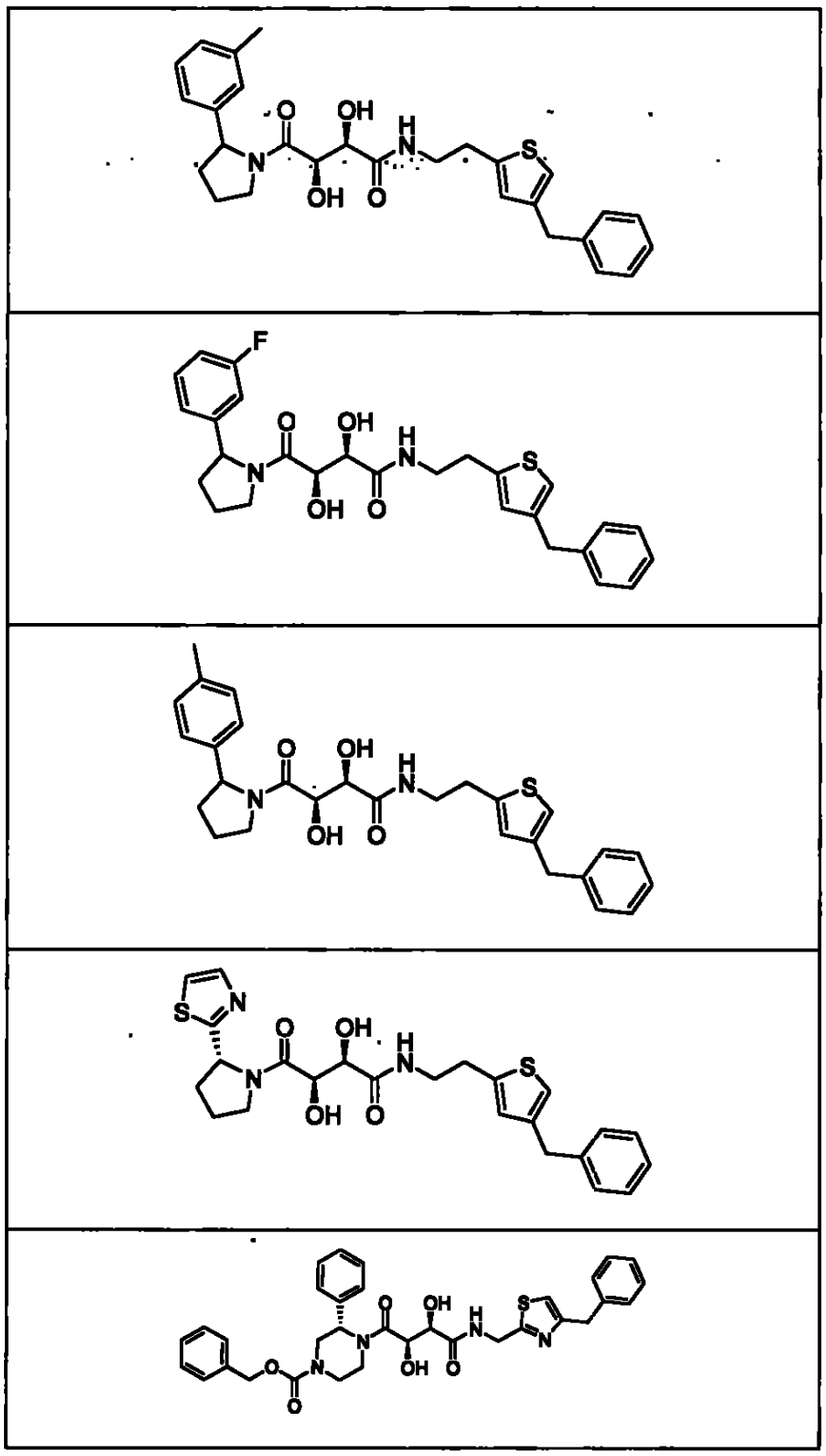




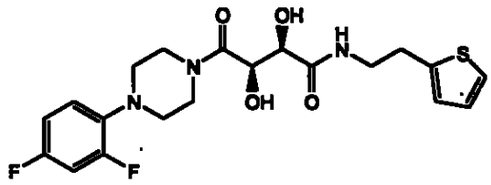
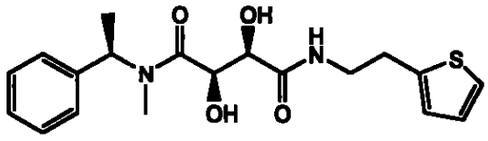
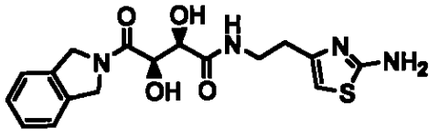
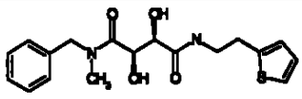
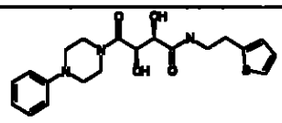
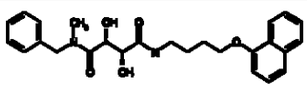
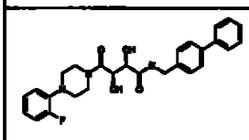




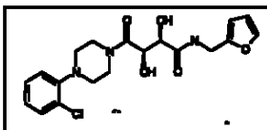
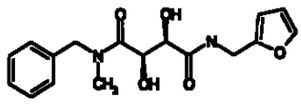
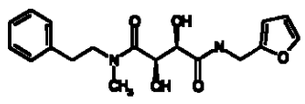
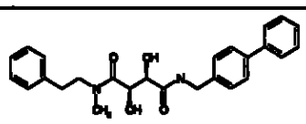
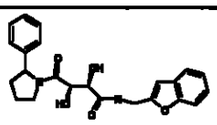
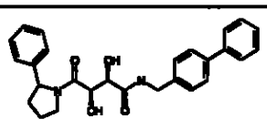
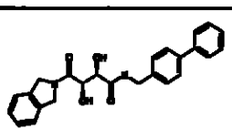


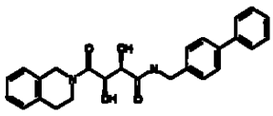
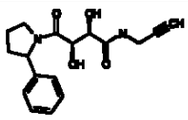
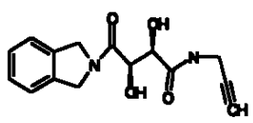
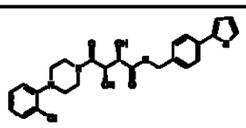
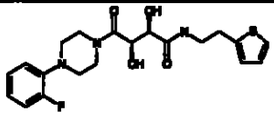
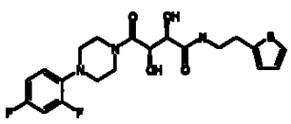
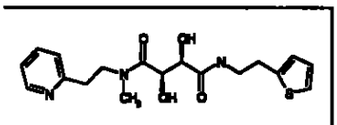


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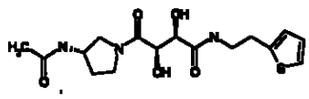
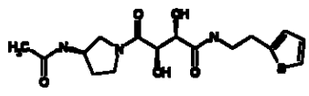
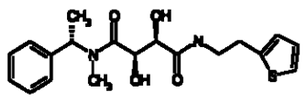
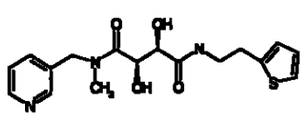
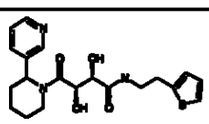
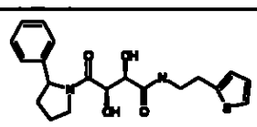
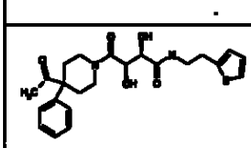
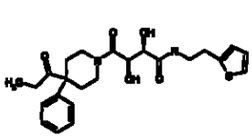
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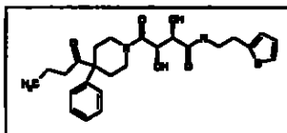
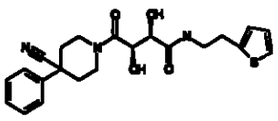
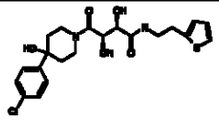
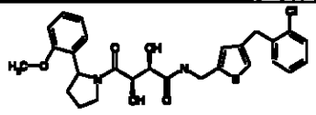
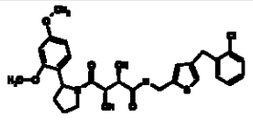
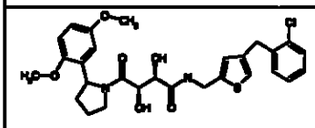
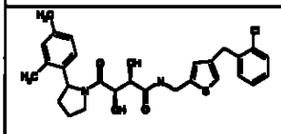








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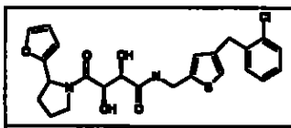
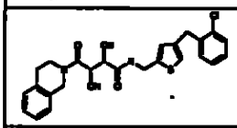
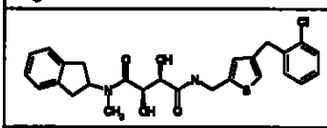
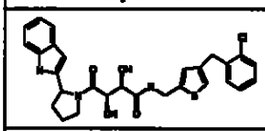
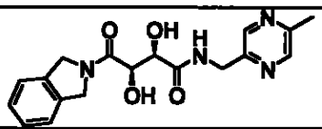
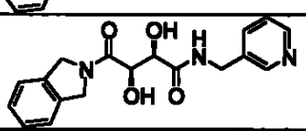
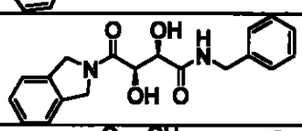
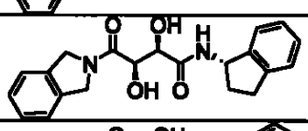
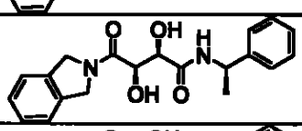
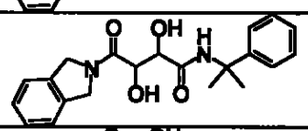
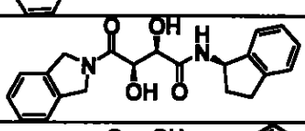
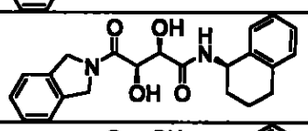
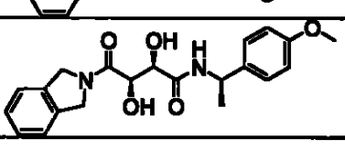









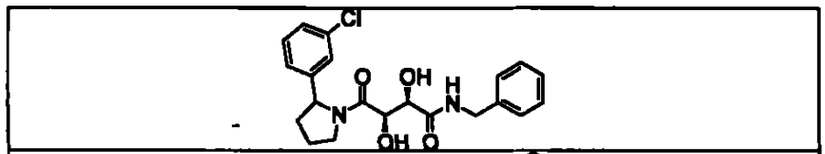
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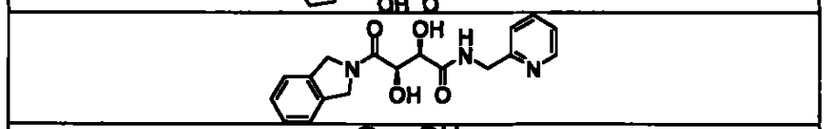








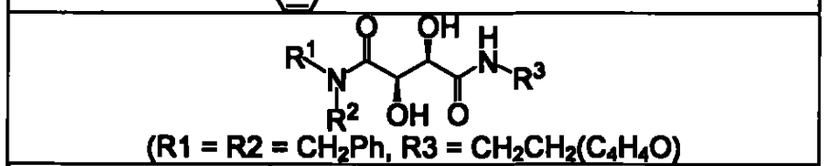
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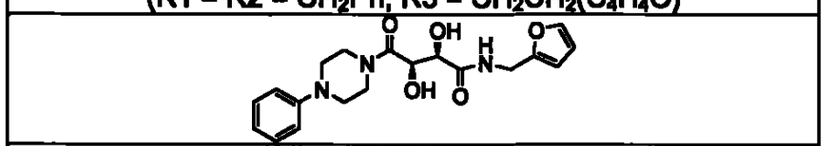














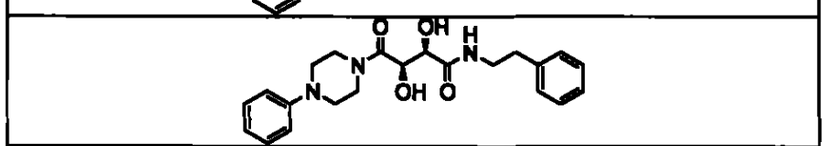


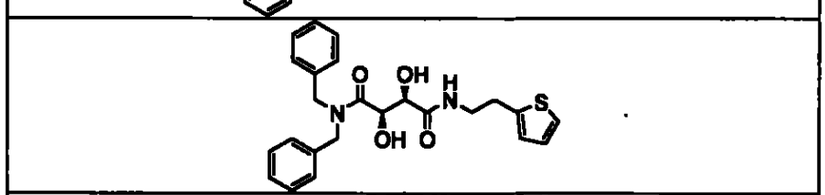


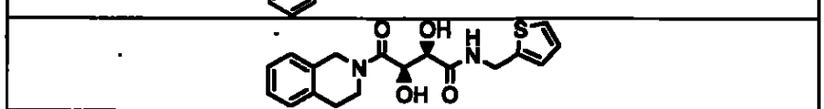


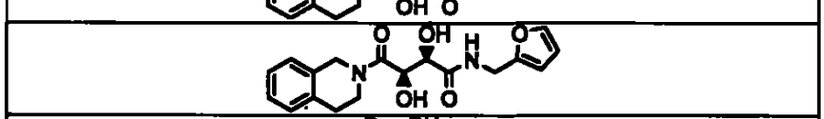
(R1 = R2 = CH_2Ph, R3 = $CH_2CH_2(C_4H_4O)$

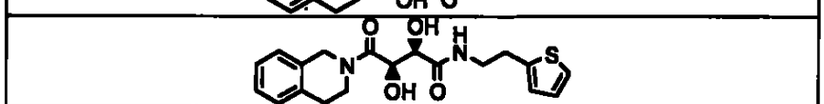


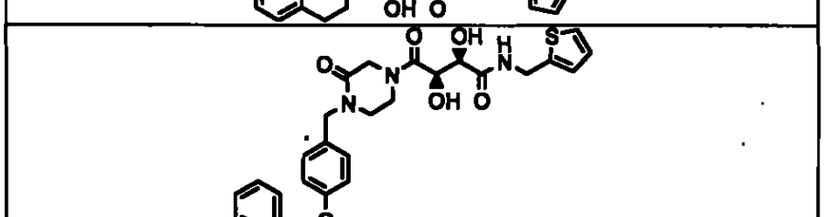


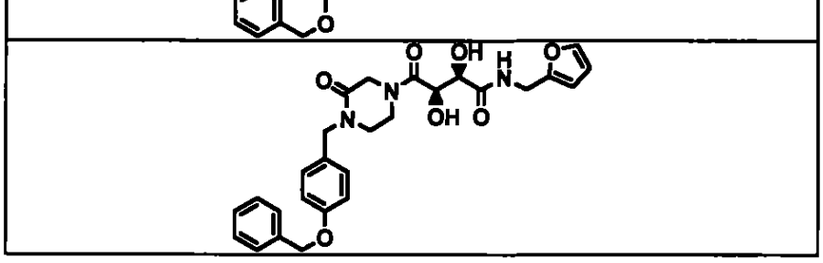






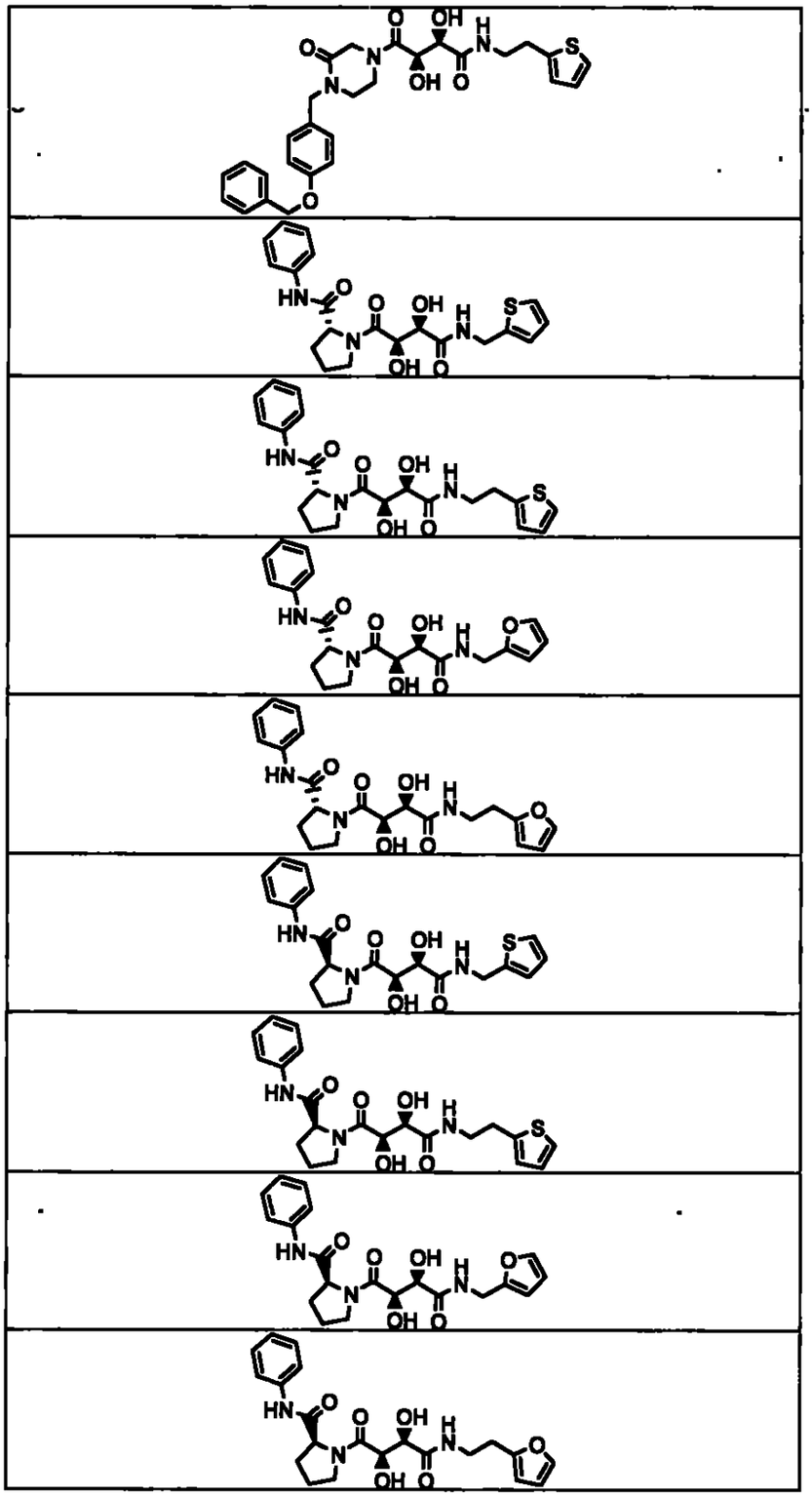


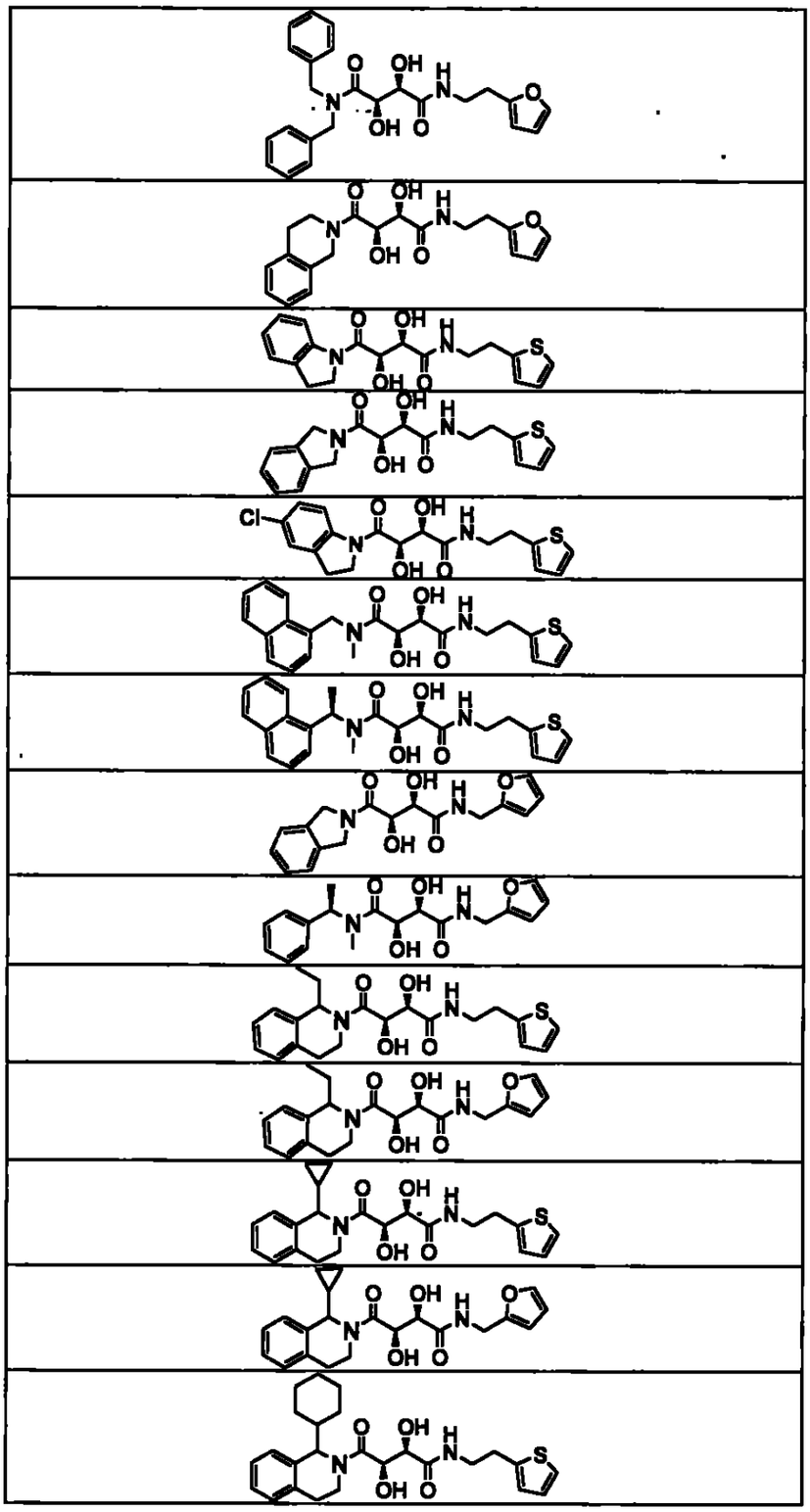


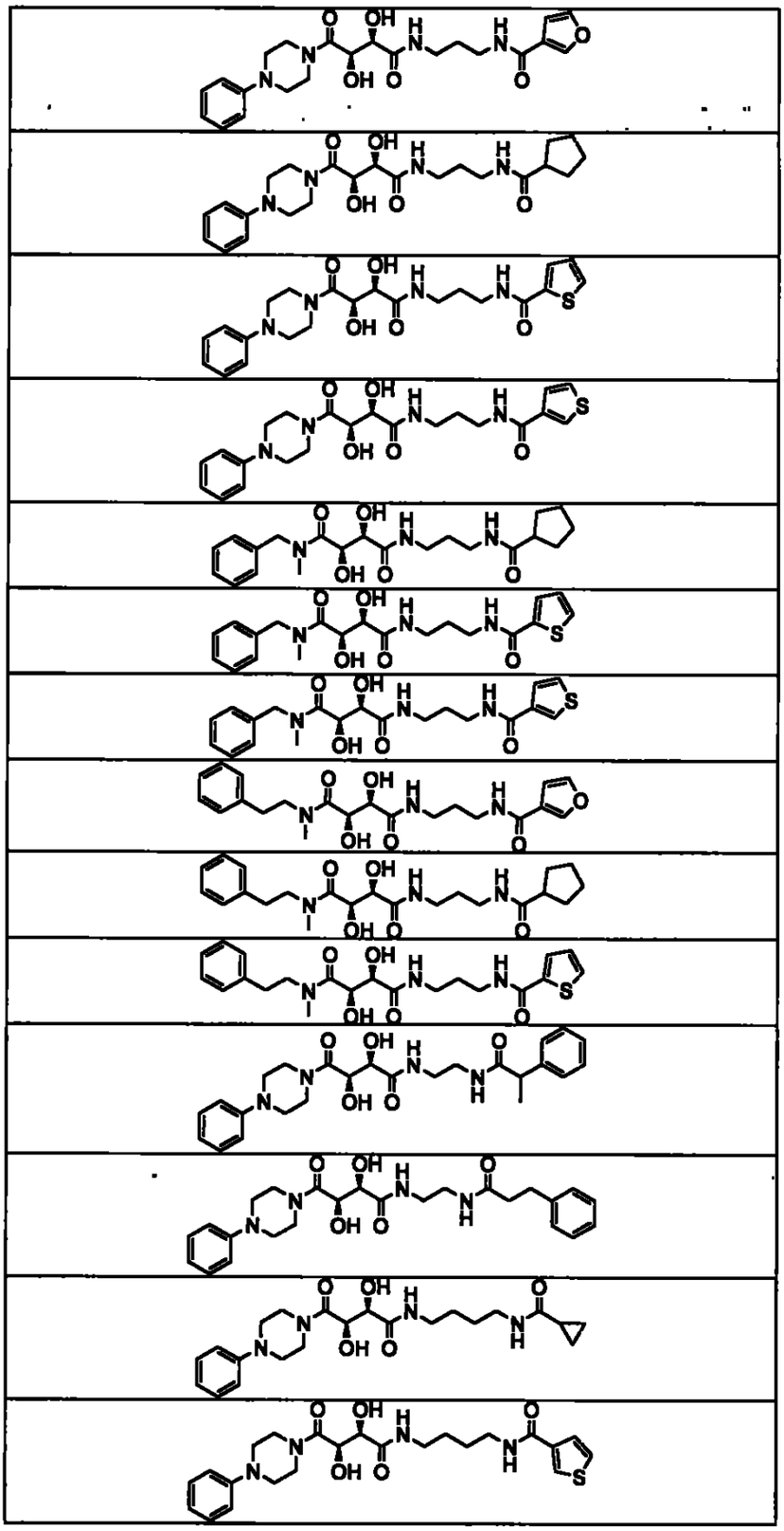


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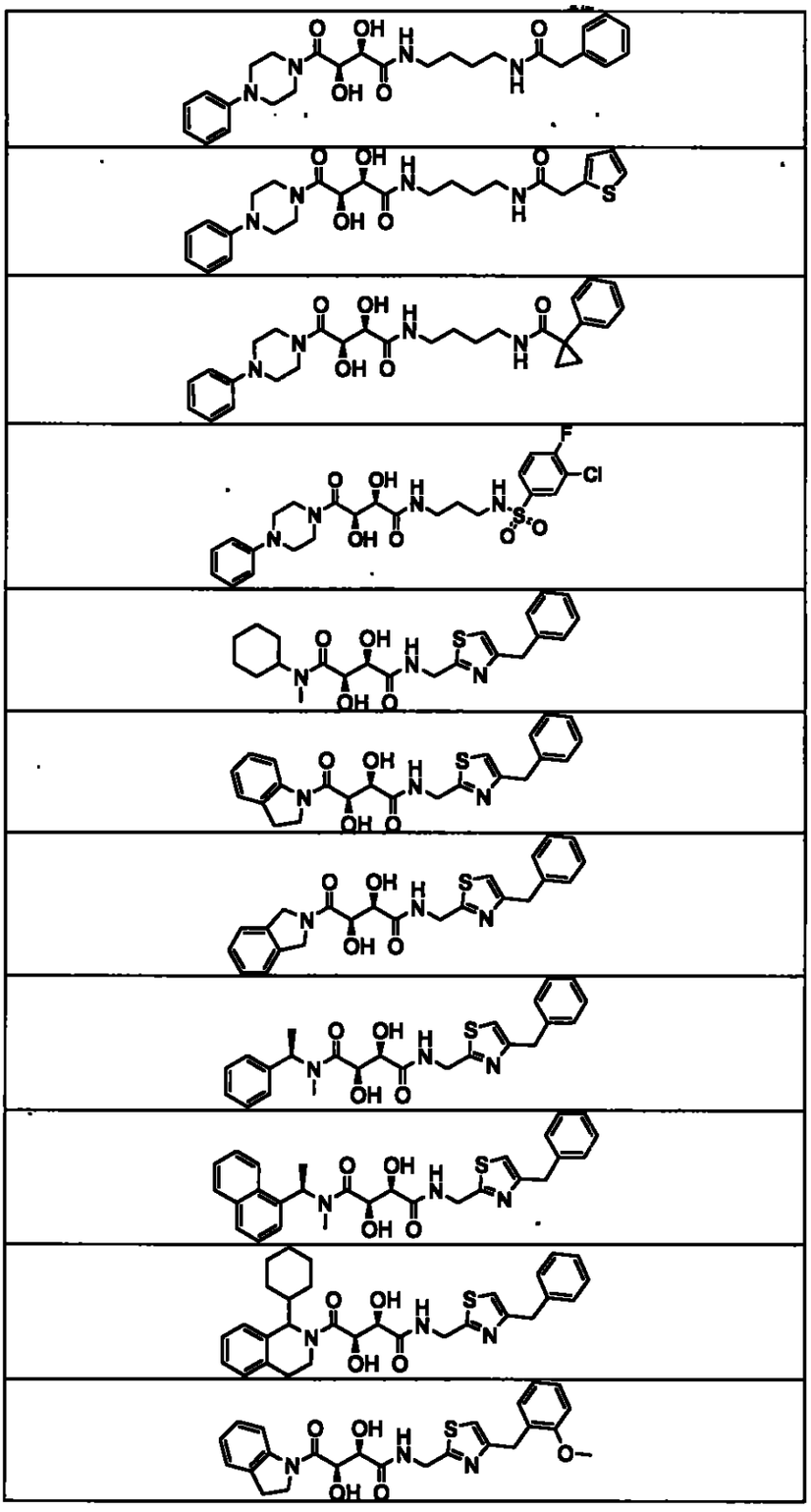


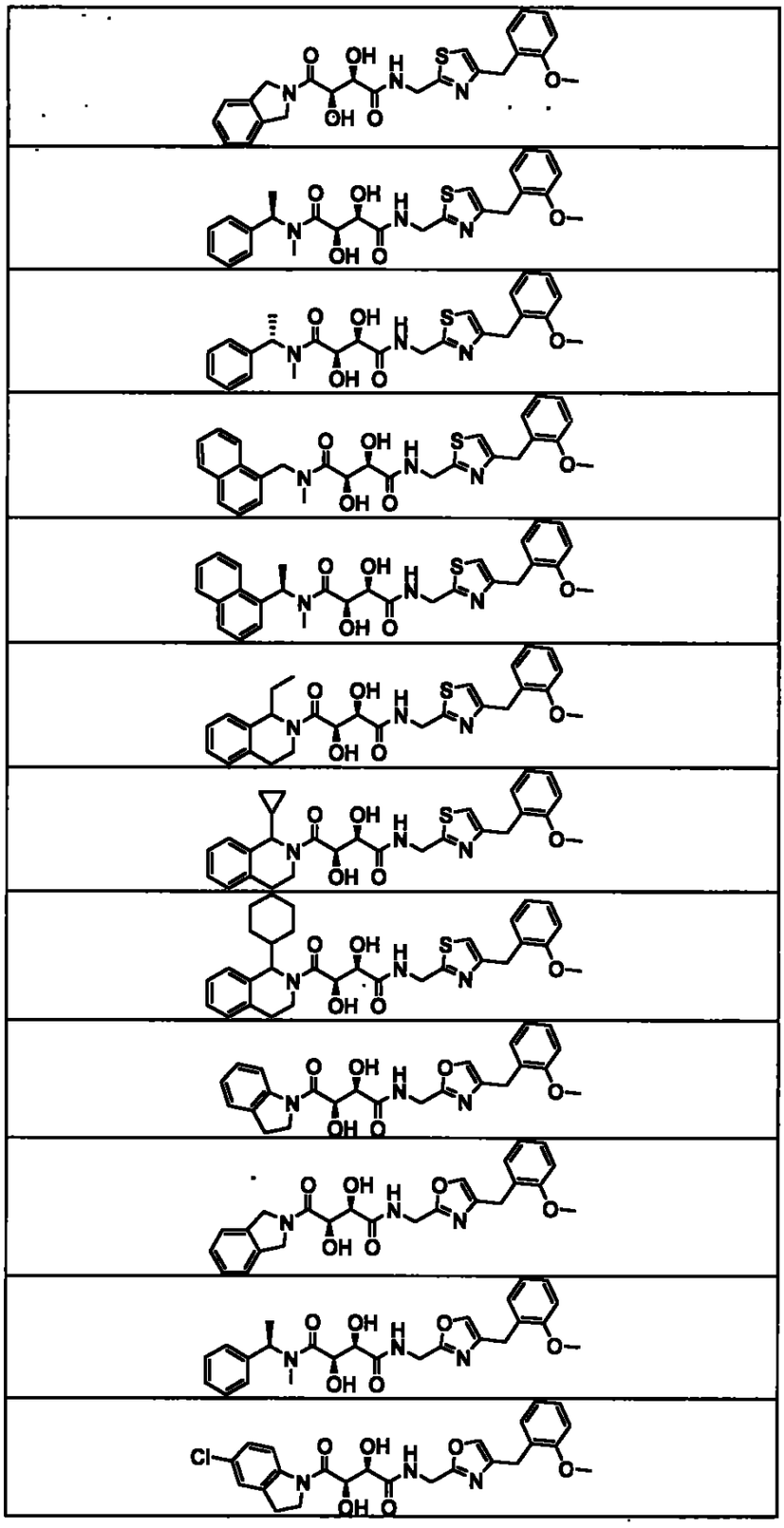


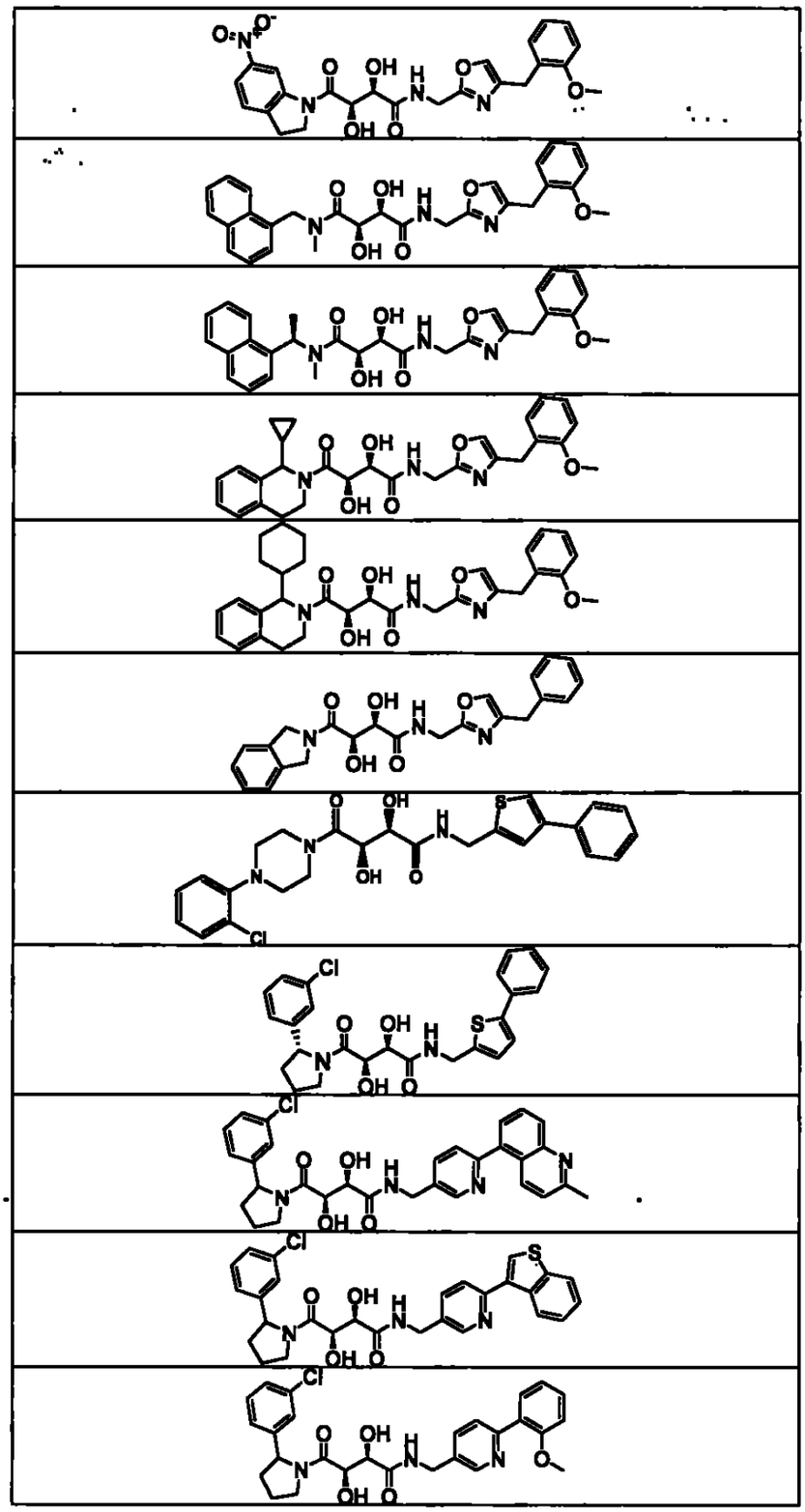


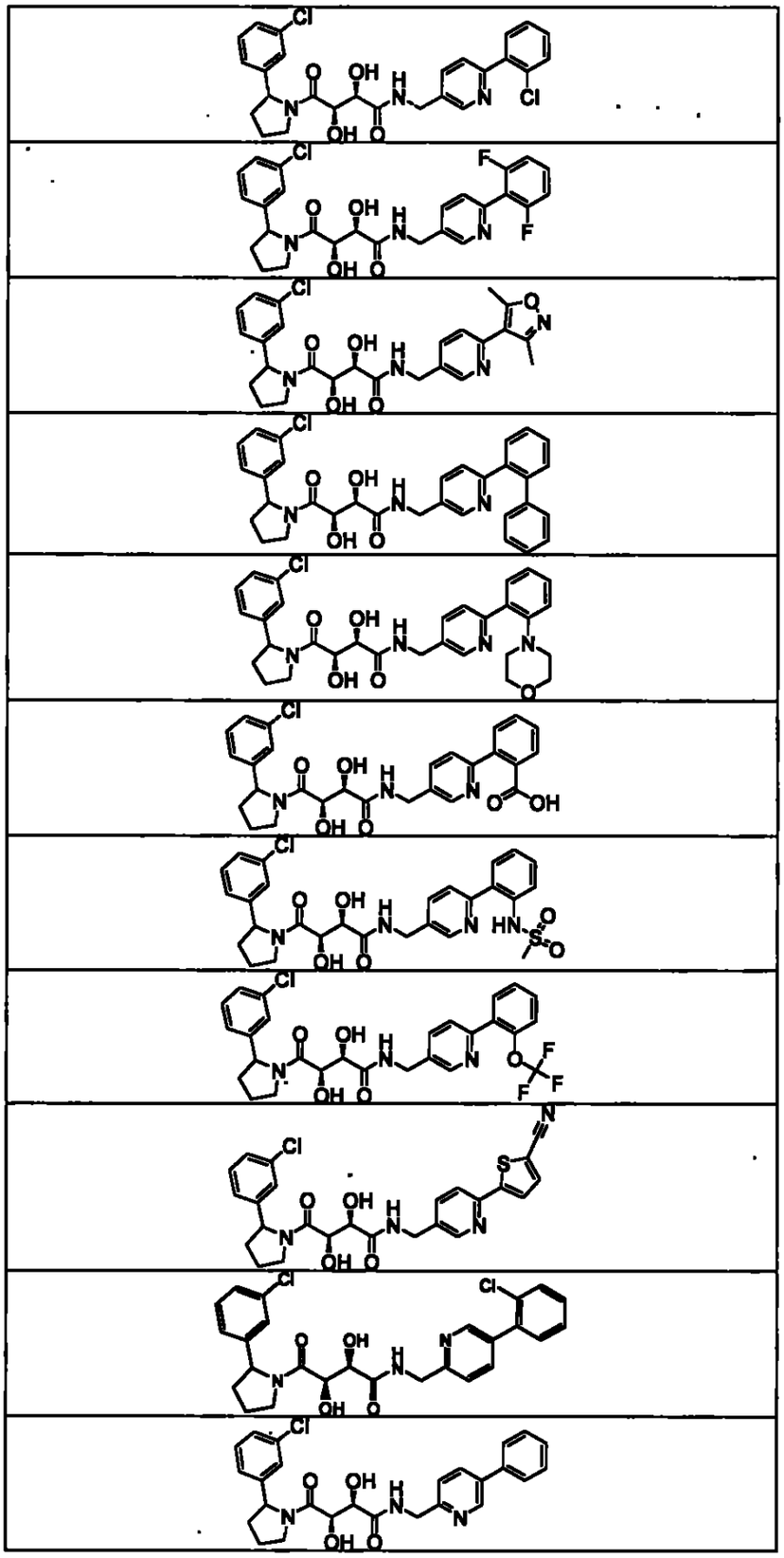
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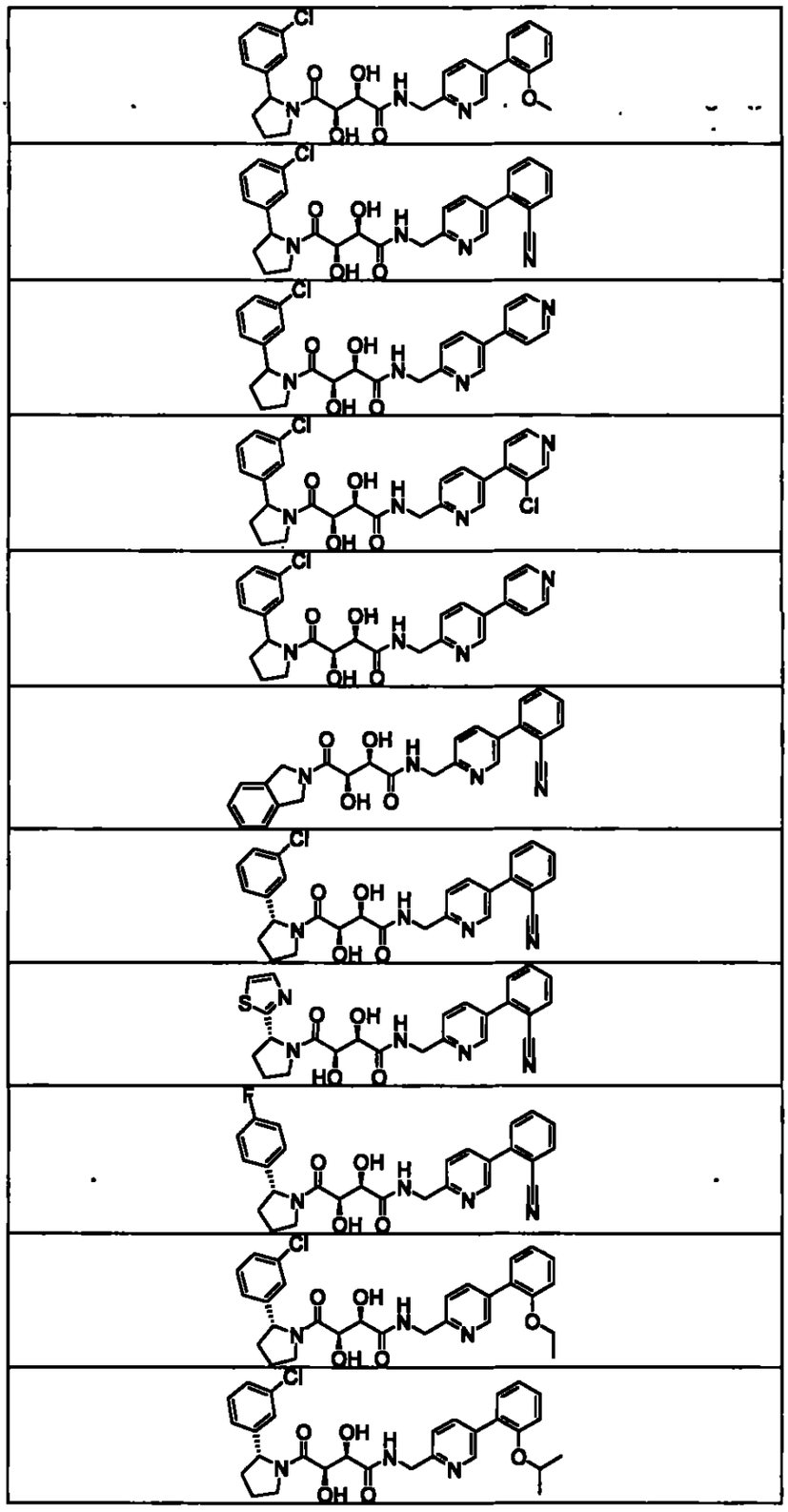
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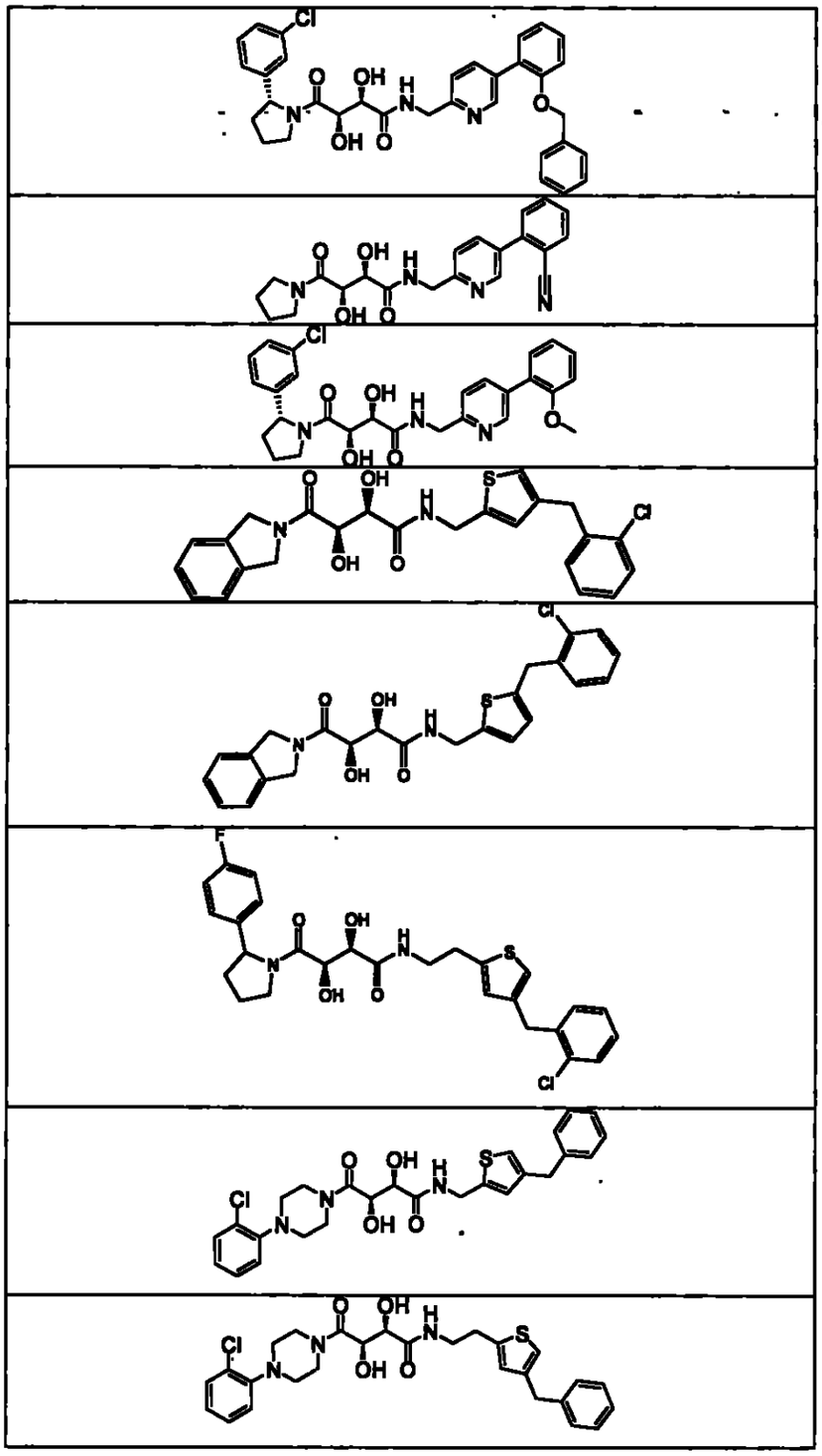


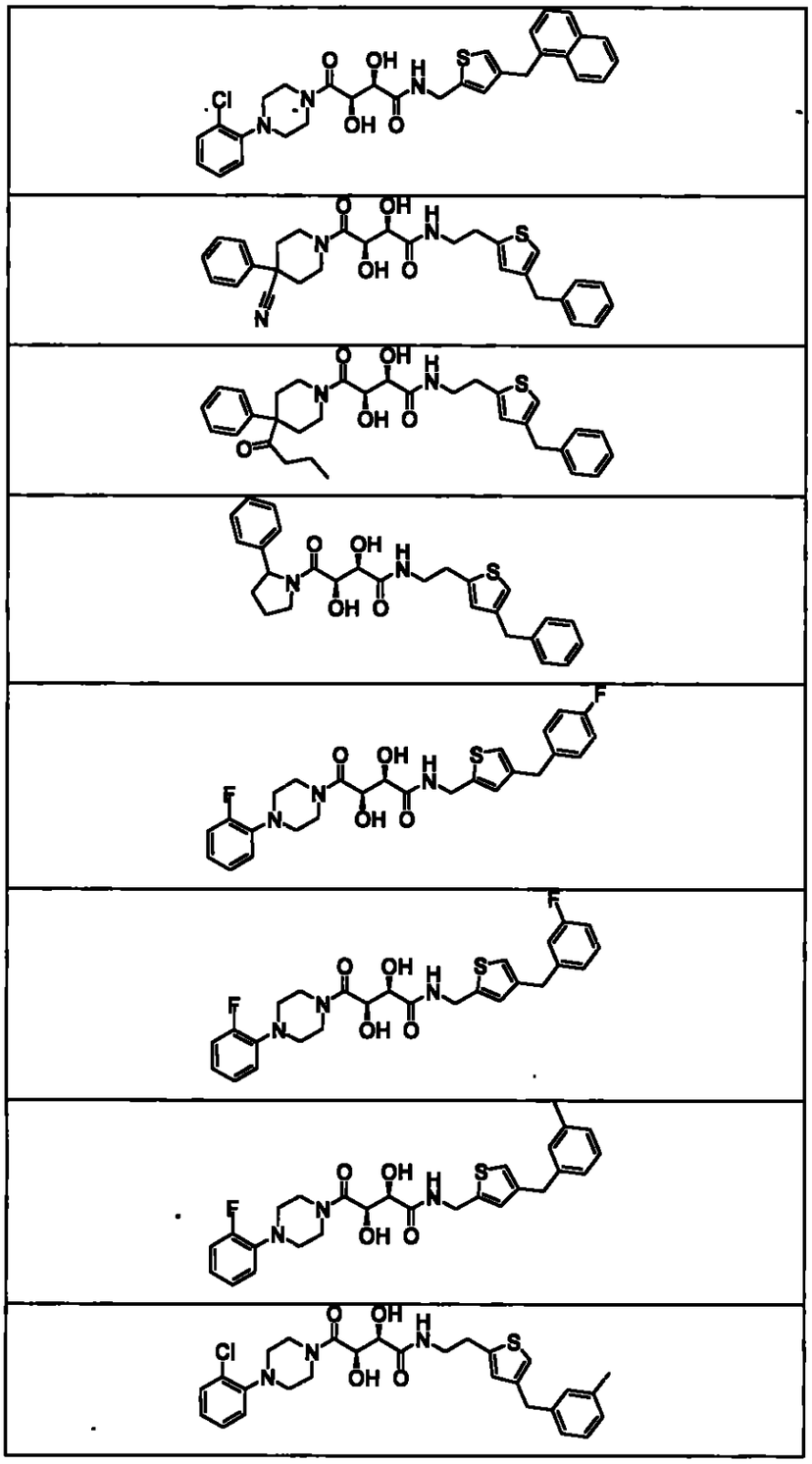


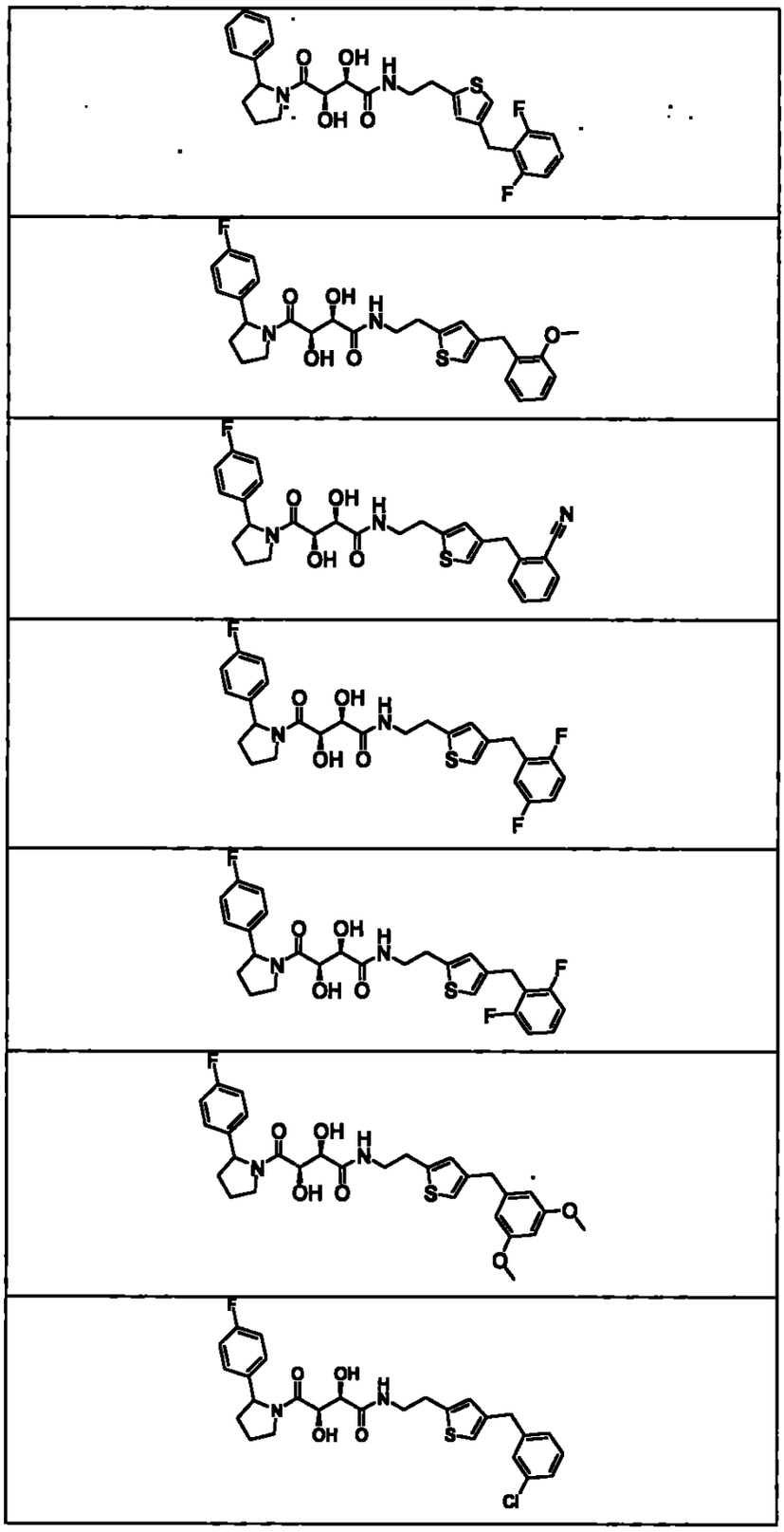




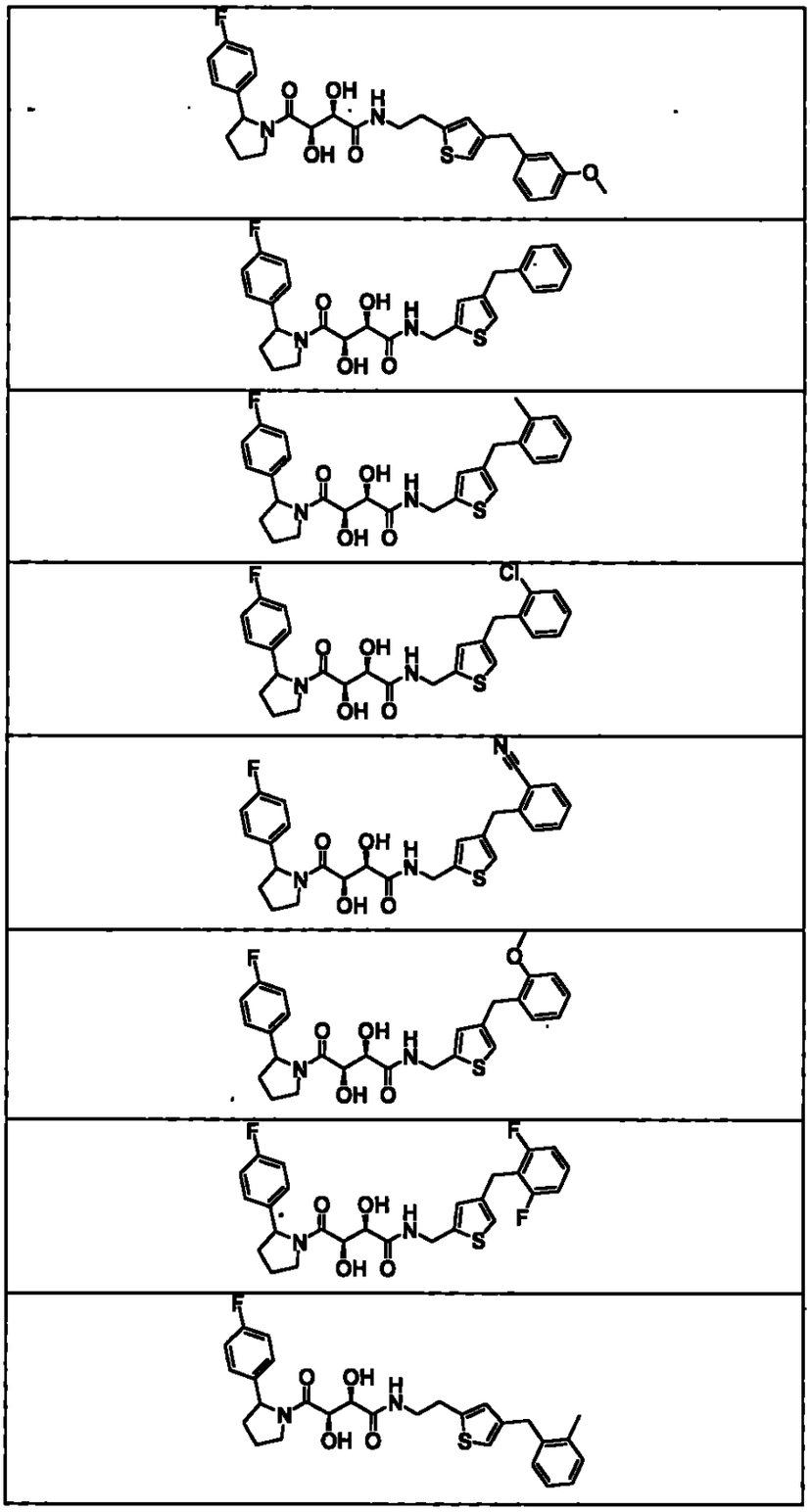


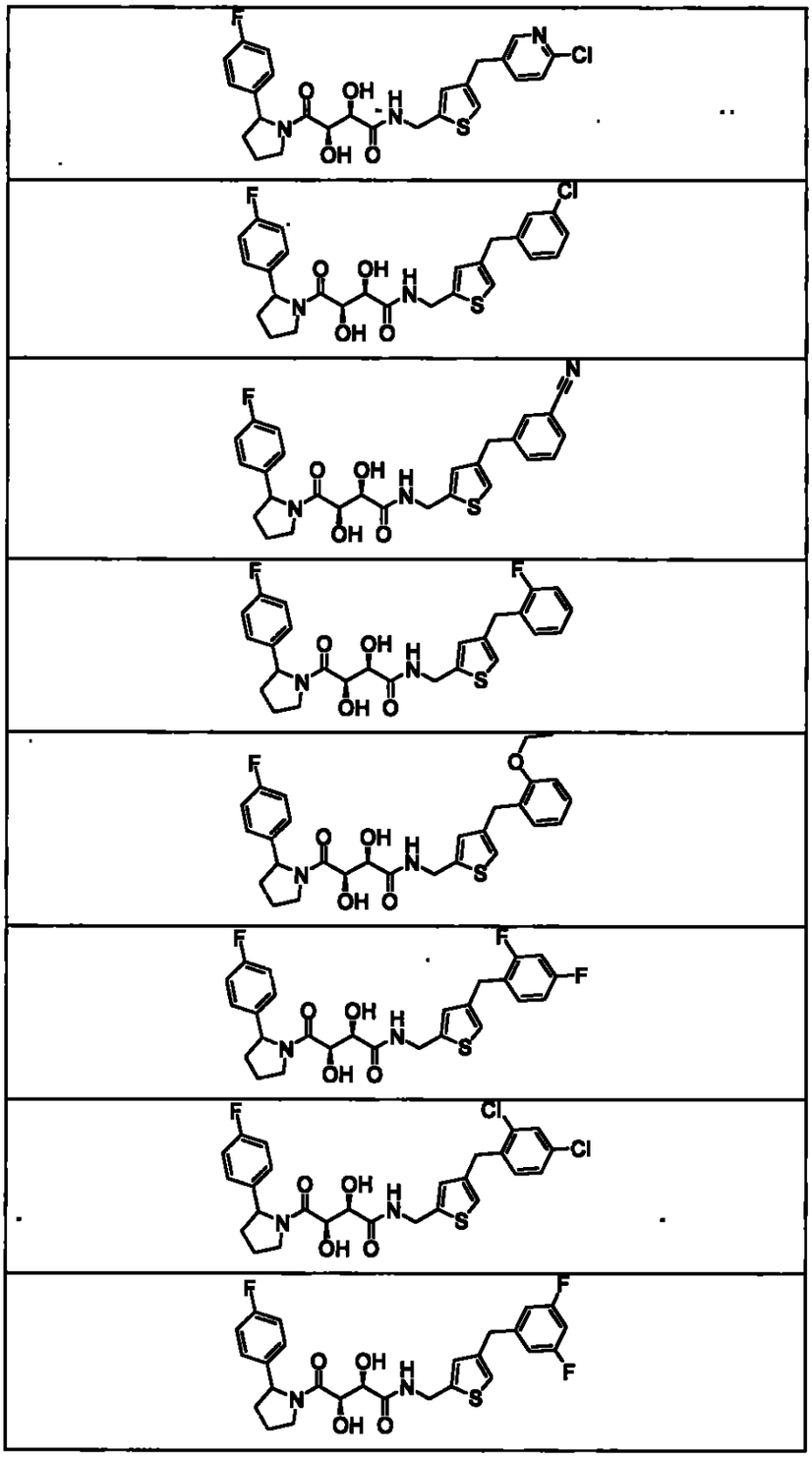


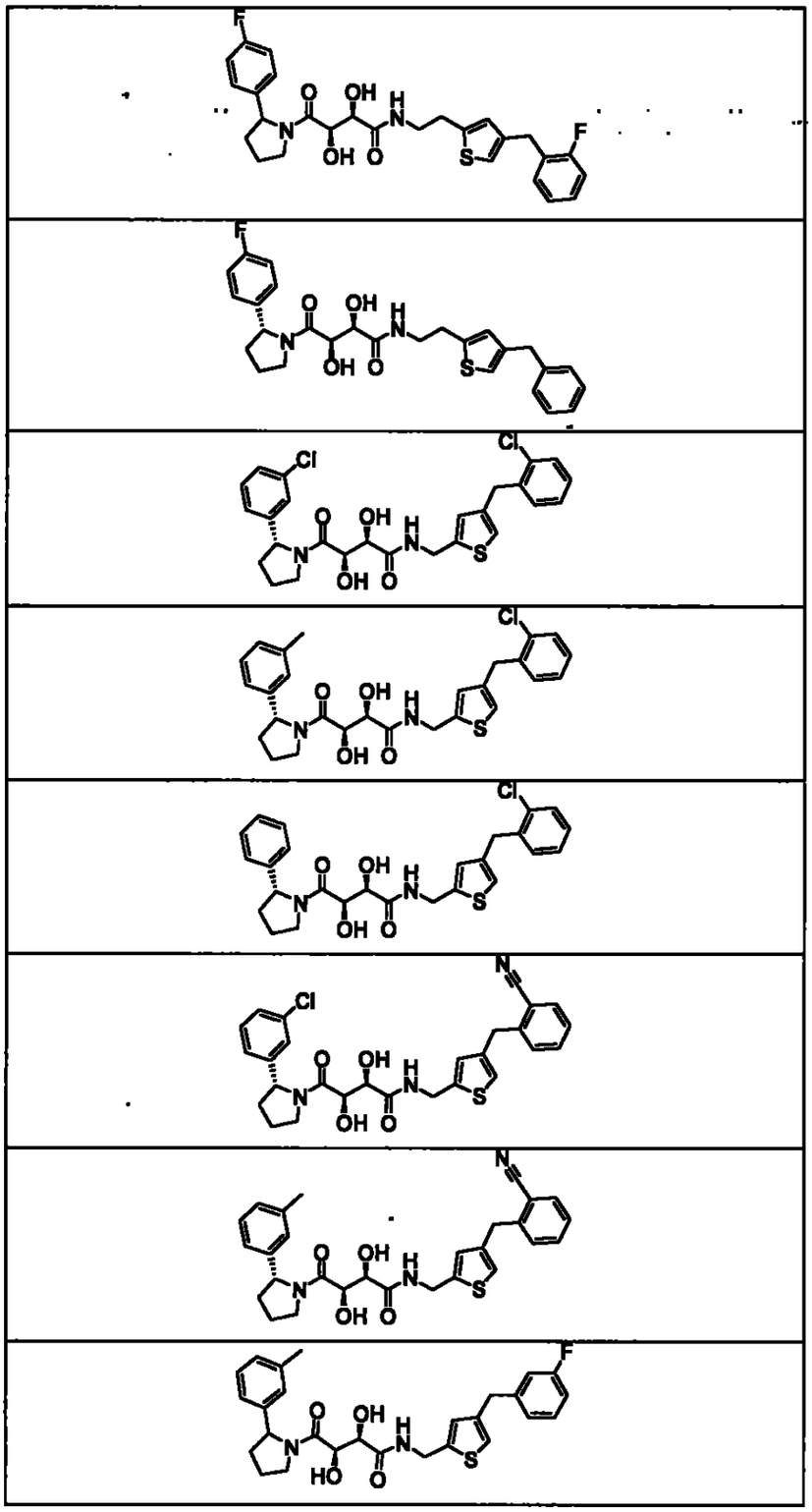


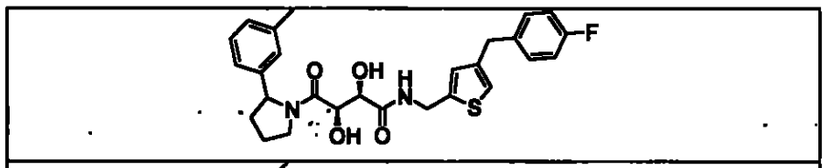


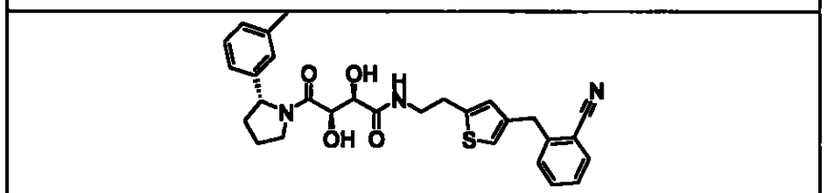
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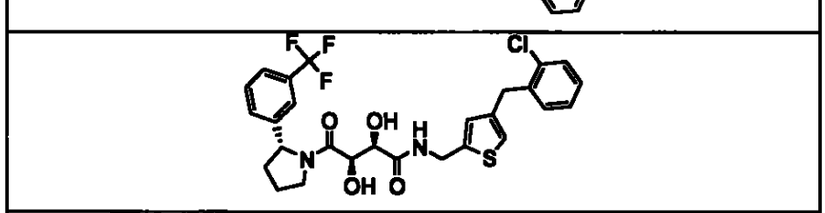


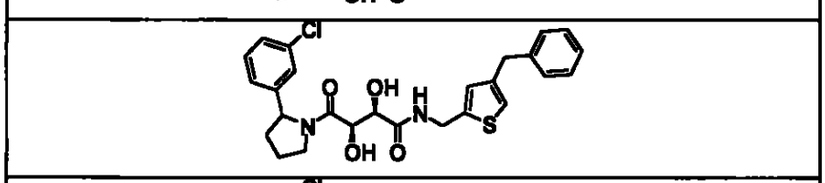


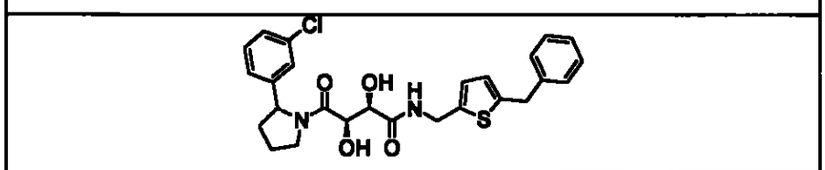


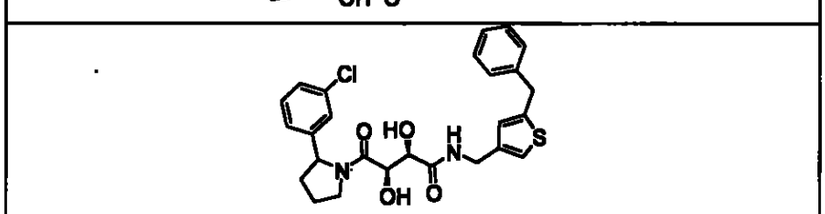


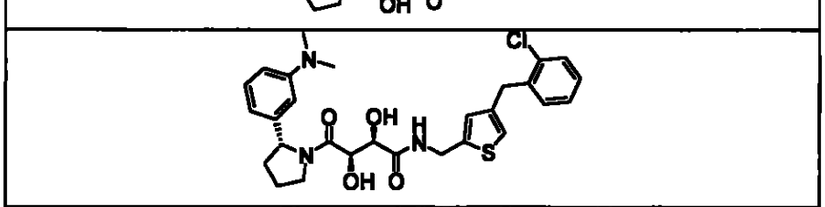


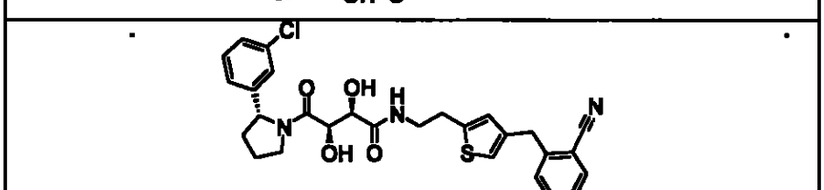


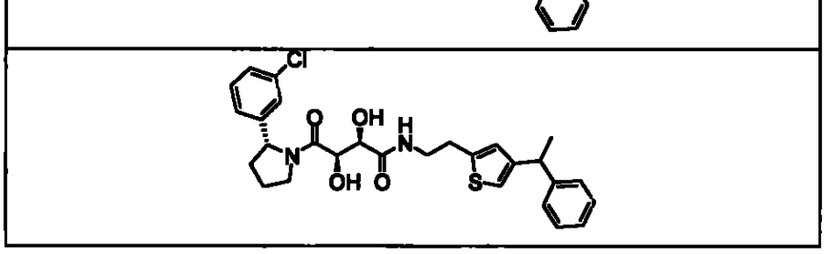




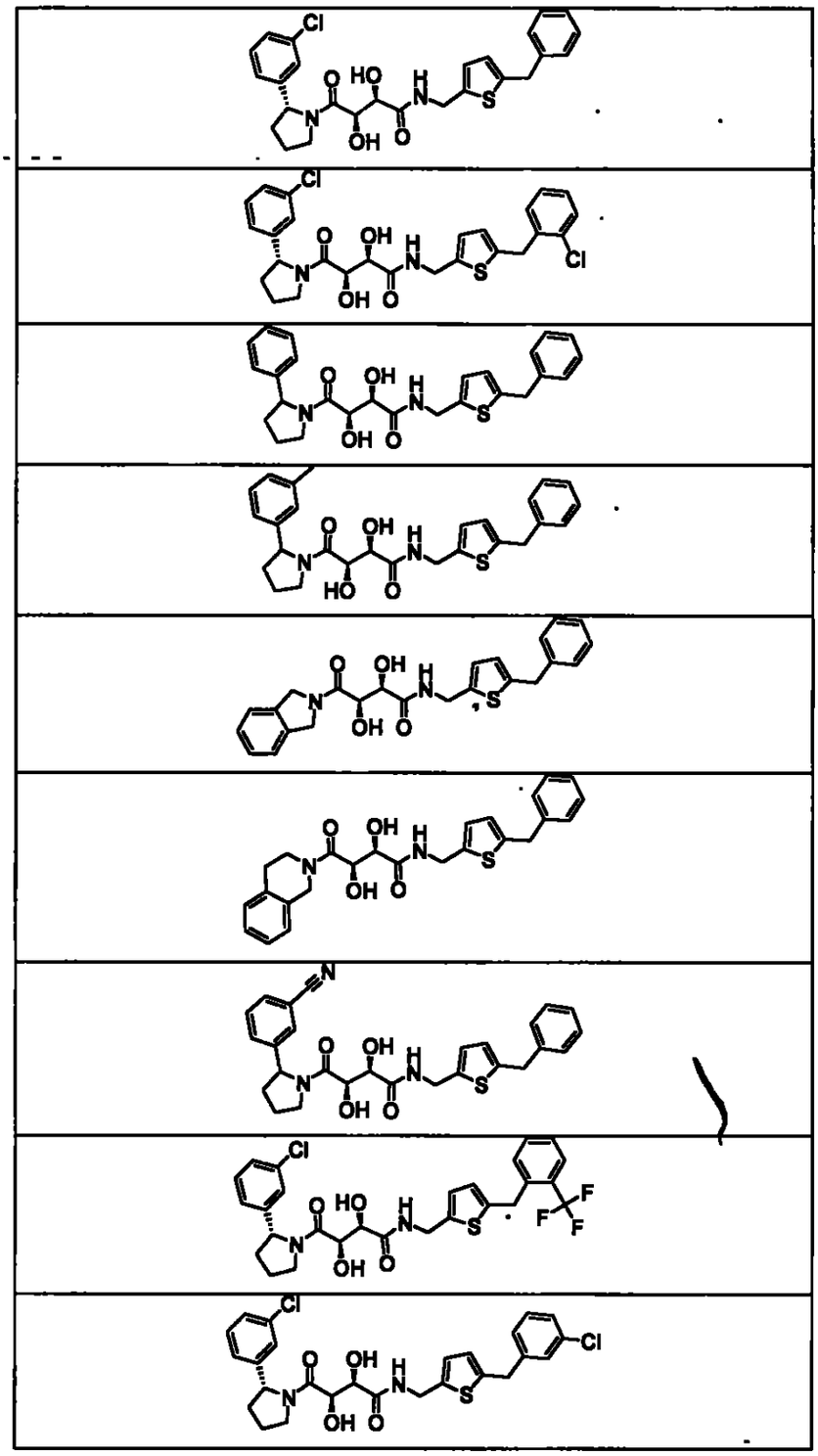


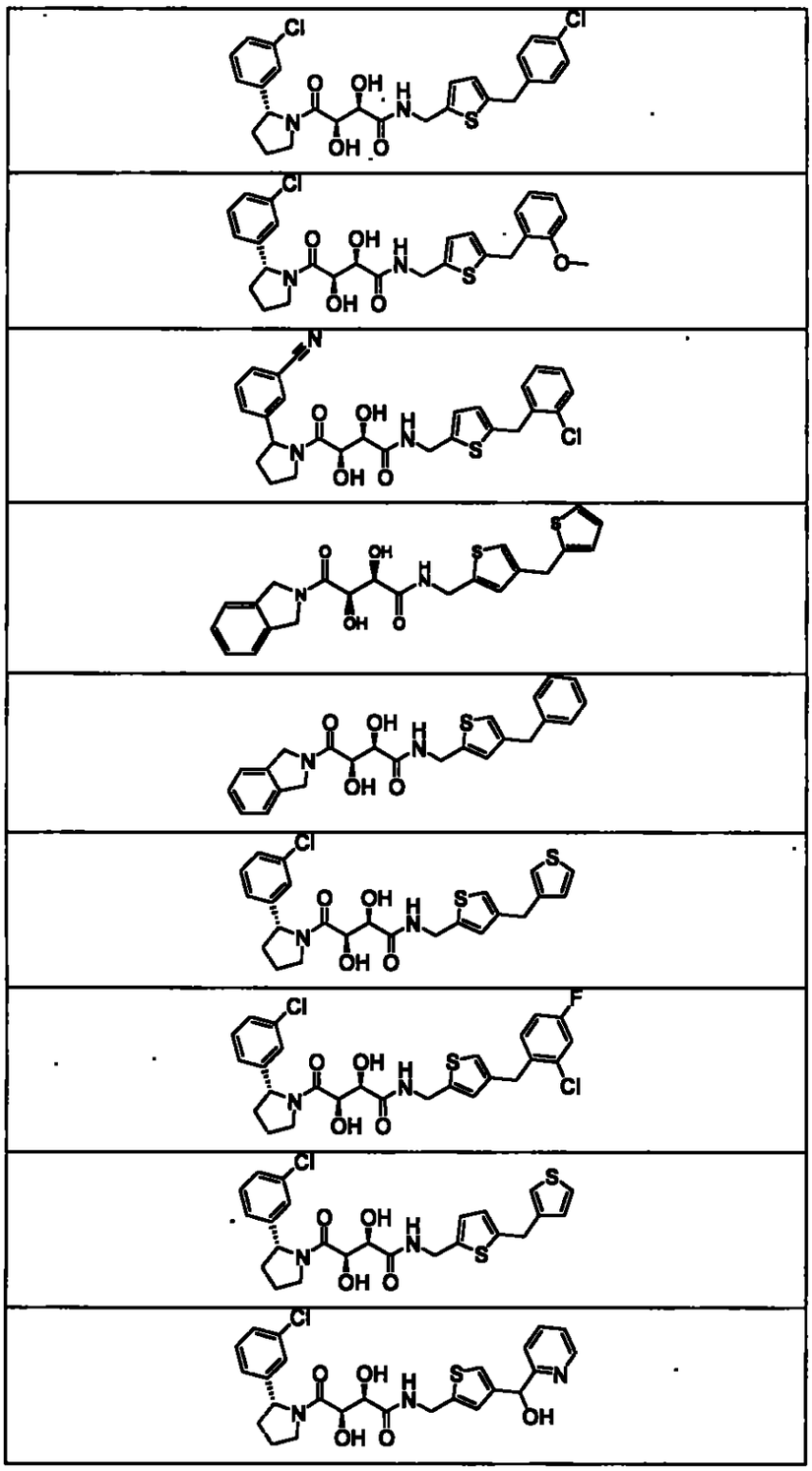


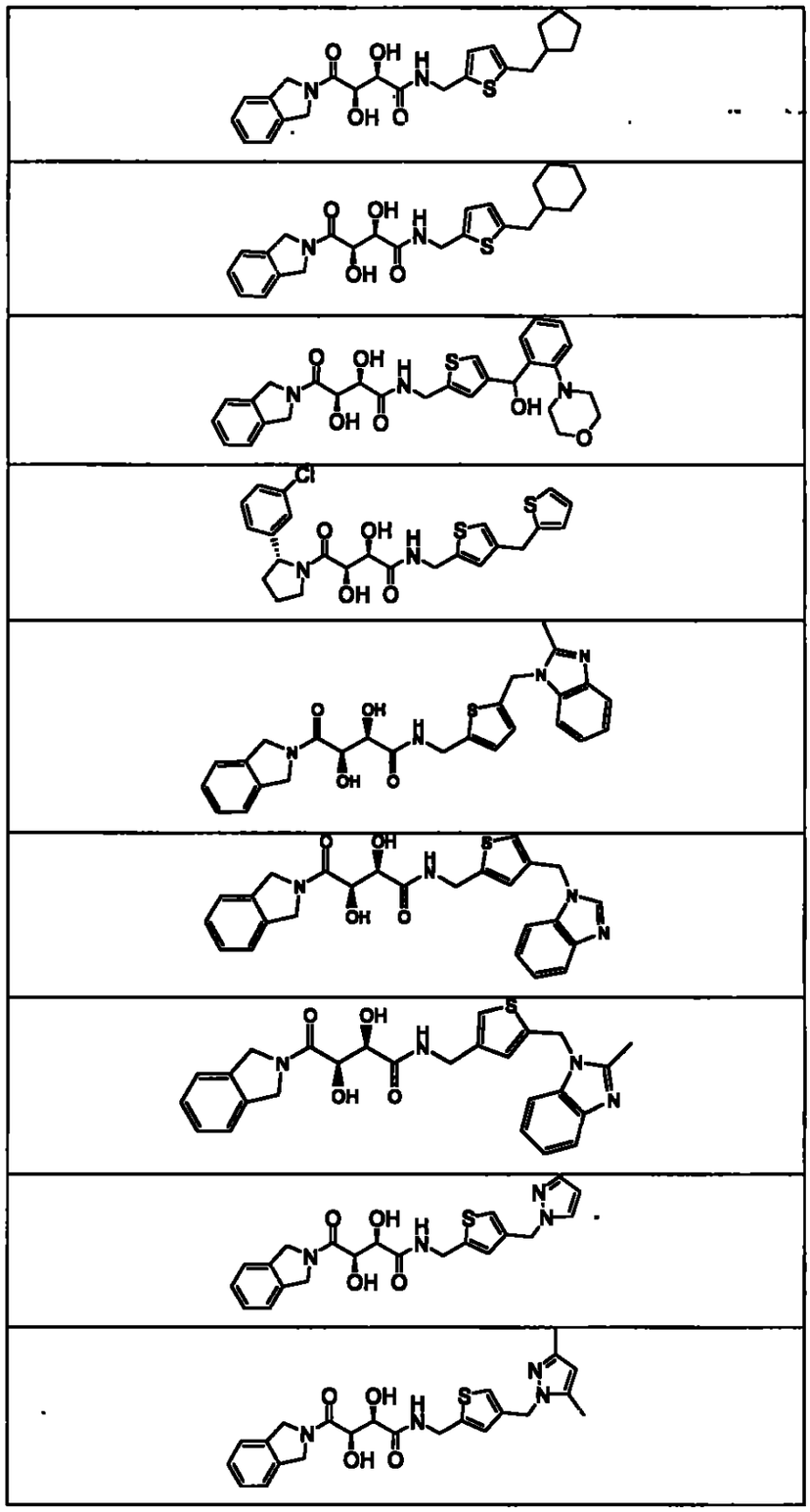


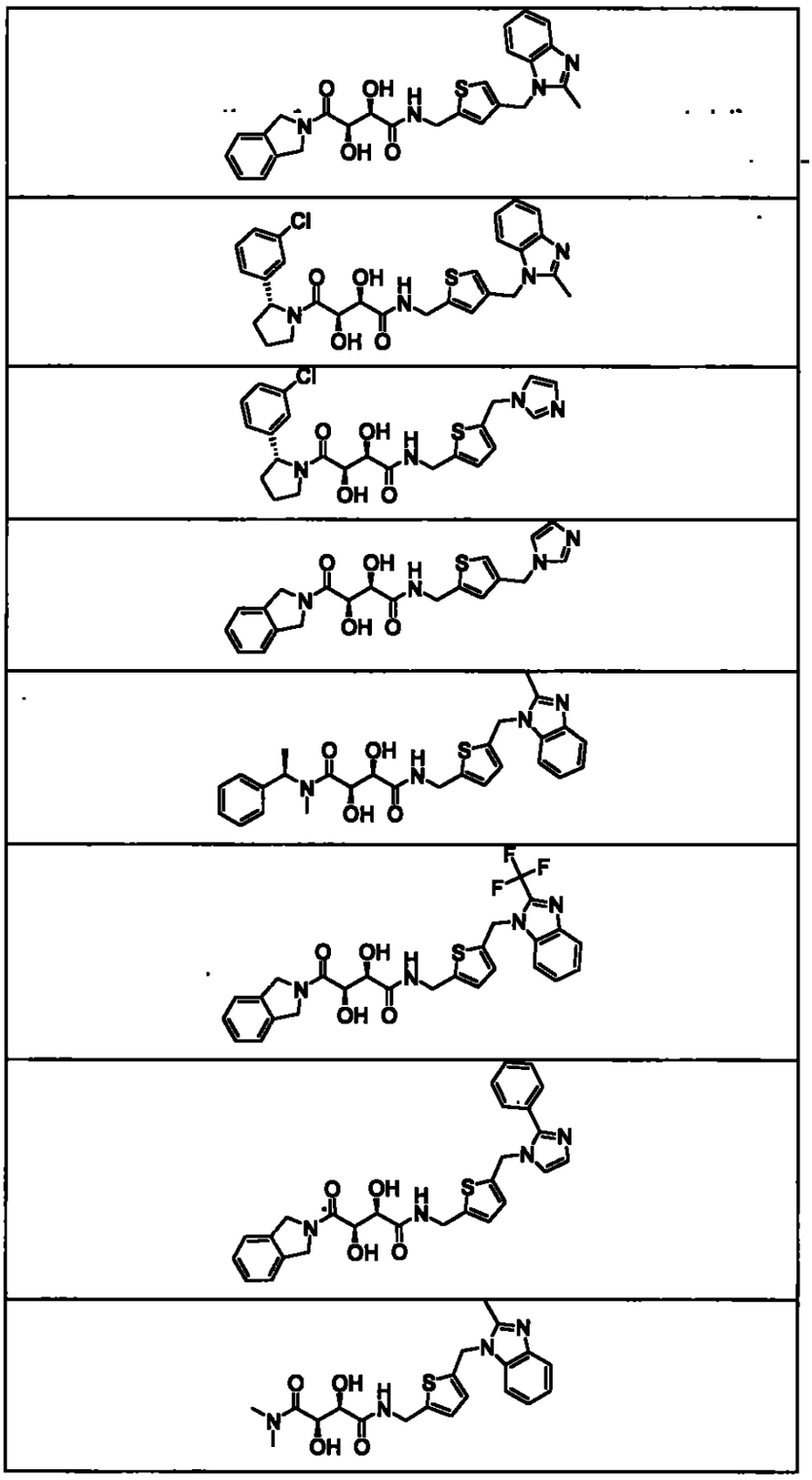


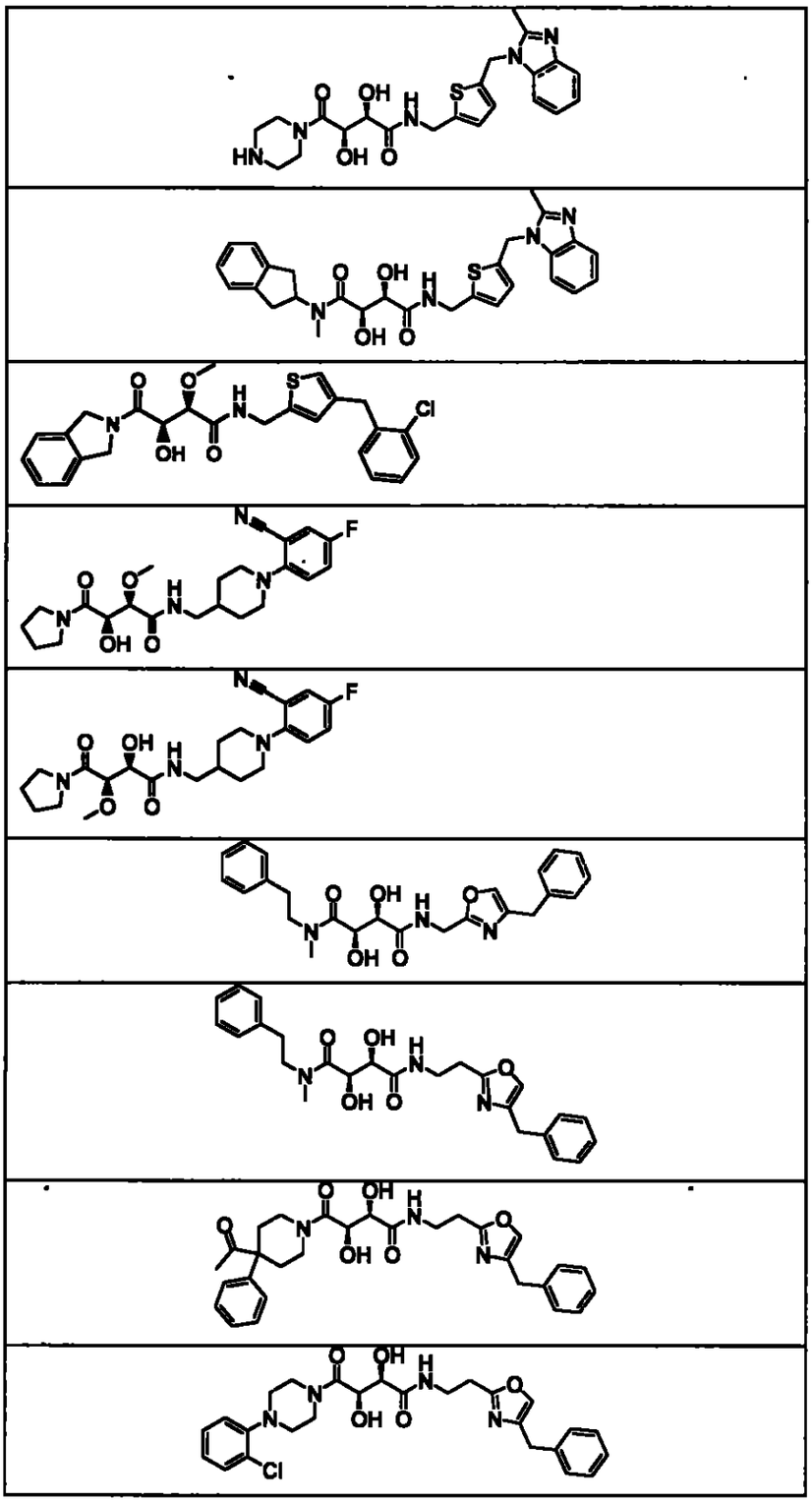
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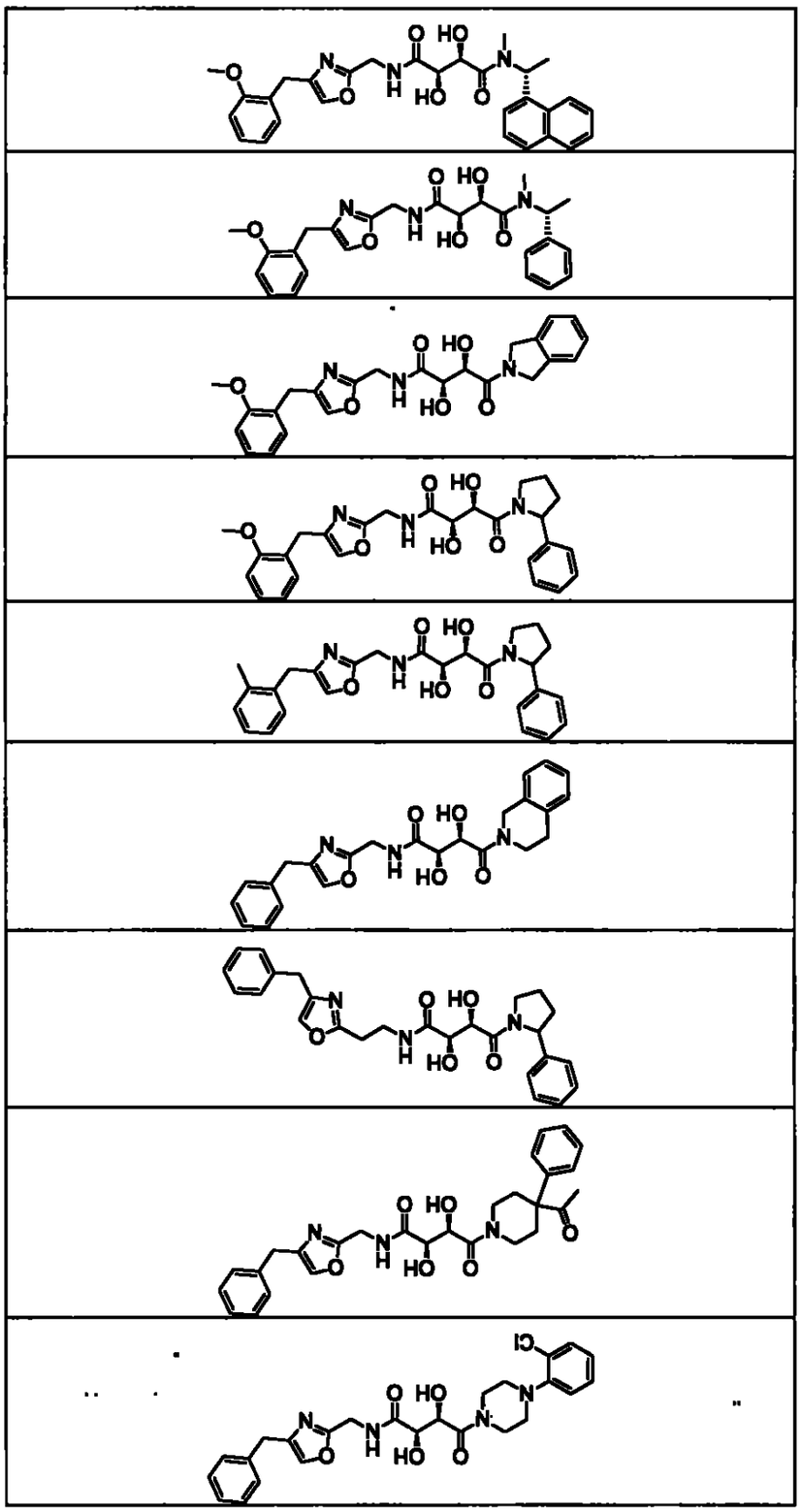


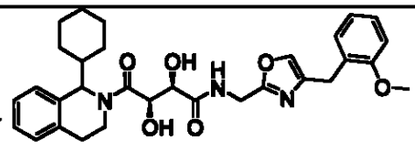
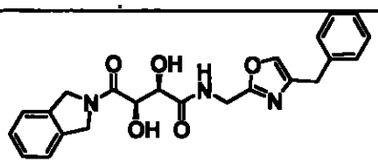
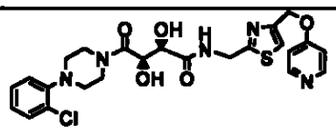
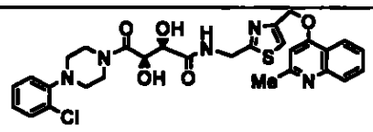
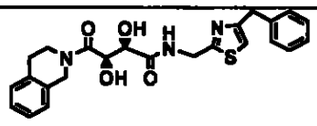
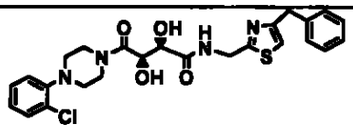
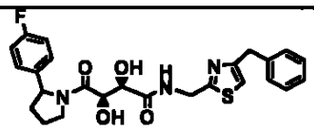
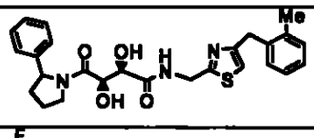
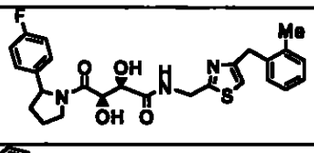
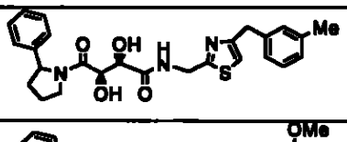
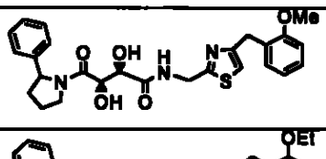
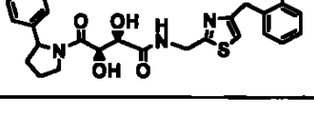




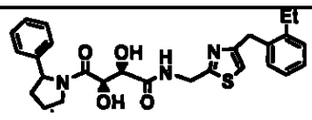
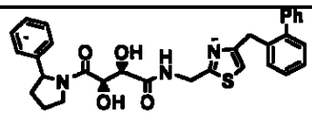
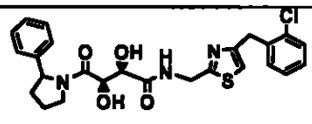
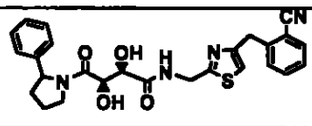
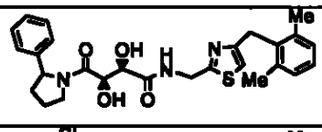
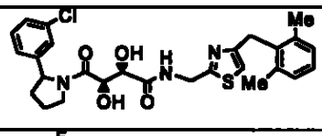
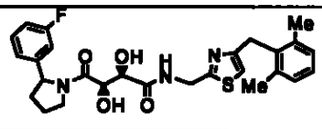
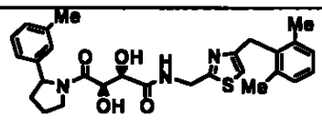
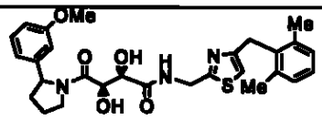
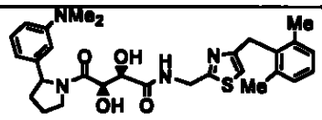
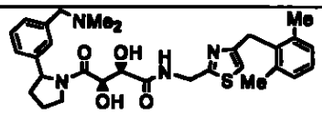
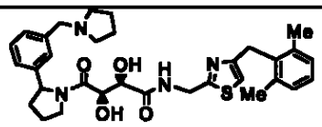
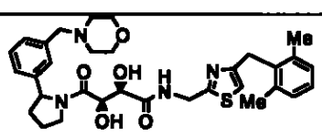


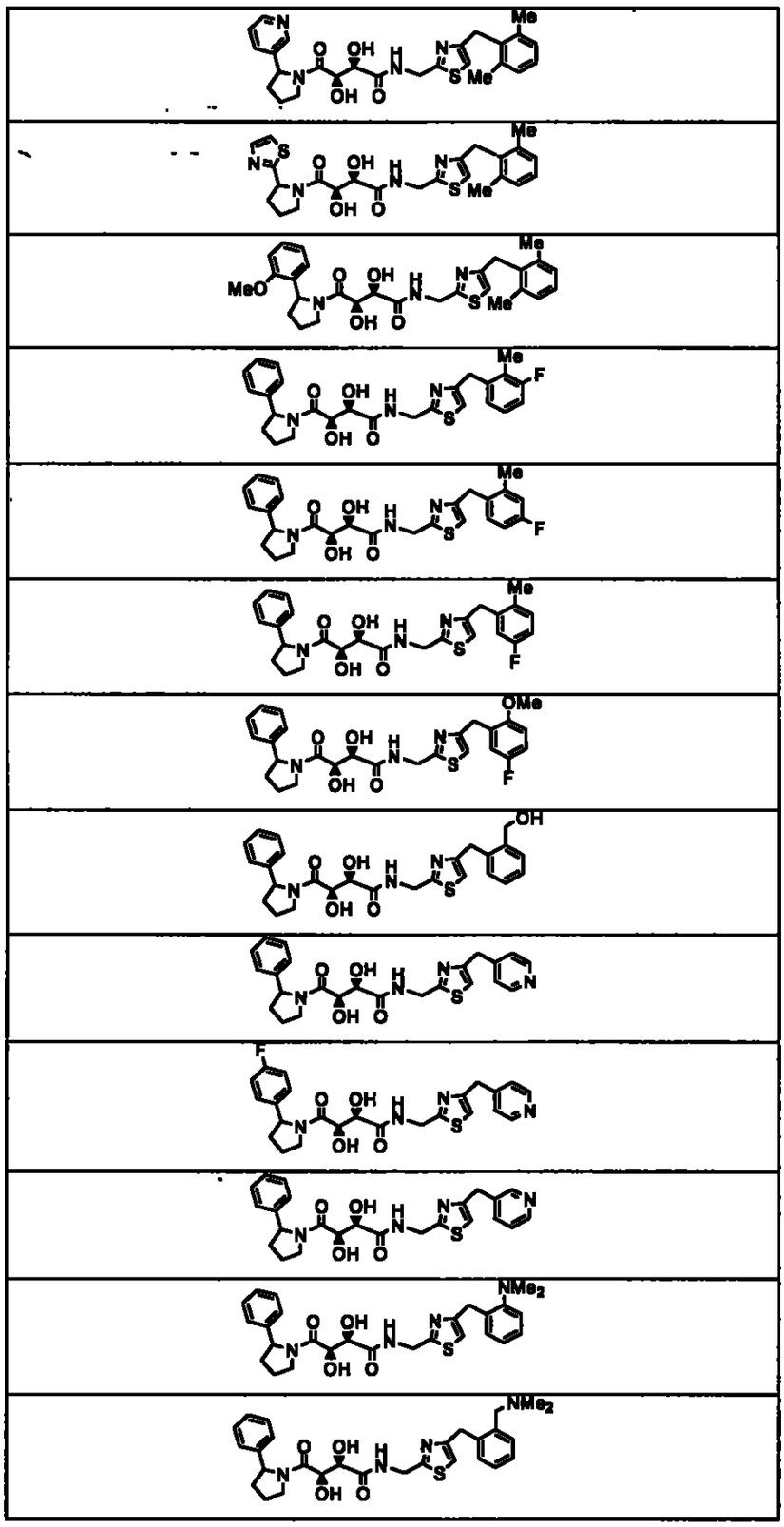


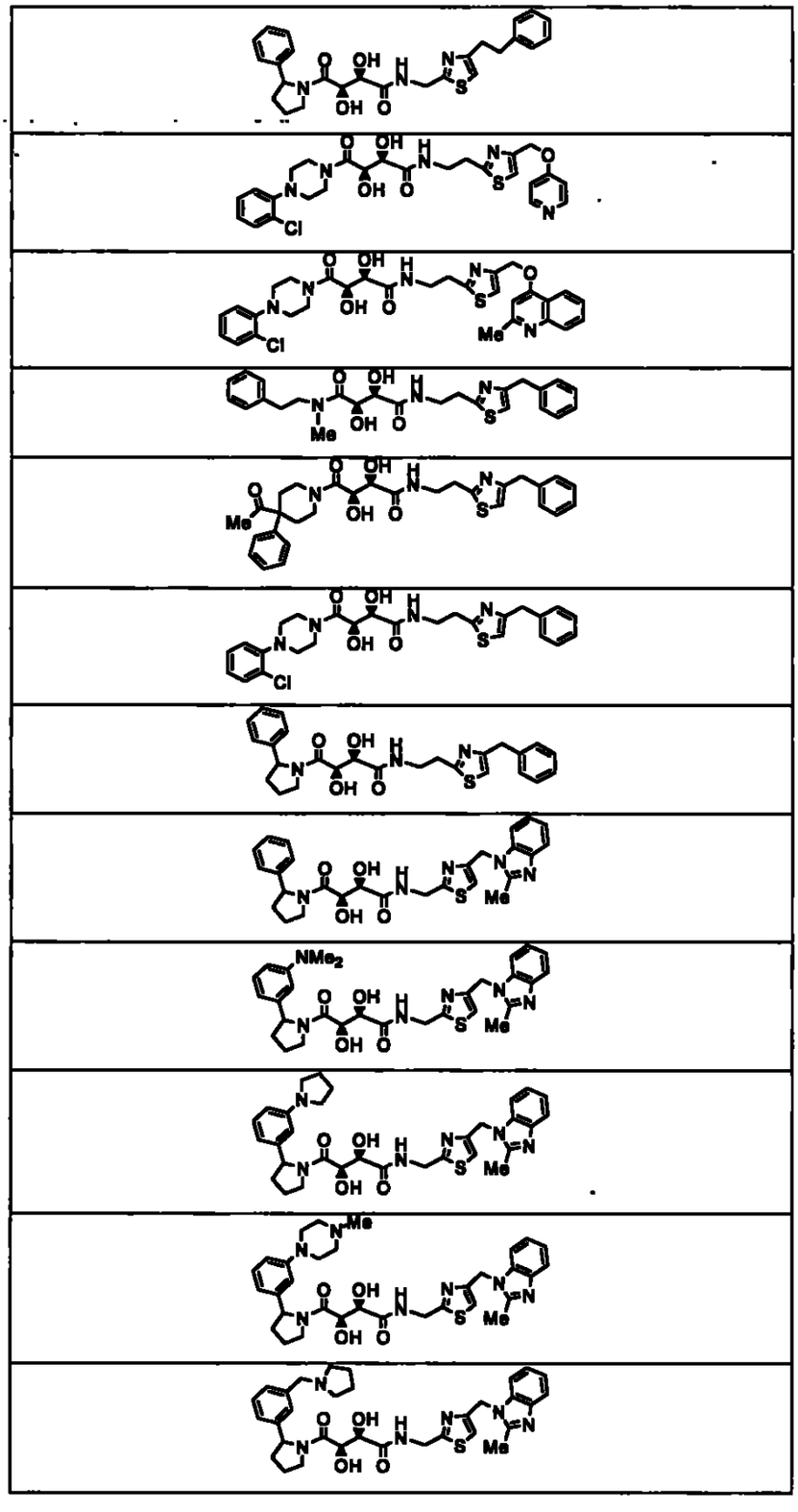


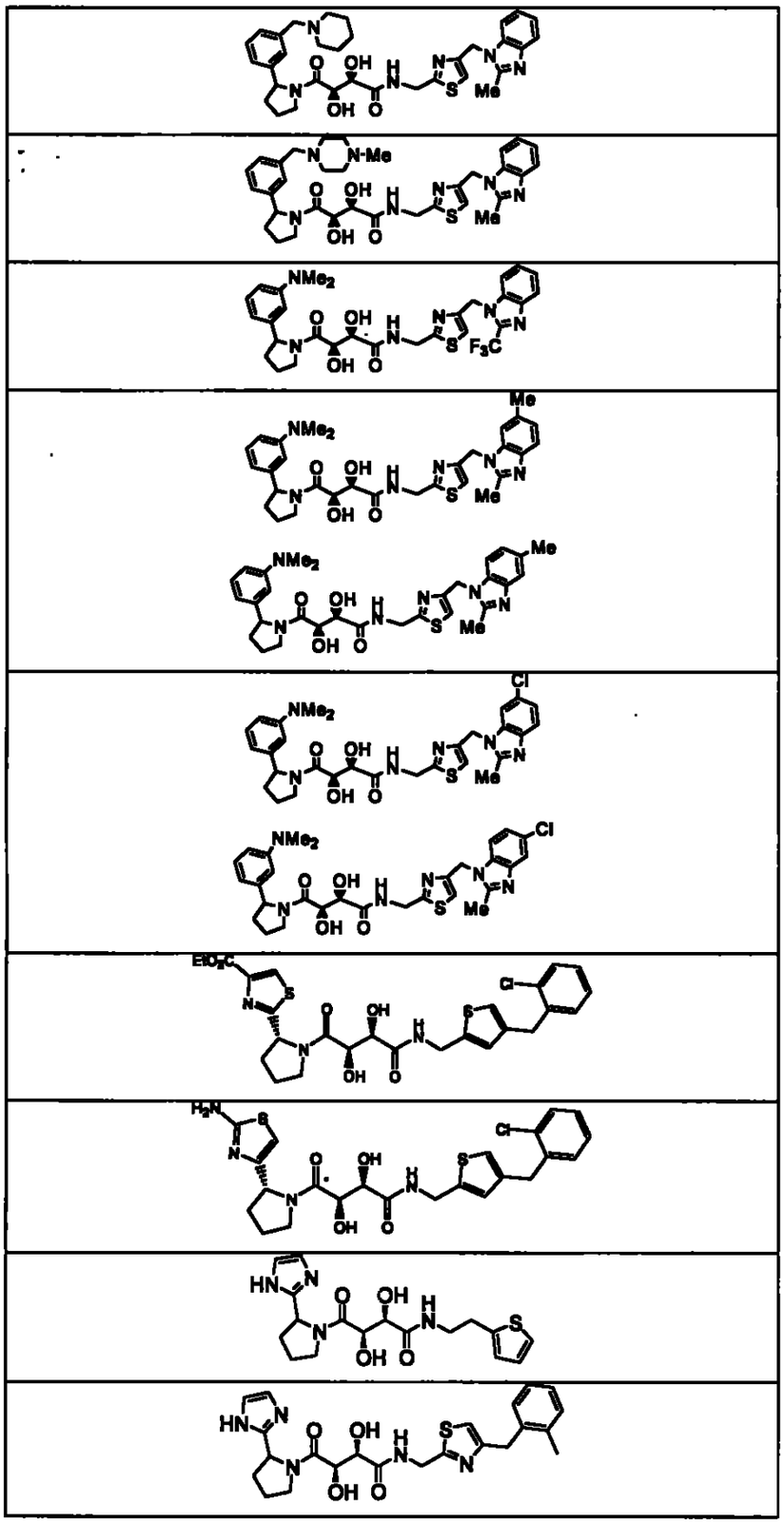













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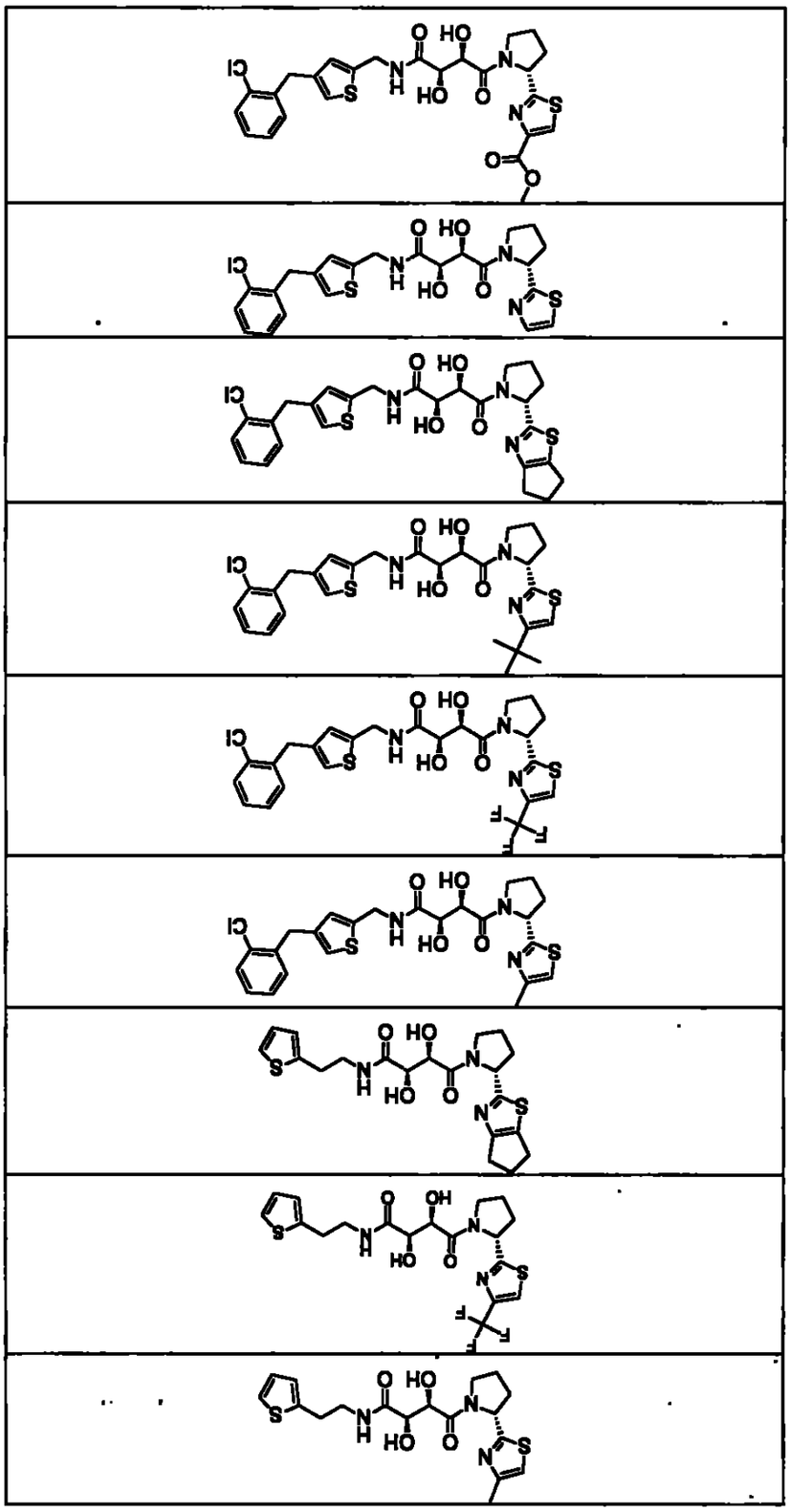














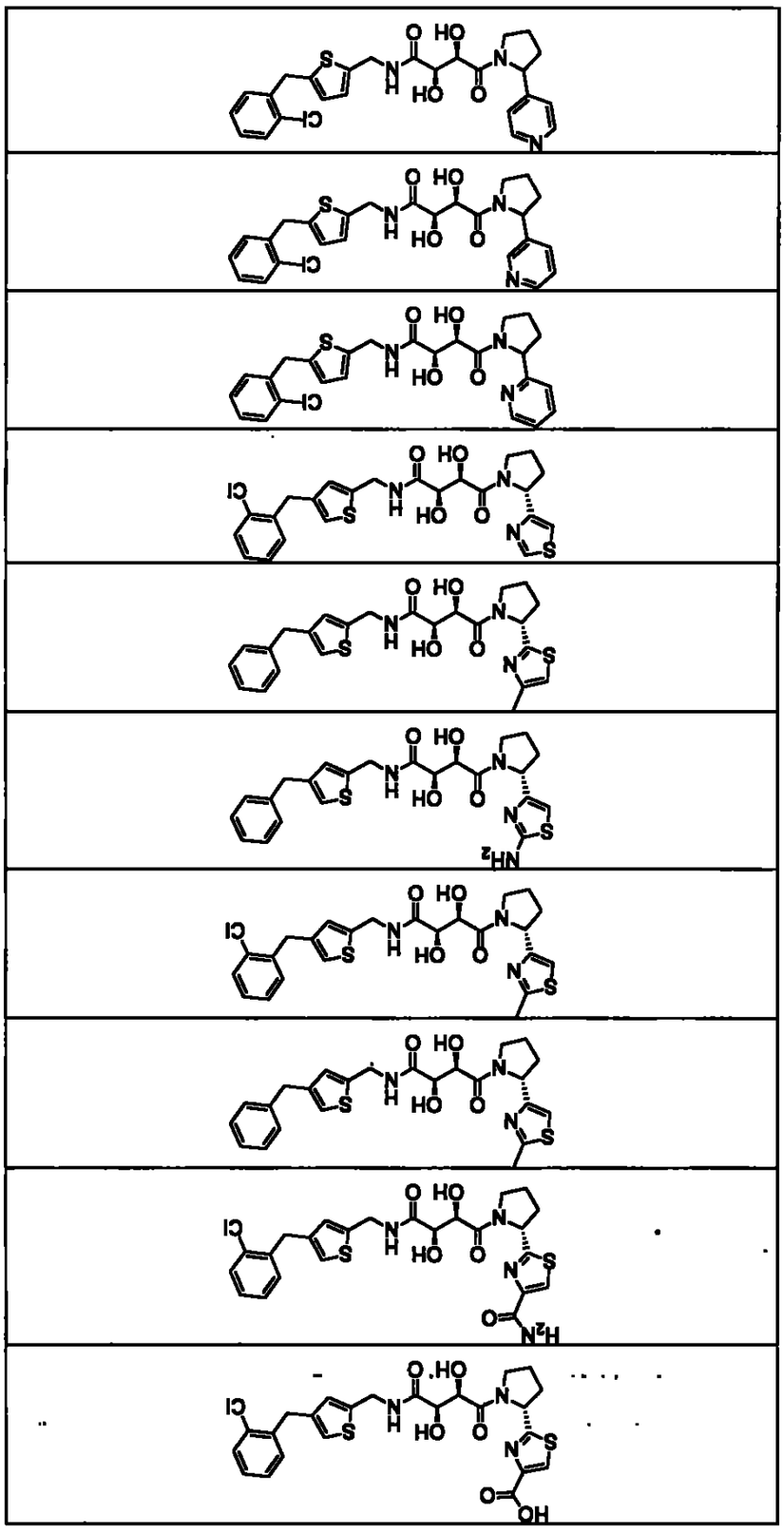


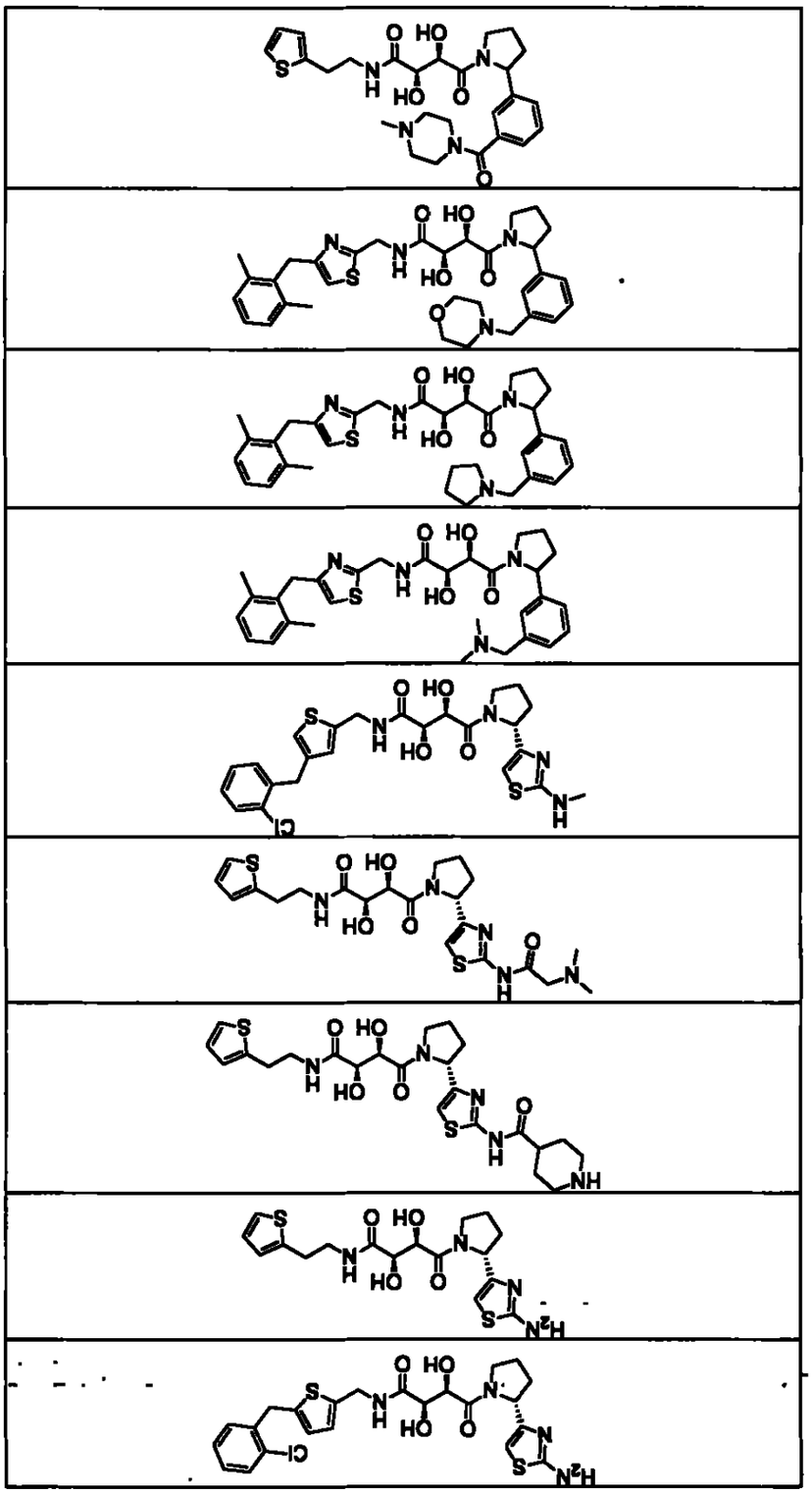


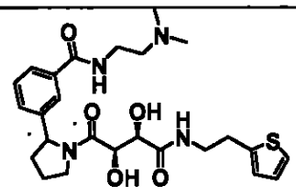
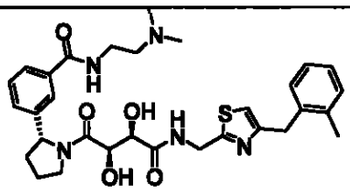
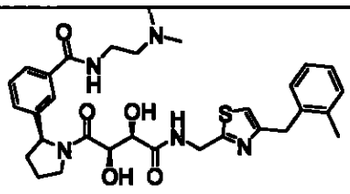
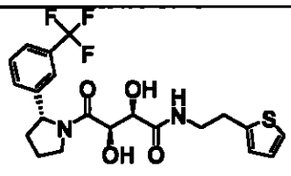
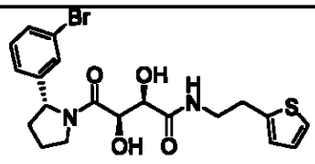
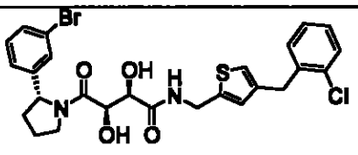
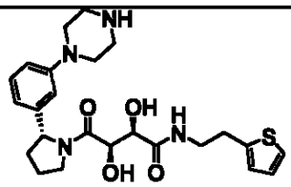
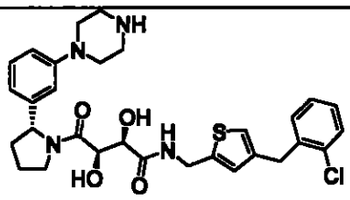


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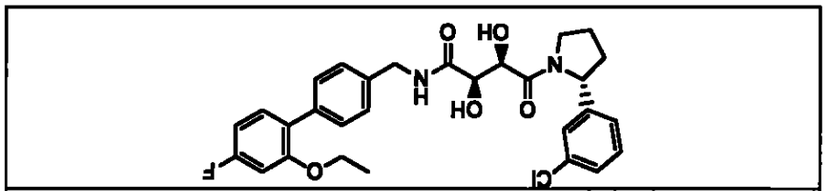


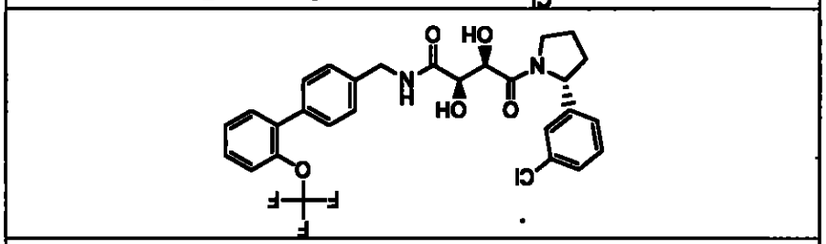


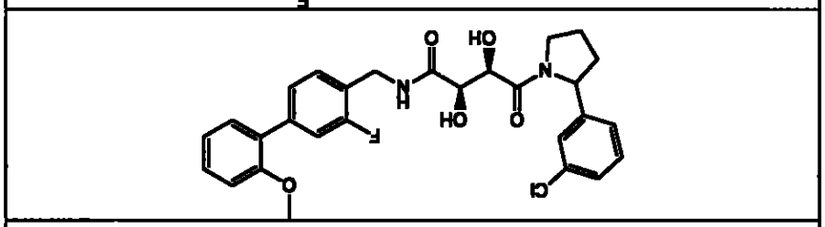









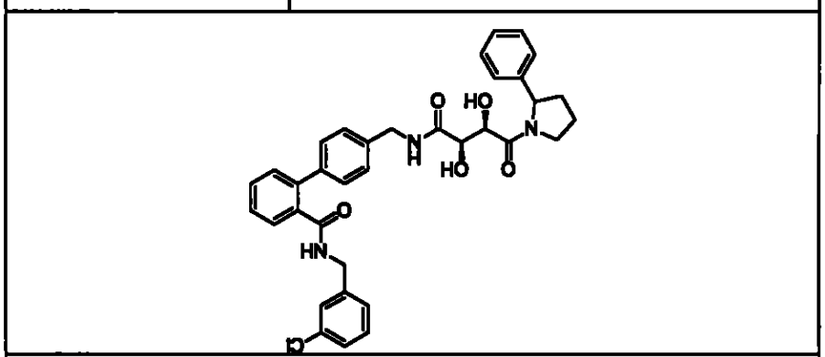
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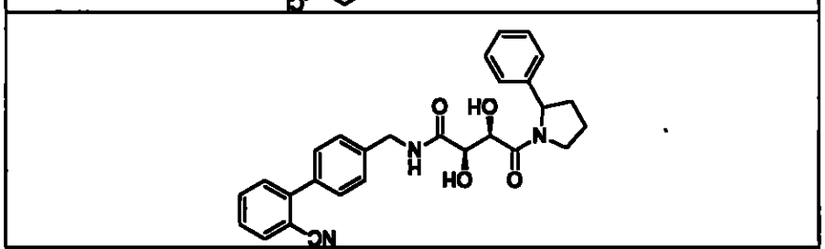
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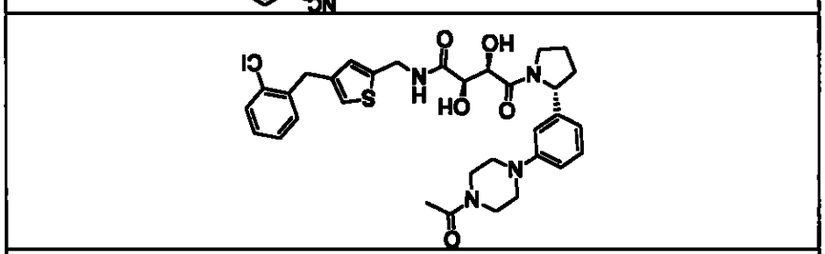


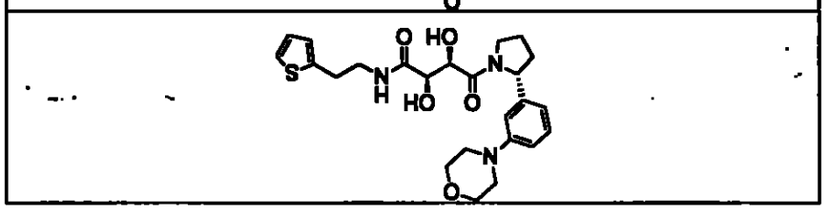




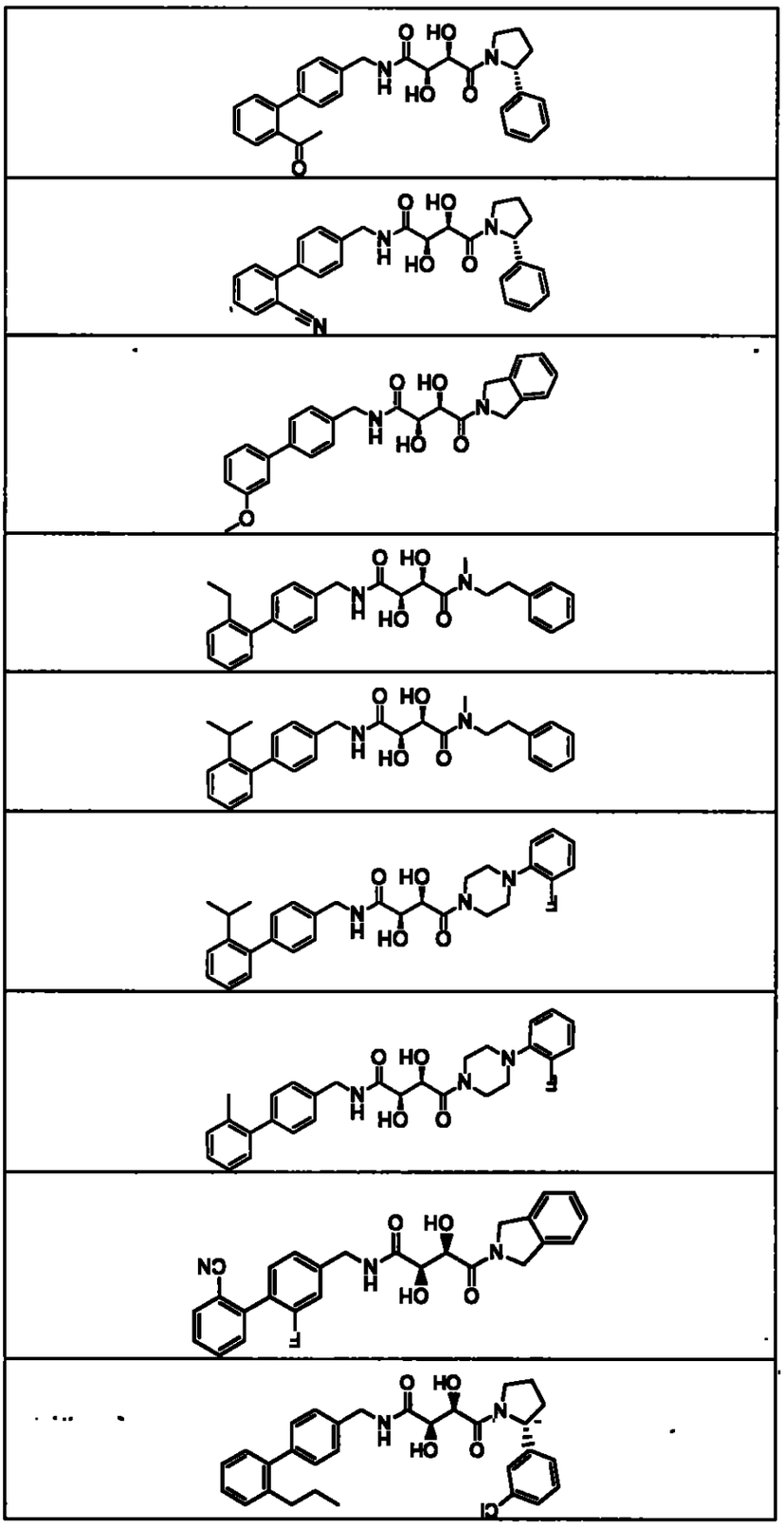


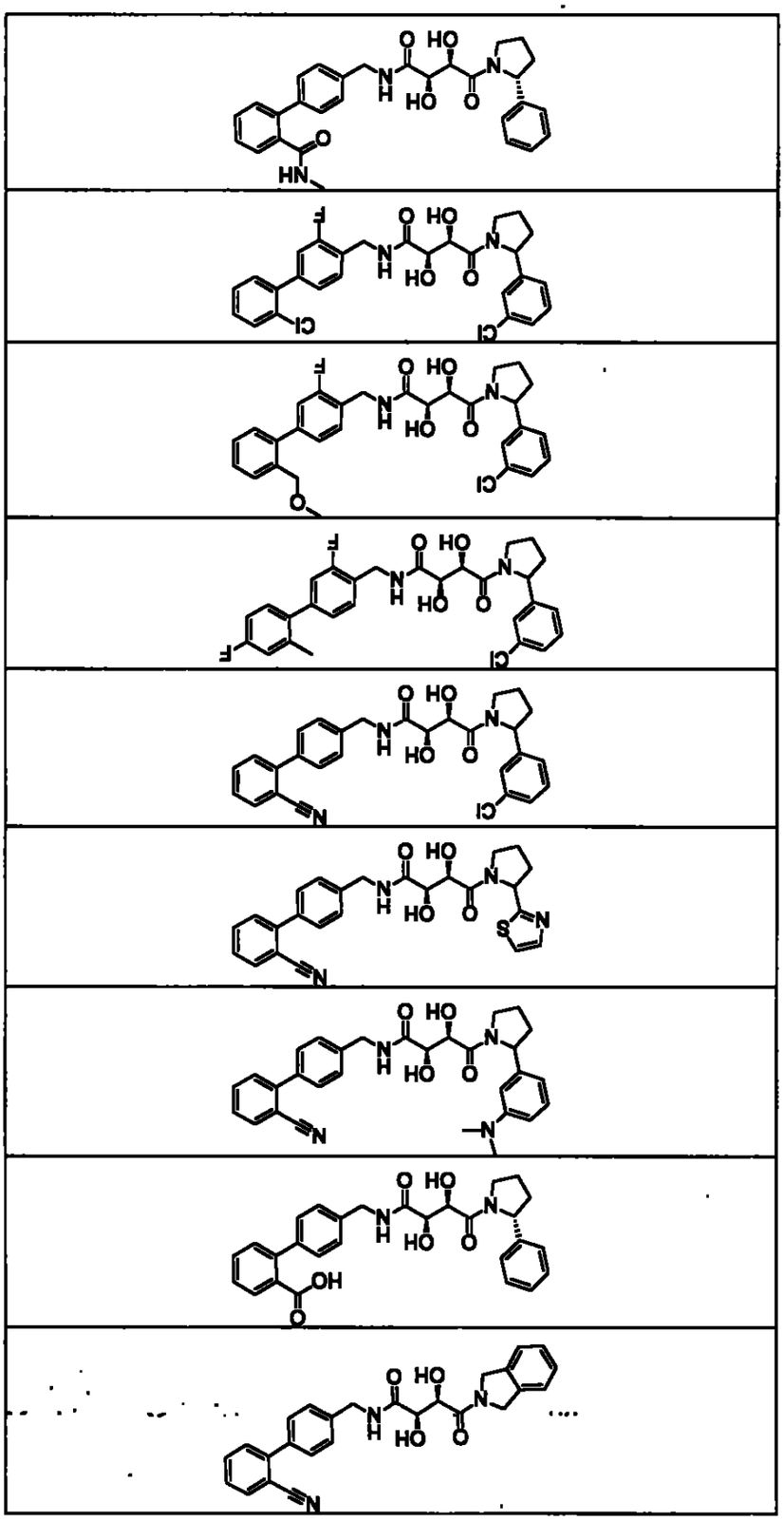


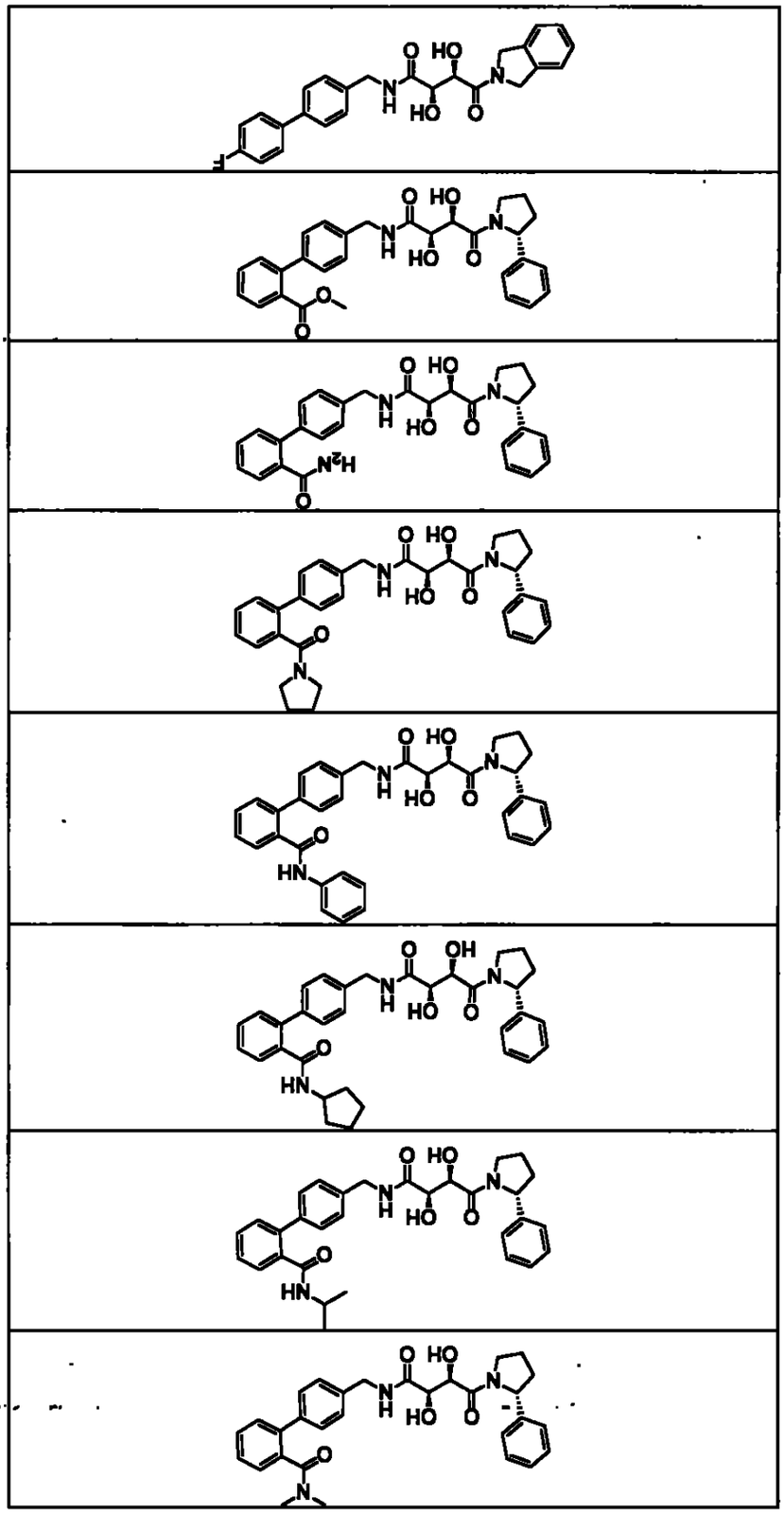




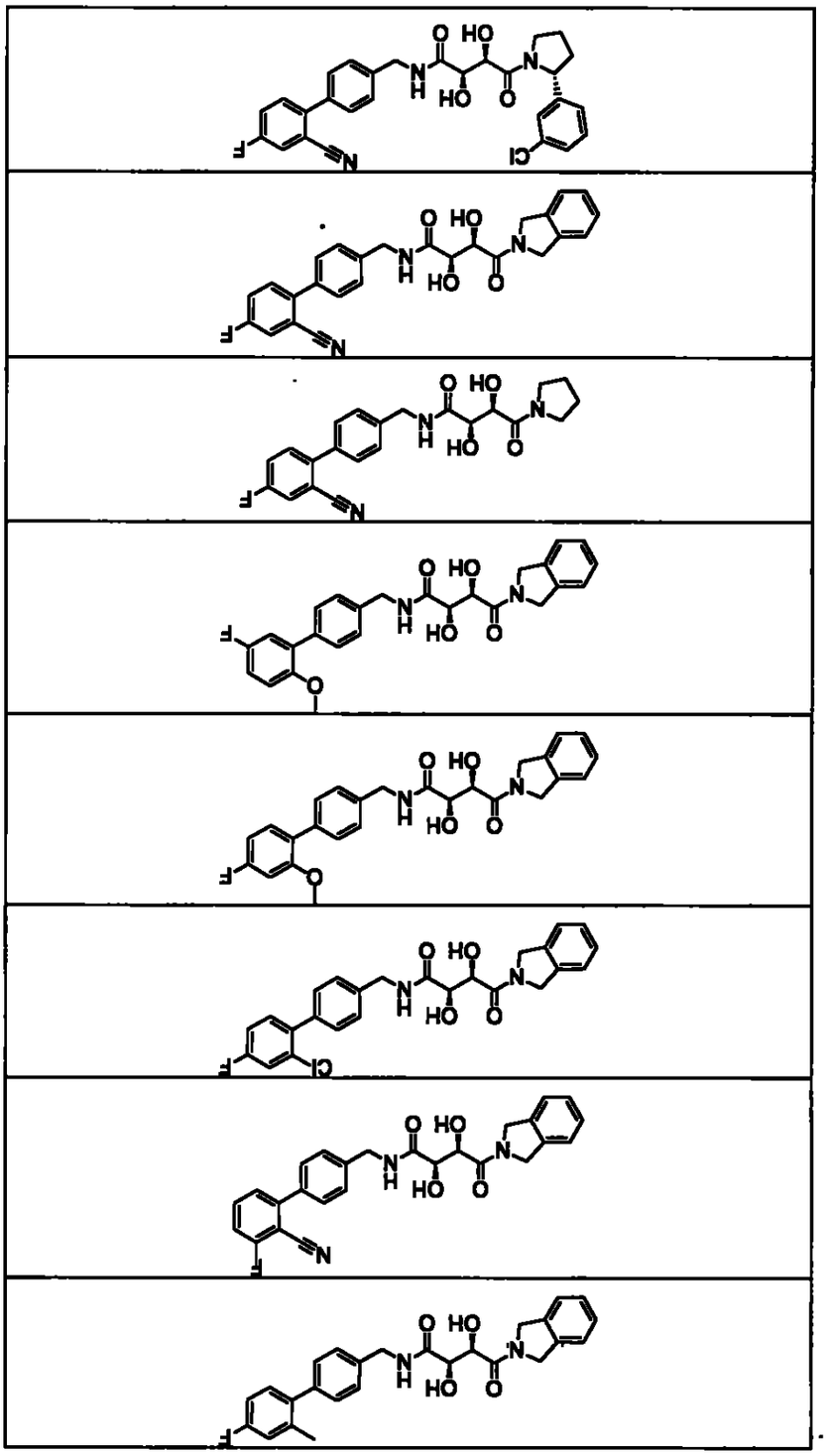
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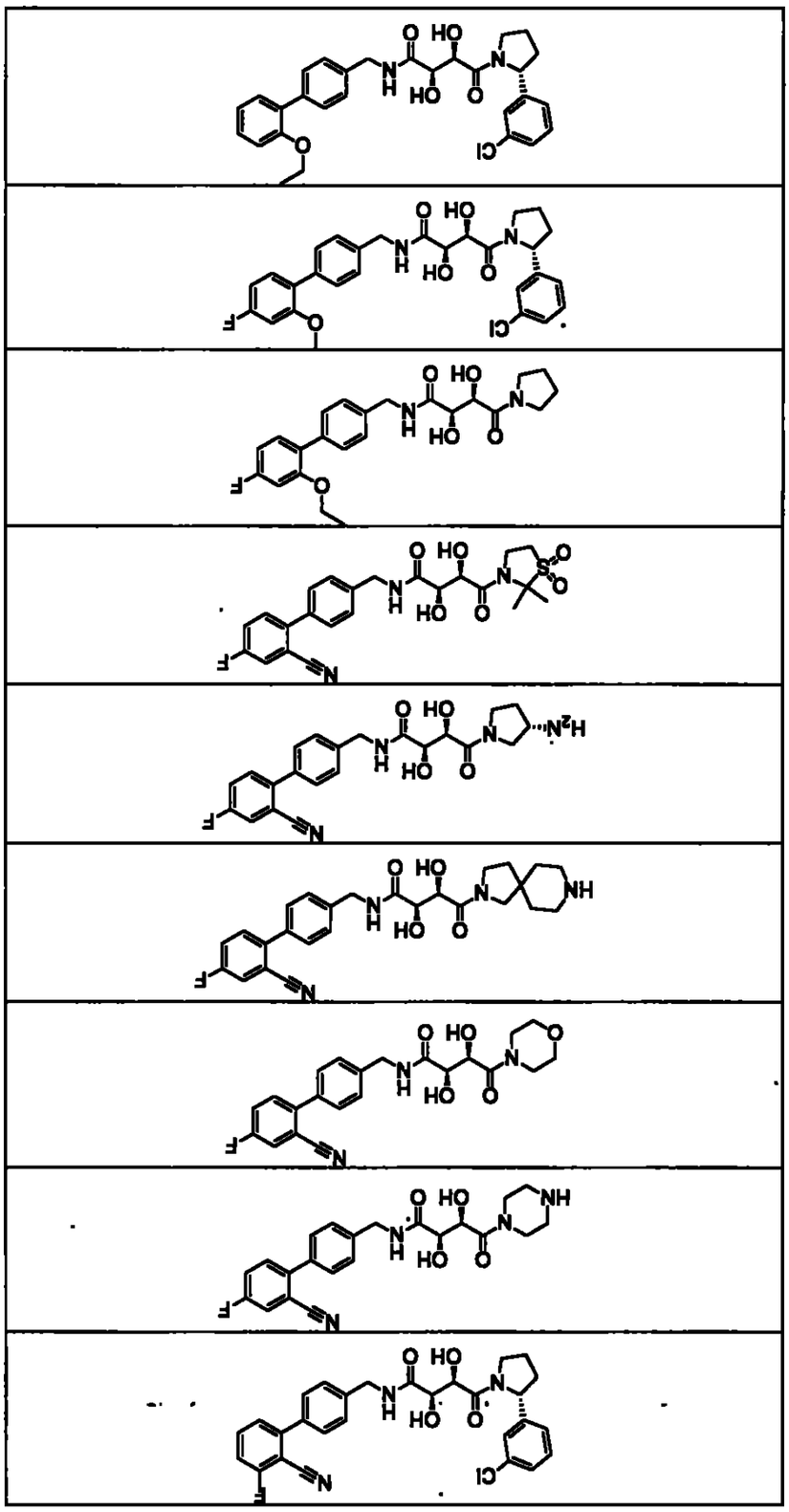


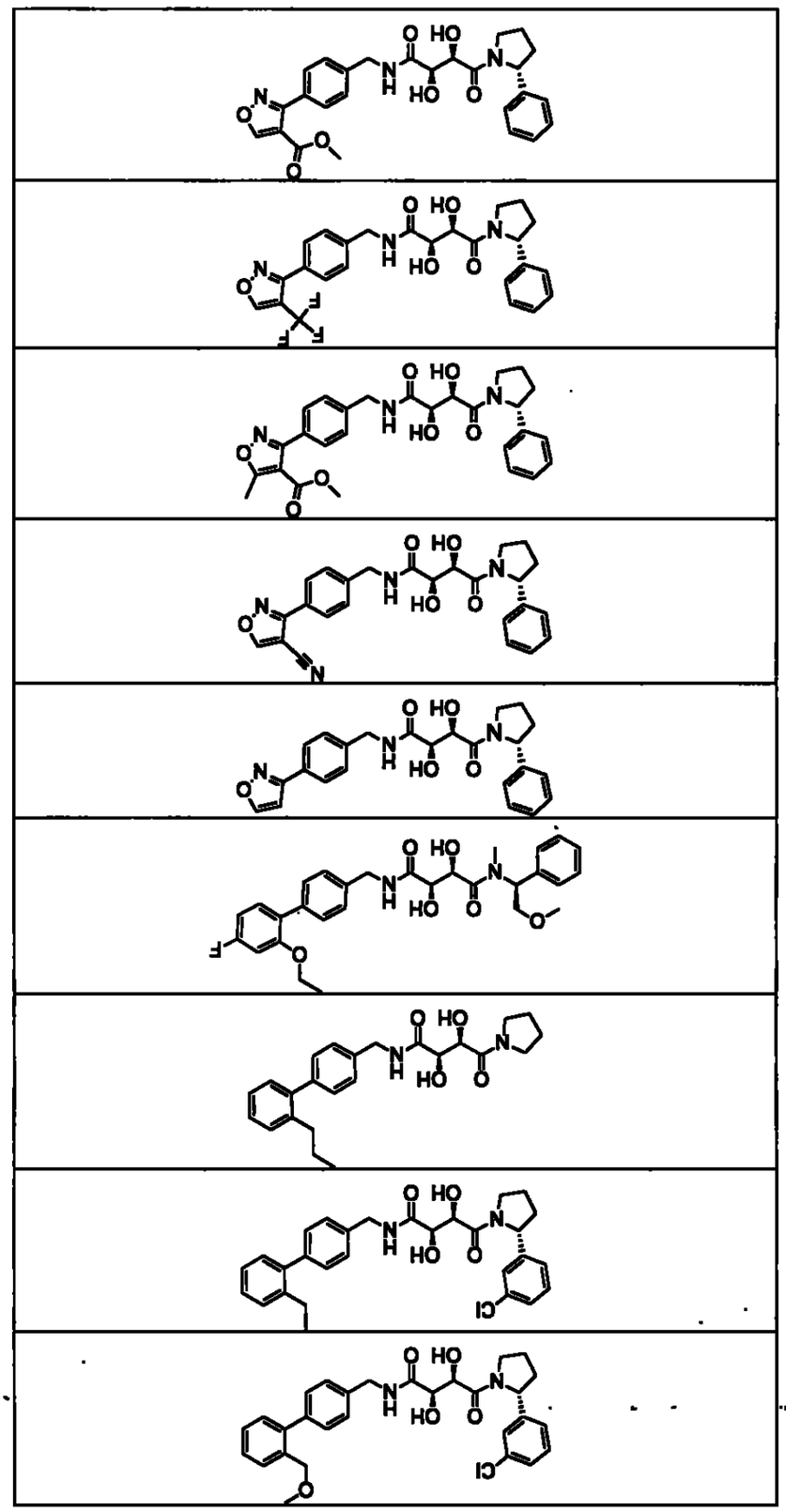


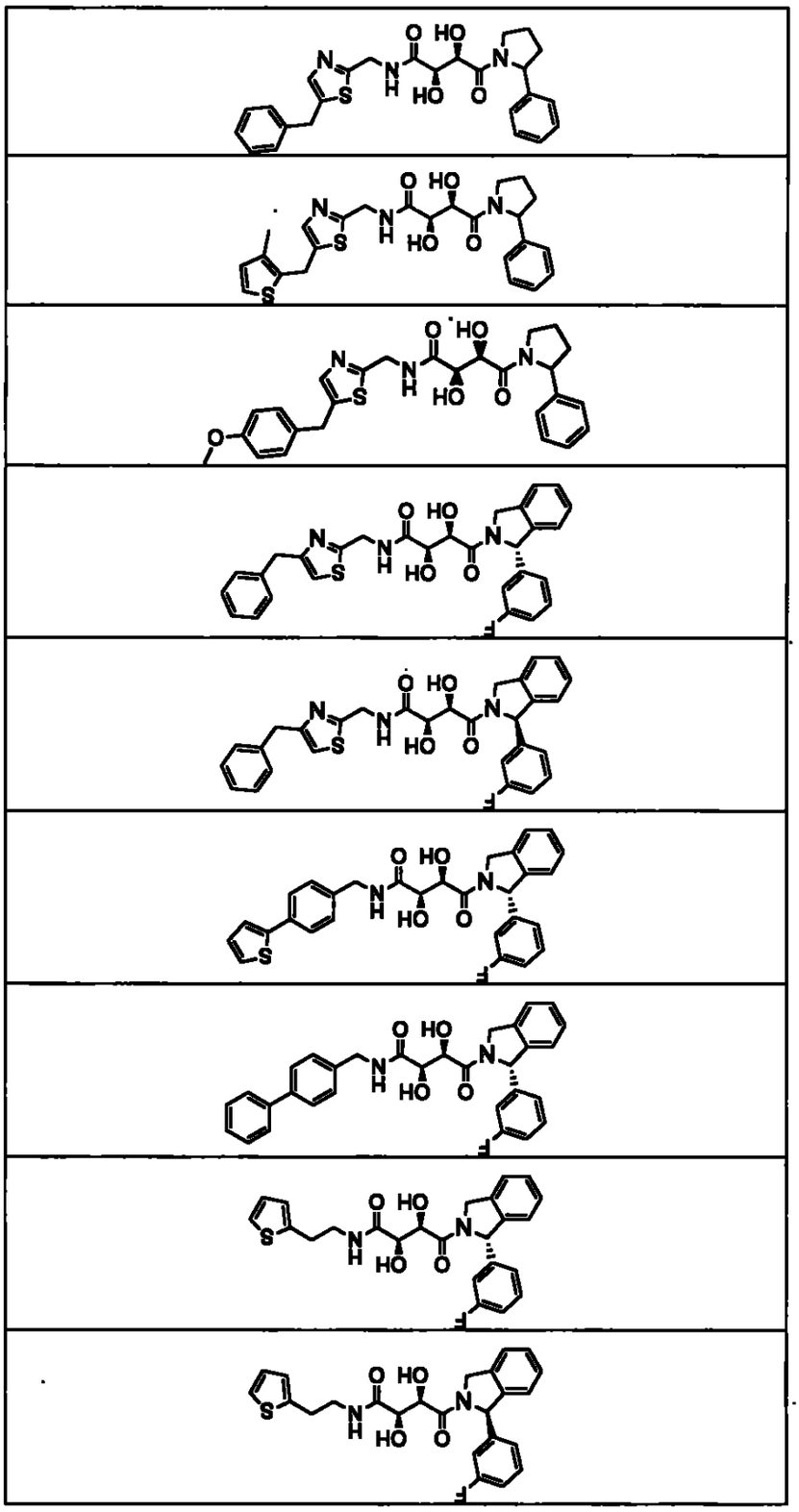


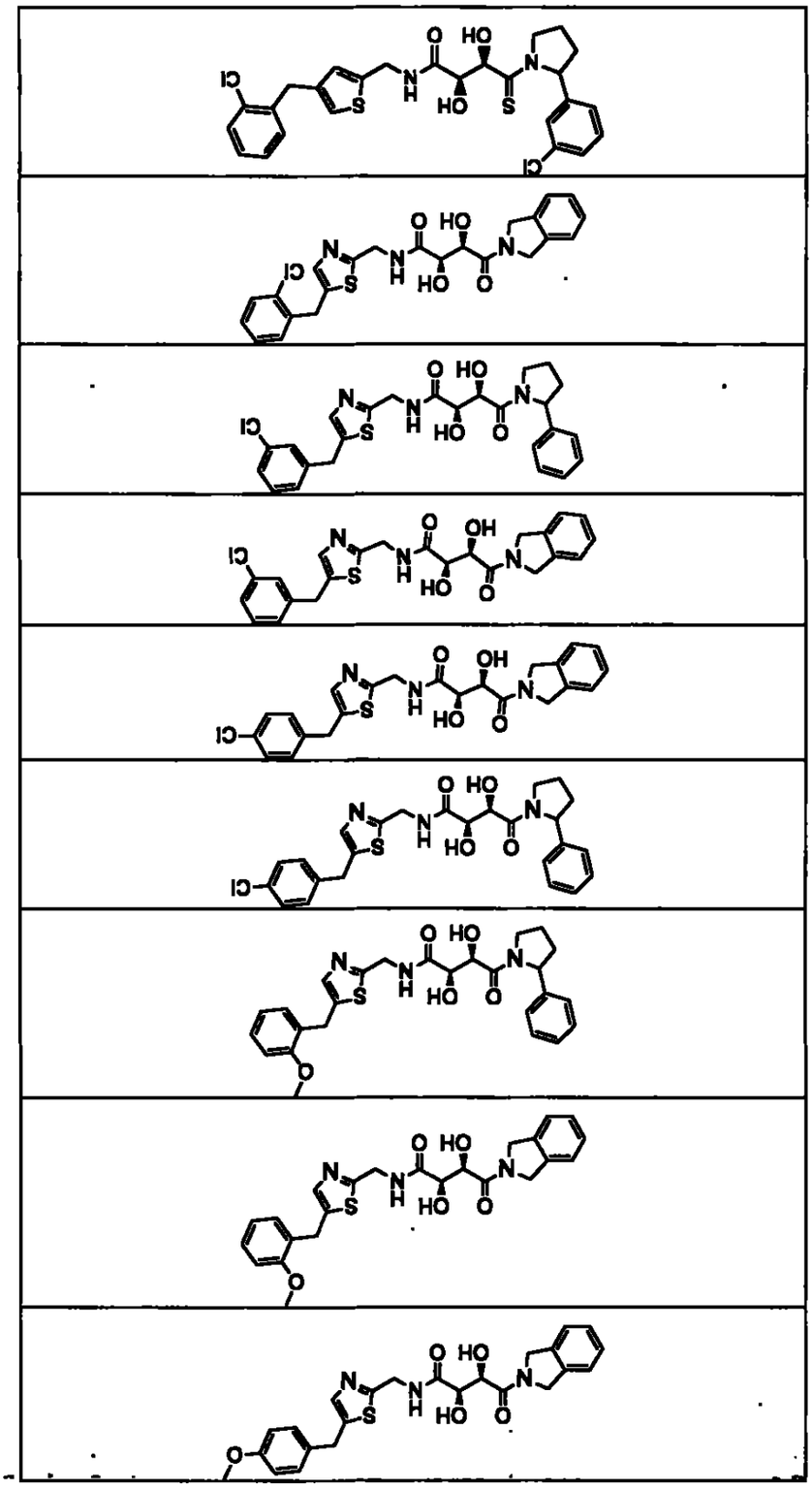
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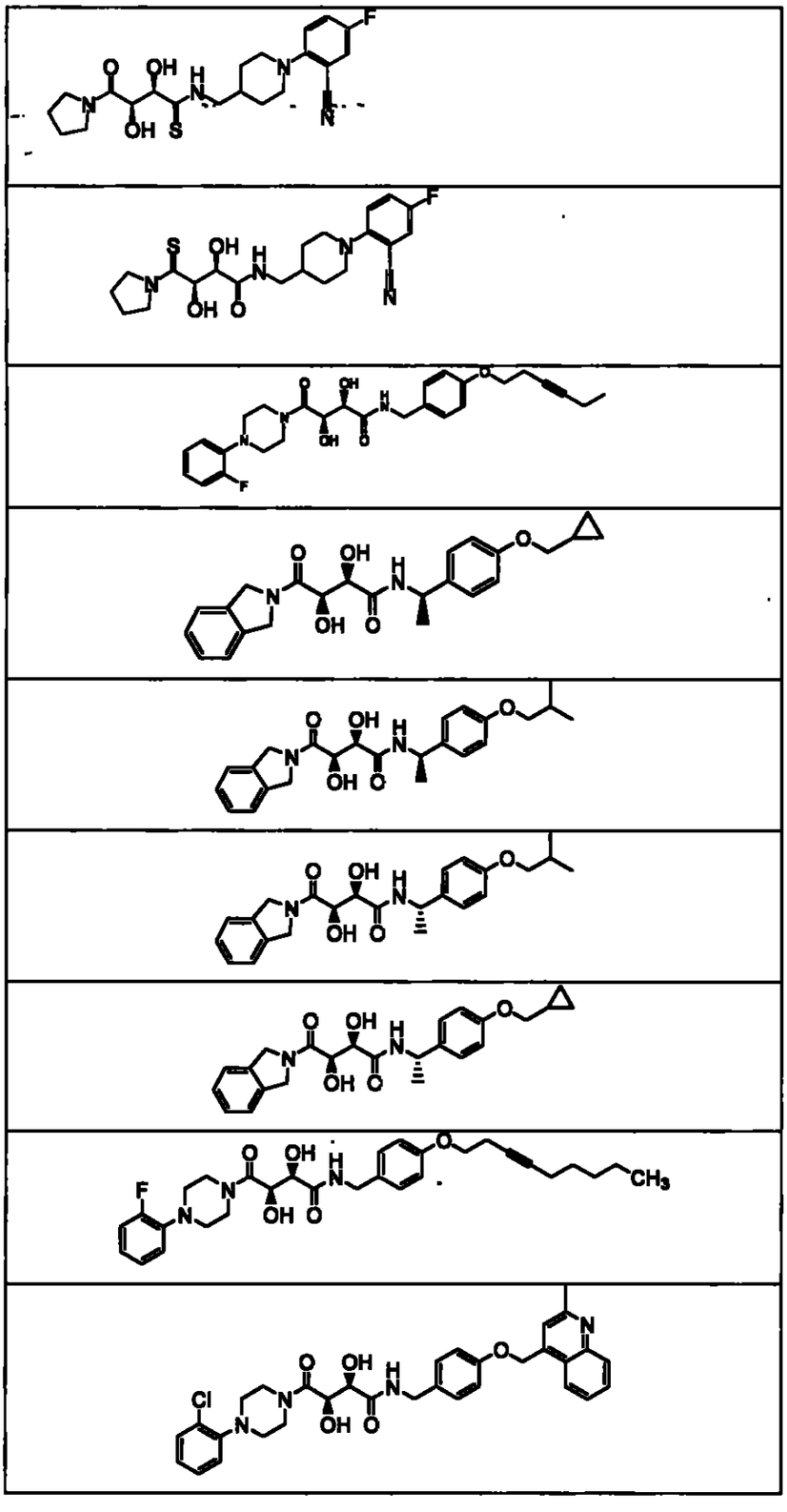




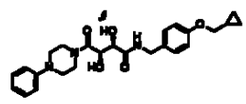
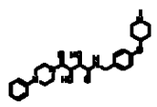
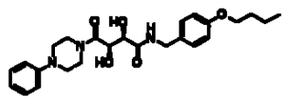
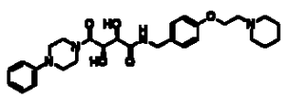
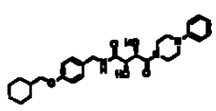
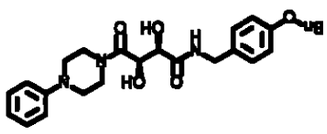
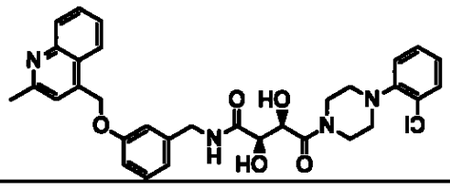
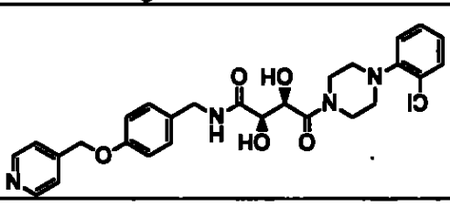
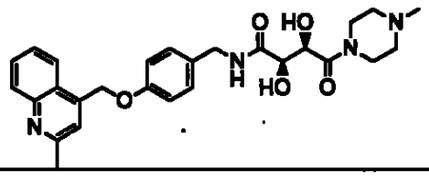


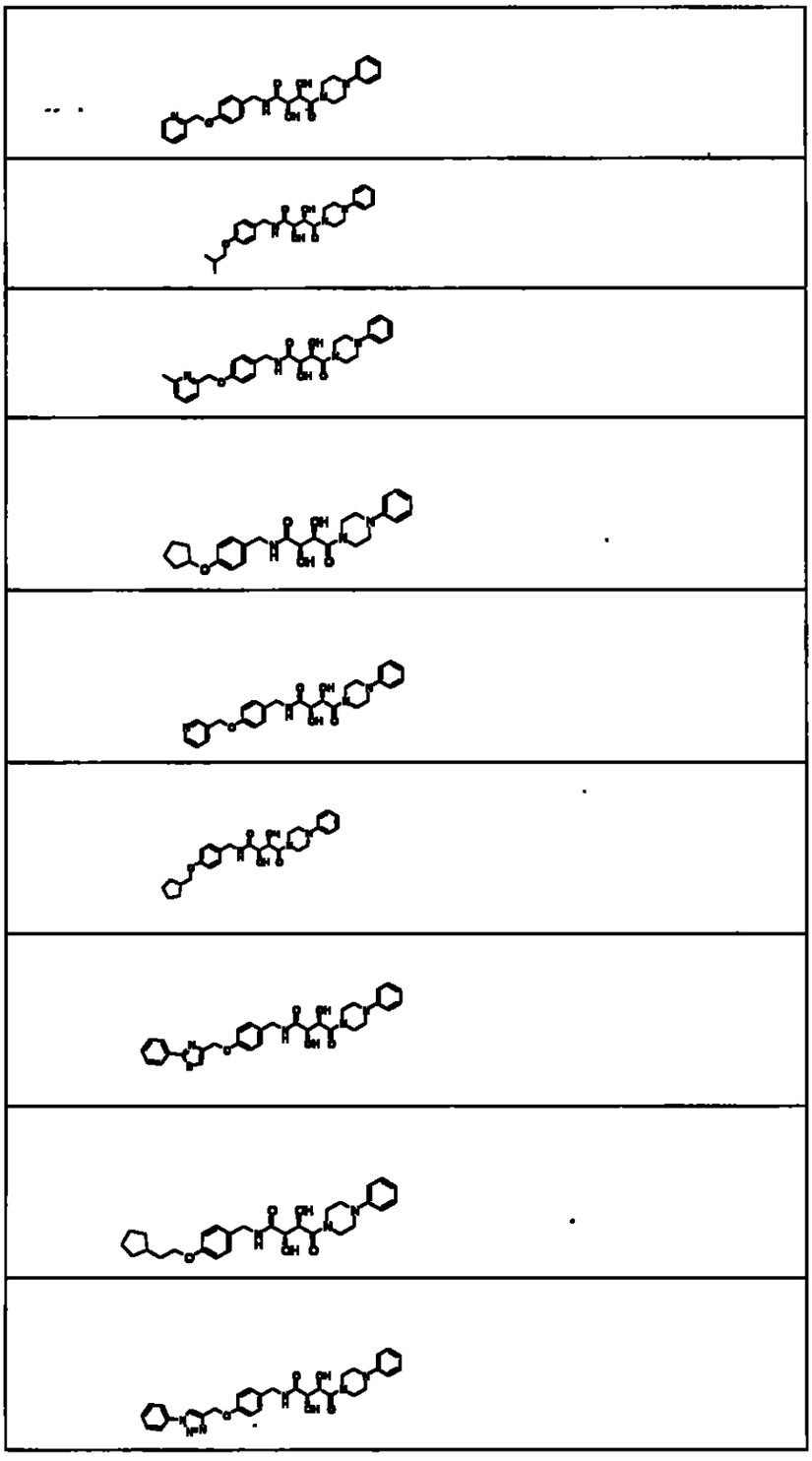




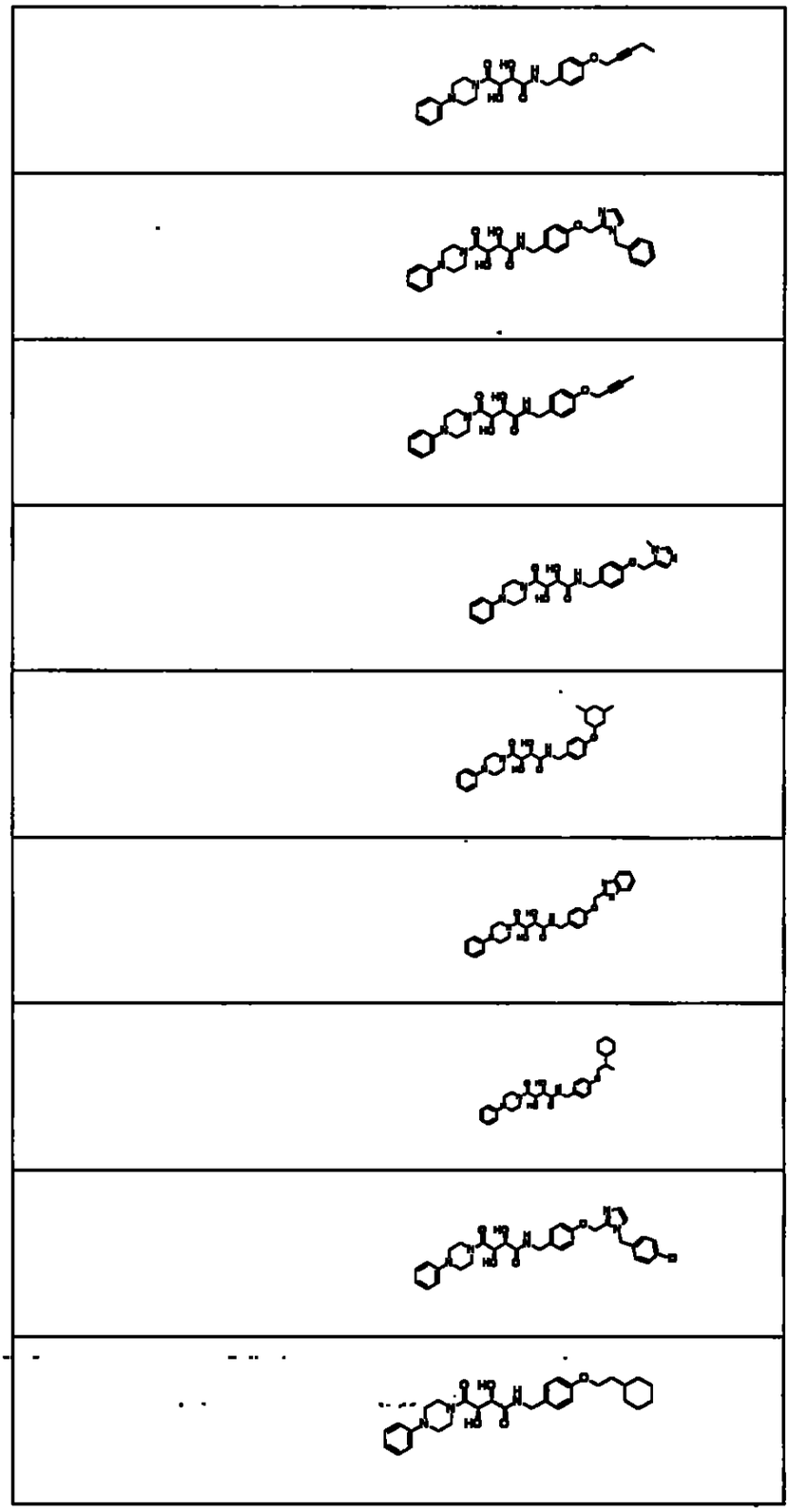


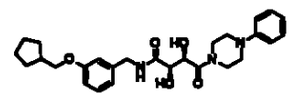
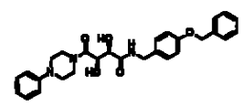
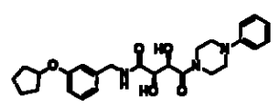
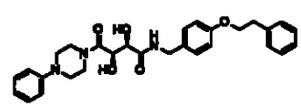
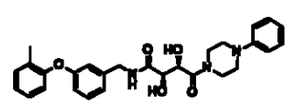
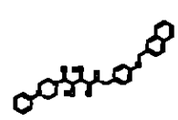
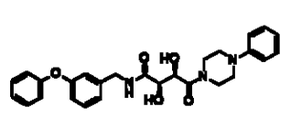
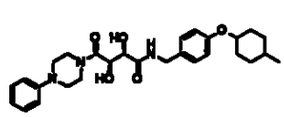
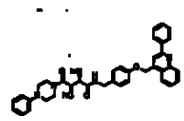
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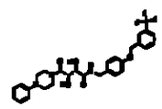
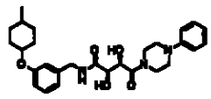
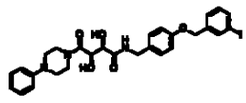
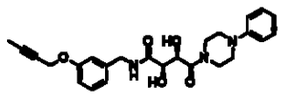
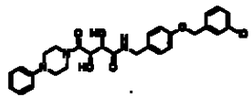
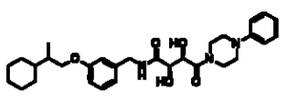
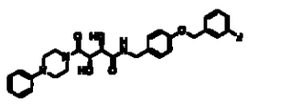
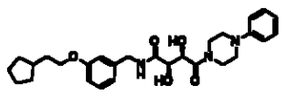
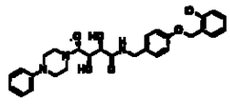


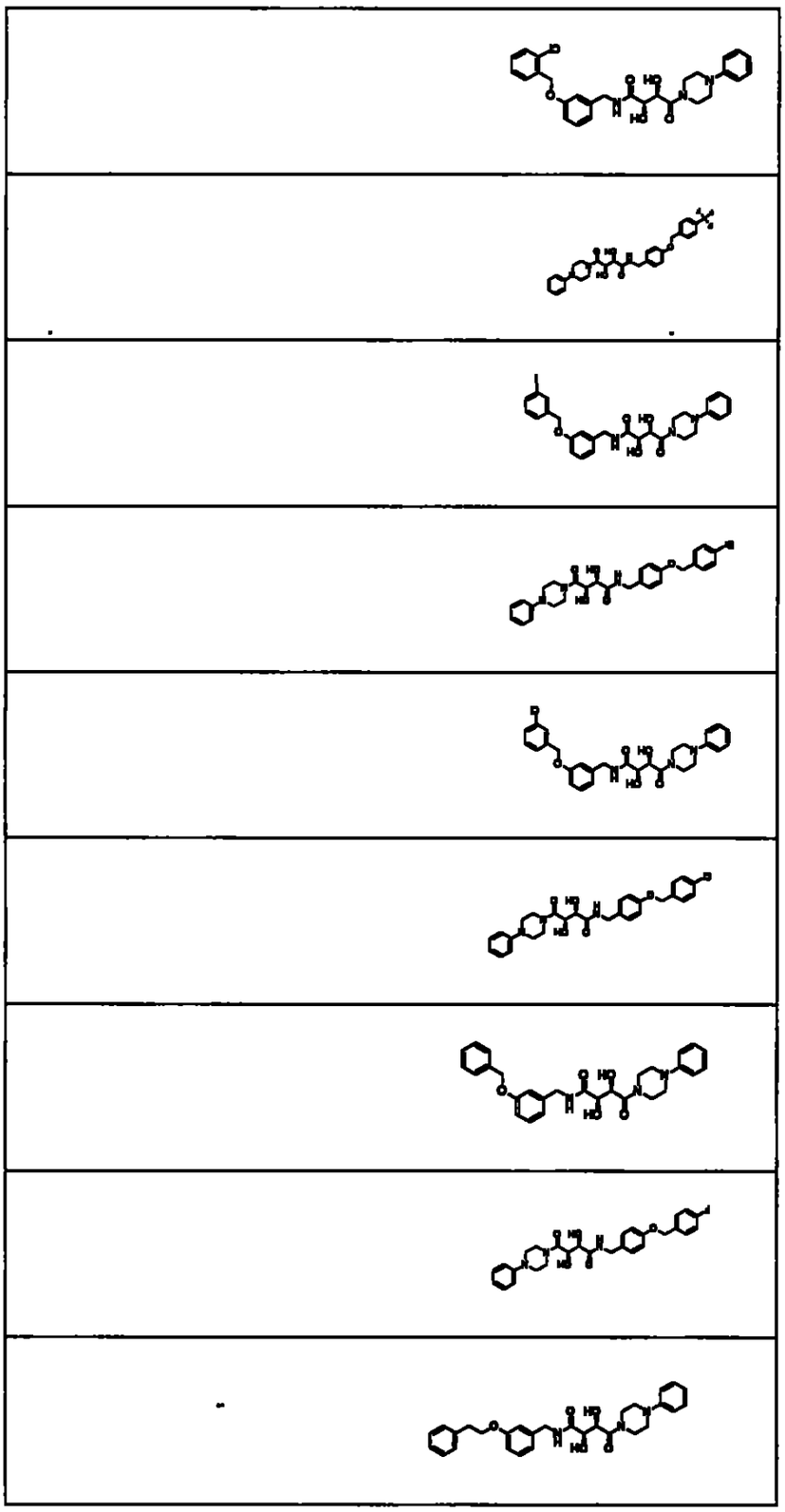
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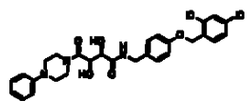
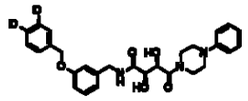
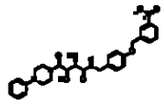
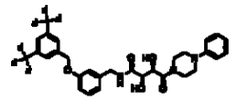
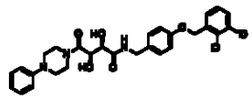
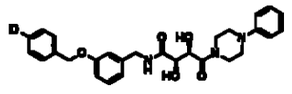
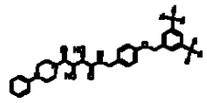
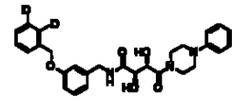
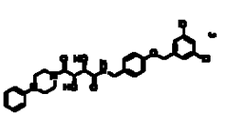










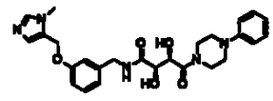
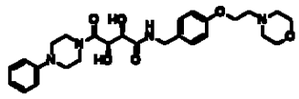
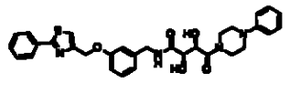
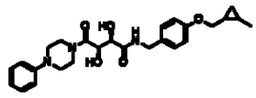
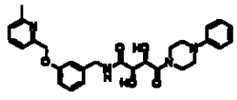
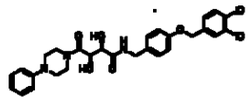
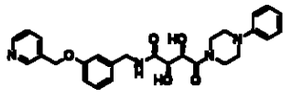
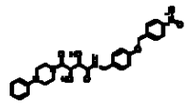
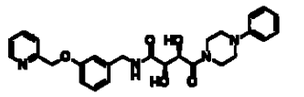
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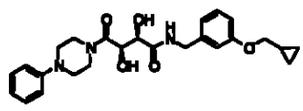
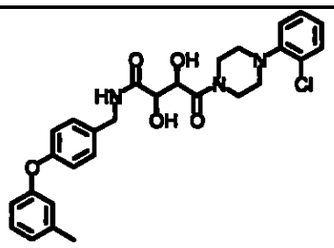
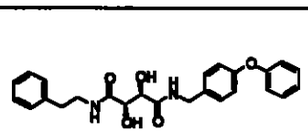
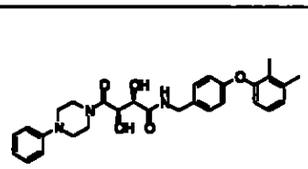
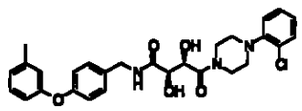
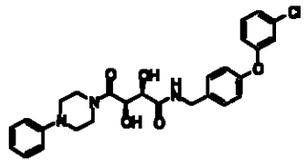
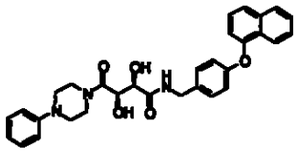
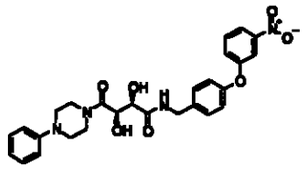












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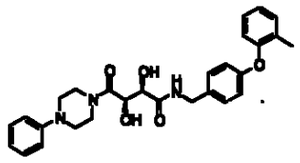
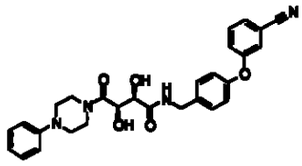
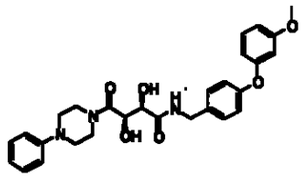
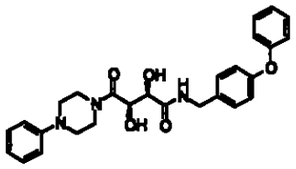
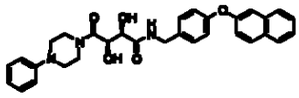
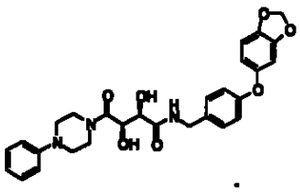
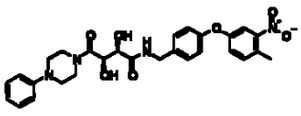










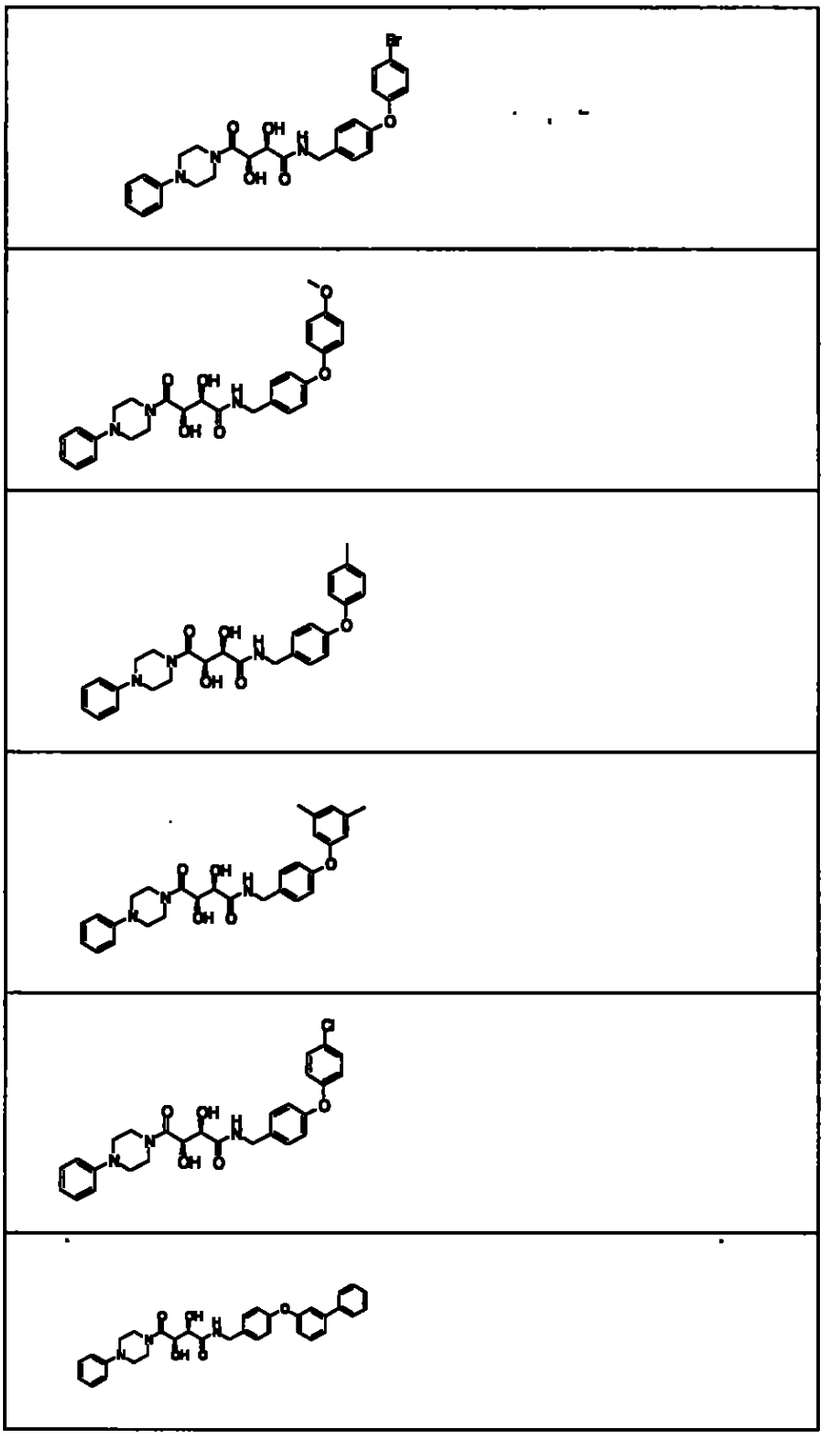










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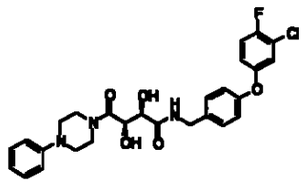
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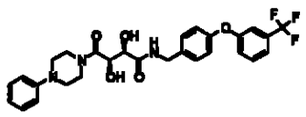








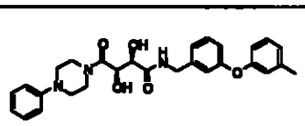


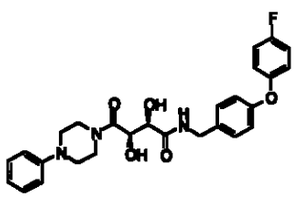
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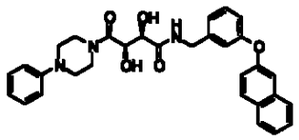
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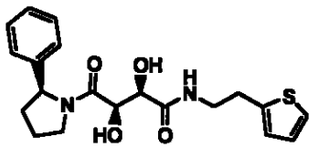


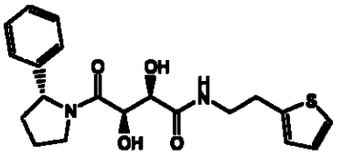


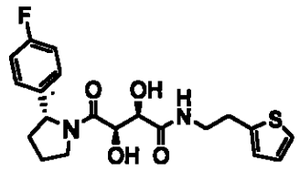
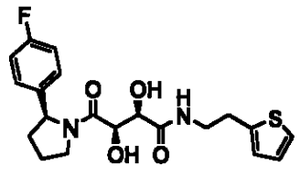
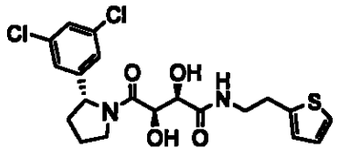
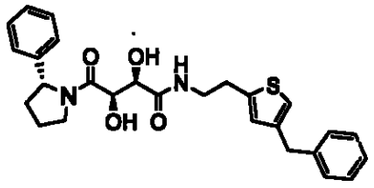
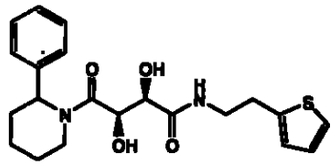
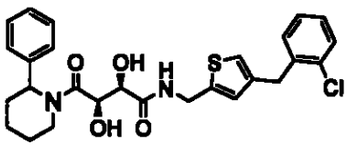
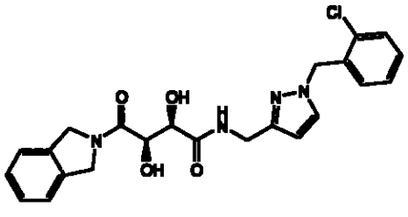


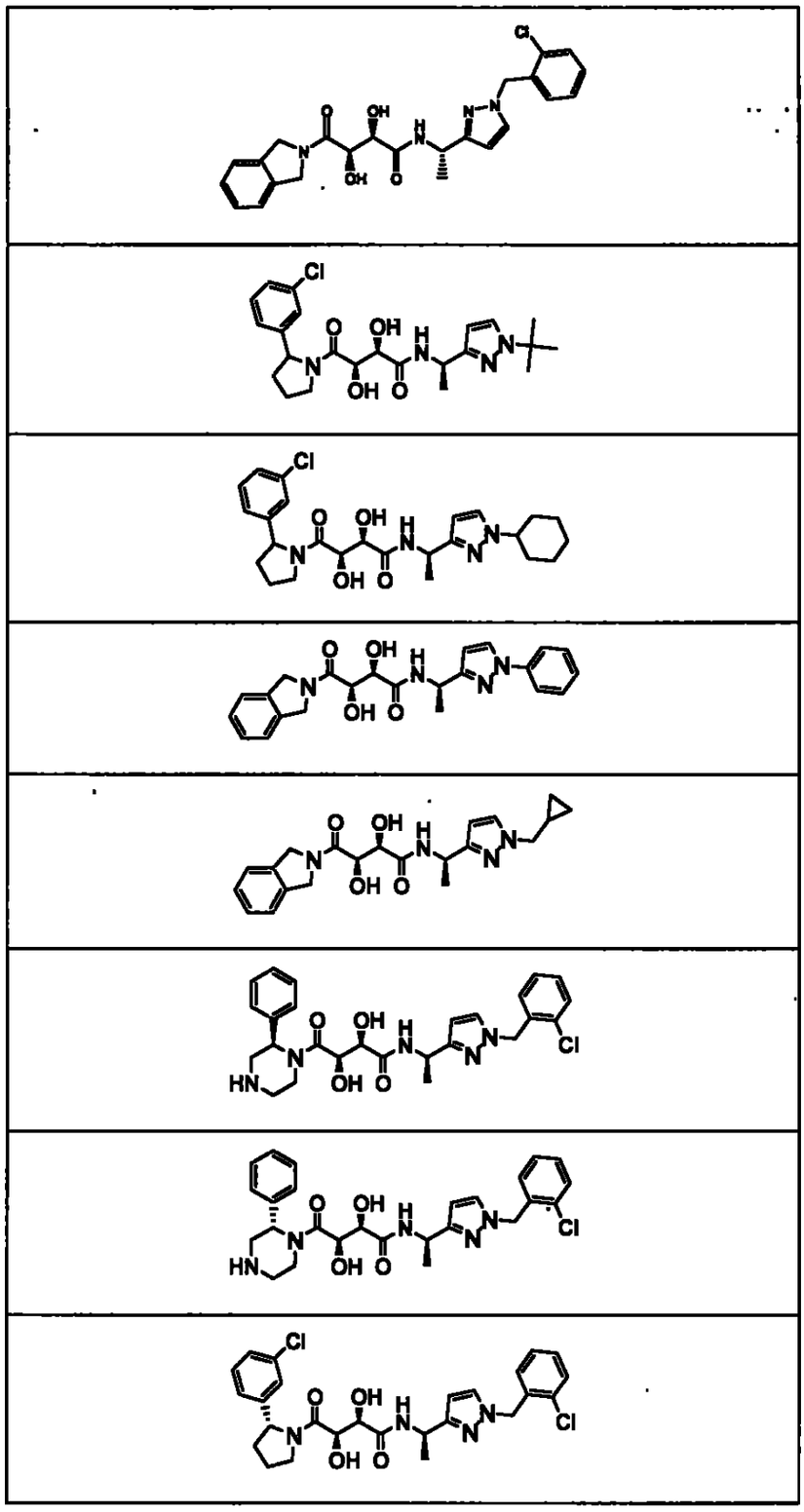


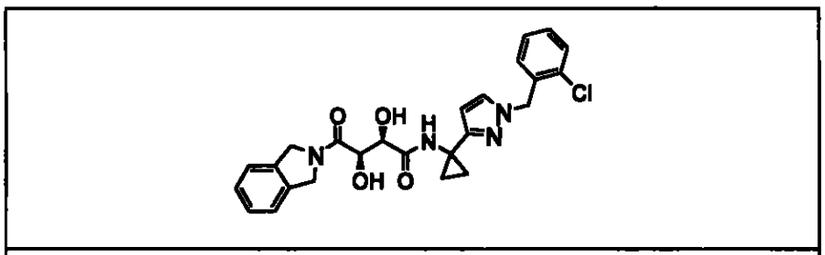


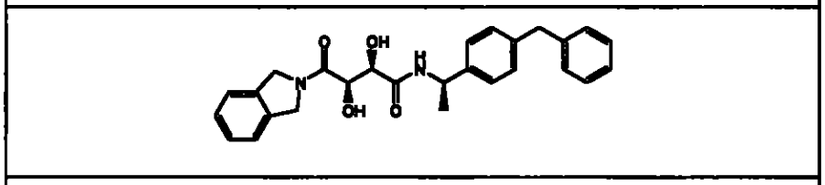


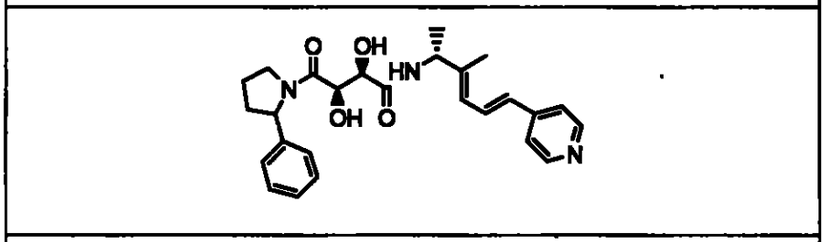


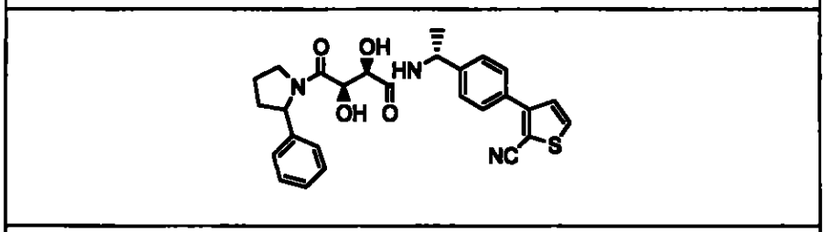








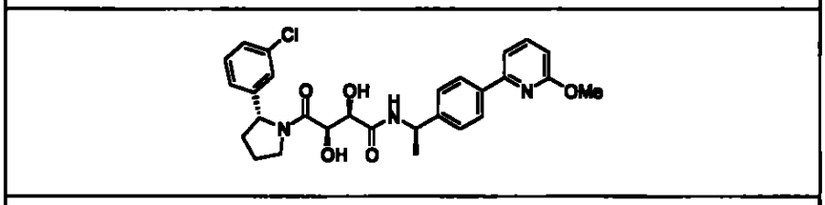


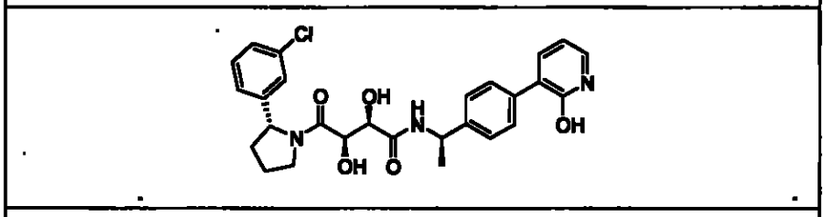


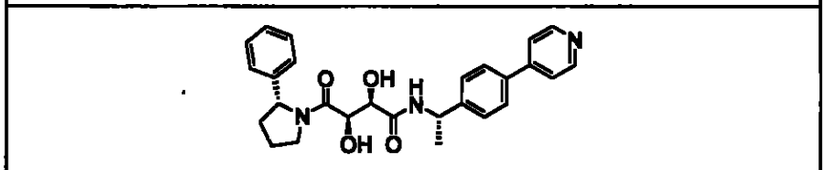


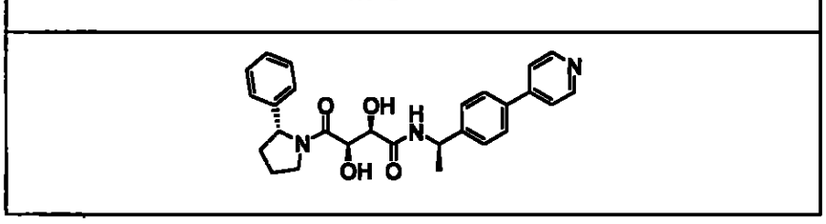




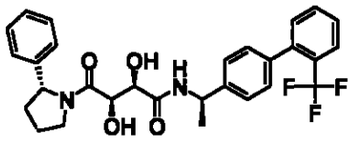
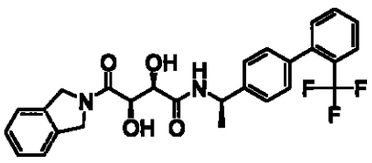
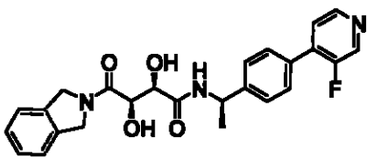
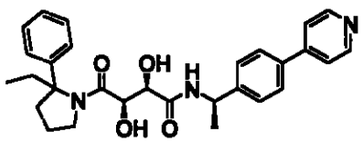
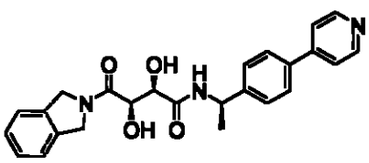
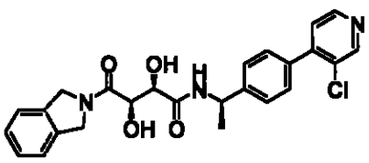
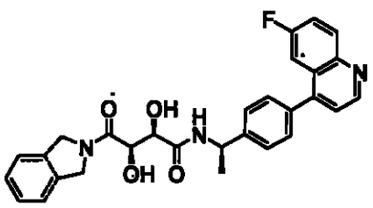
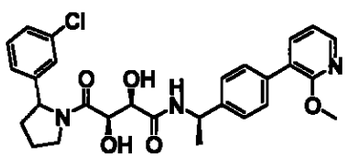






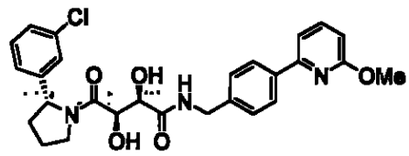
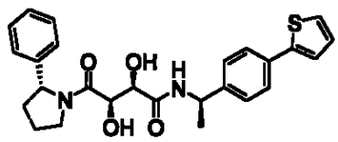
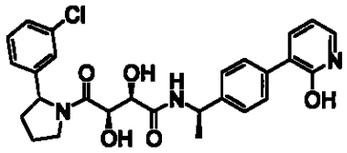
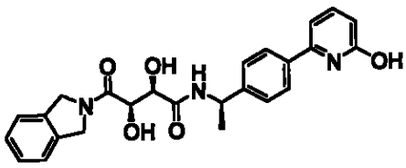
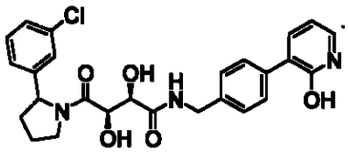
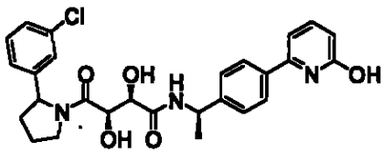
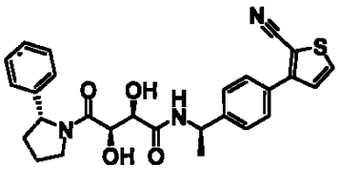
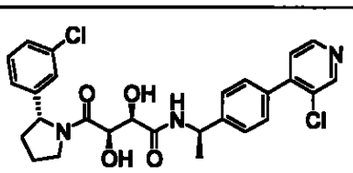


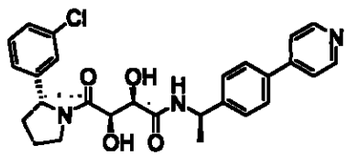
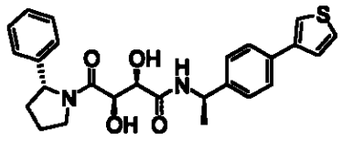
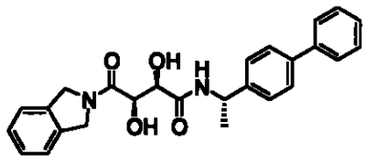
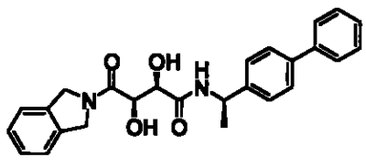
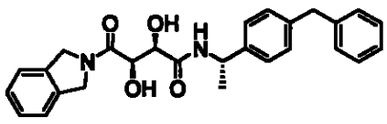
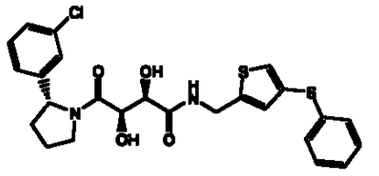
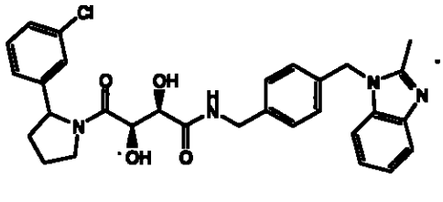
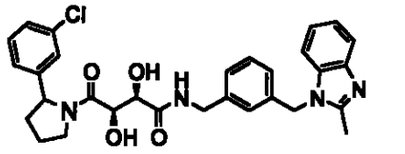
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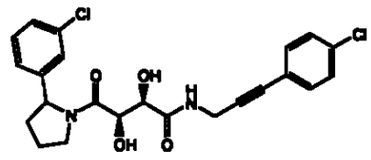
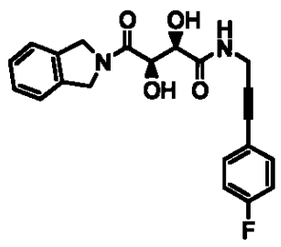
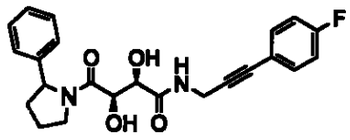
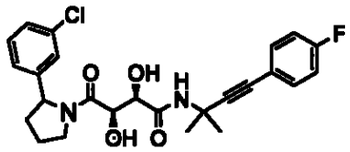
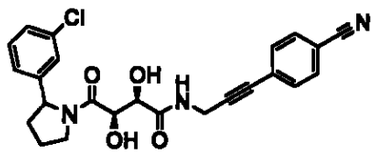
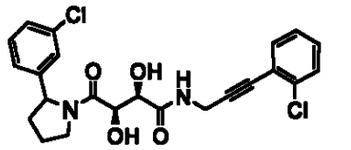
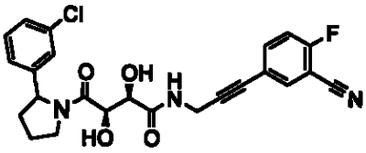
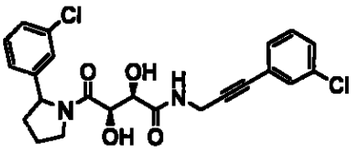
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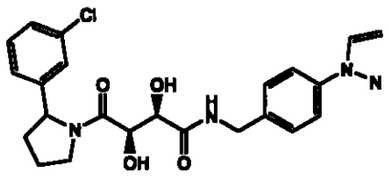
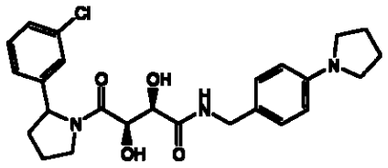
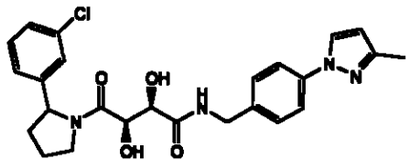
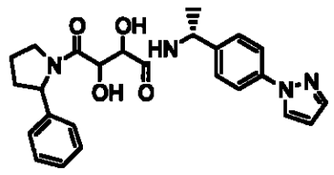
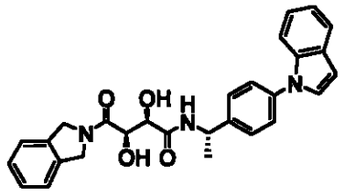
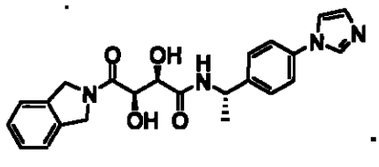
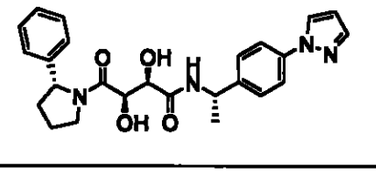









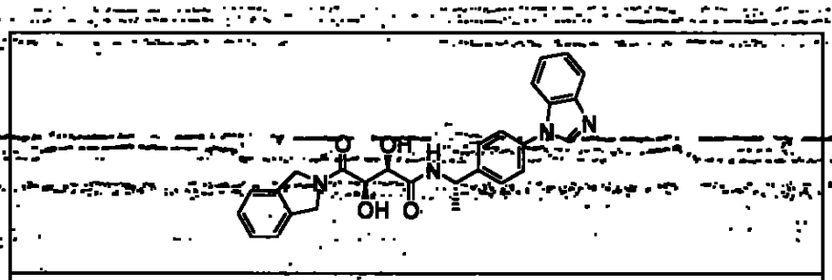
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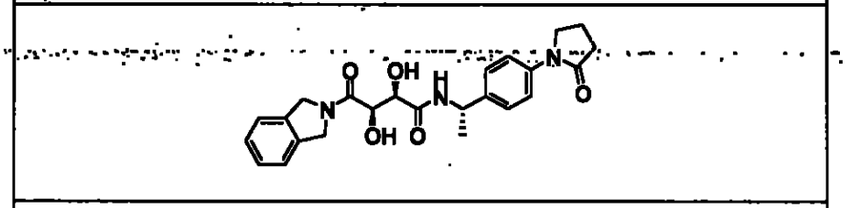
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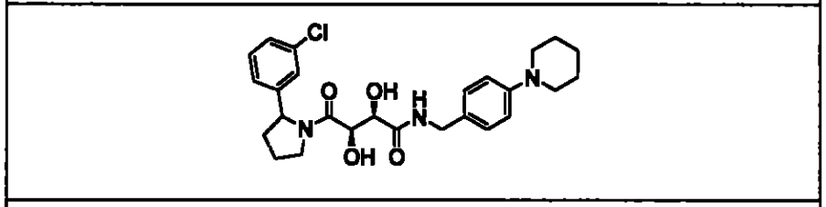









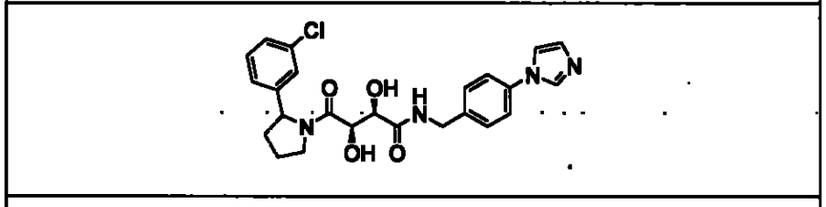
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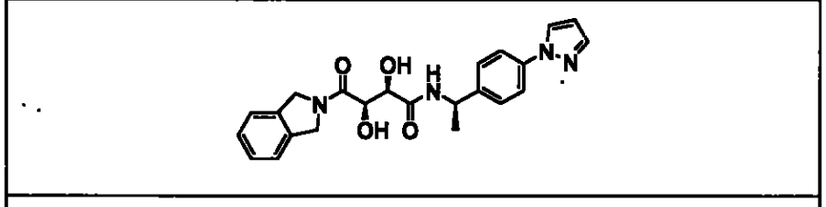








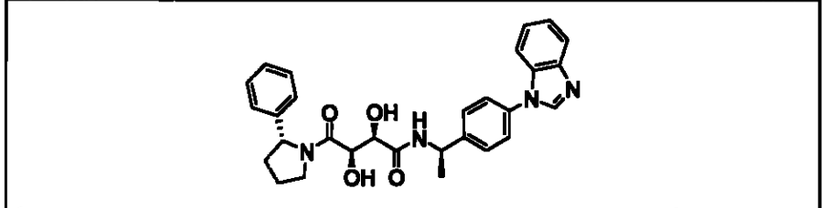


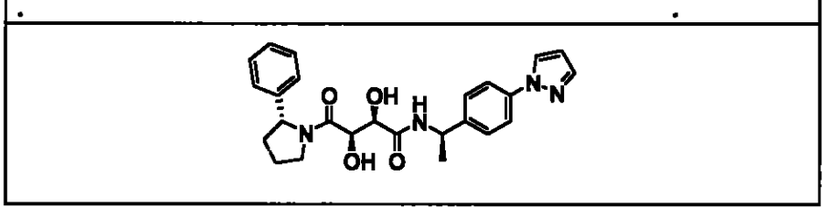






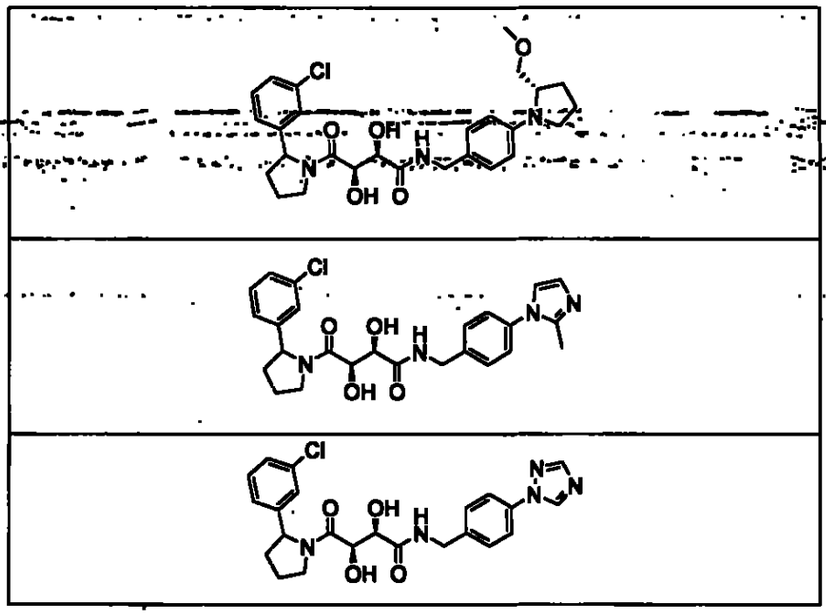


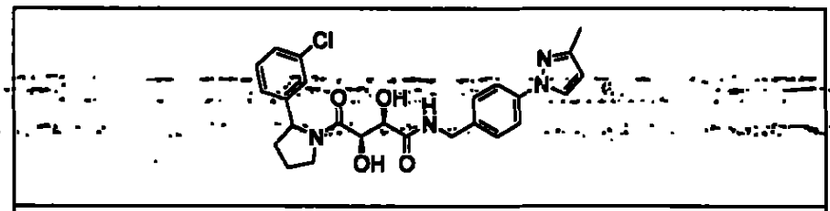


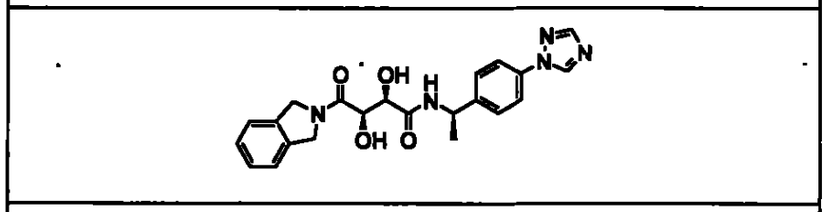


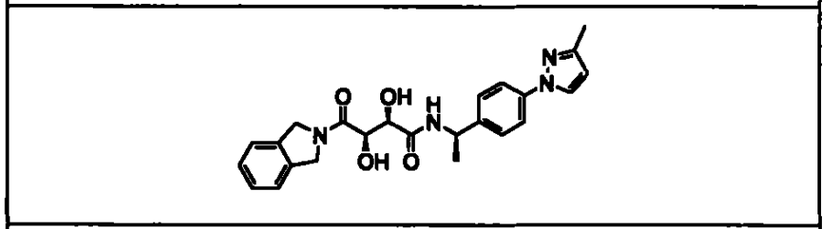
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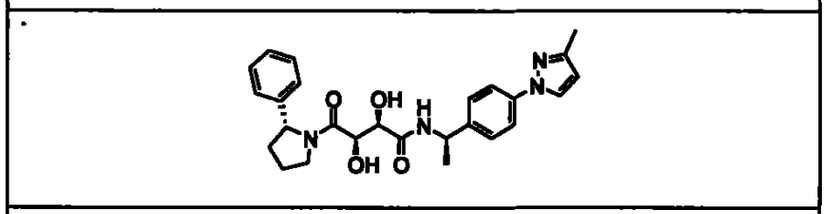
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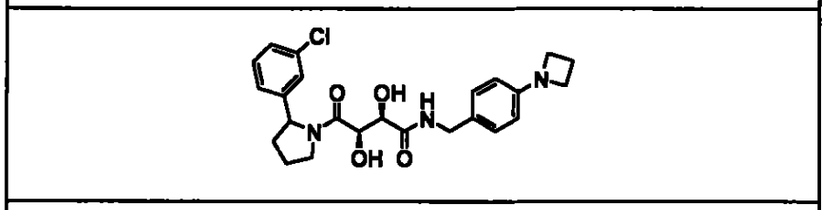


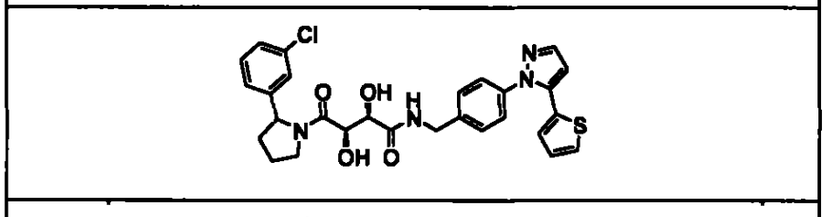


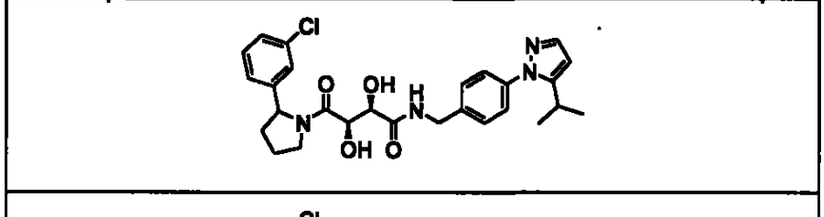


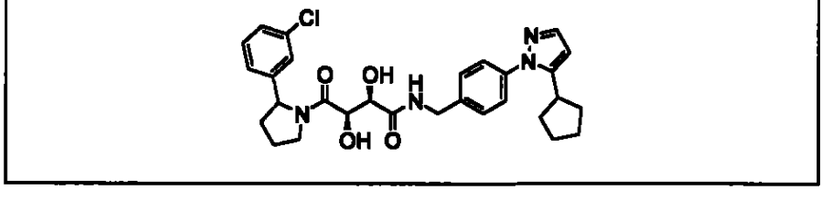






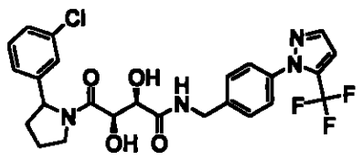
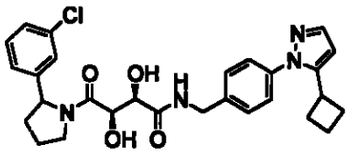
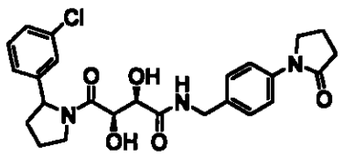
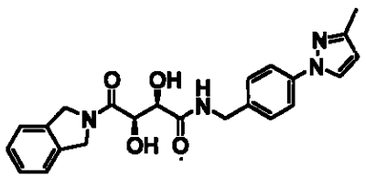
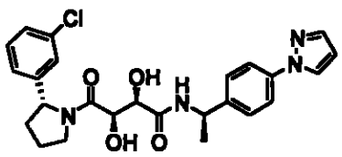
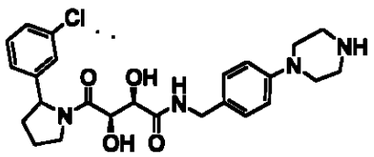
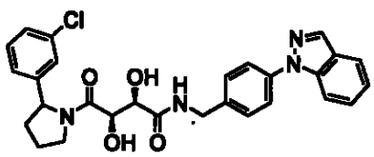
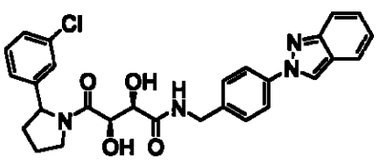






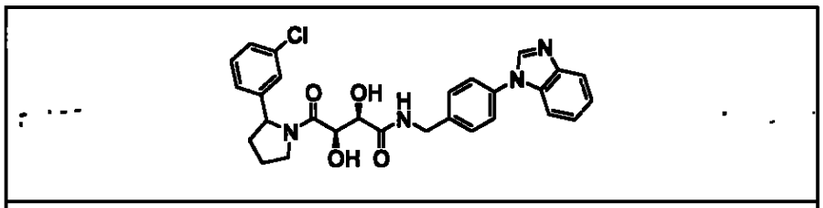
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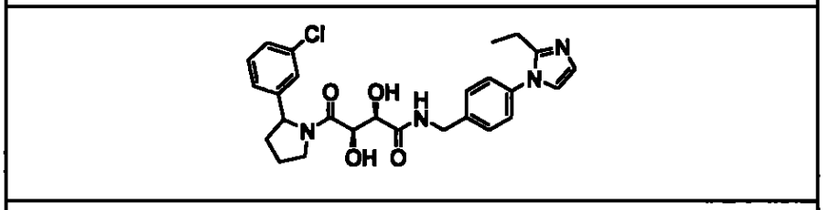
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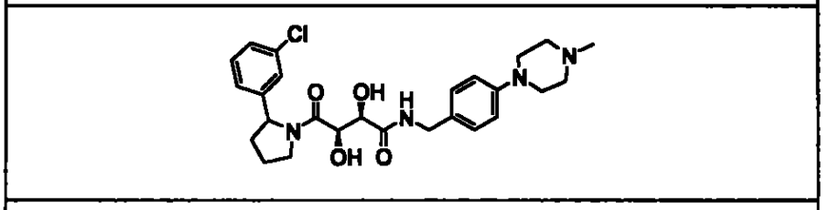









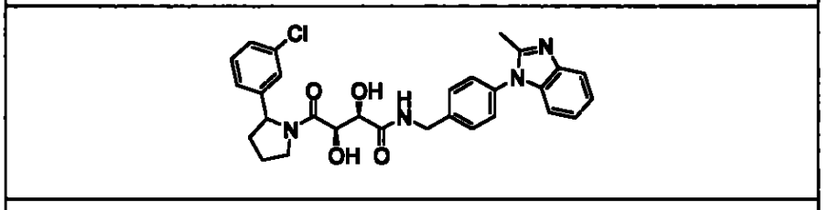
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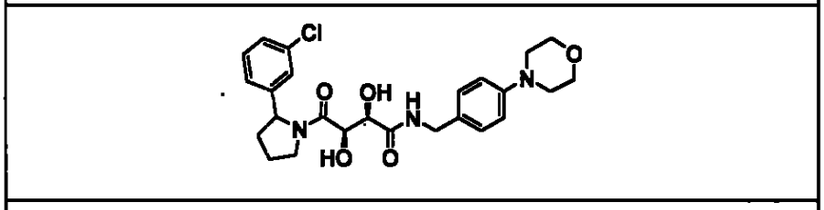
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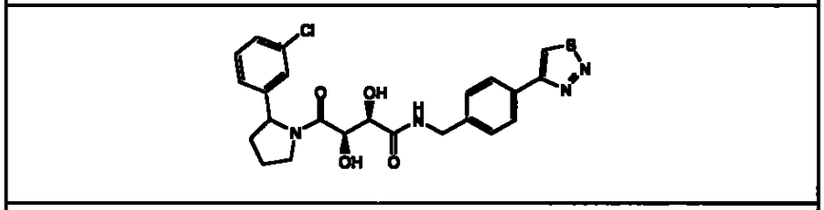


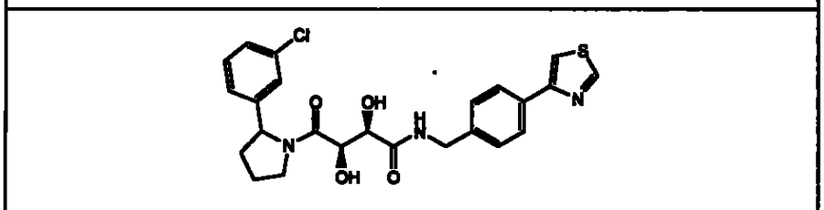


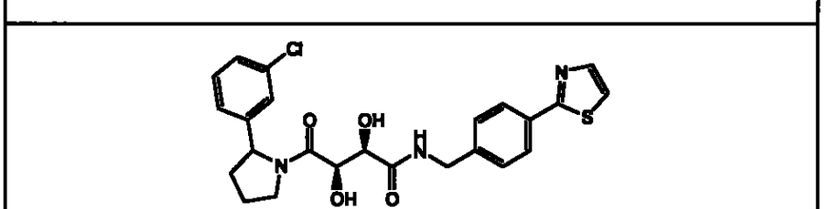






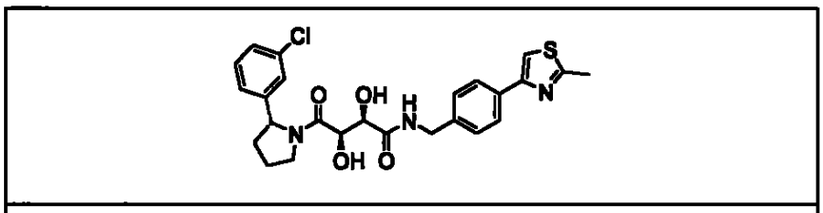


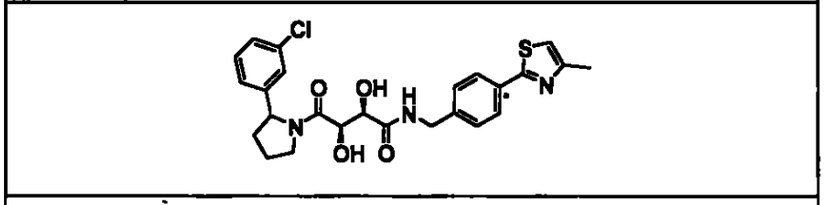


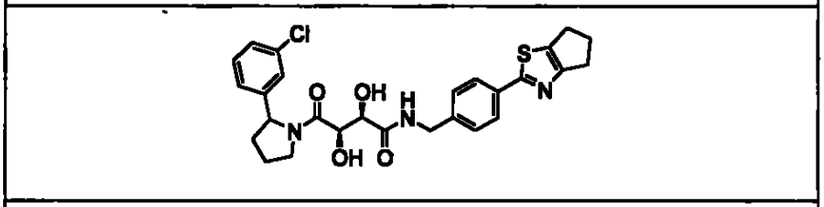


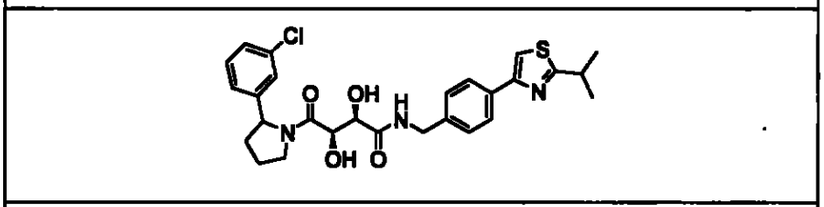
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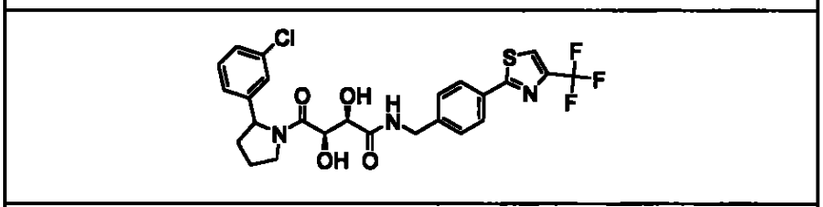
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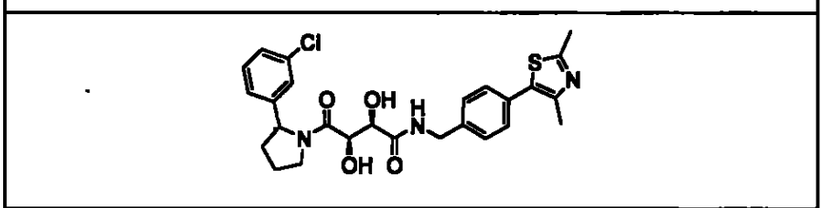


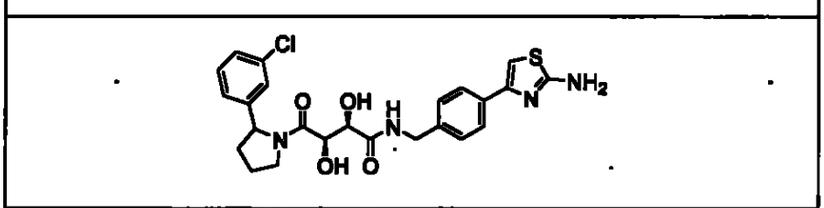


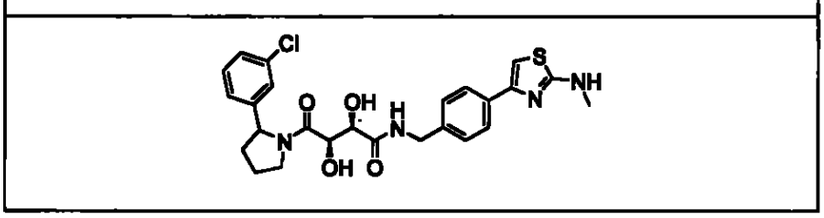




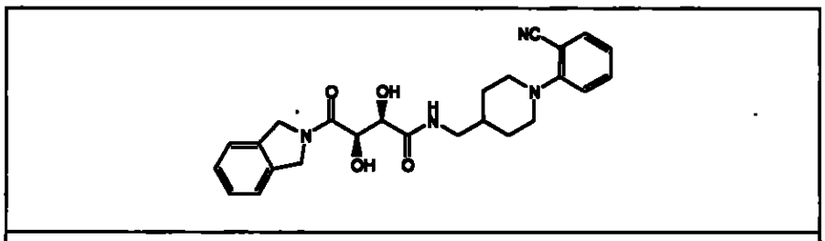


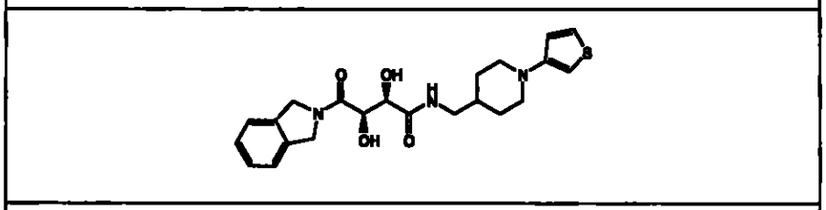


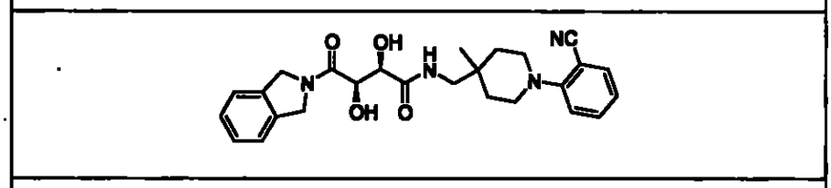


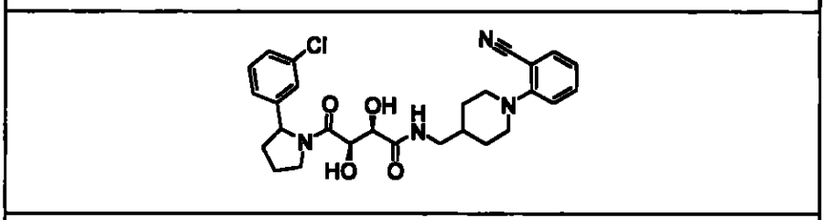


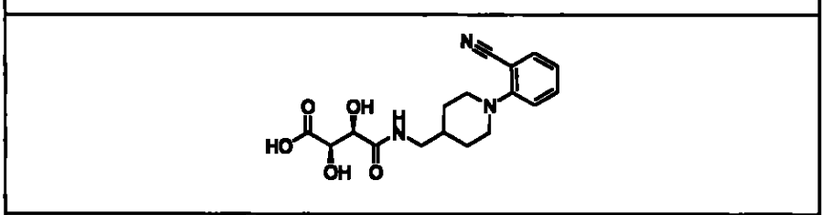
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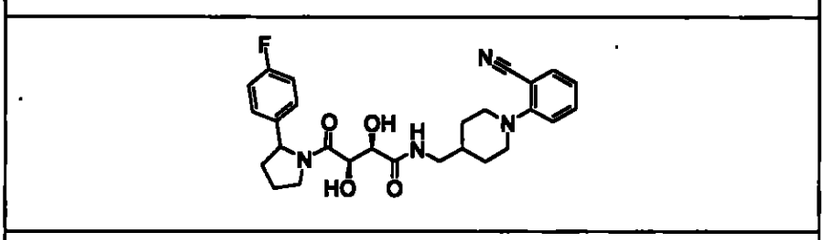


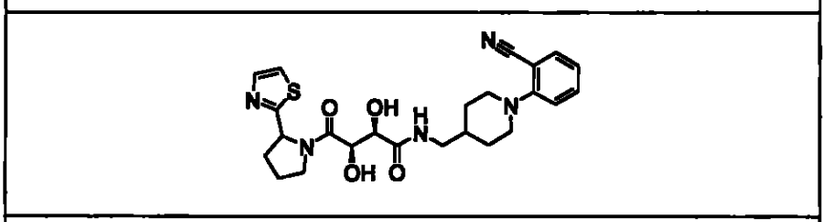


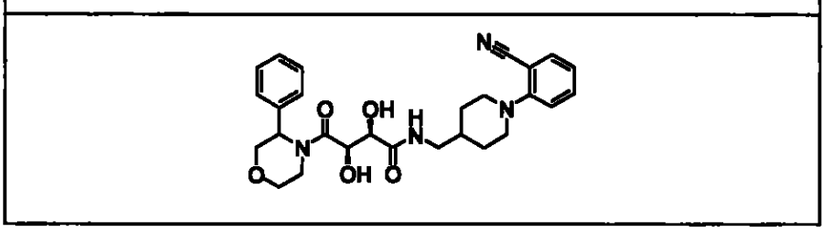




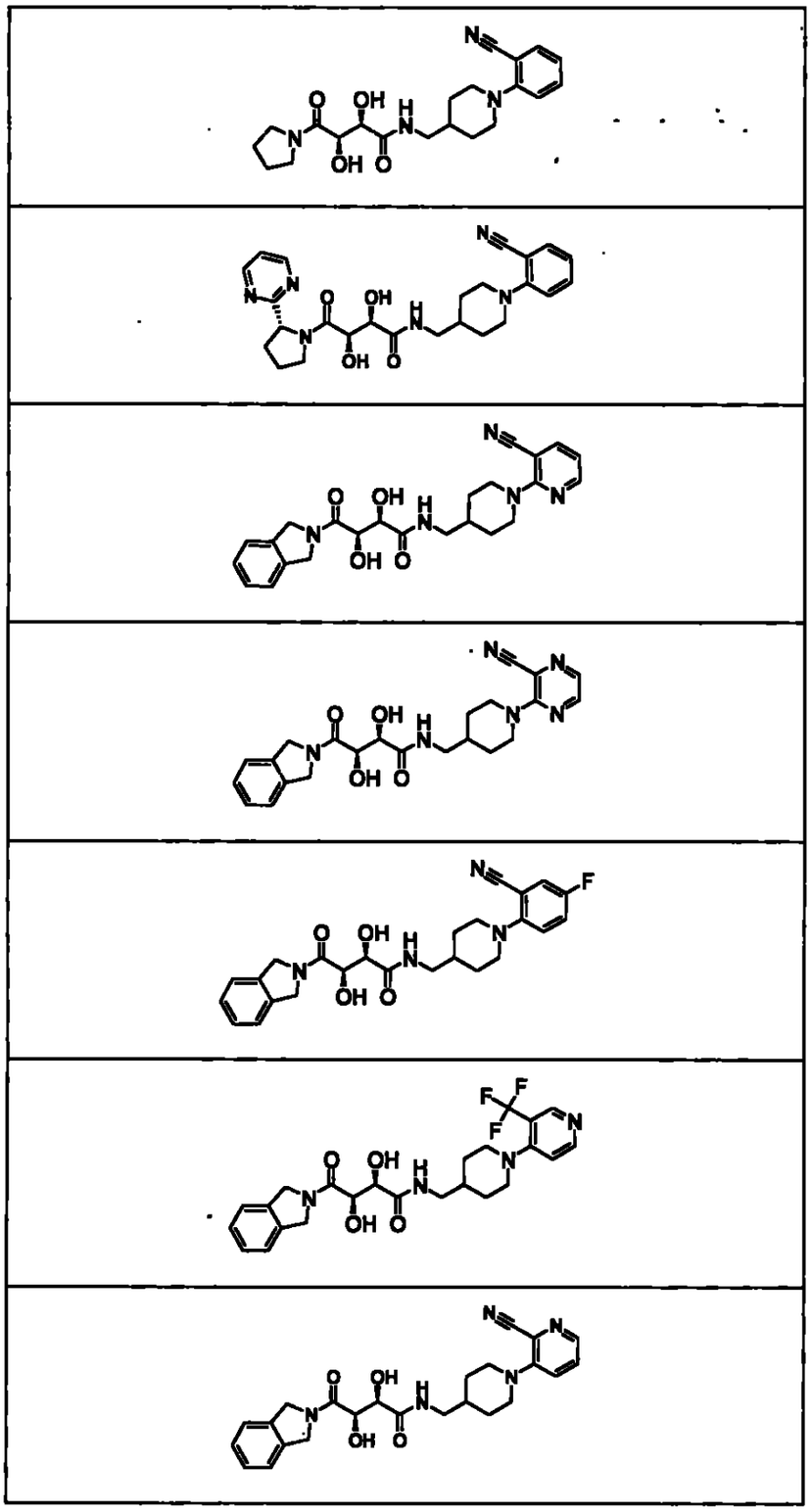


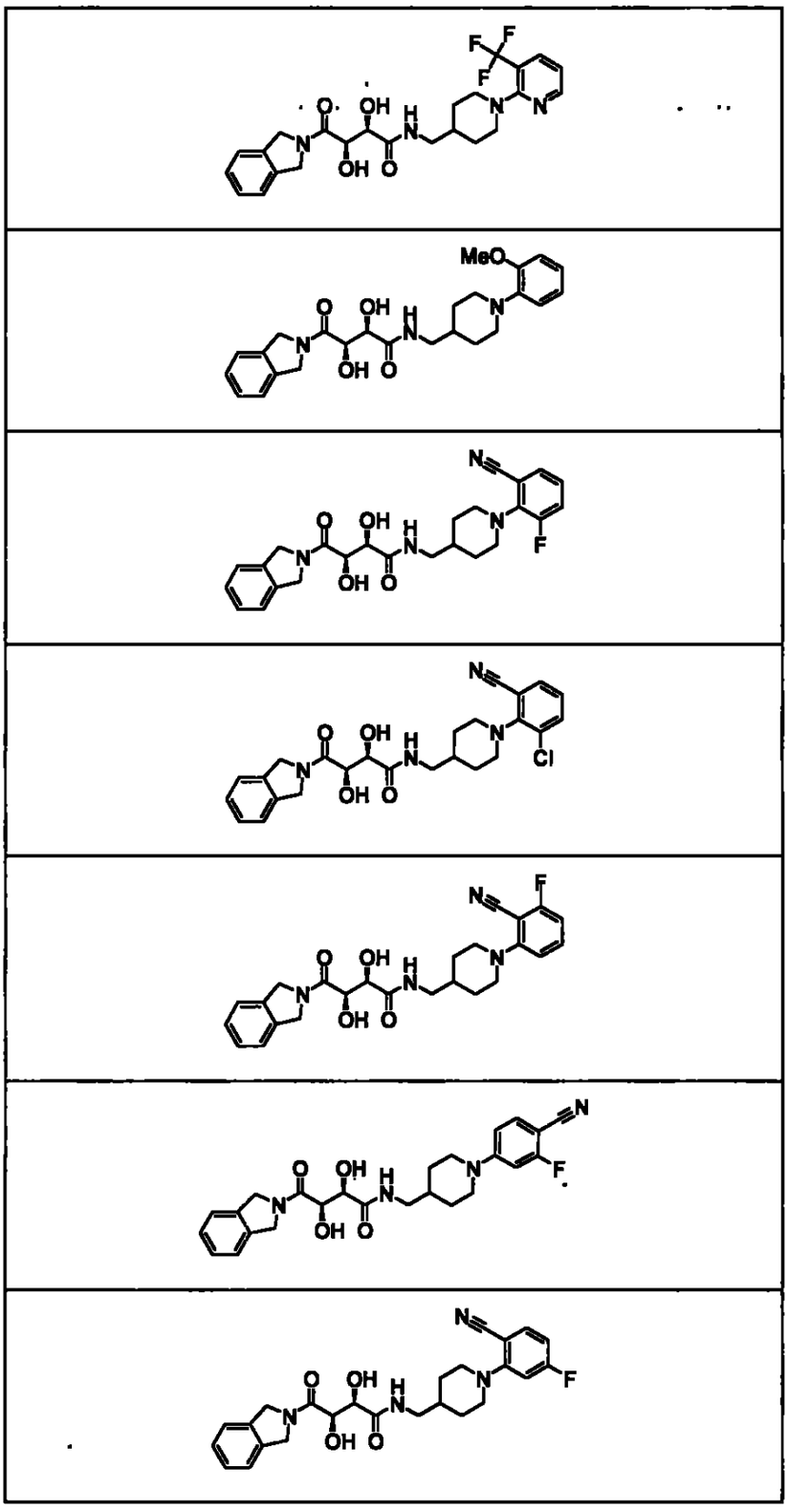


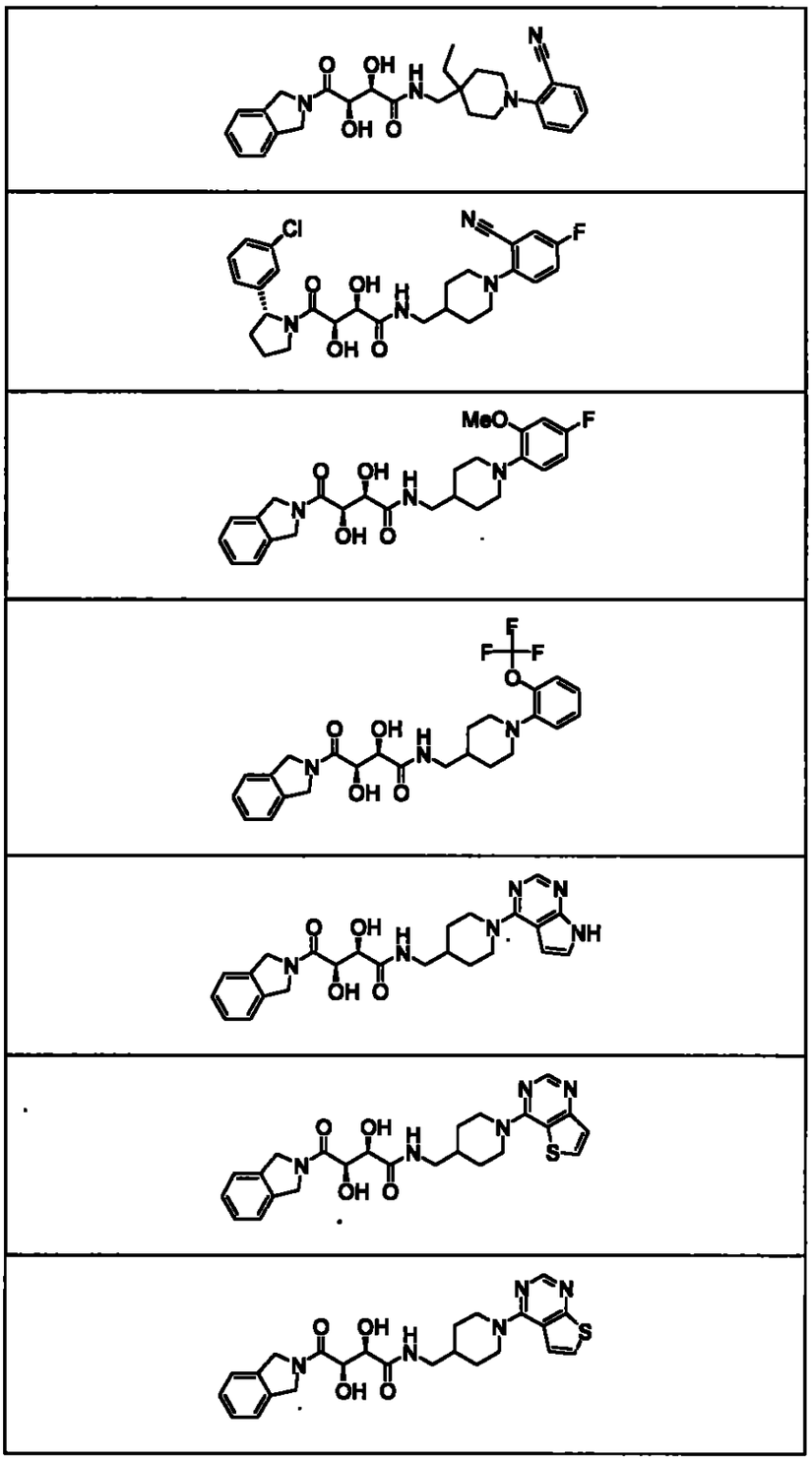


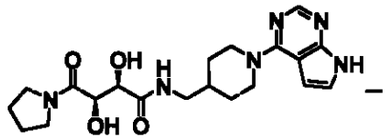
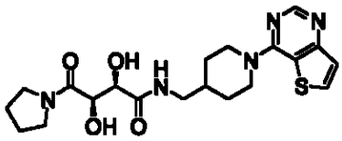
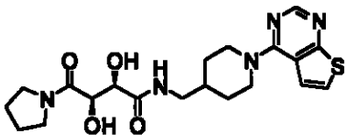
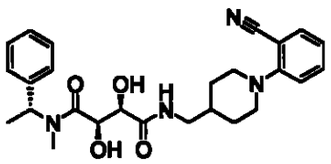
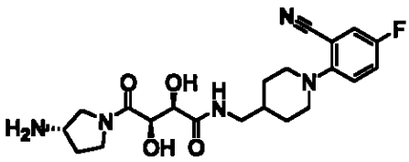
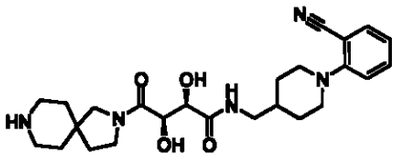
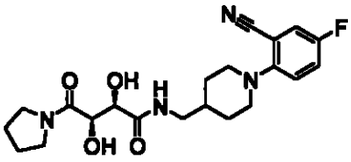
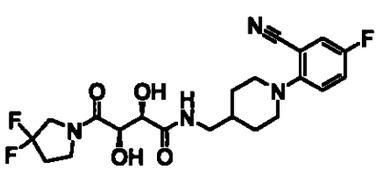


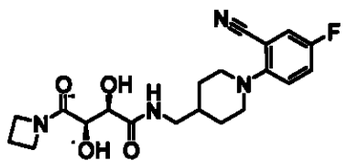
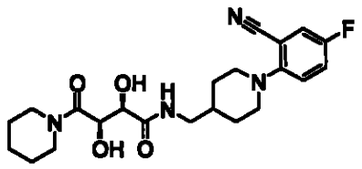
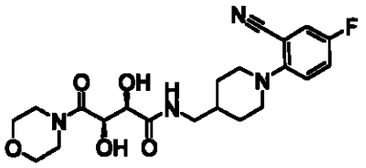
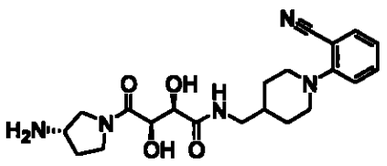
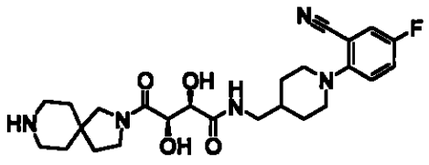
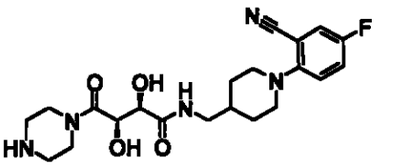
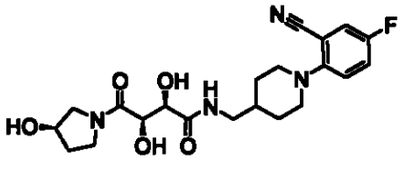
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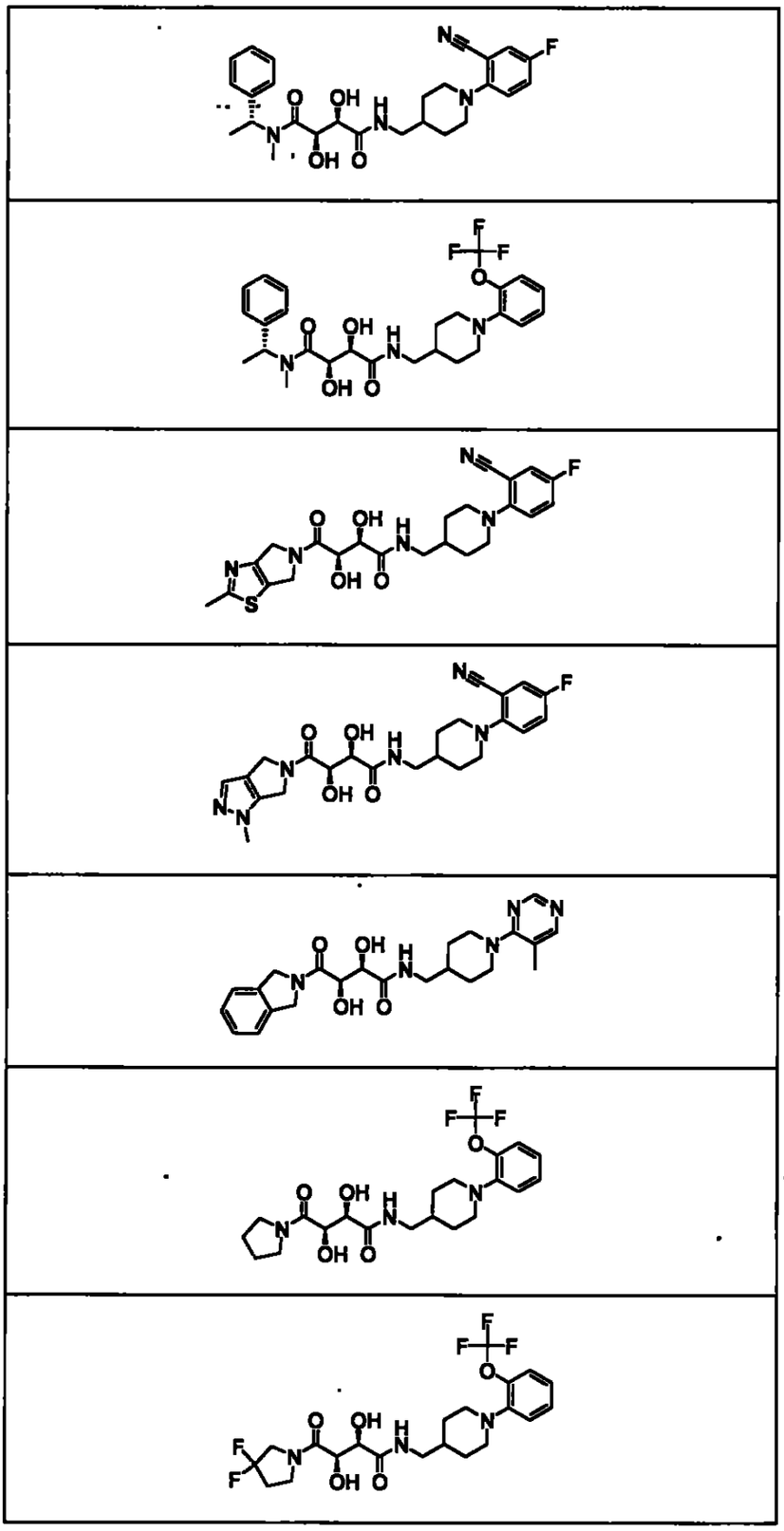


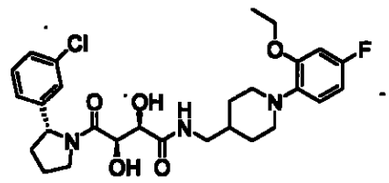
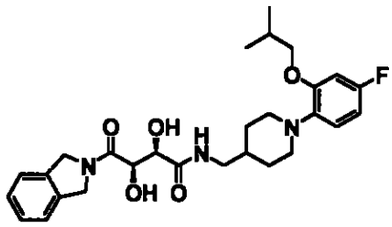
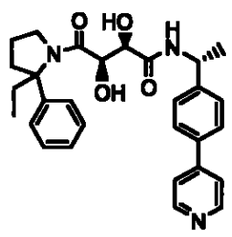
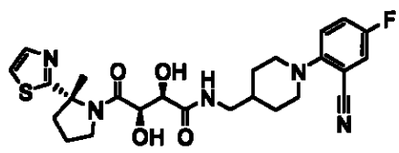
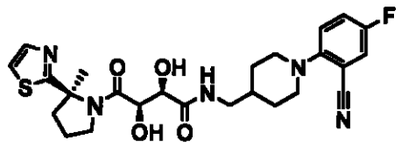
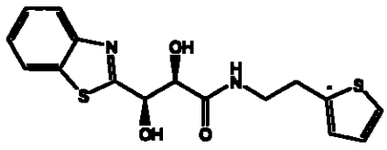
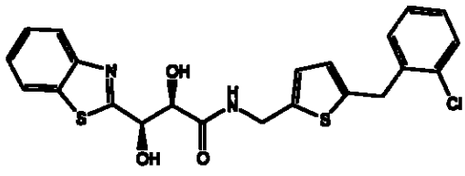









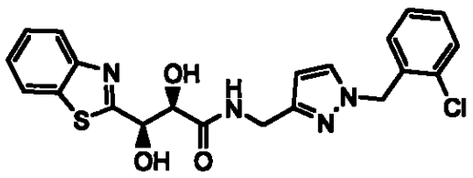
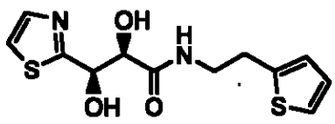
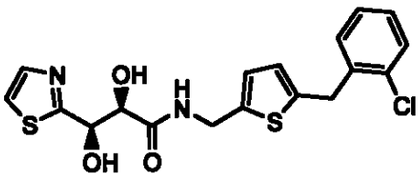
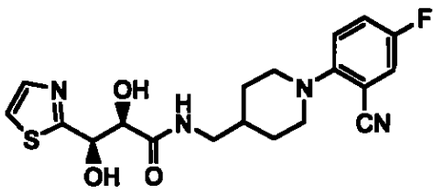
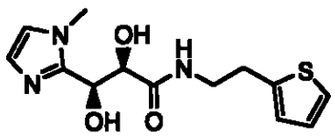
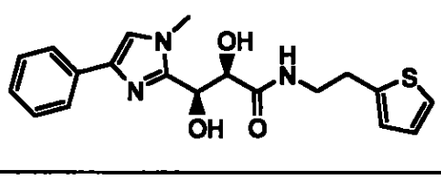
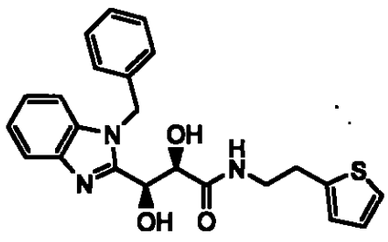








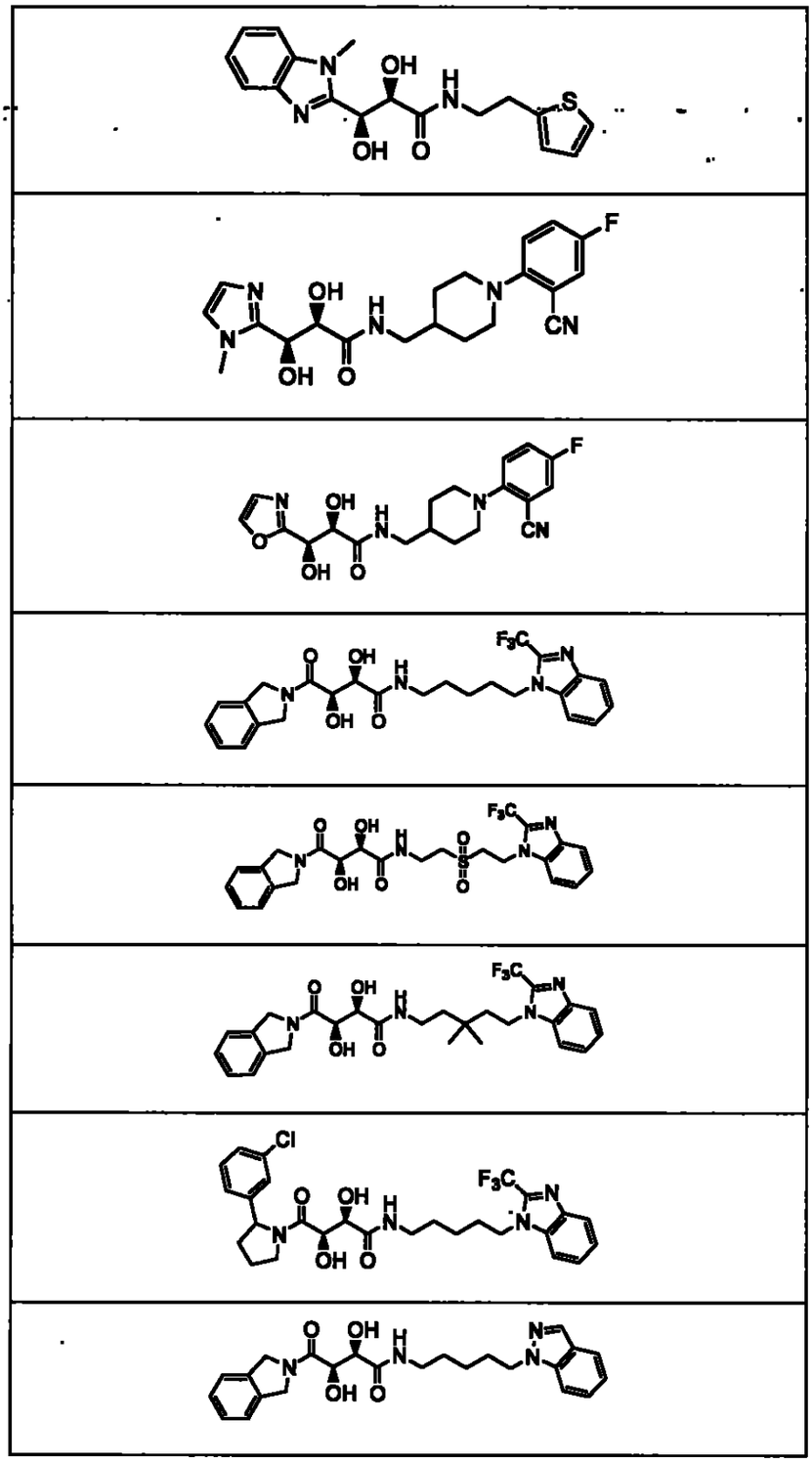
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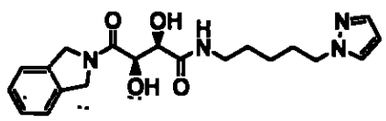
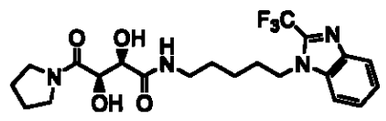
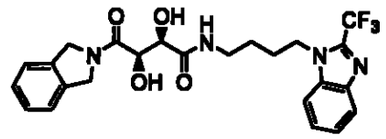
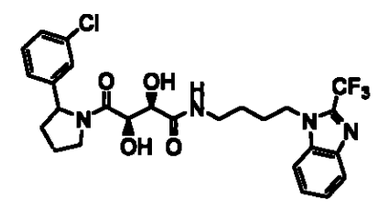
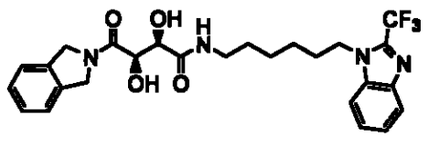
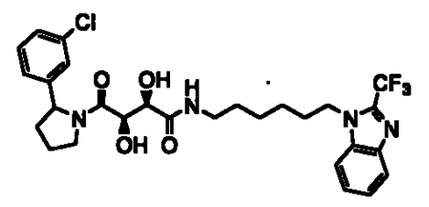
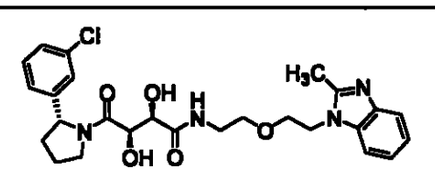
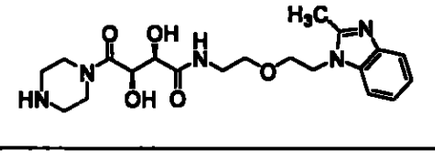
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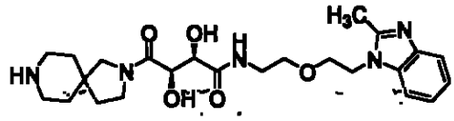
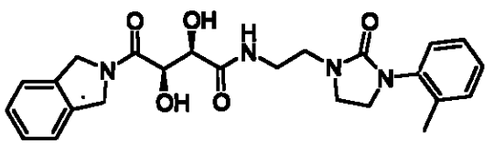
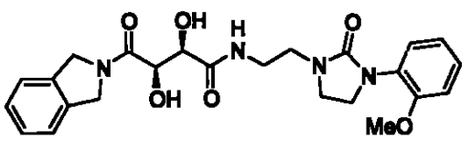
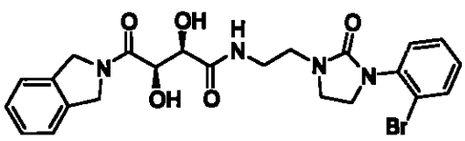
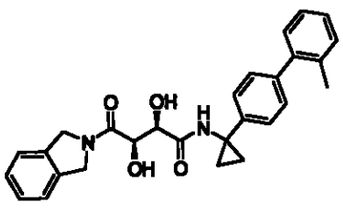
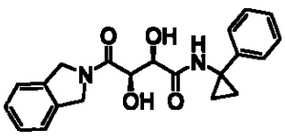
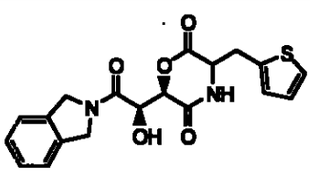
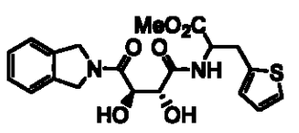








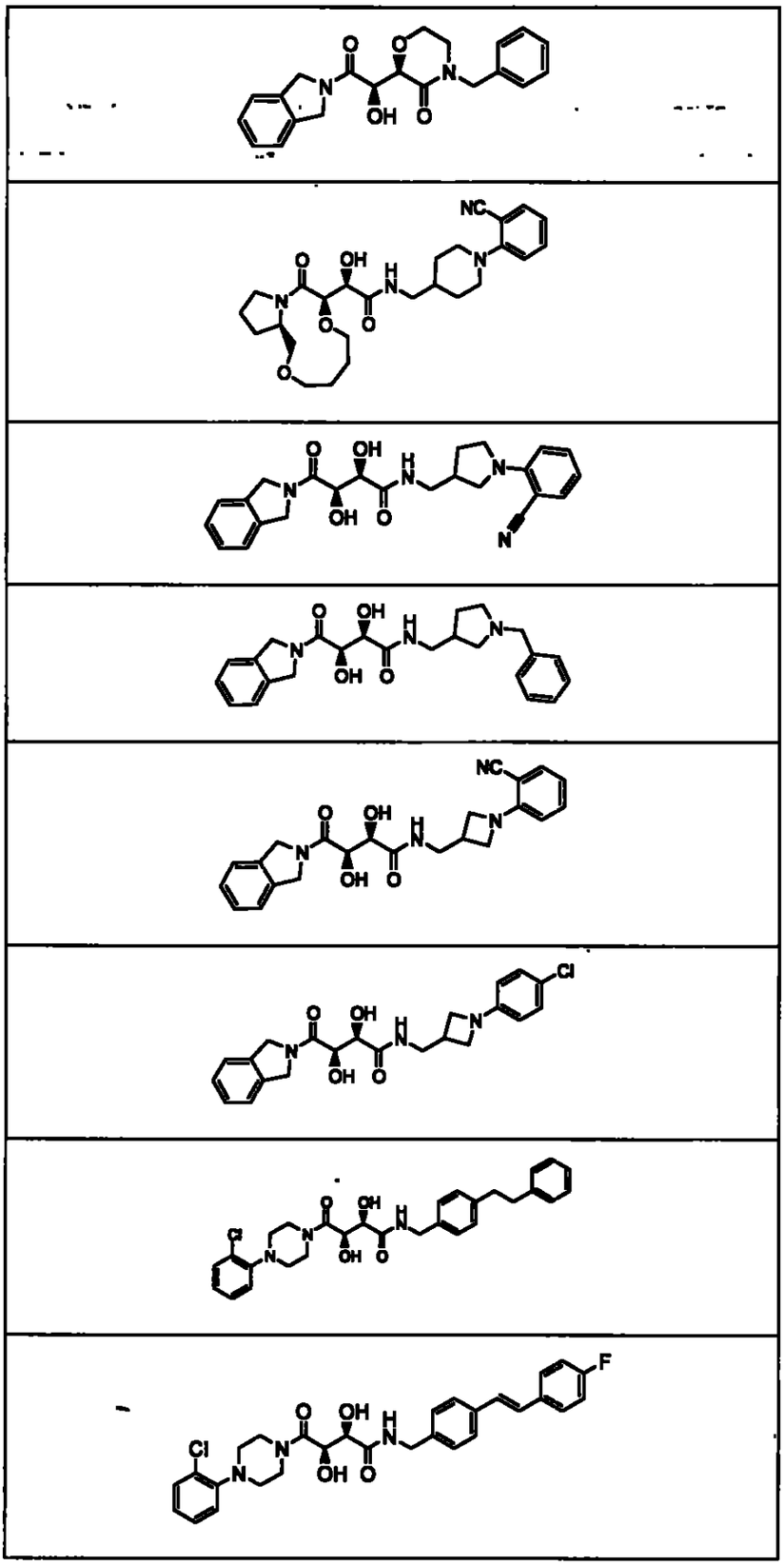


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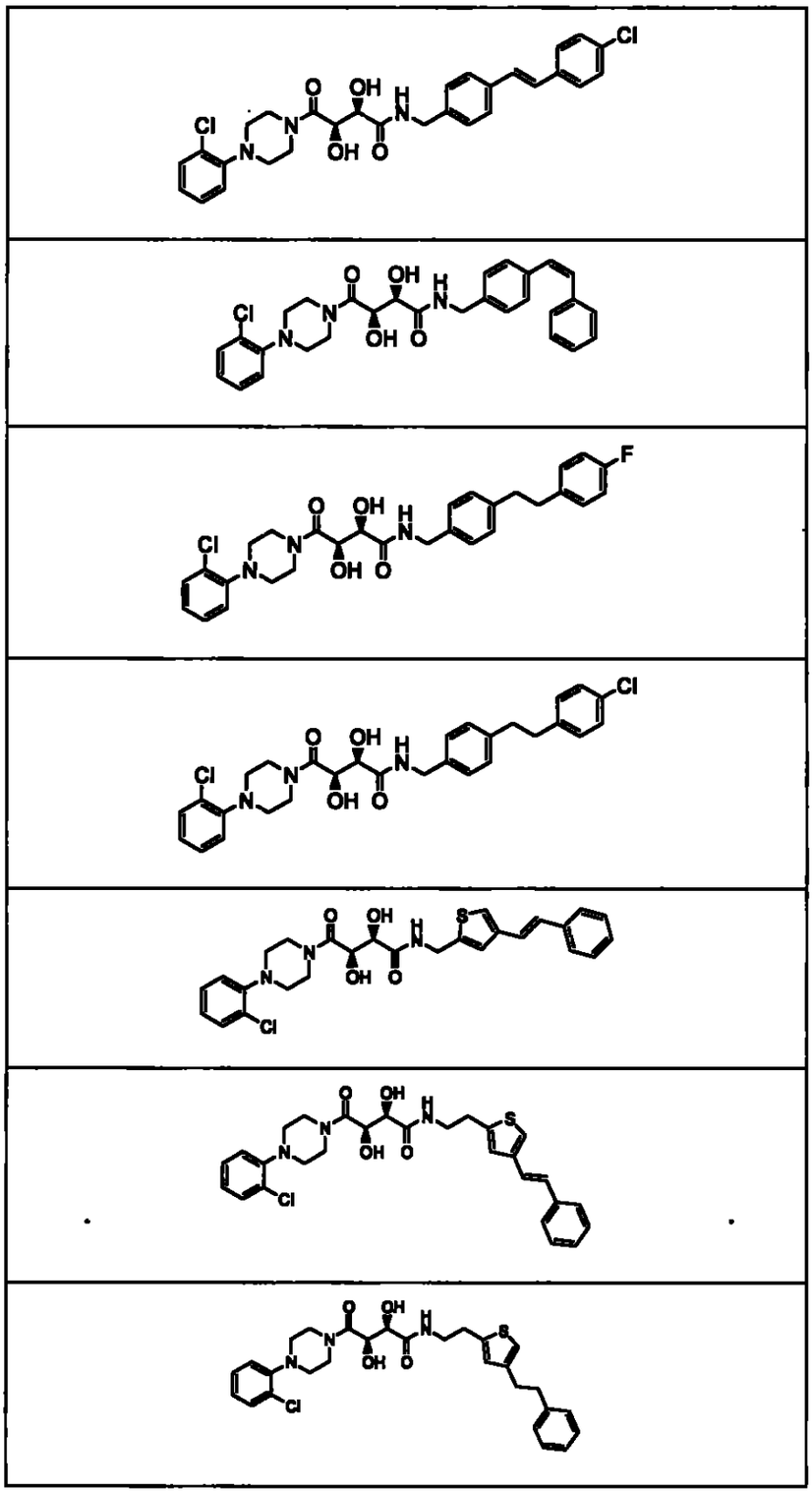
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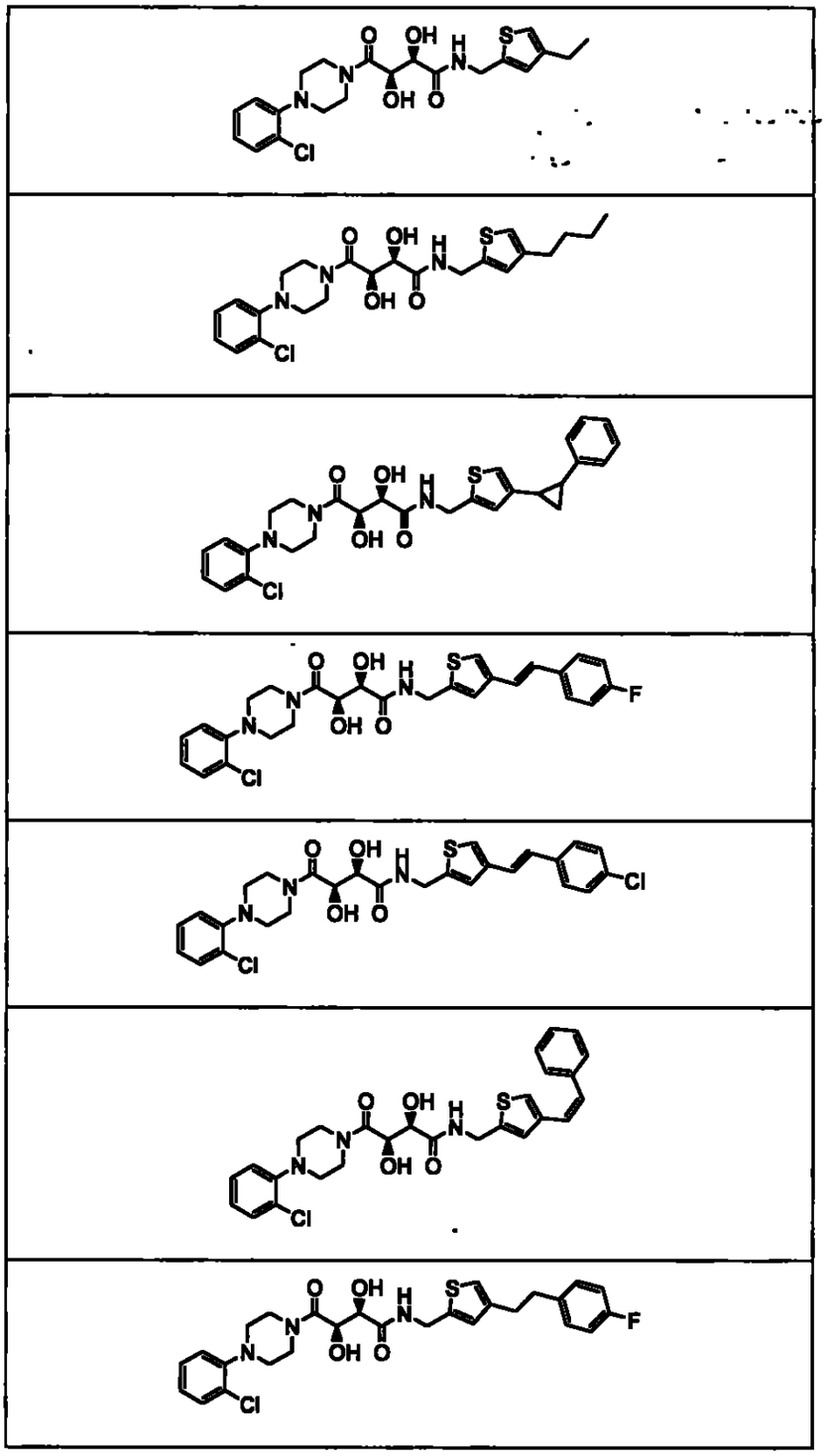
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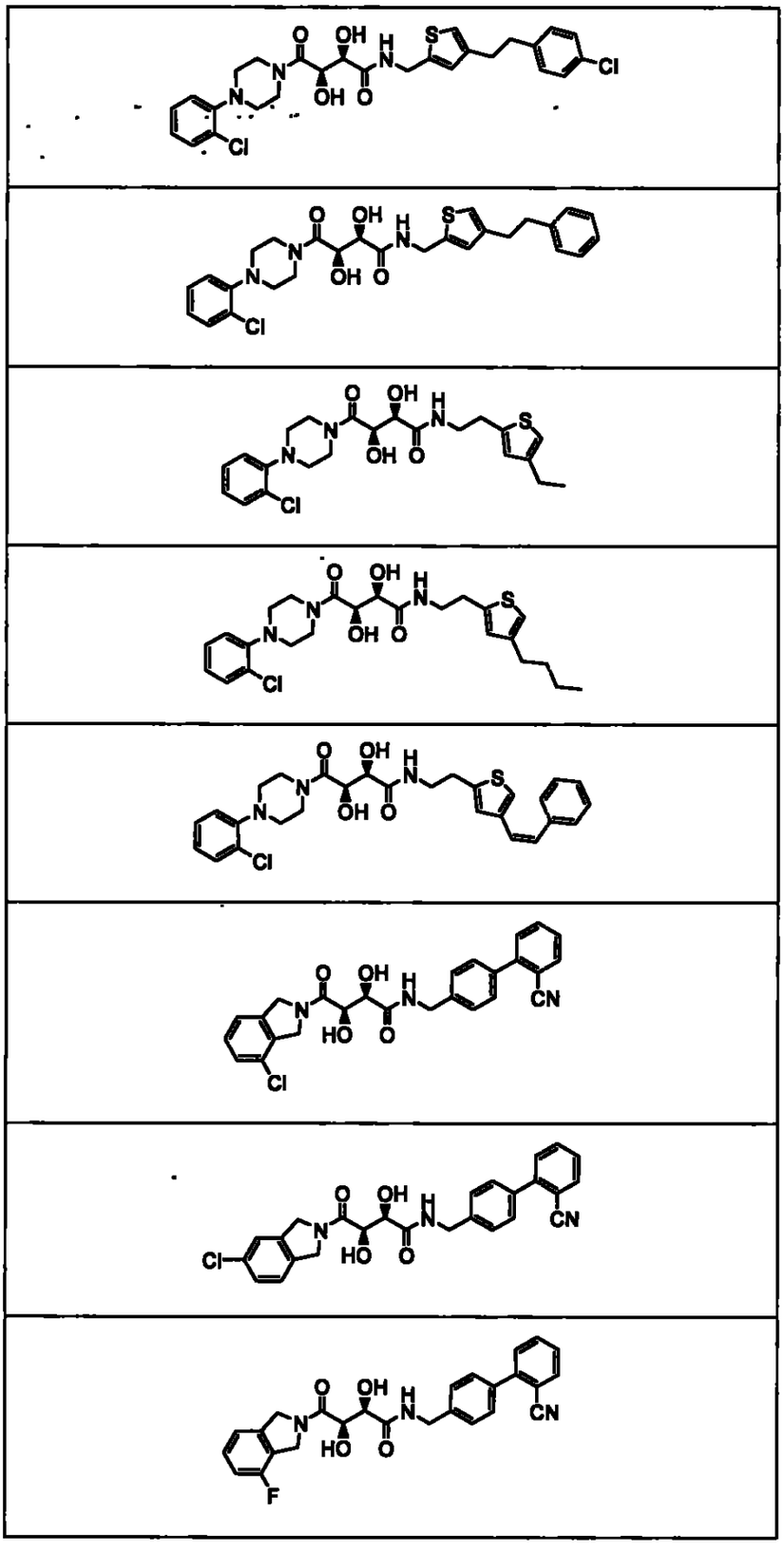
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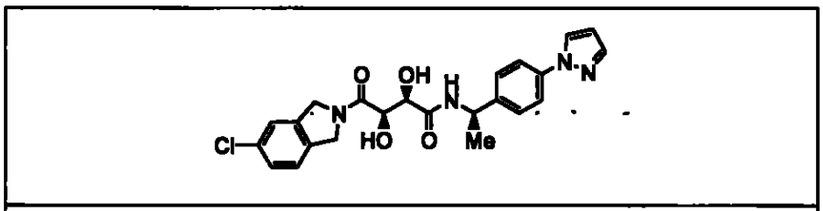
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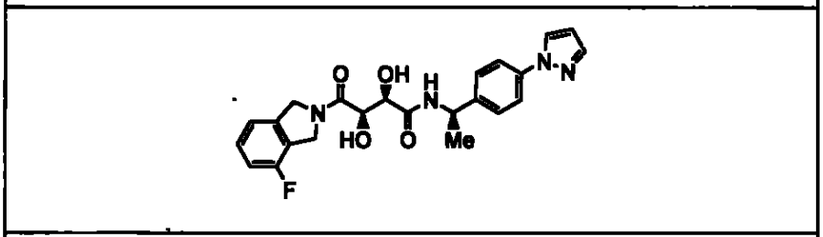


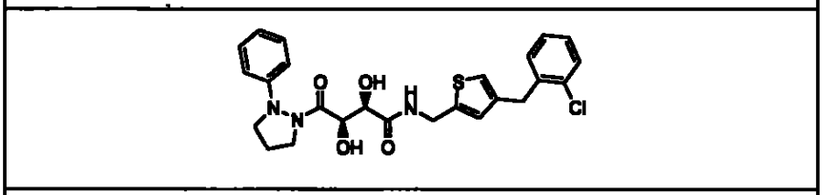
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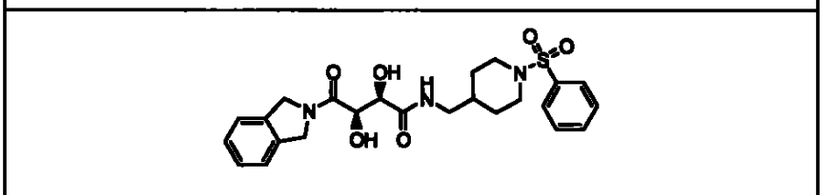
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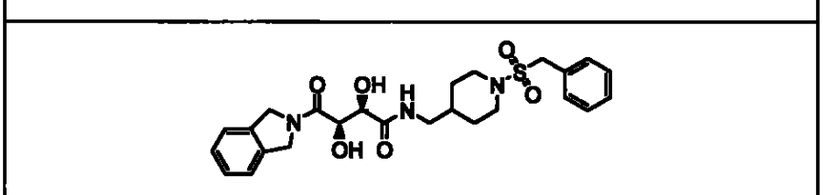


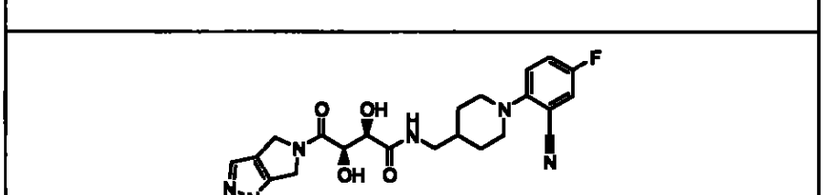


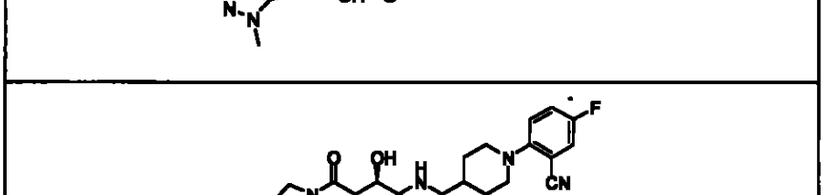


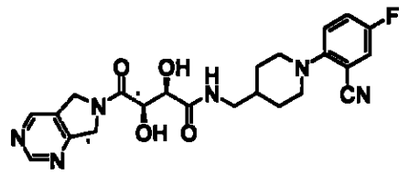
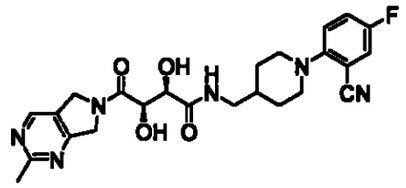
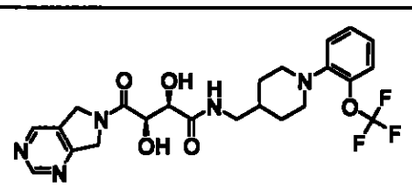
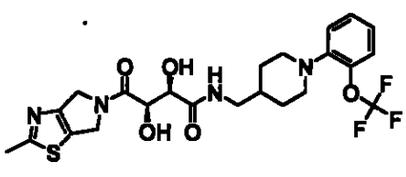
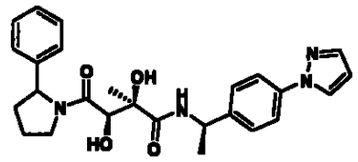
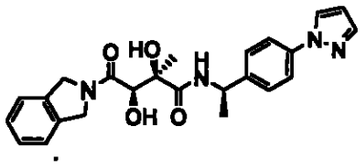
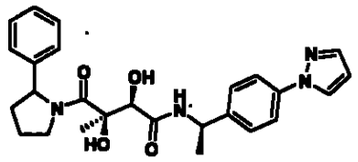


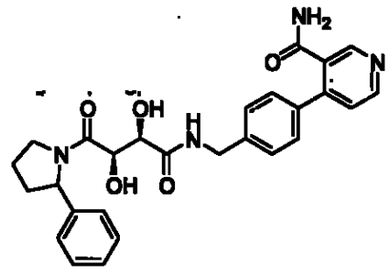
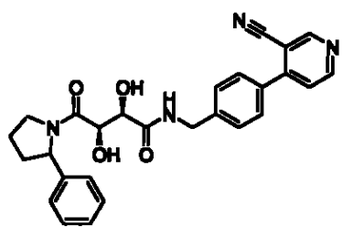
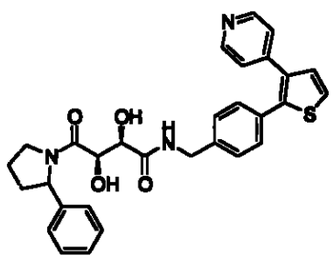
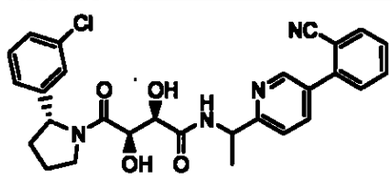
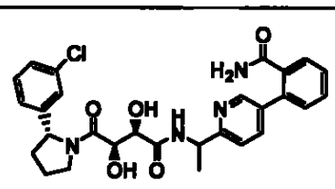
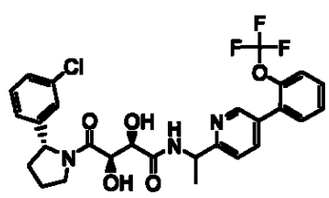


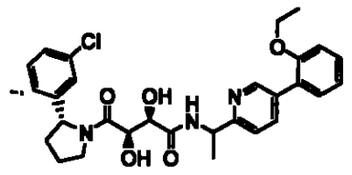
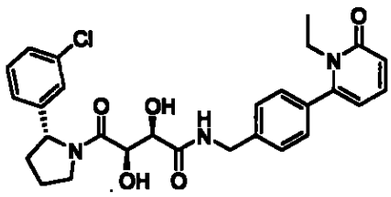
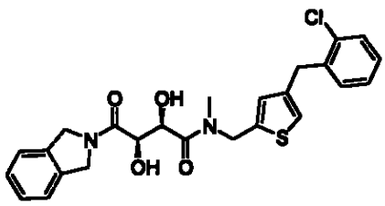
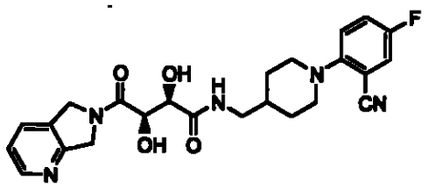
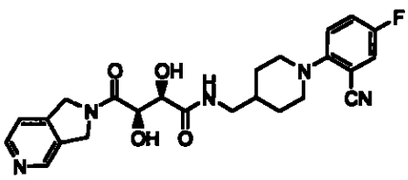
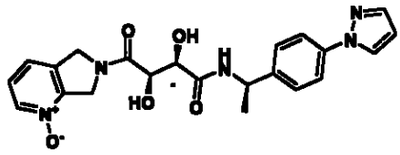
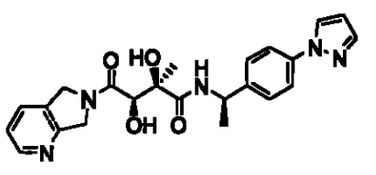






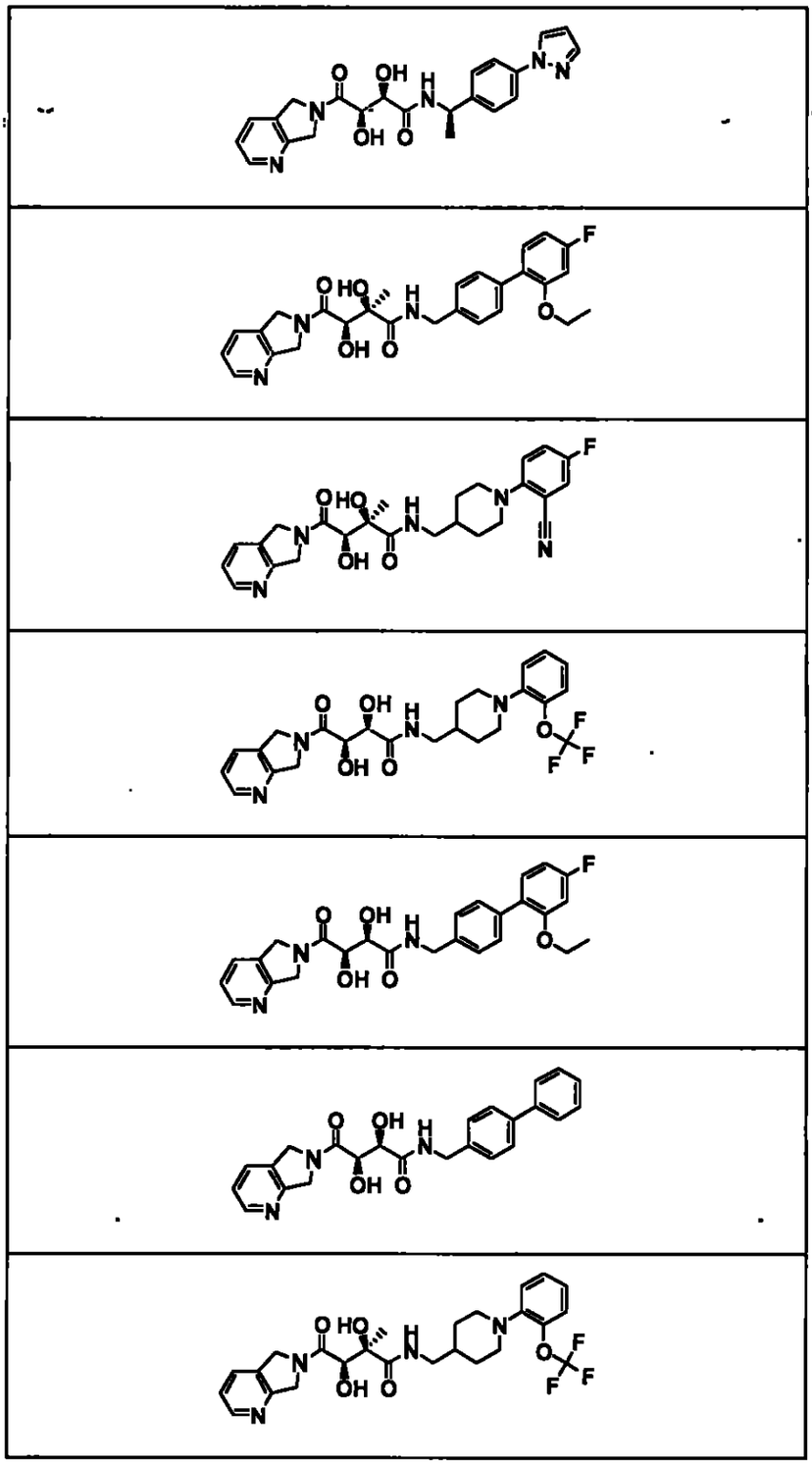








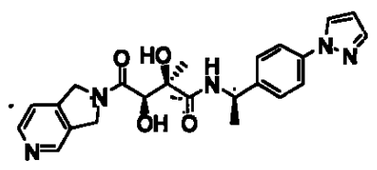
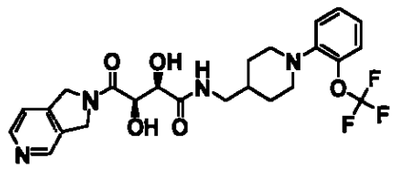
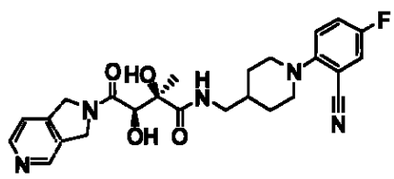
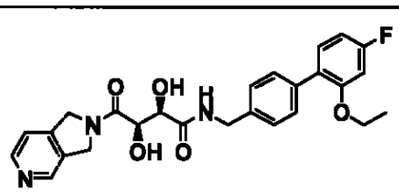
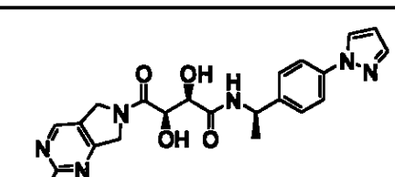
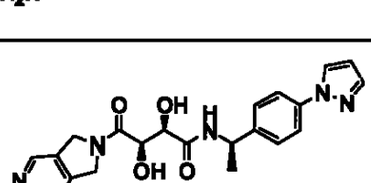
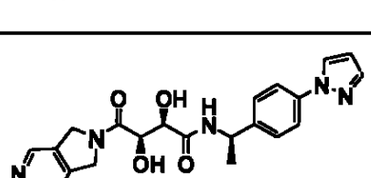
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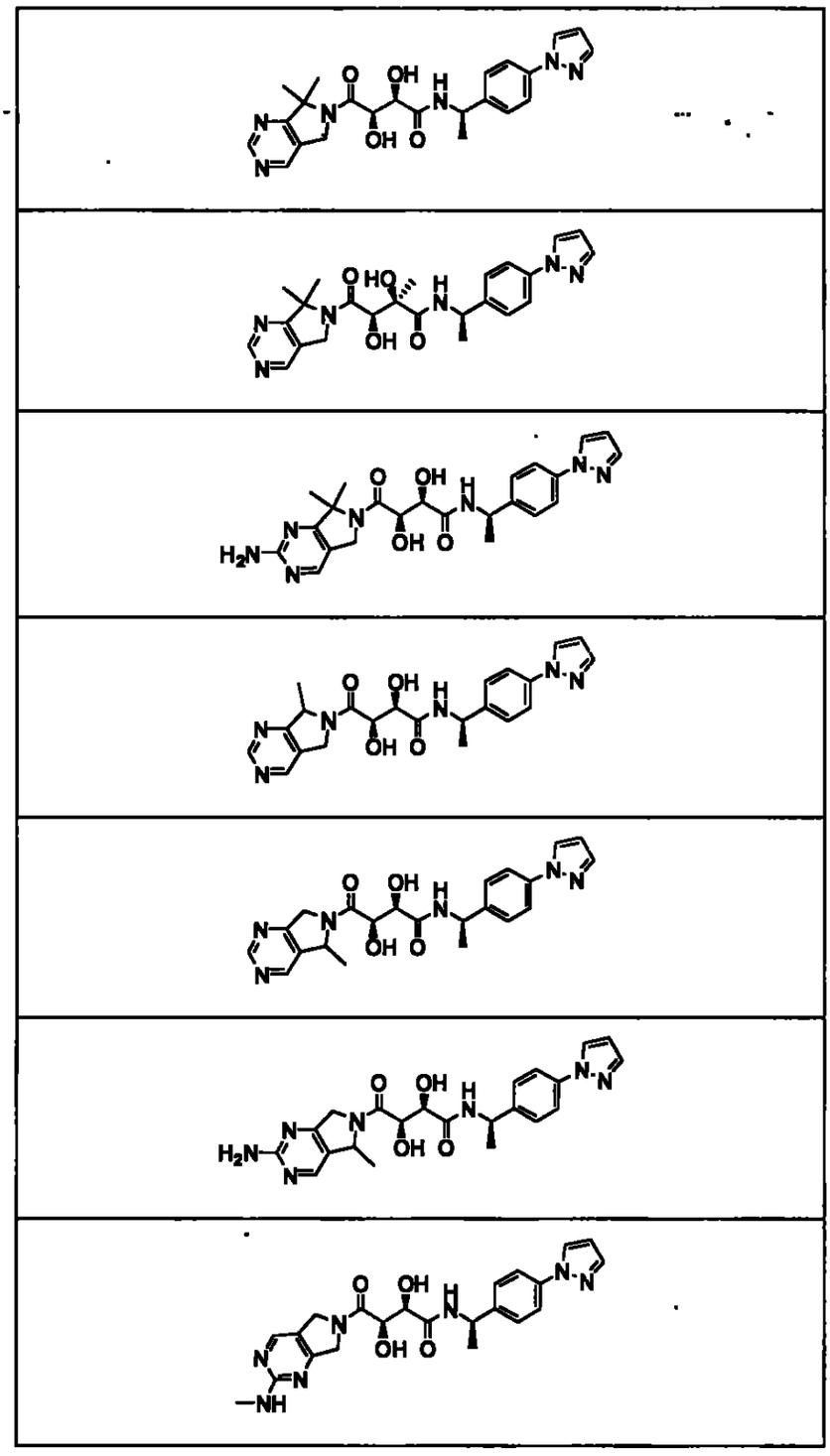
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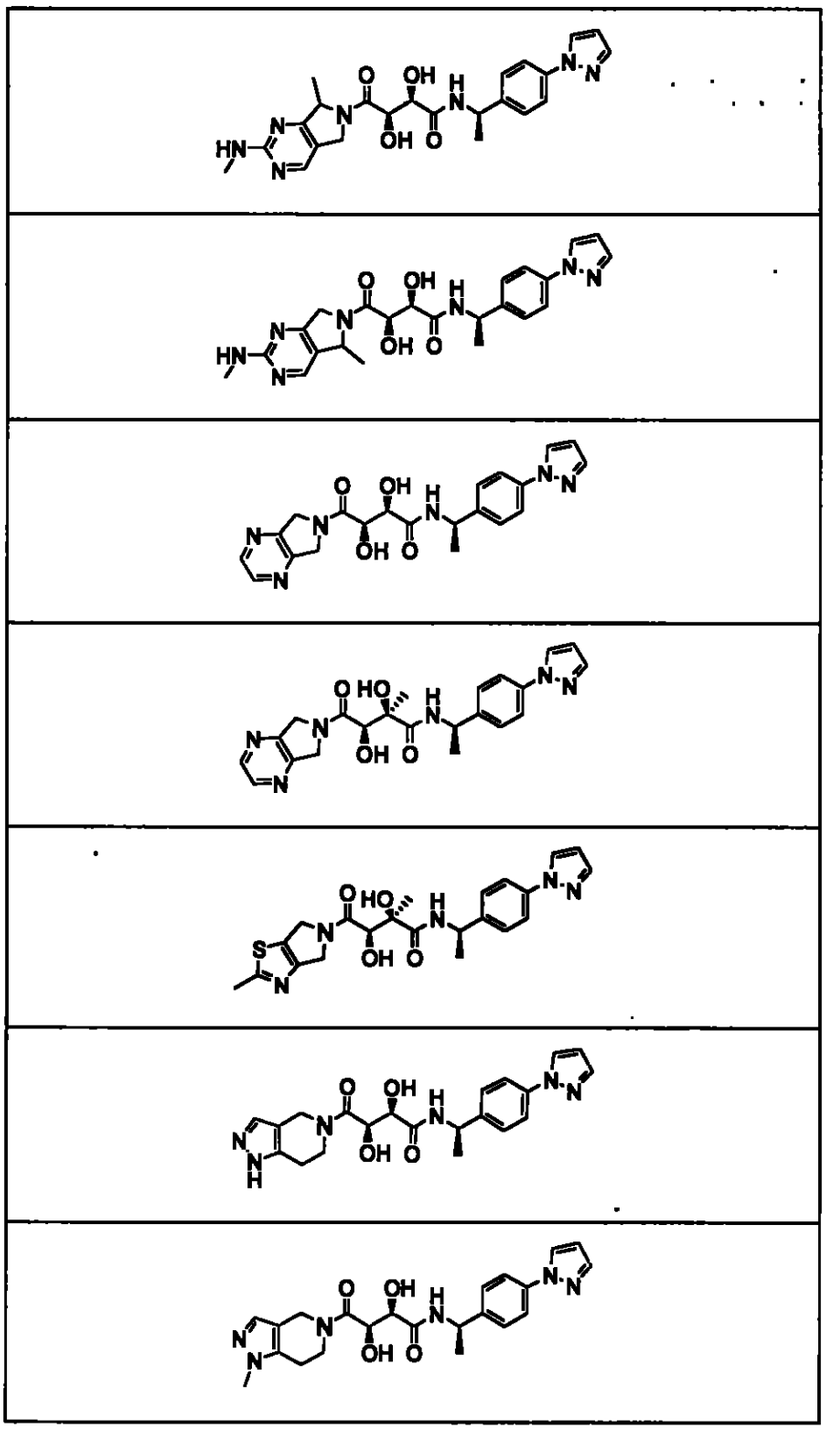


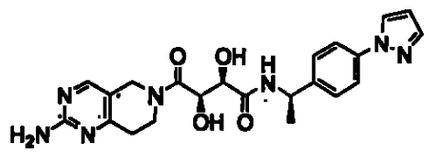
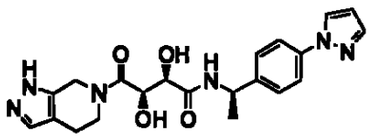
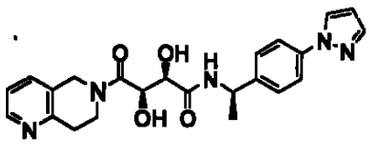
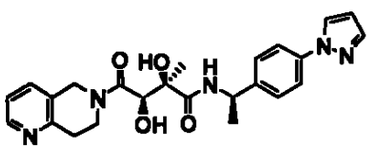
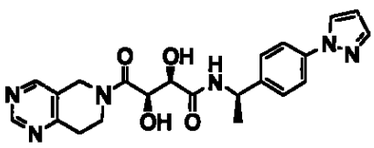
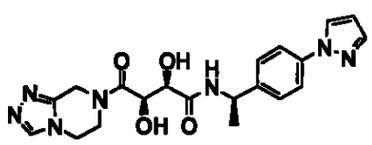
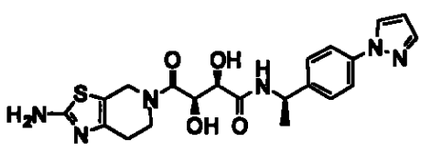
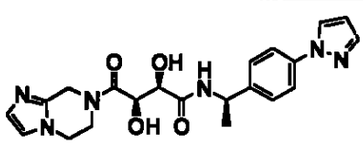
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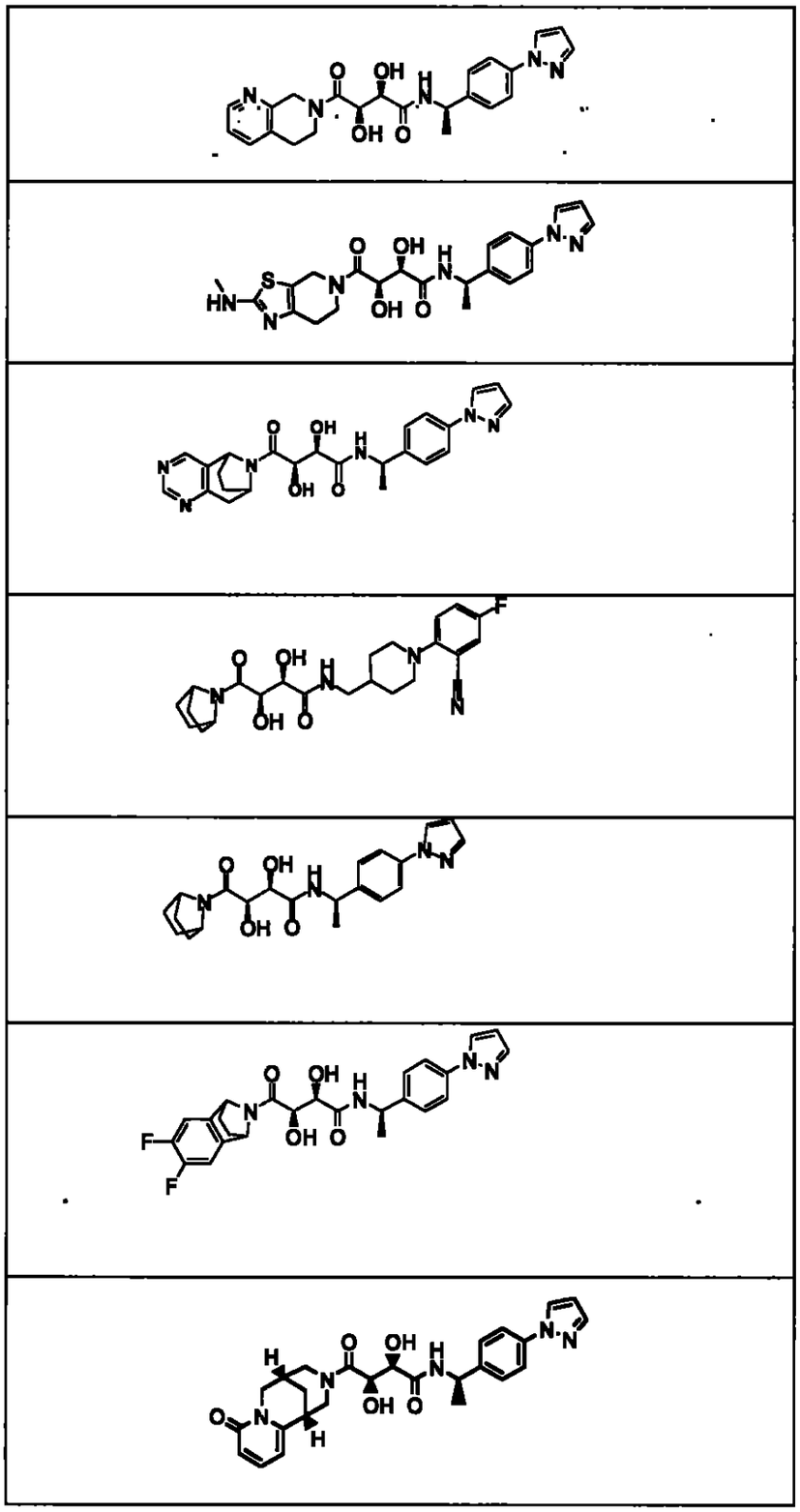








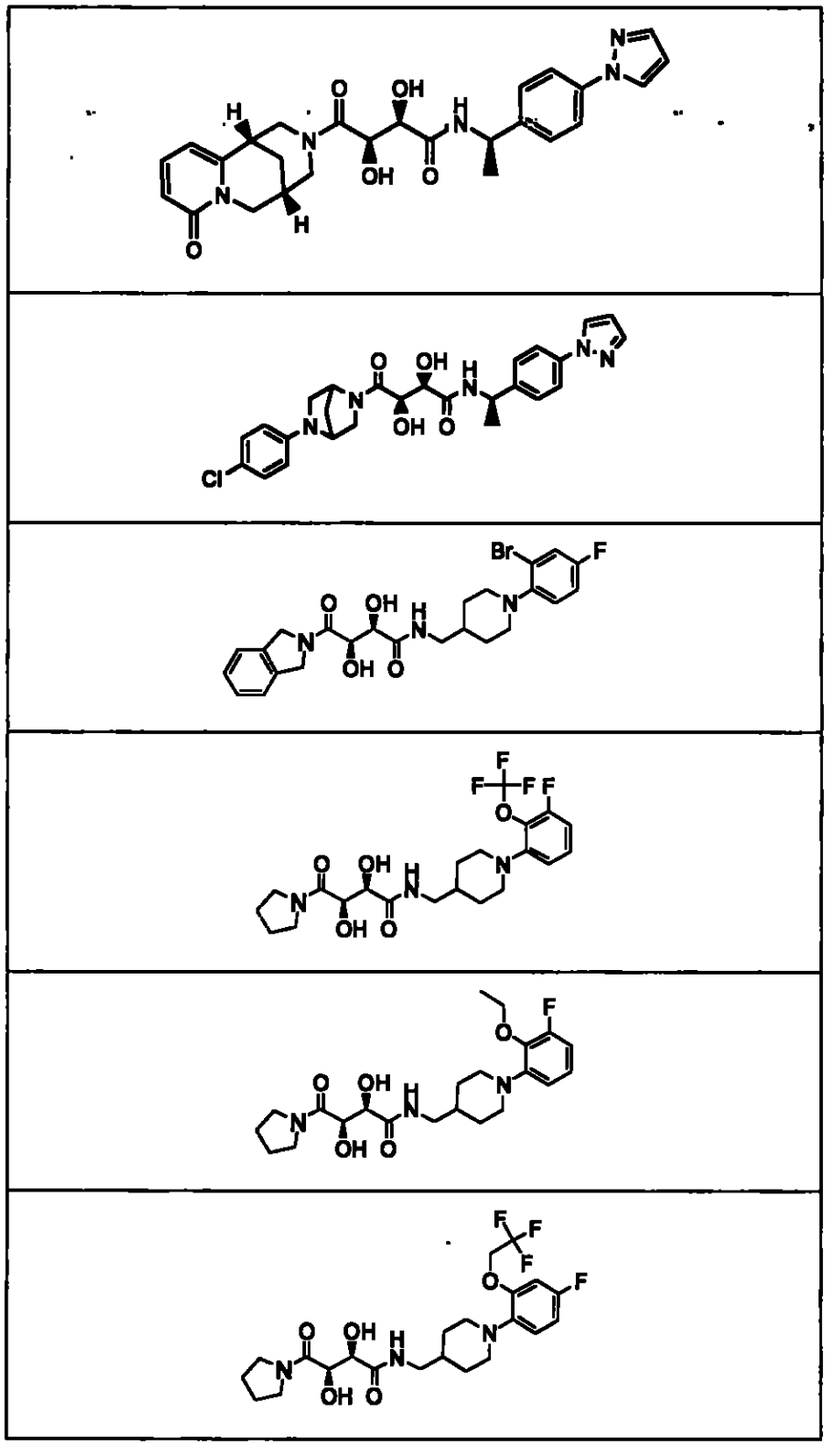




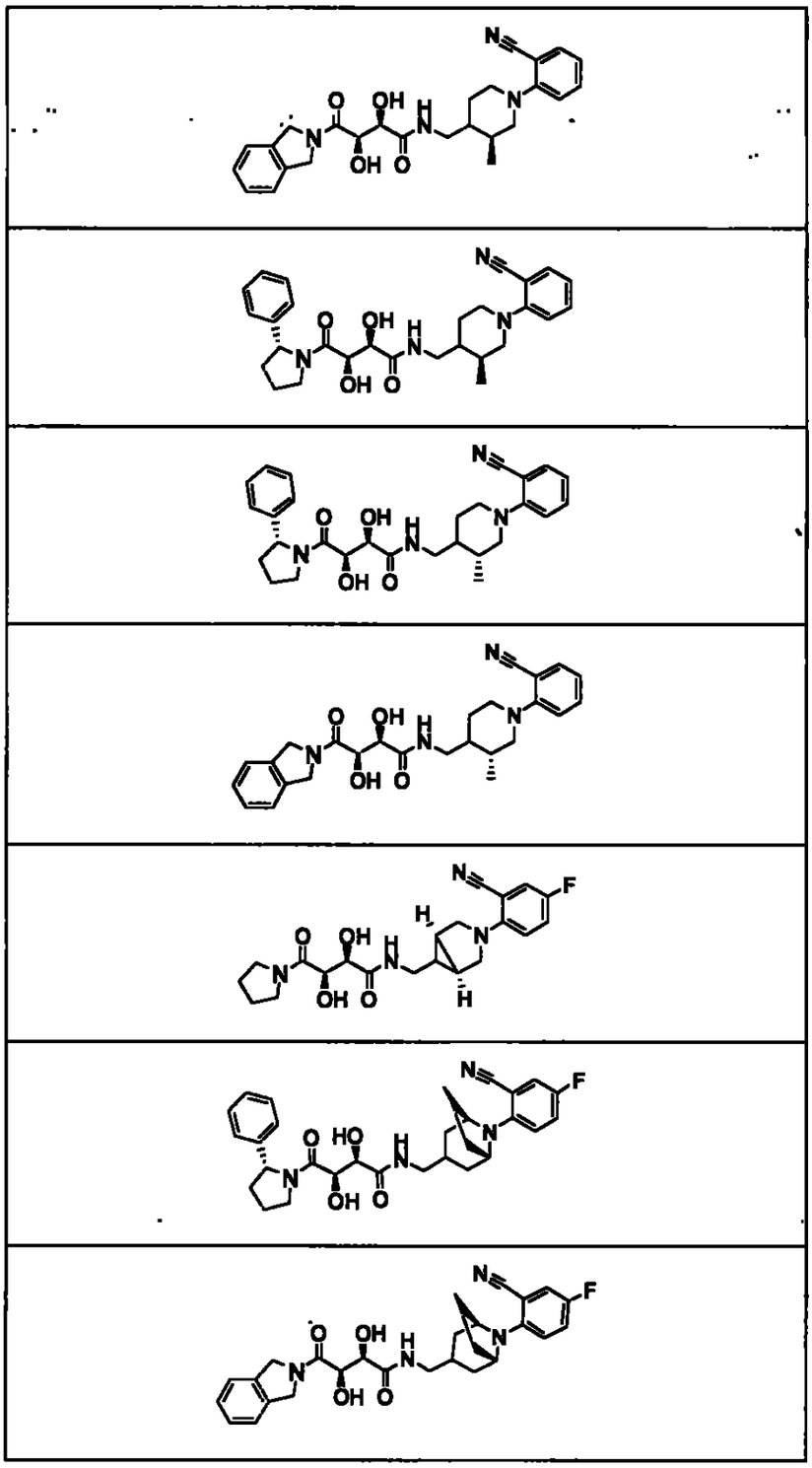
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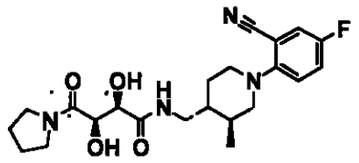
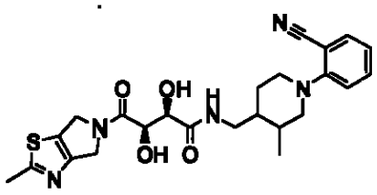
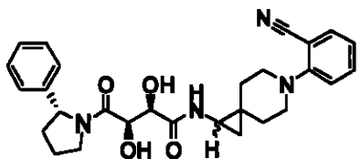
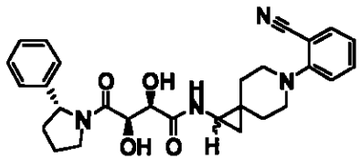
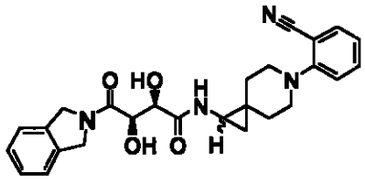
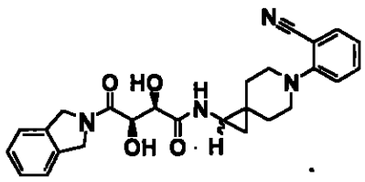
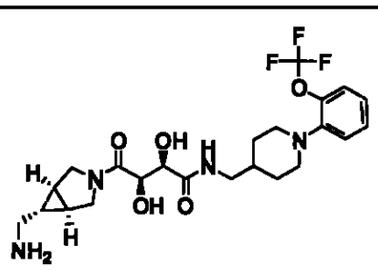


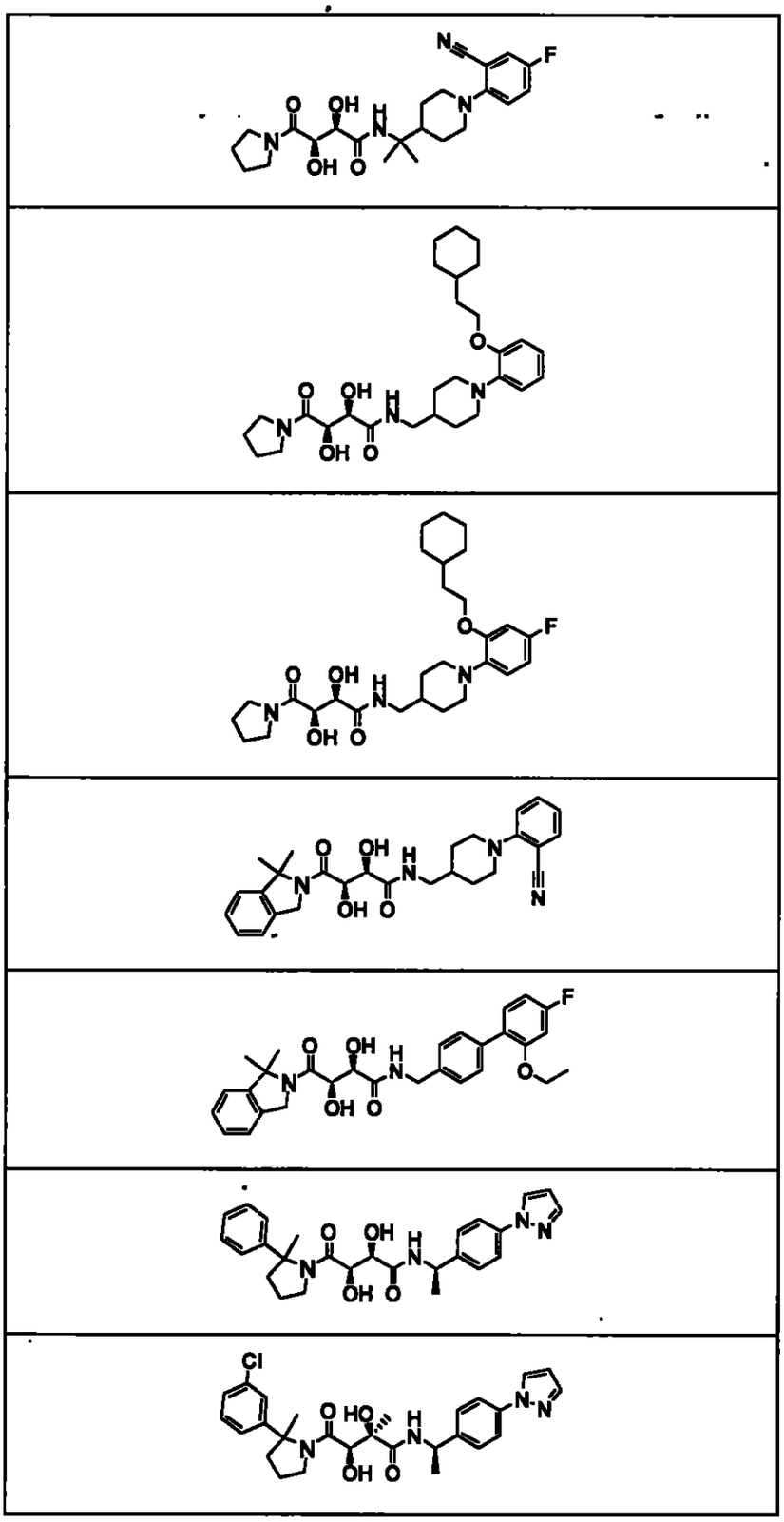


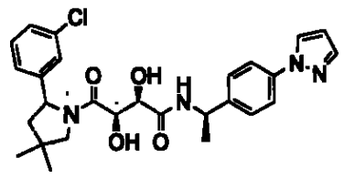
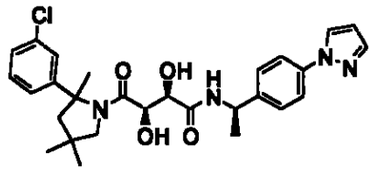
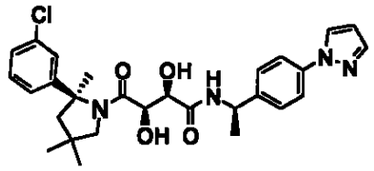
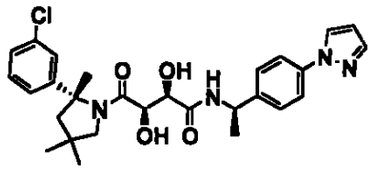
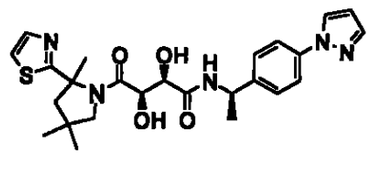
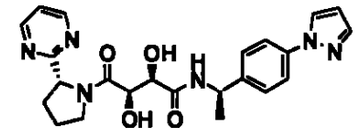
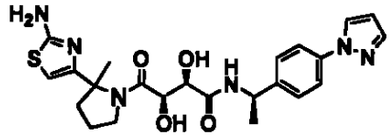
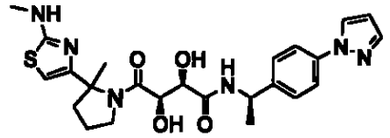
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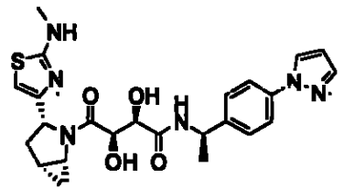
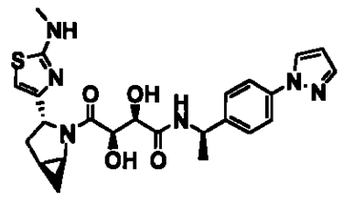
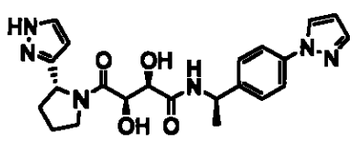
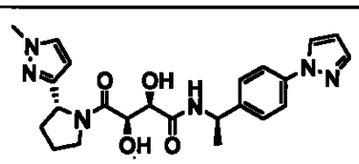
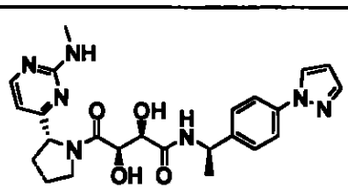
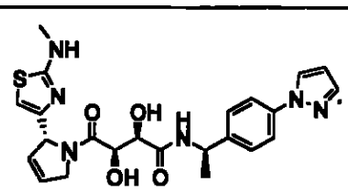
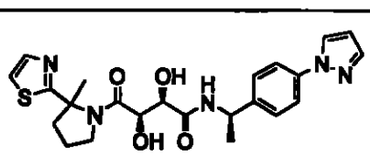
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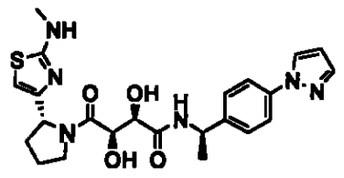
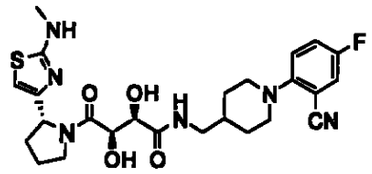
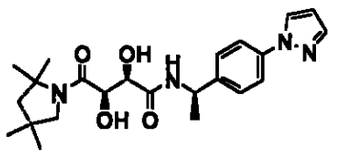
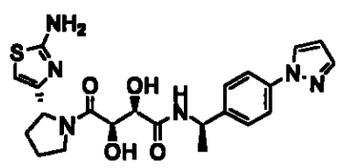
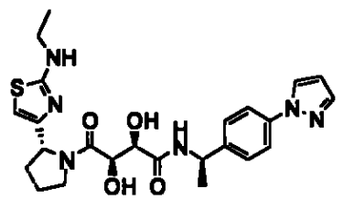
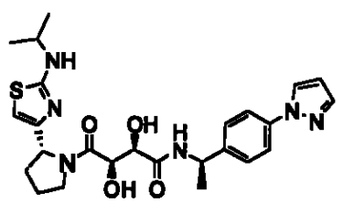
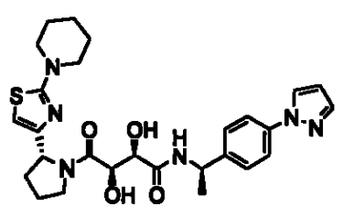










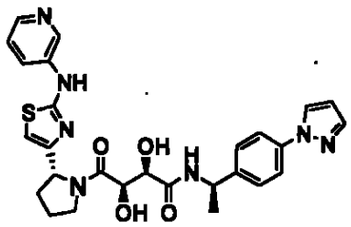
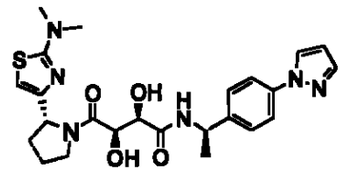
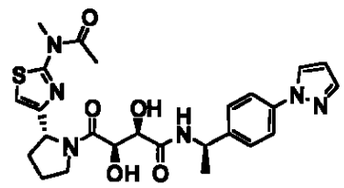
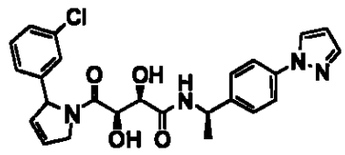
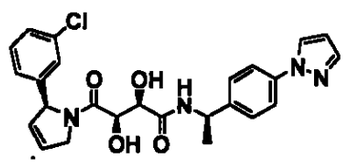
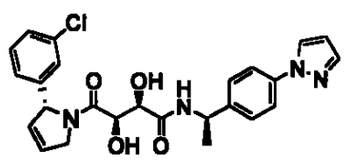
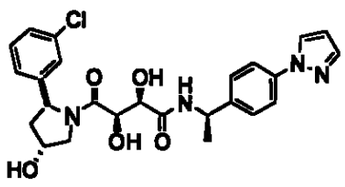








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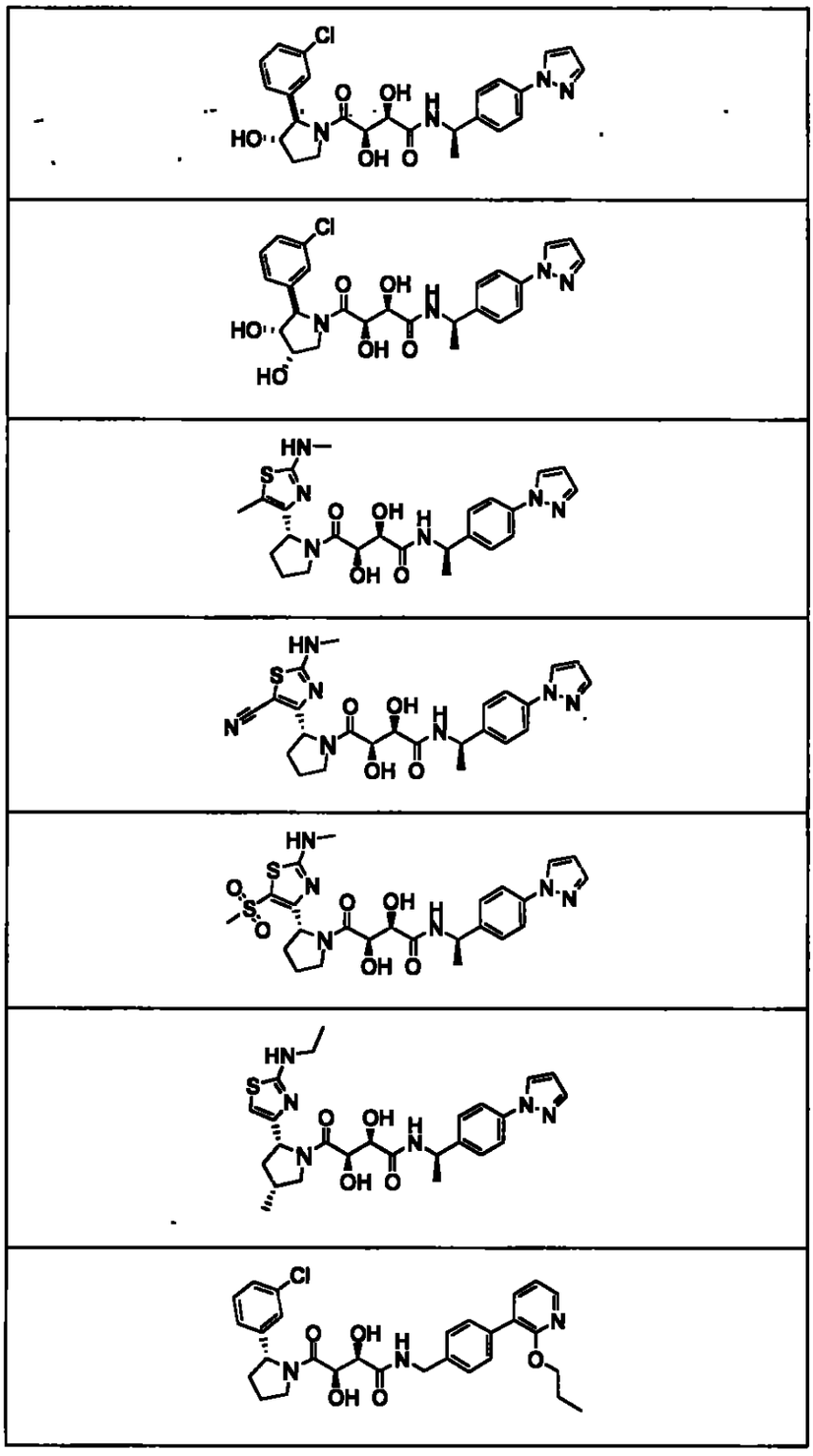
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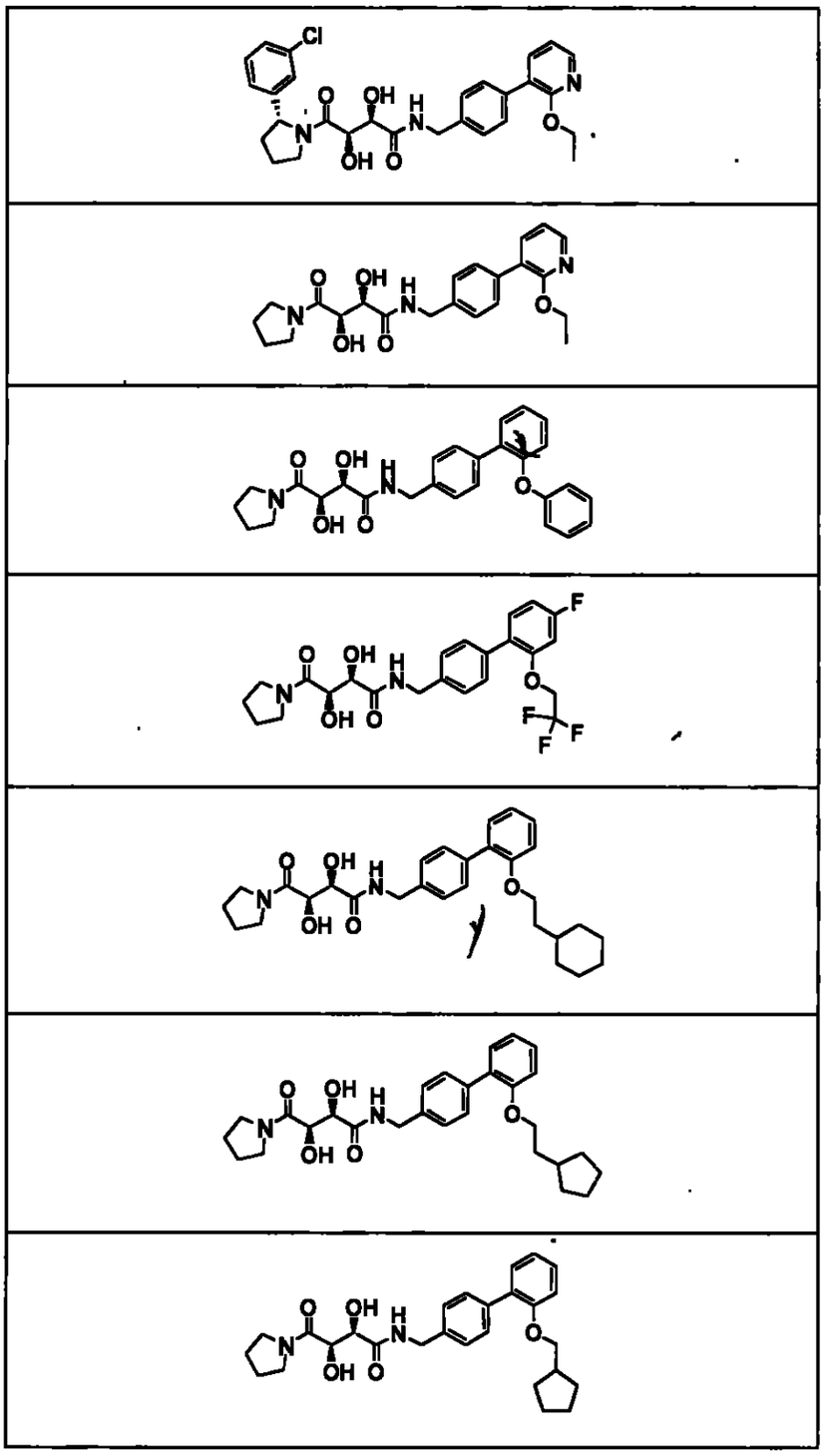








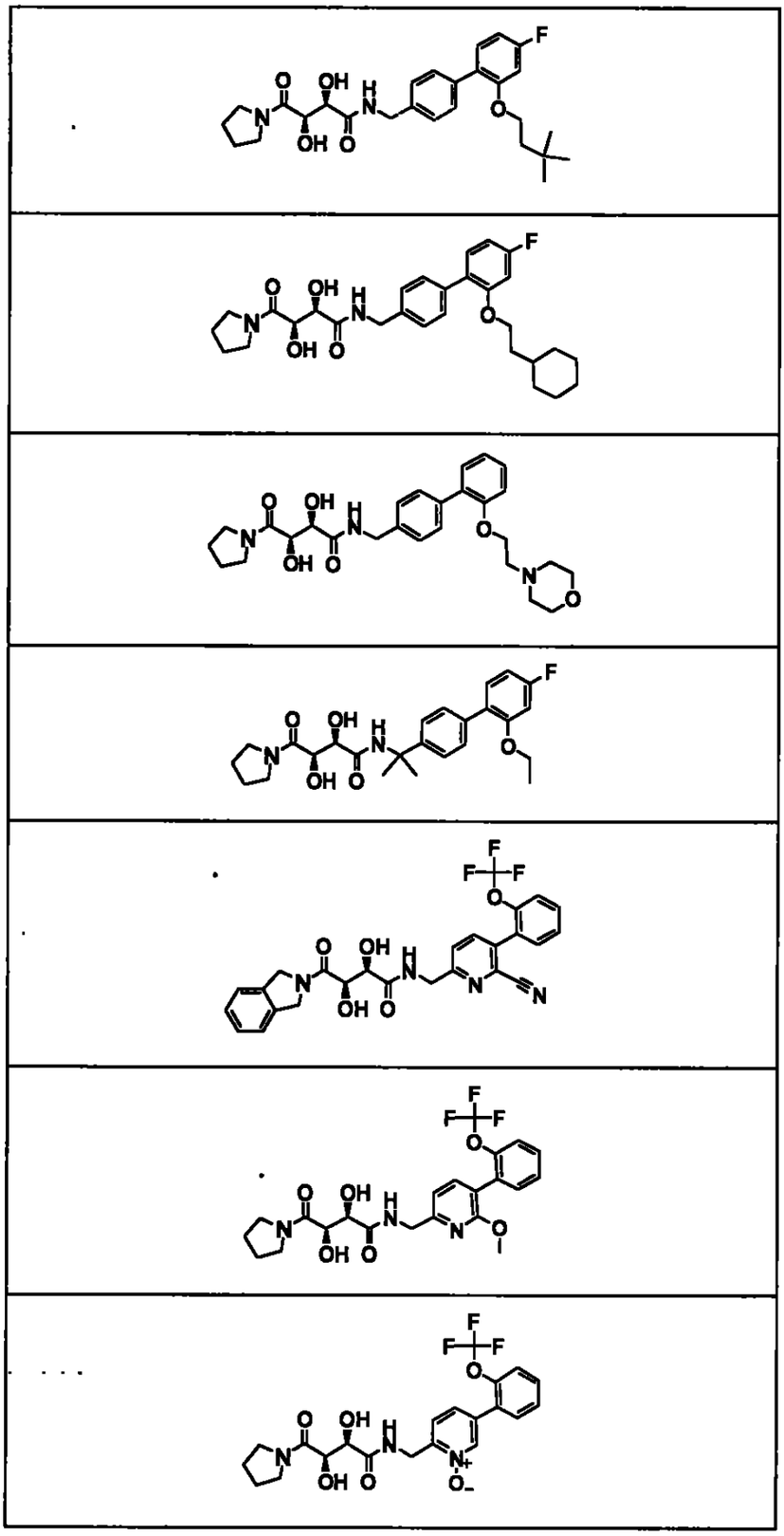
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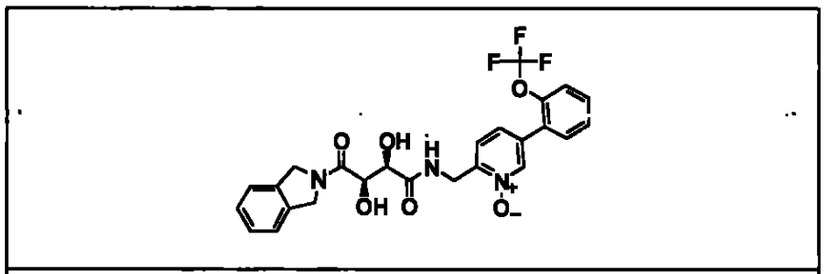
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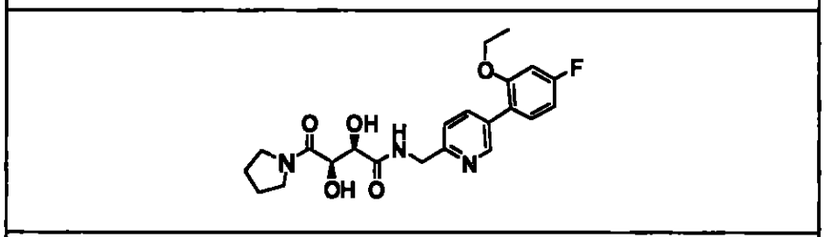


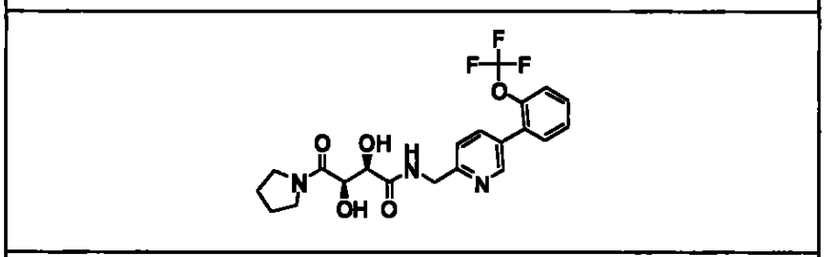


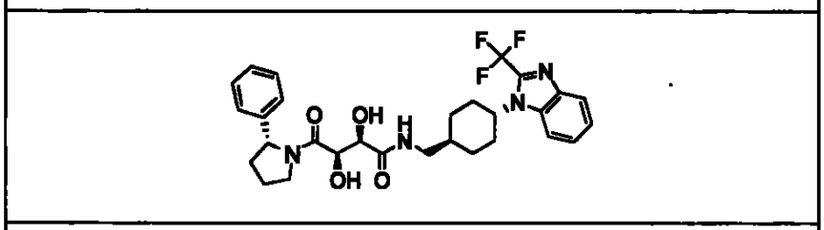
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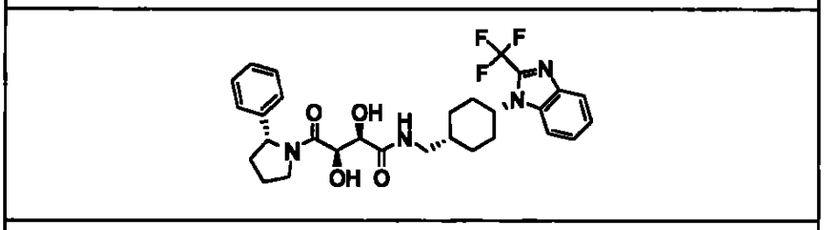
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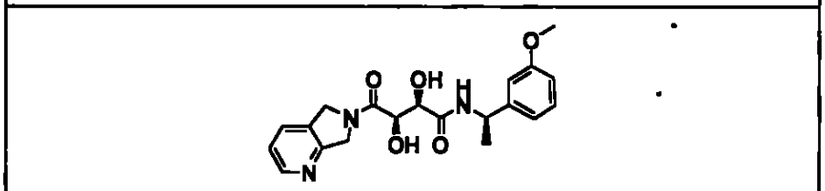


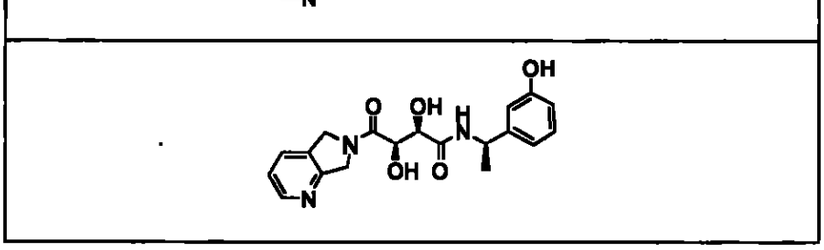






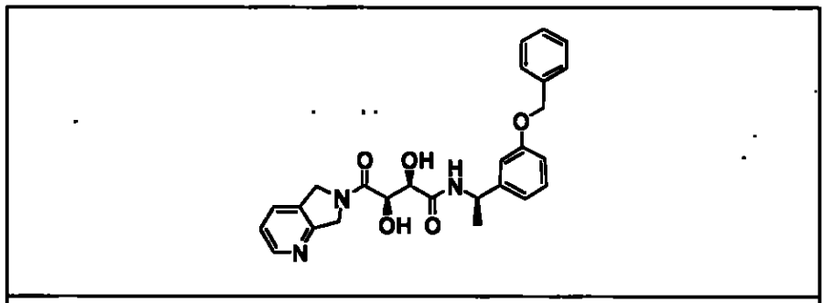


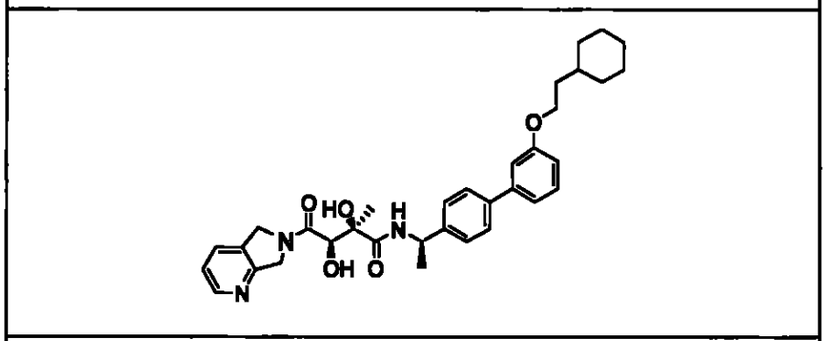


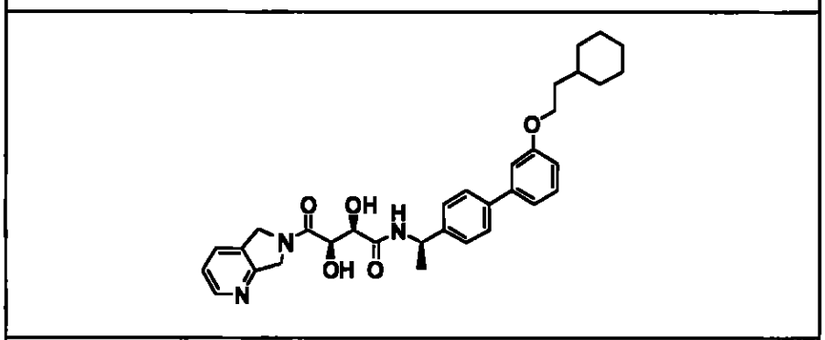


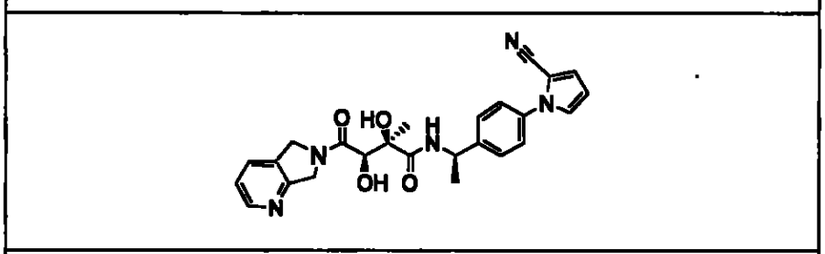
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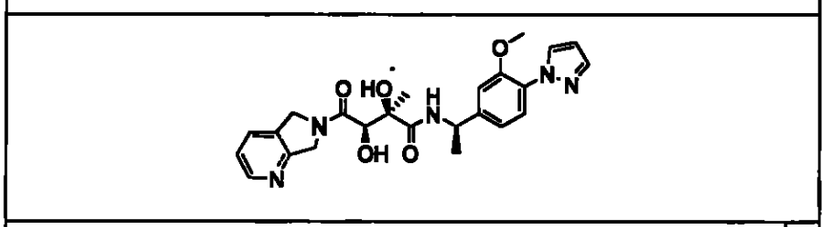
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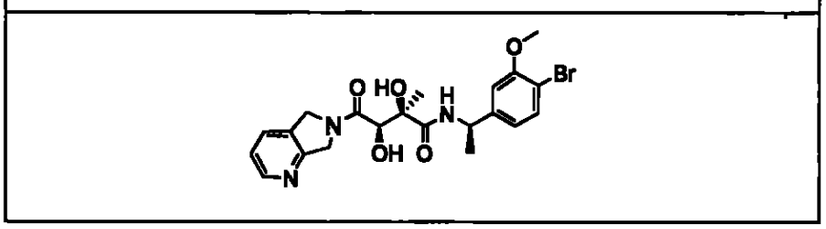


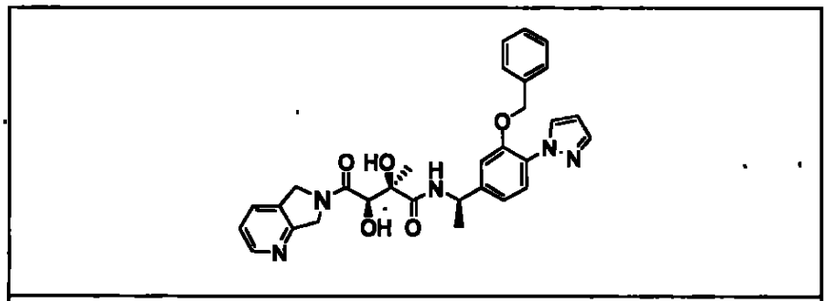


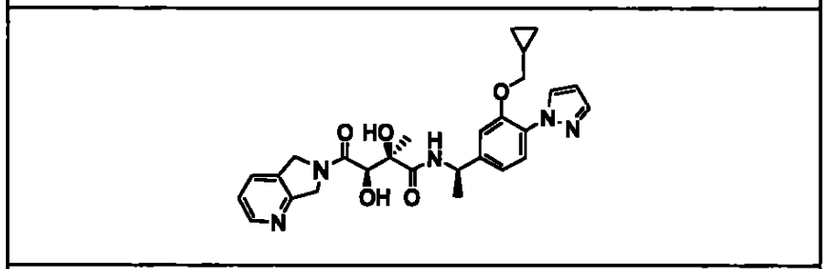


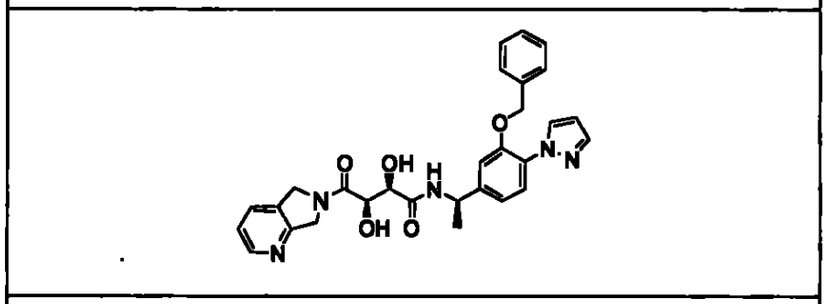


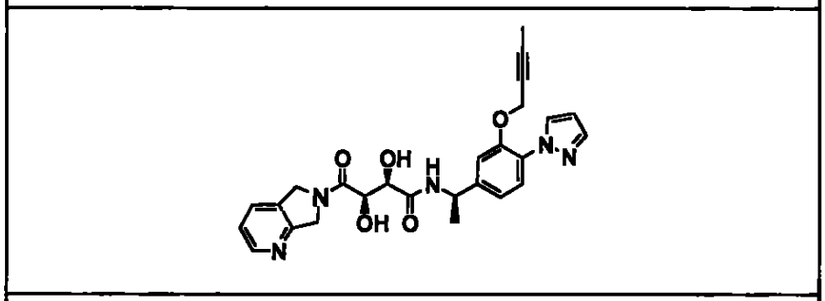


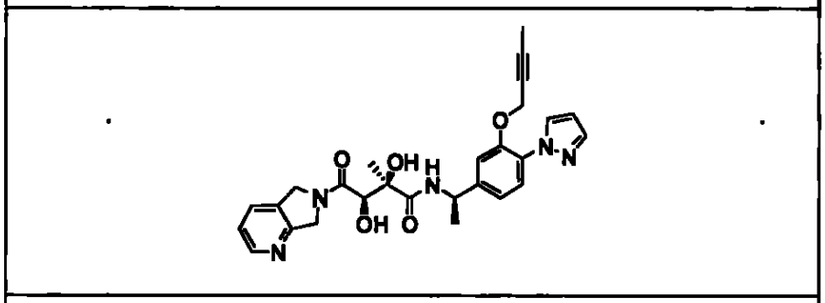


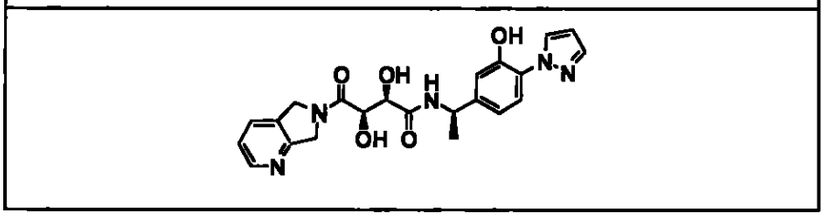






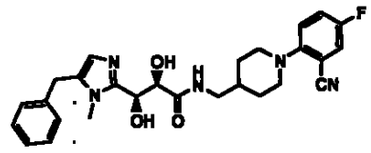
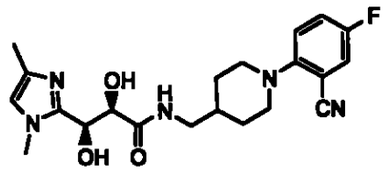
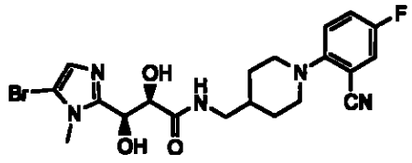
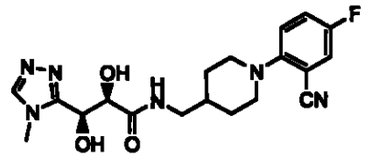
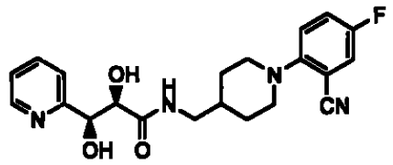
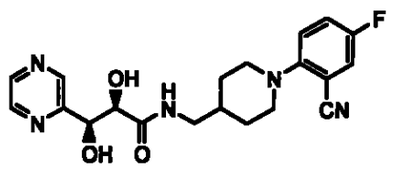
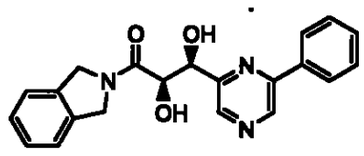


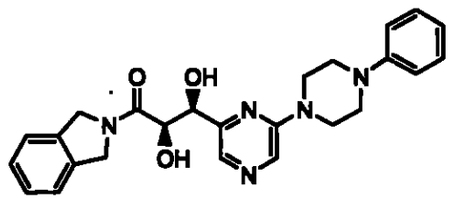
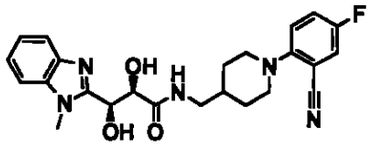
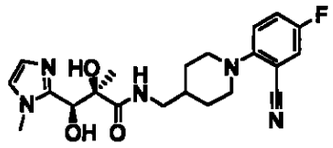
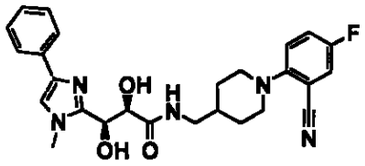
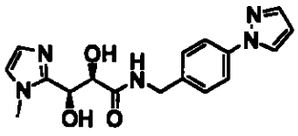
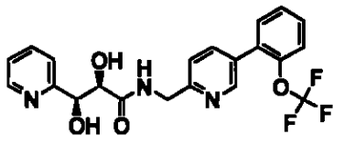
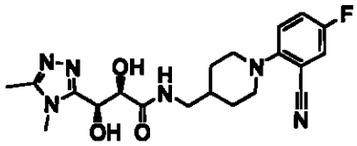
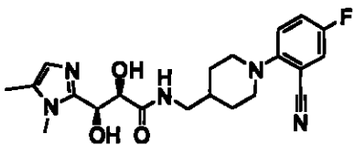


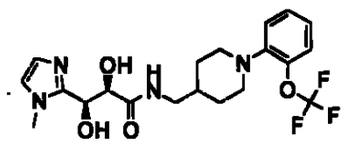
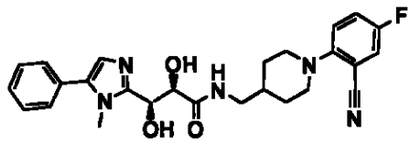
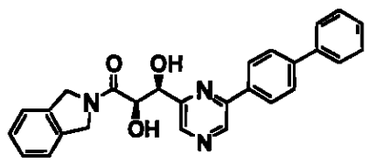
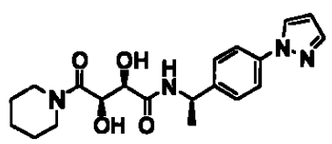
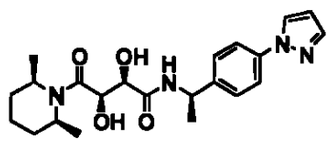
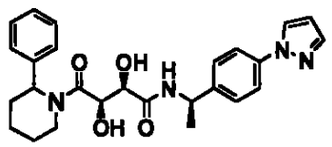
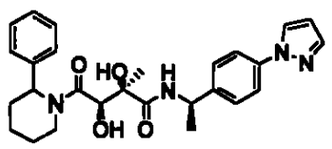
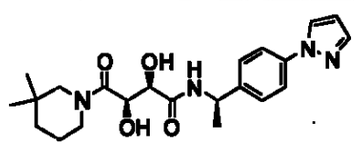


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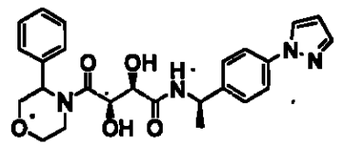
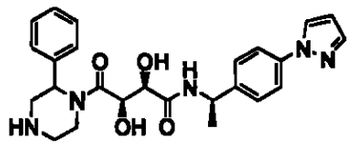
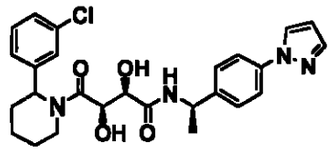
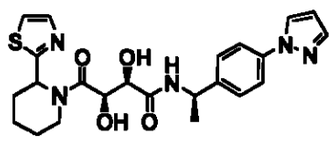
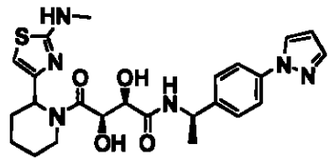
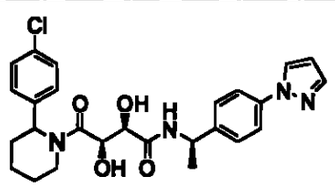
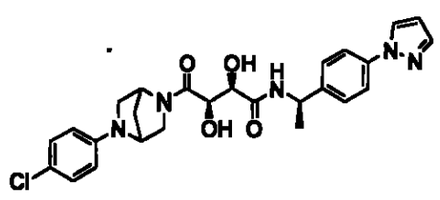
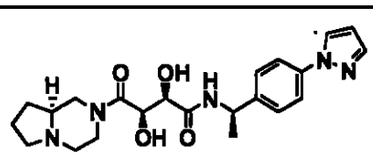








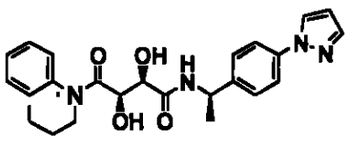
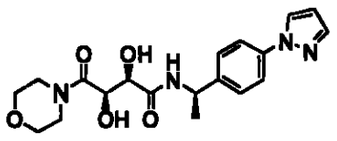
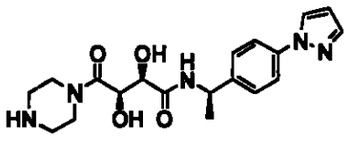
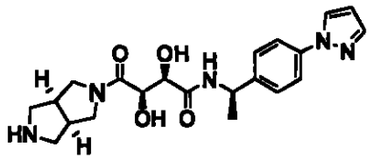
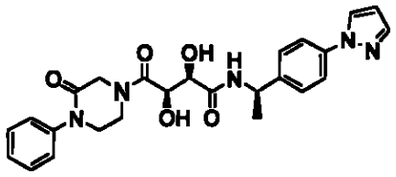
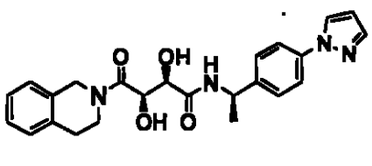
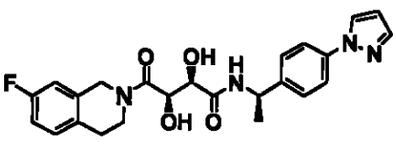
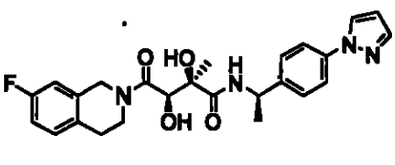









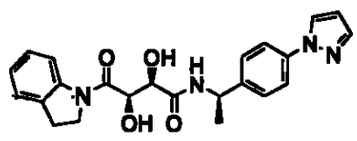
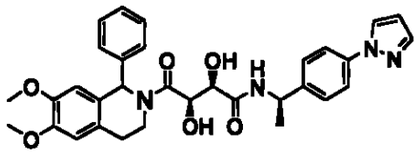
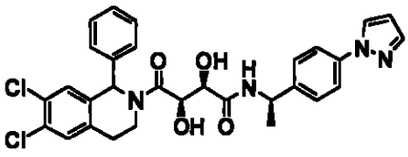
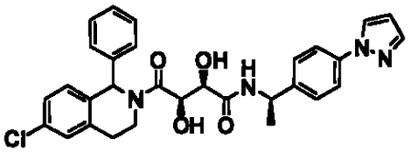
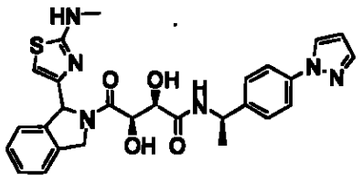
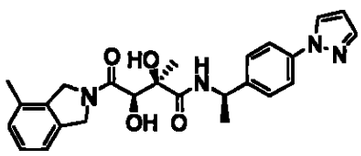
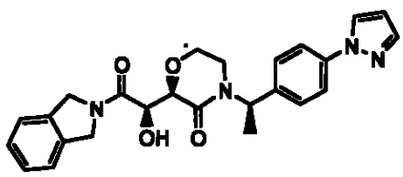
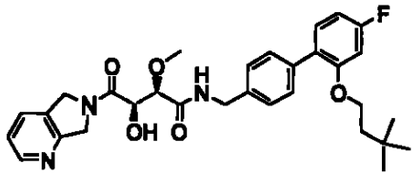









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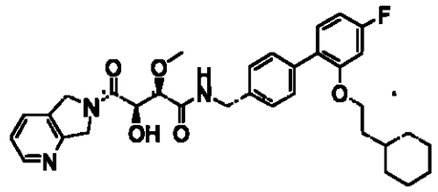
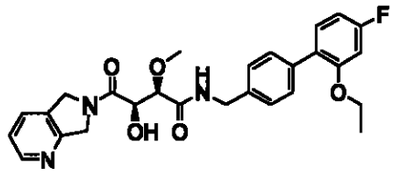
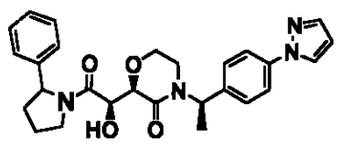
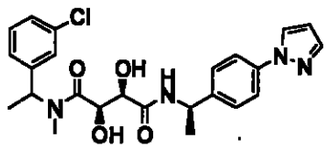
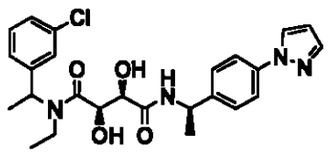
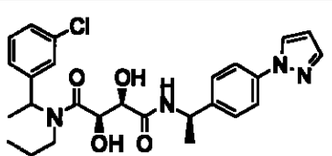
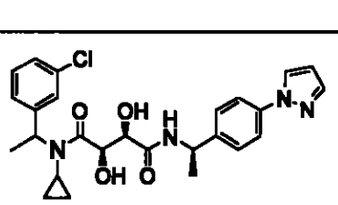
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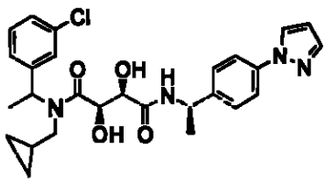
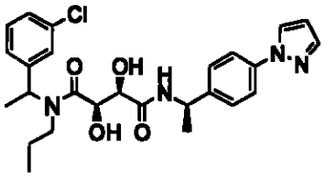
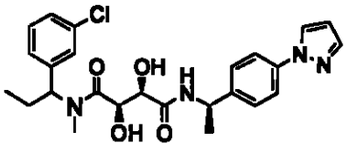
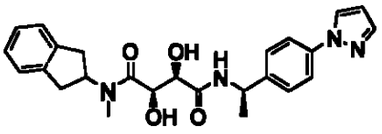
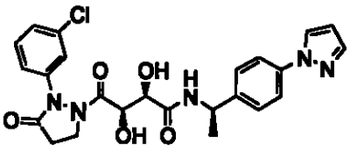
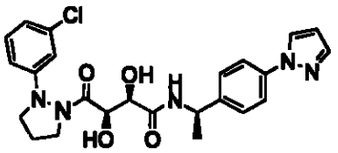
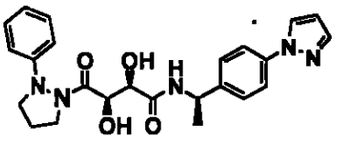
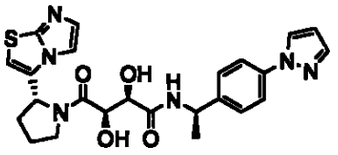









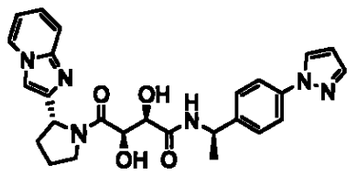
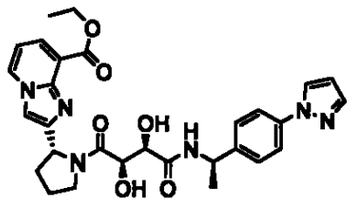
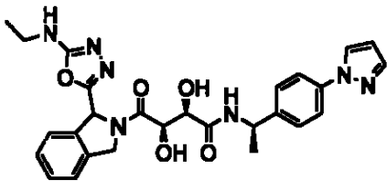
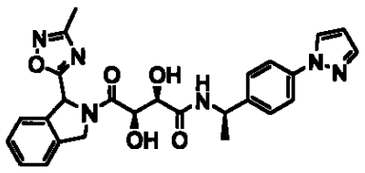
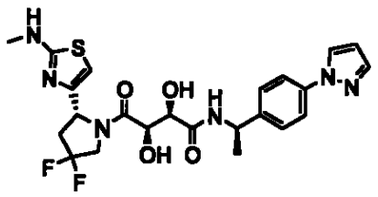
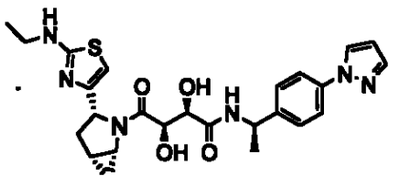
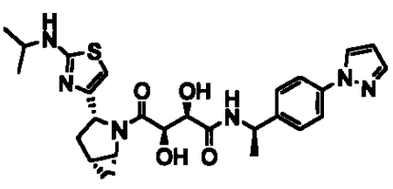









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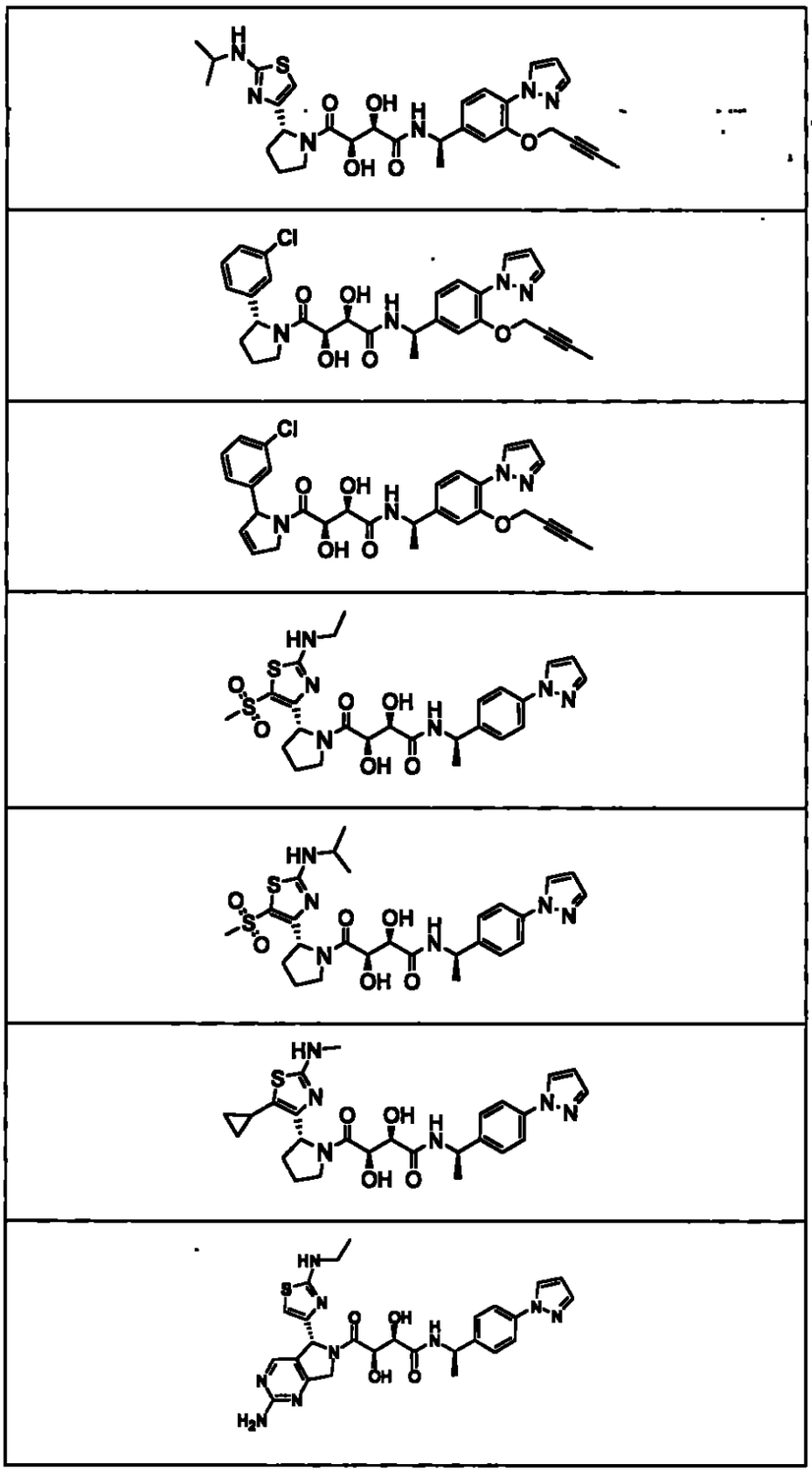
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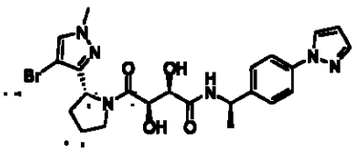
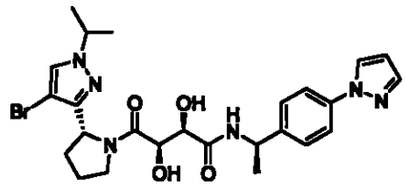
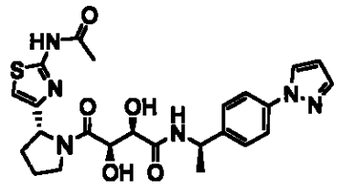
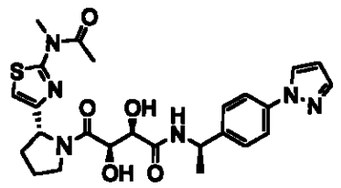
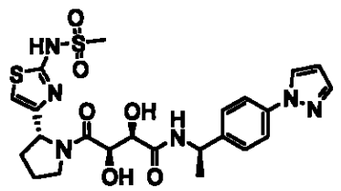
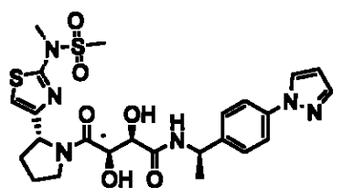
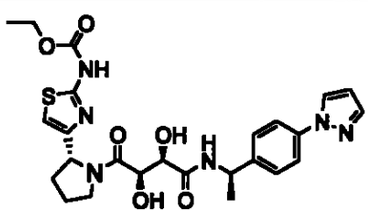









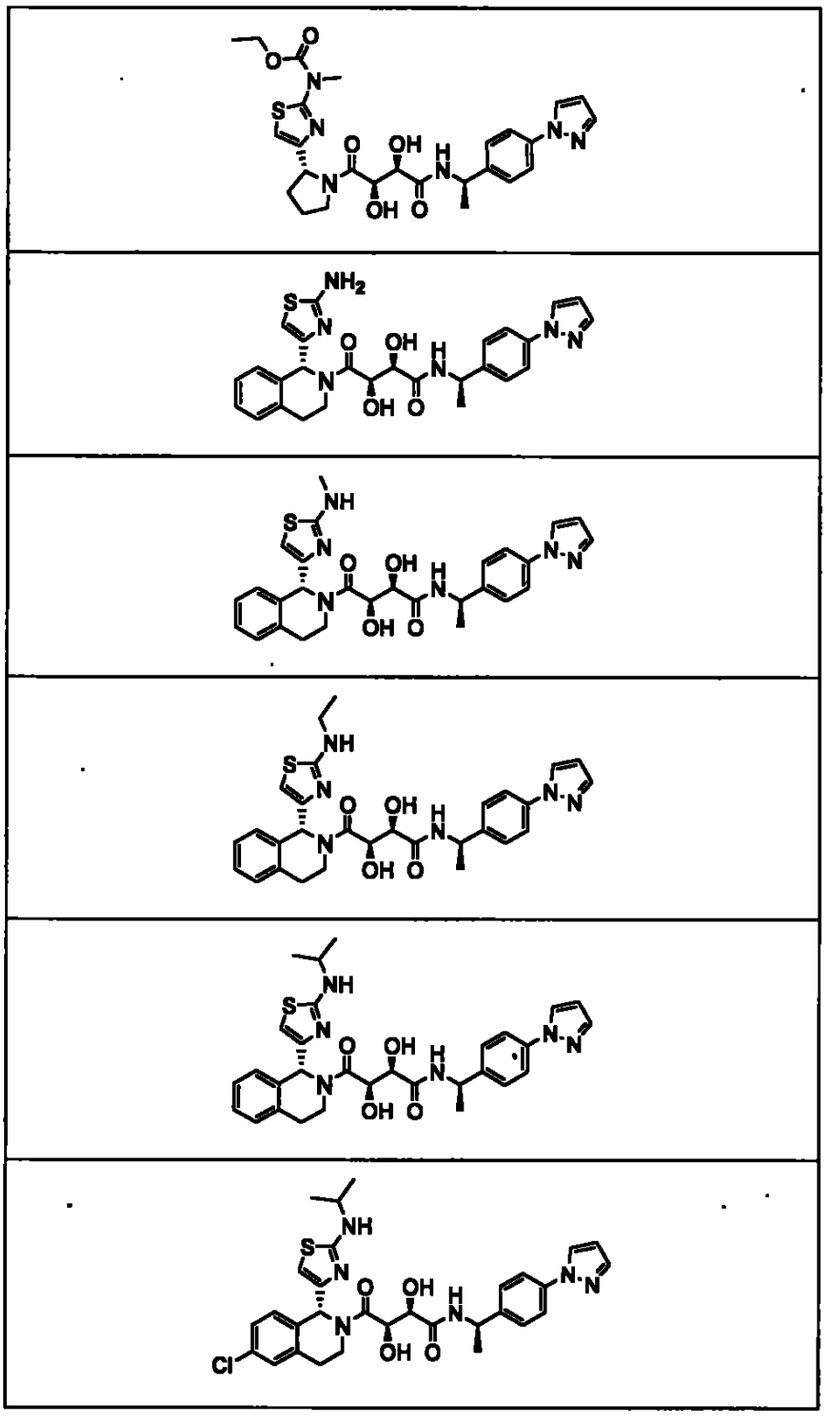
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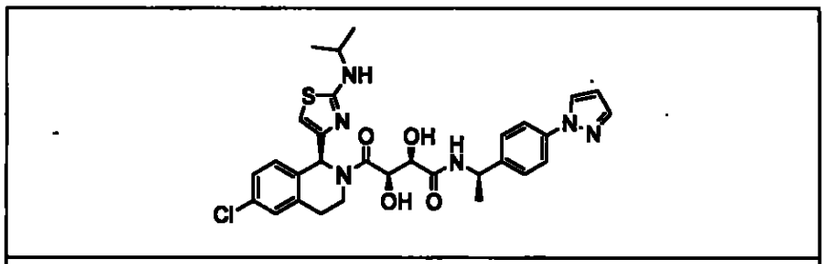








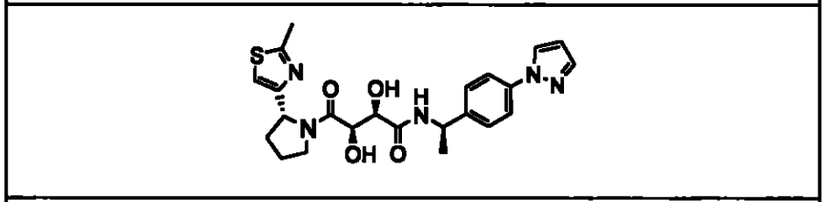
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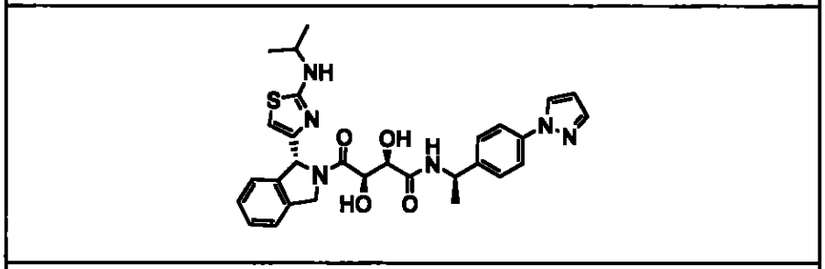


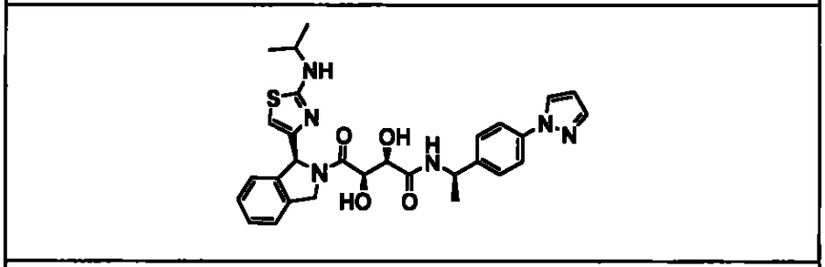
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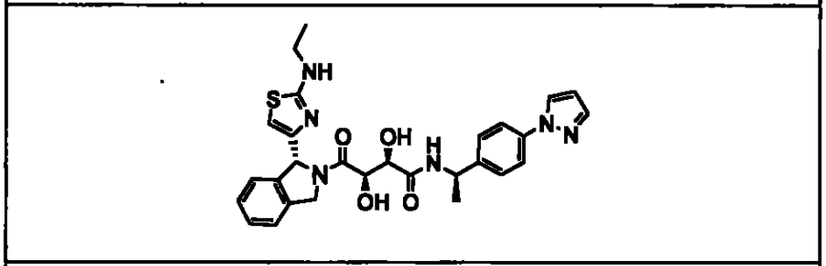
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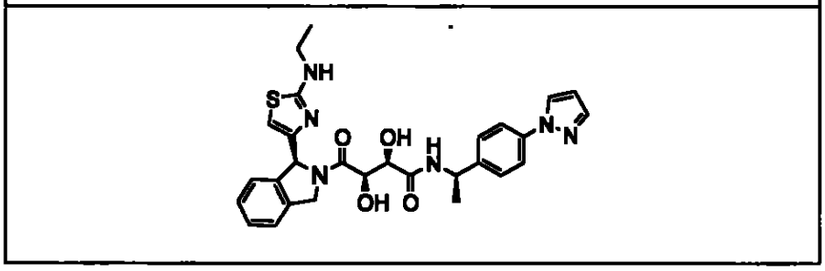


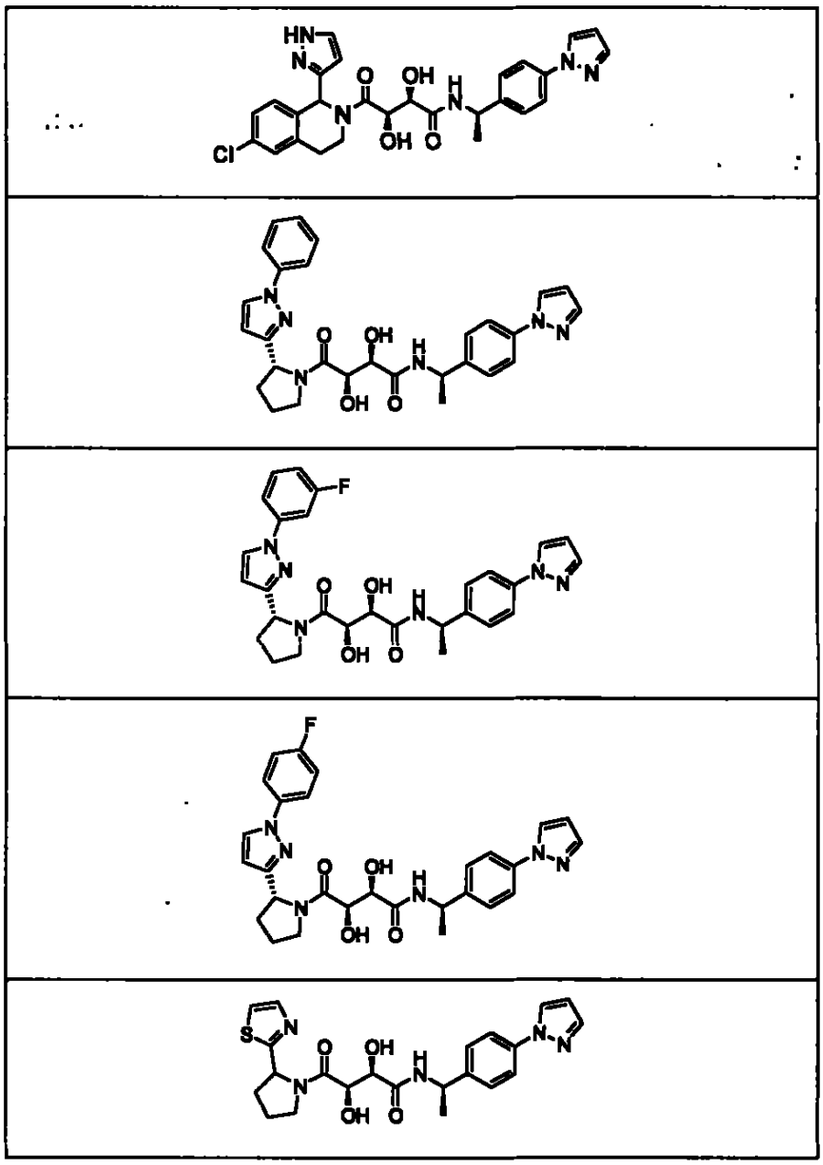




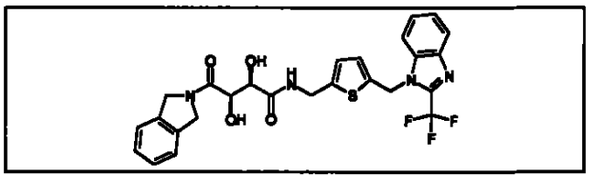


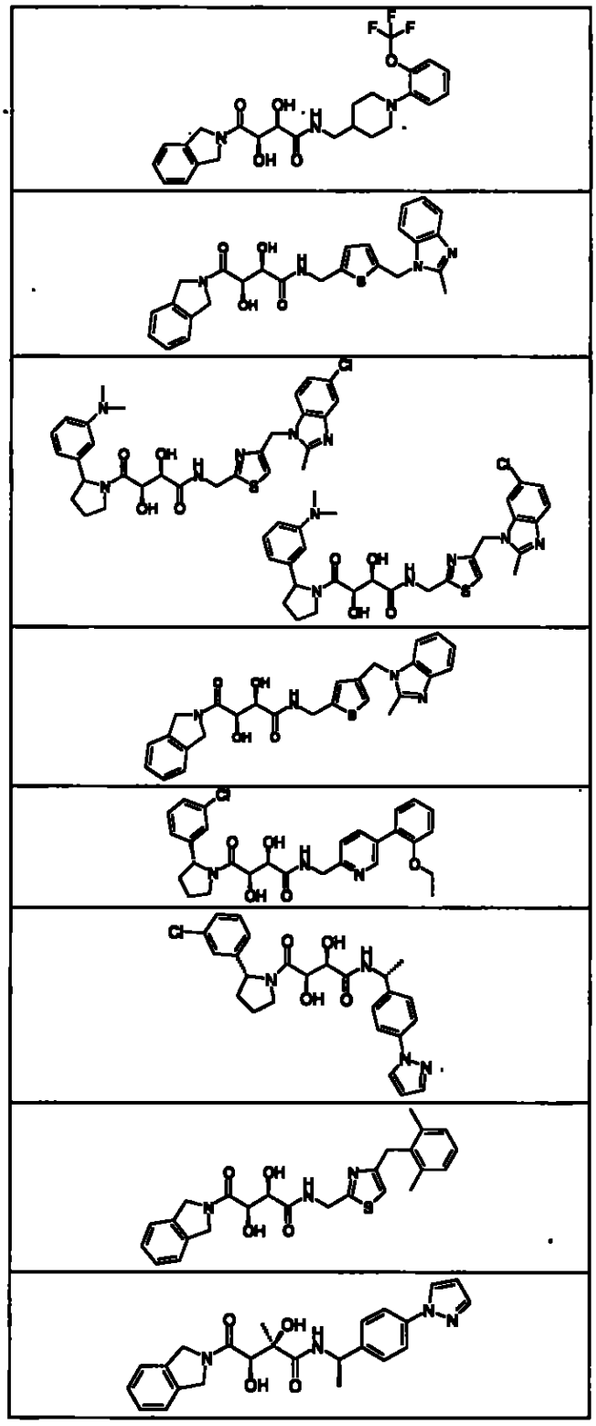


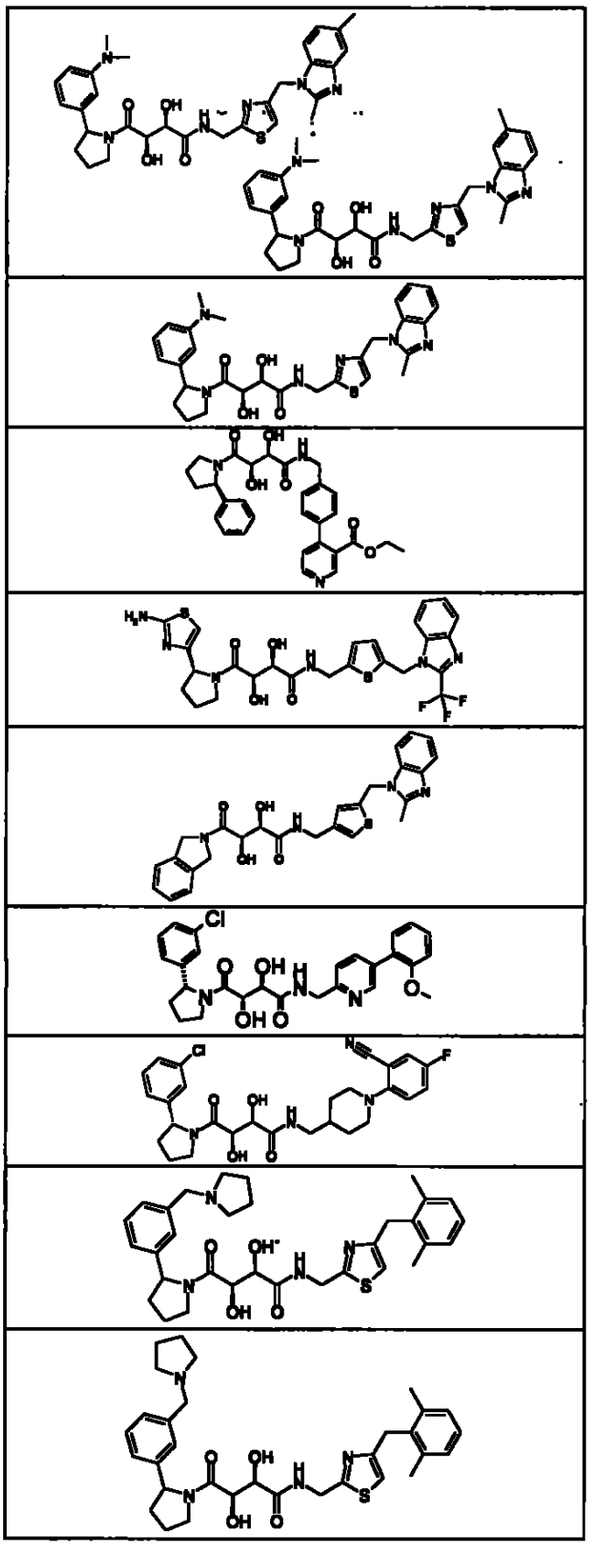


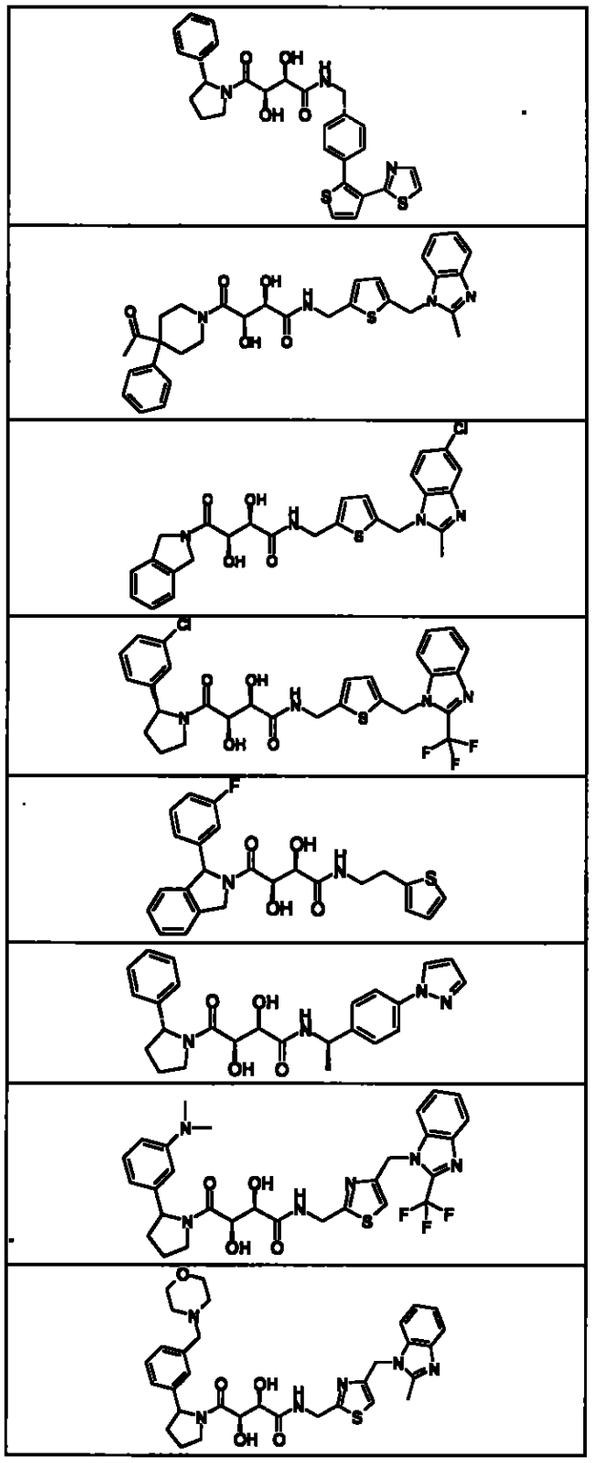


En una realización preferida, el compuesto se selecciona del grupo que consiste en:



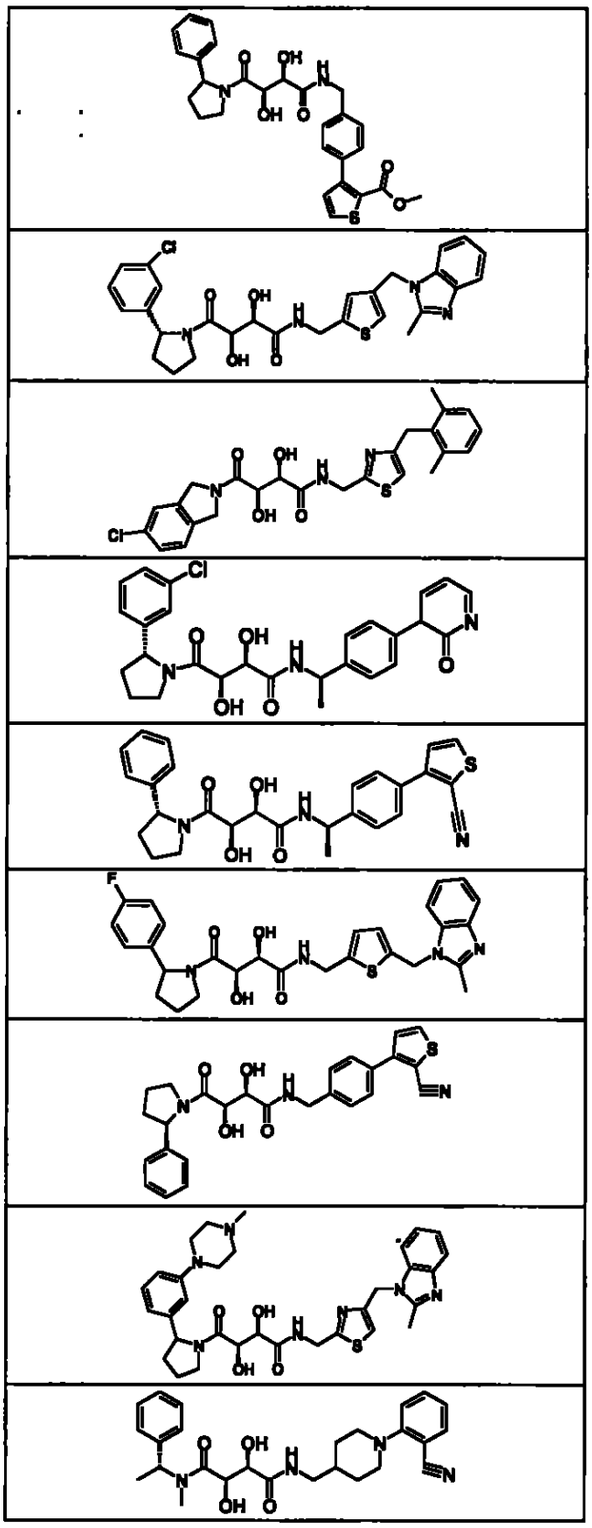


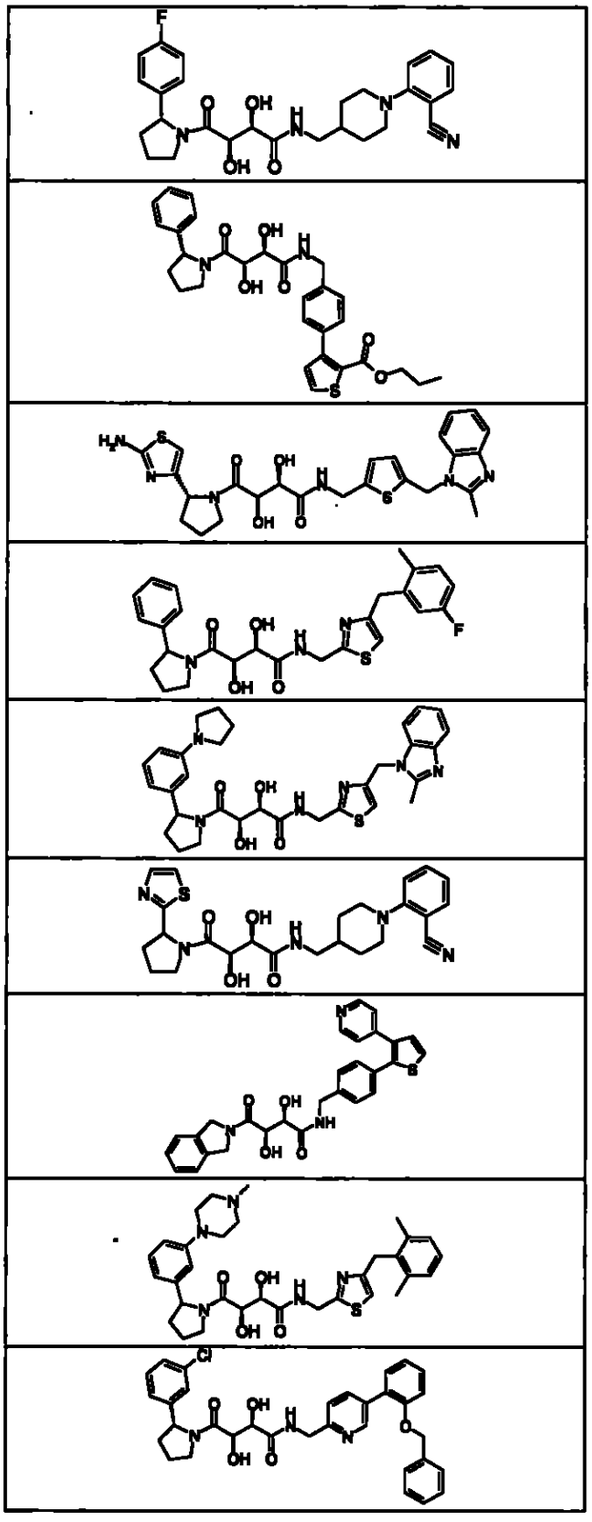


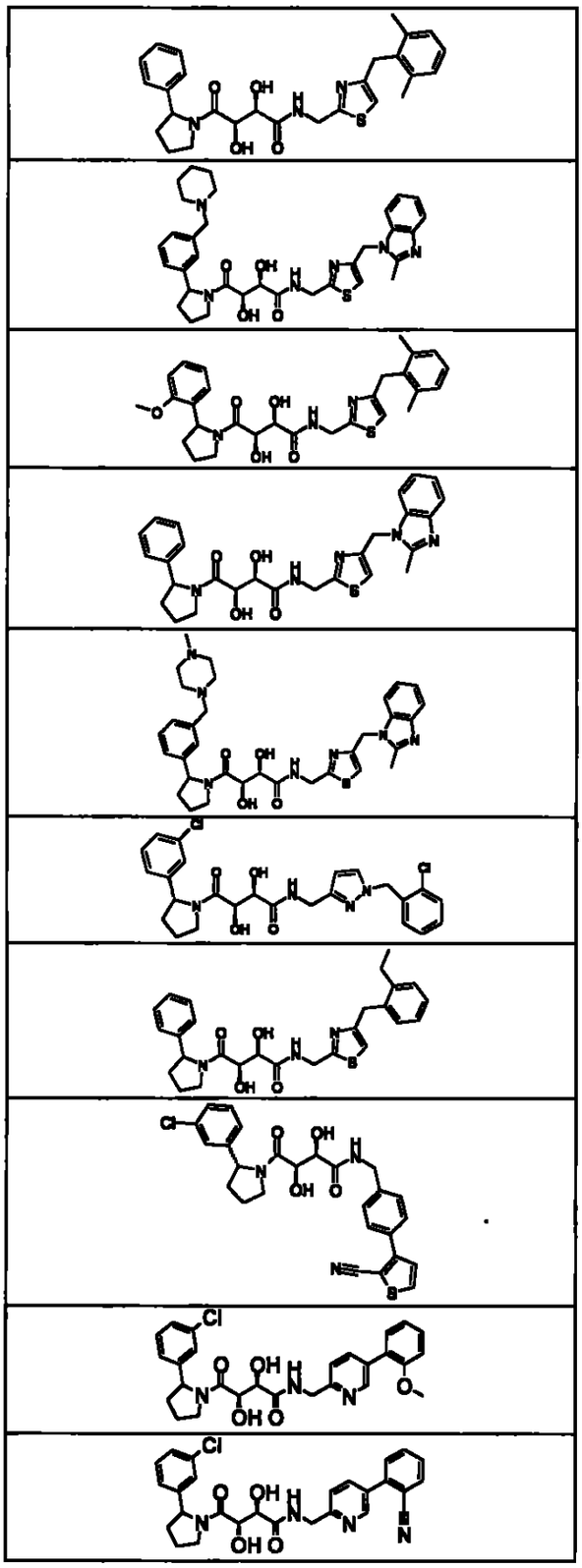


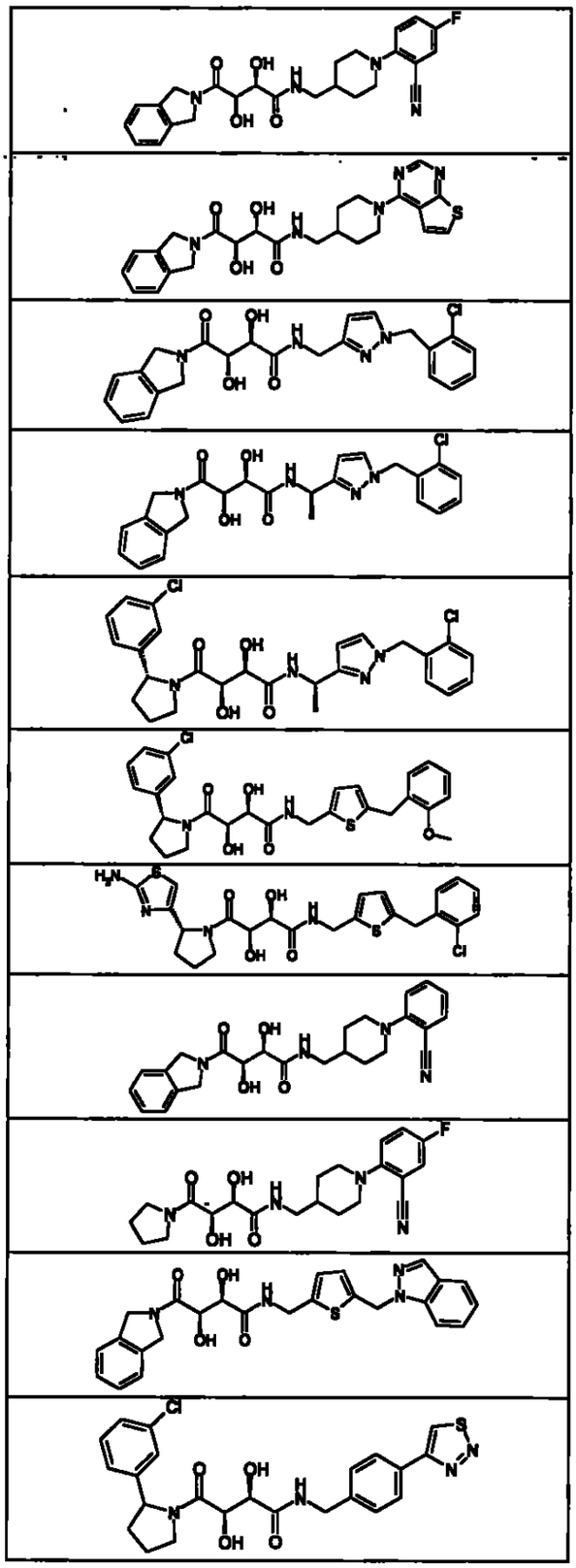
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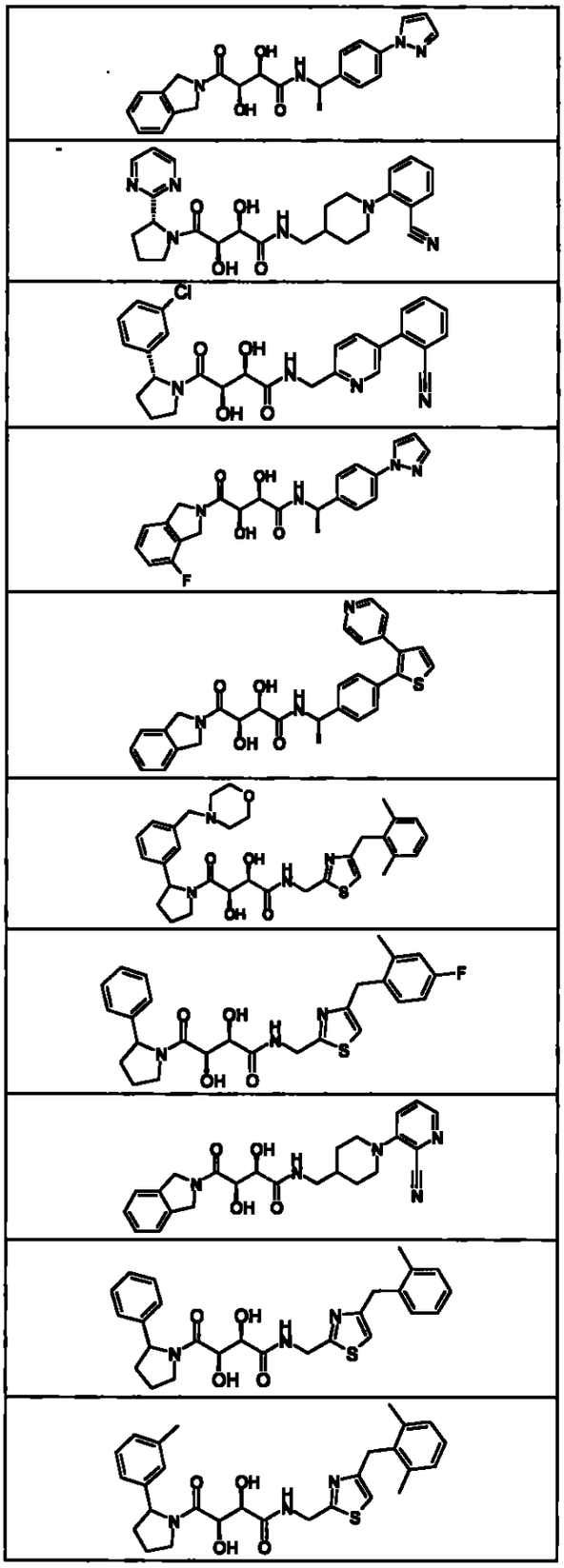
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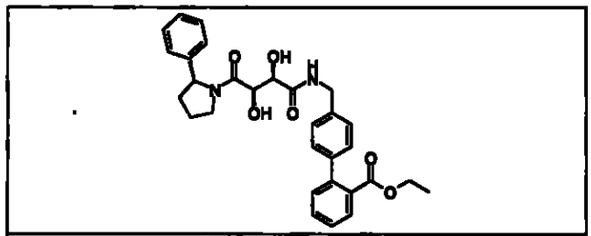


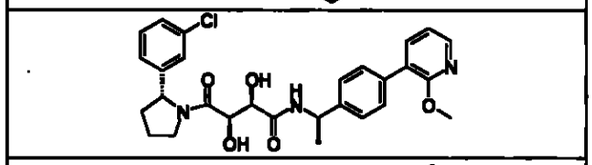


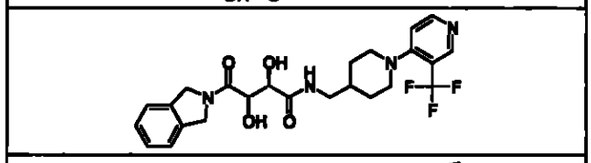


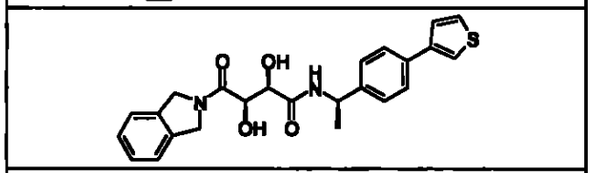


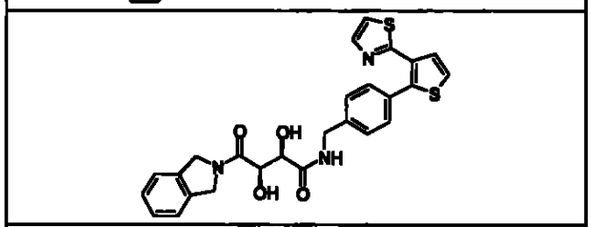


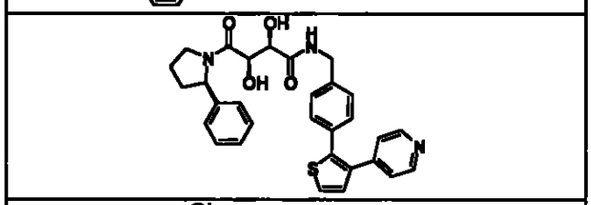


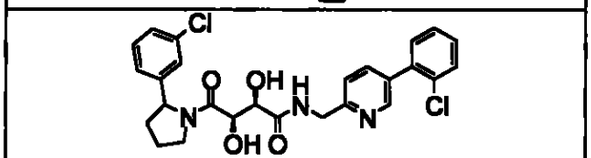


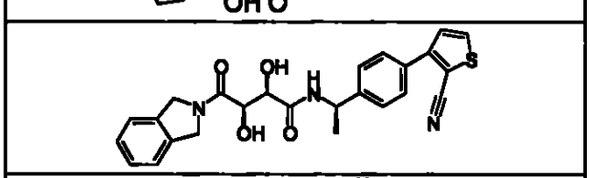


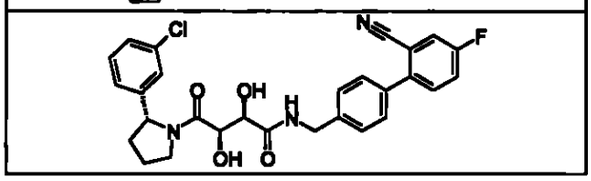


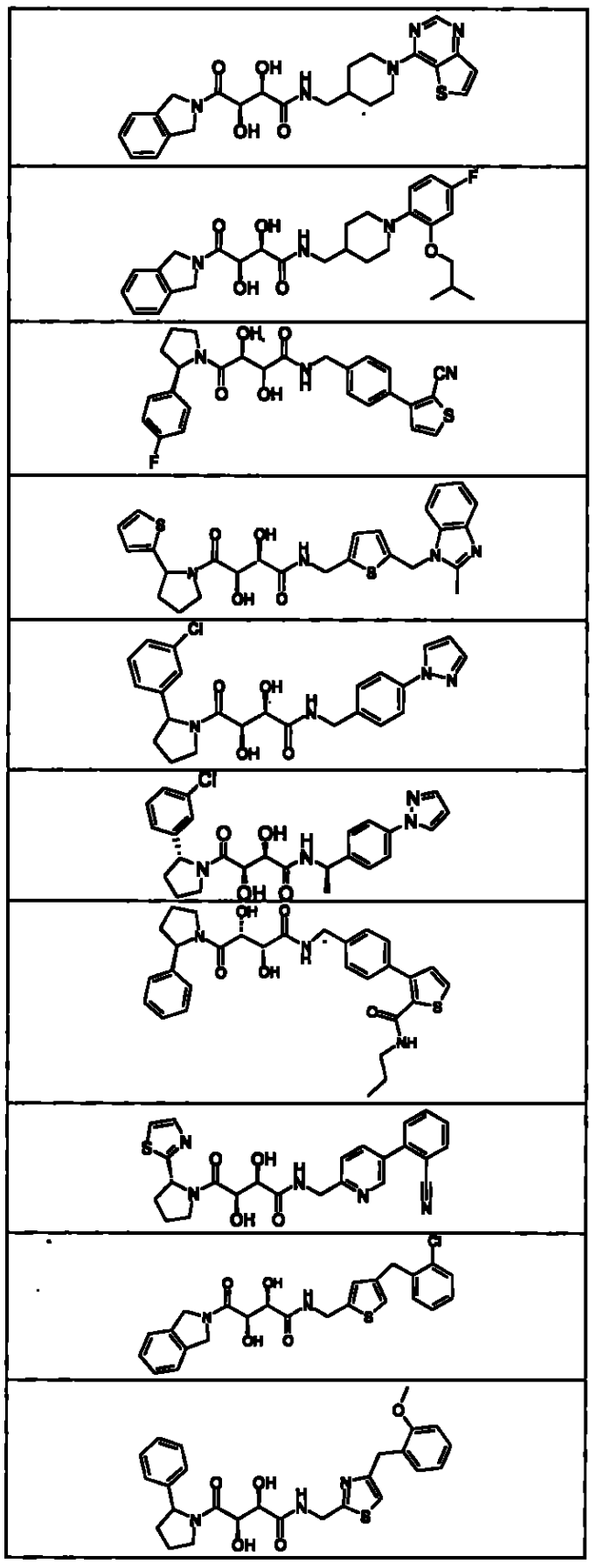




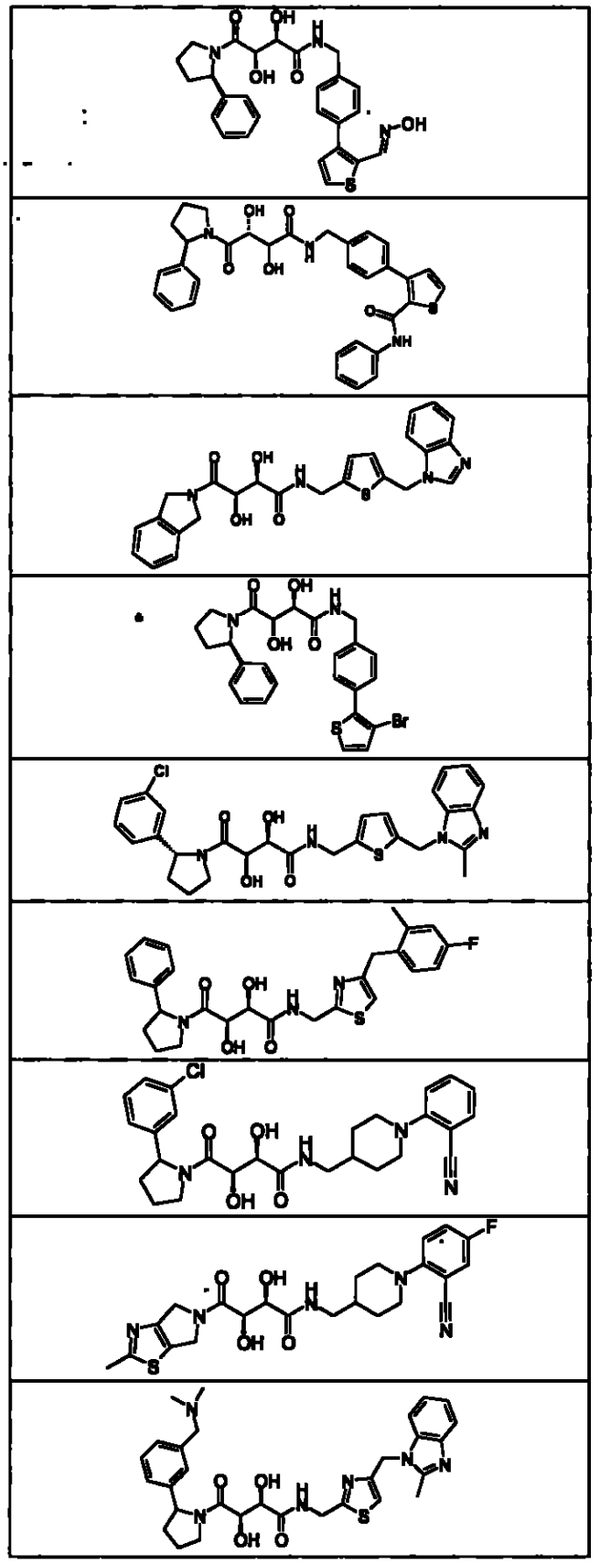


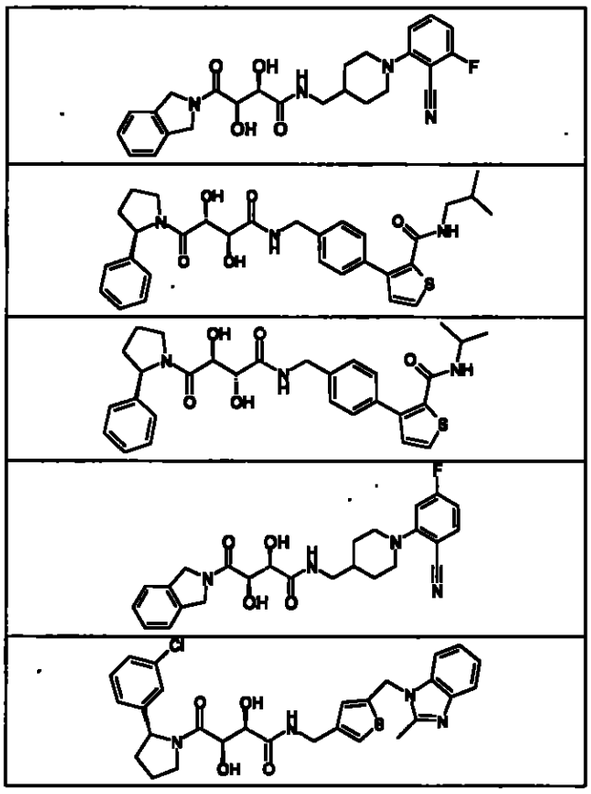


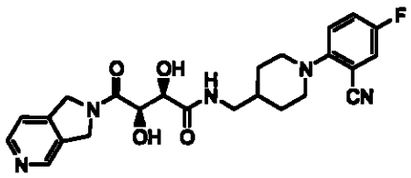


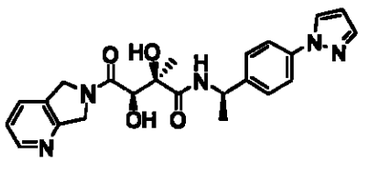


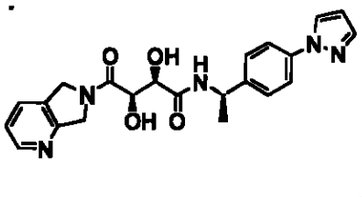
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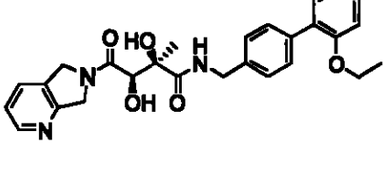


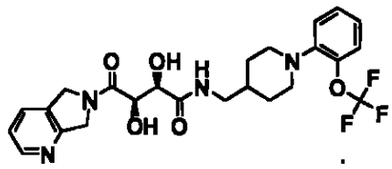


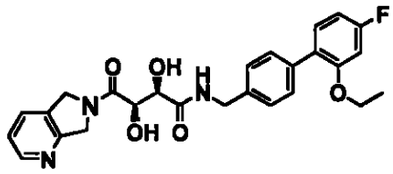


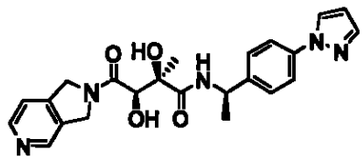


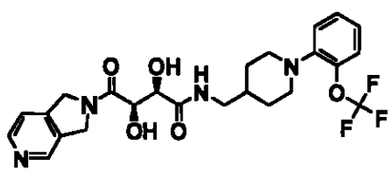


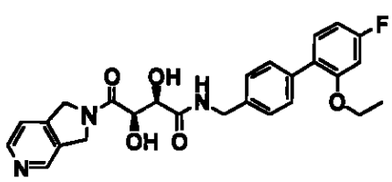


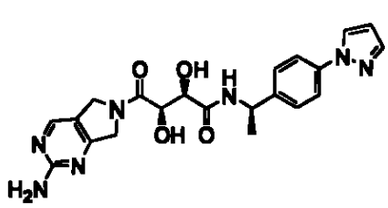


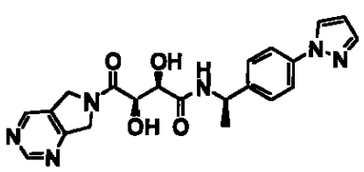


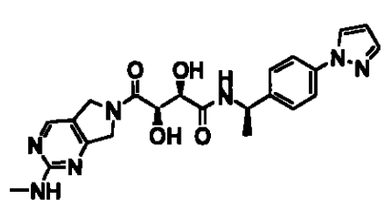


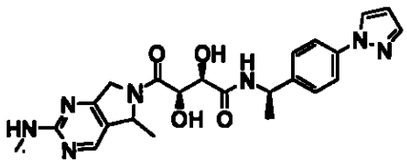


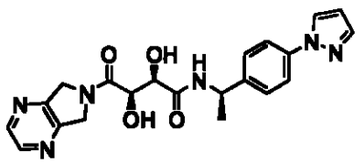


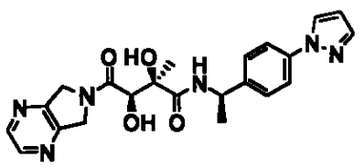


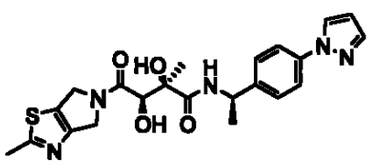


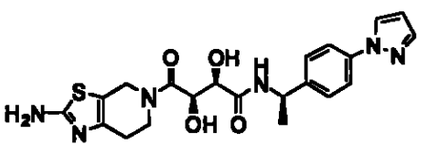


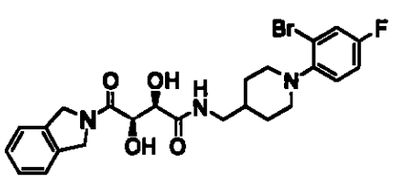


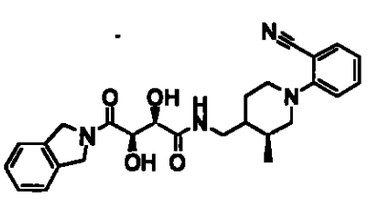


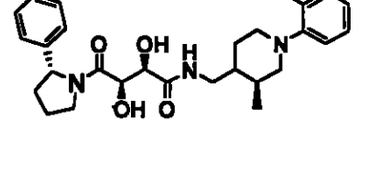


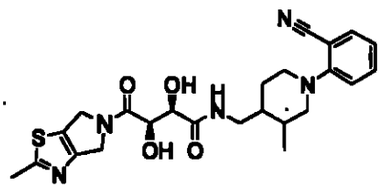


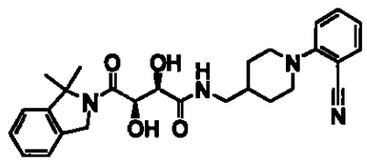


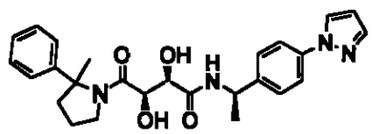


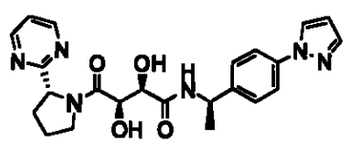


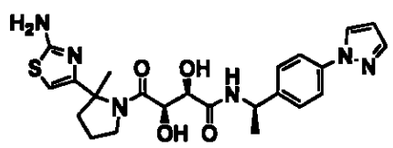


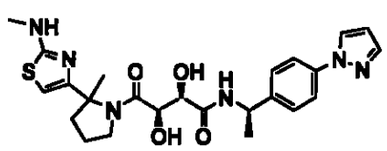


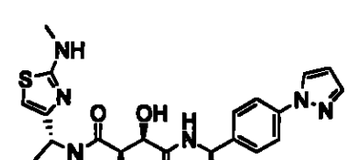


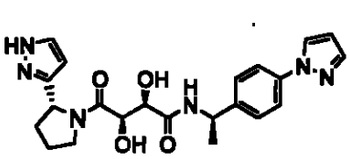


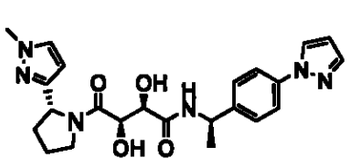


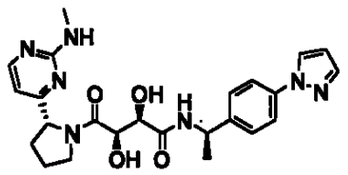


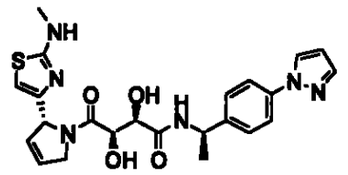


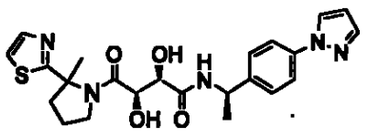


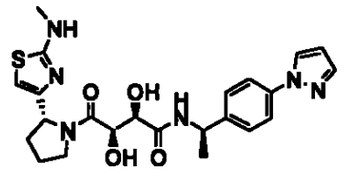


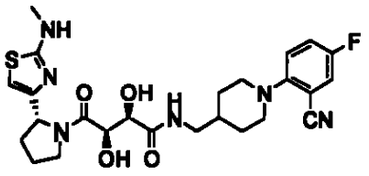


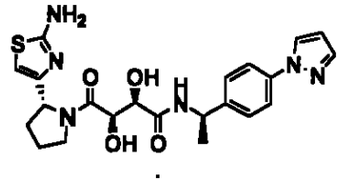


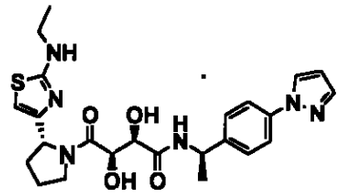


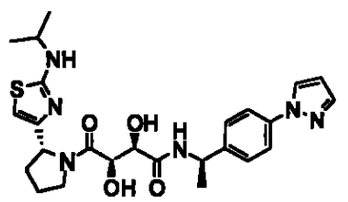


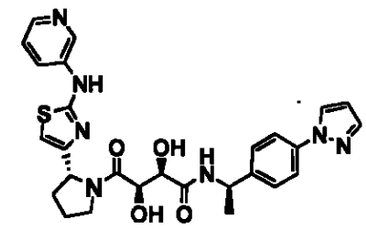


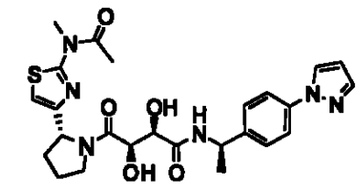


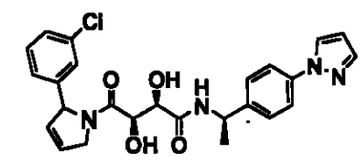


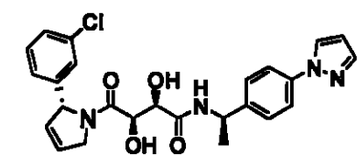


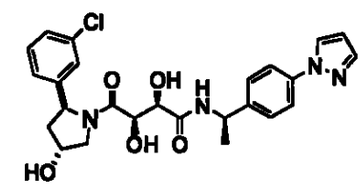


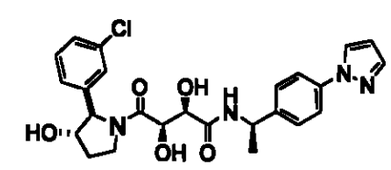


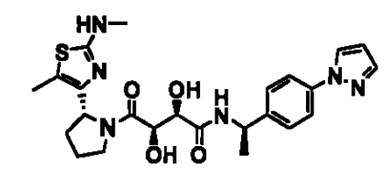


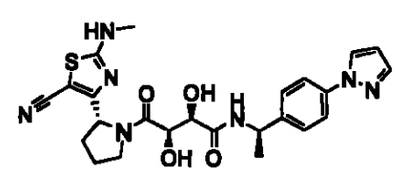


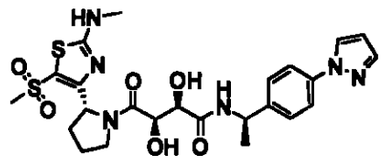


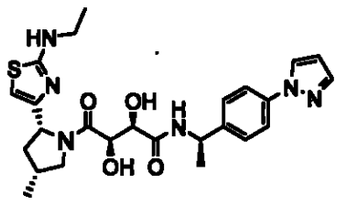


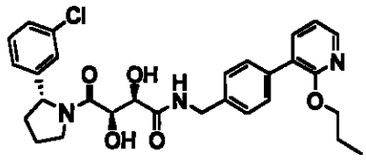


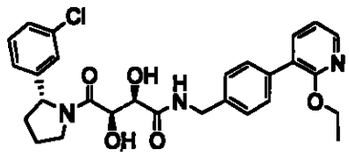


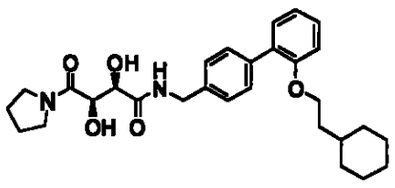


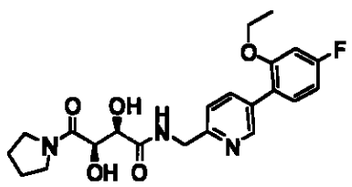


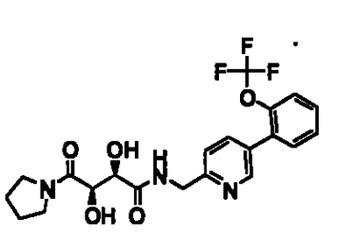




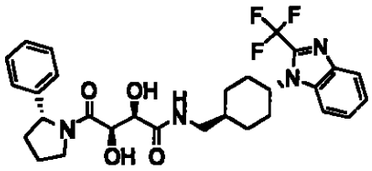


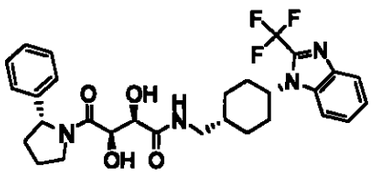


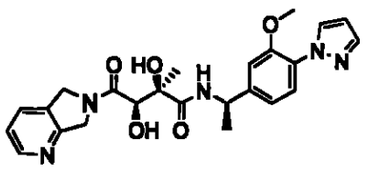


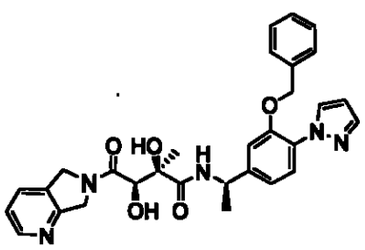


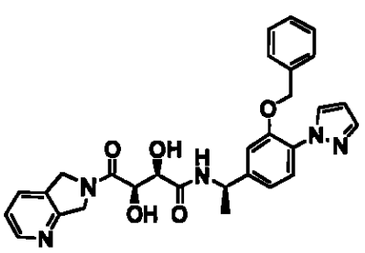
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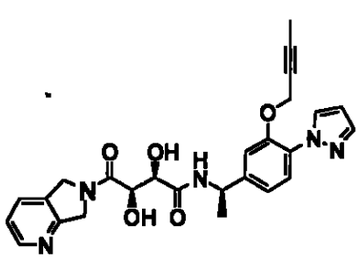


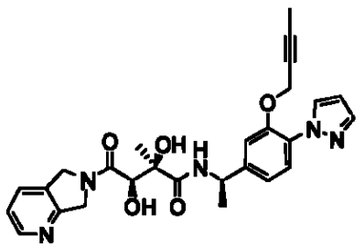


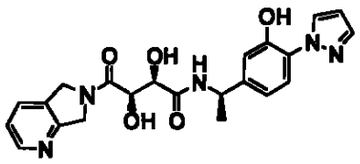


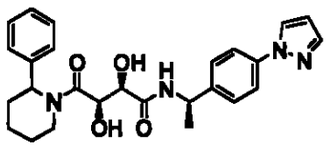


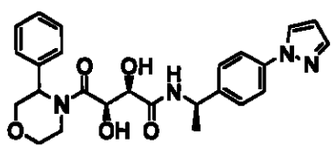


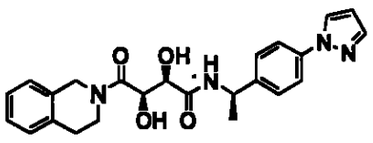


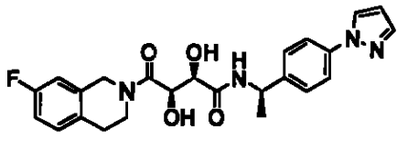


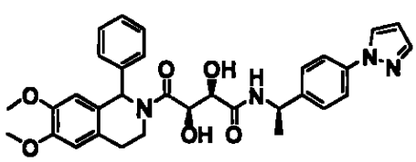


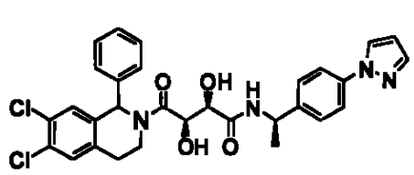


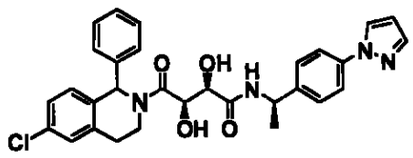


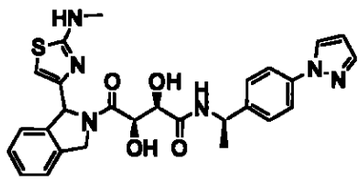


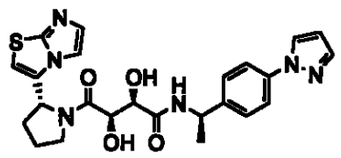


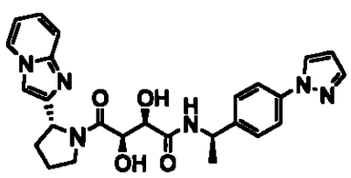


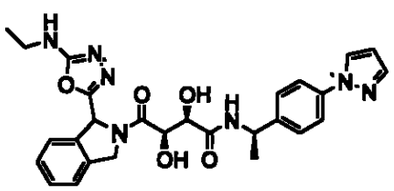


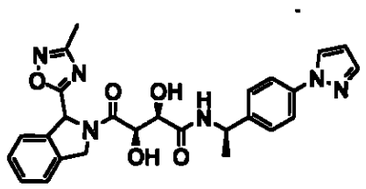


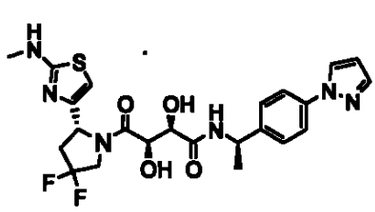


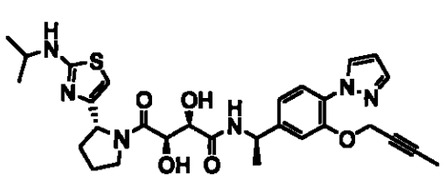


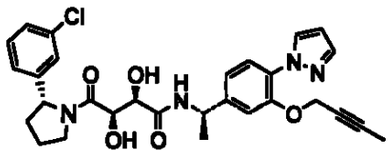


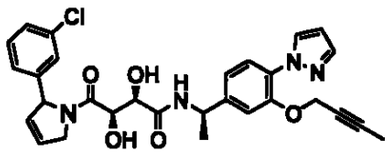


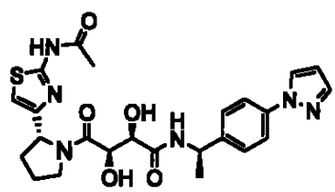


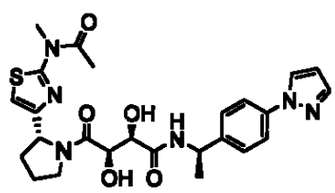


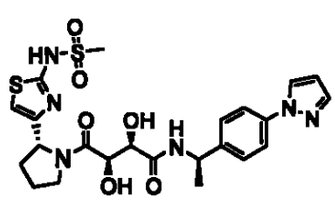


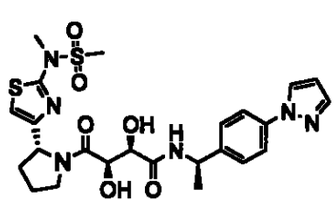


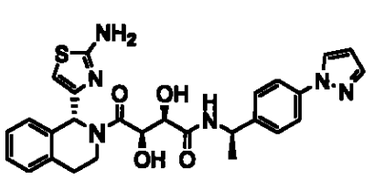


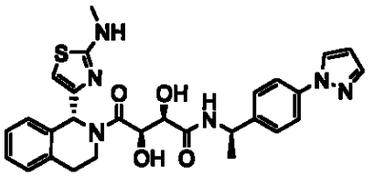


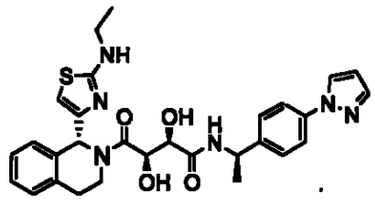


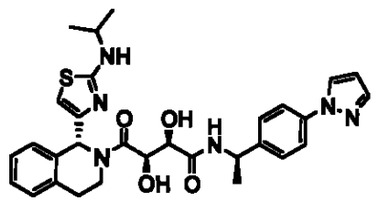


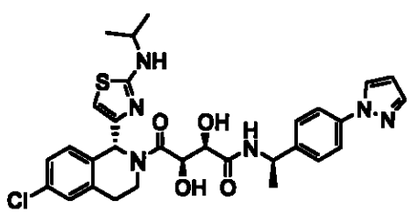


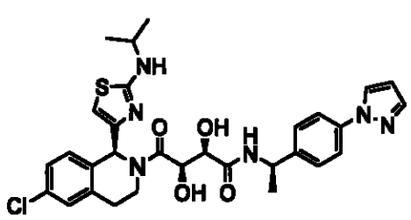


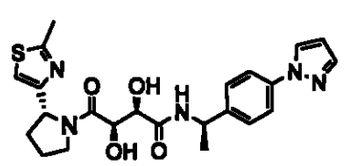


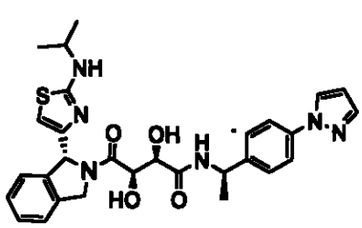


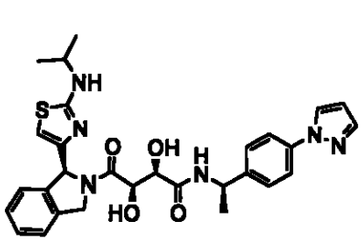


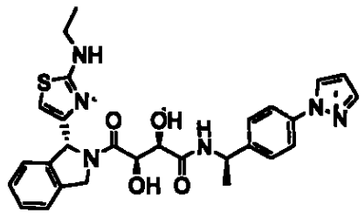


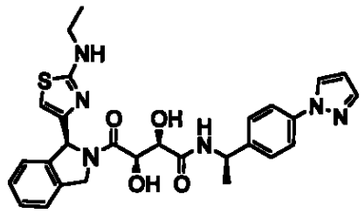


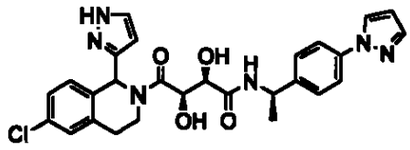


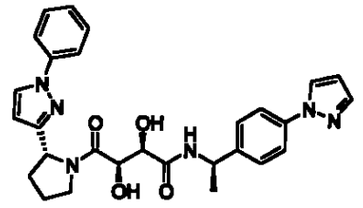


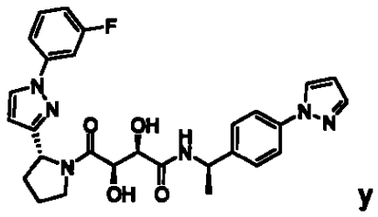




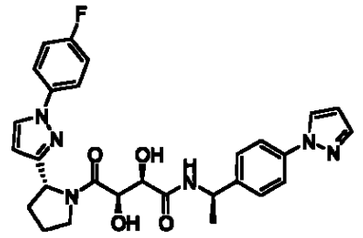






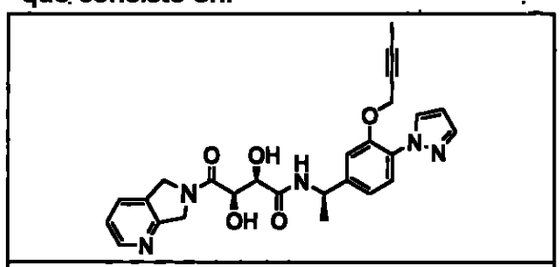


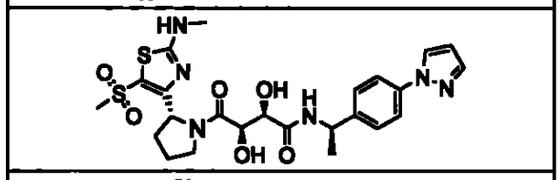
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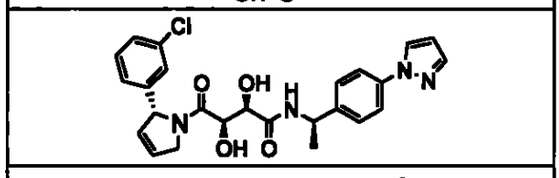


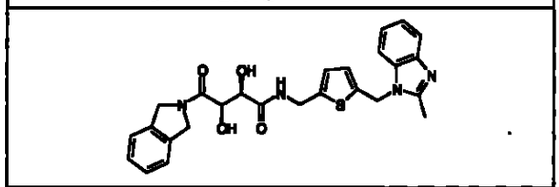
Los compuestos preferidos anteriores poseen valores de K_i para TACE menores de 20nM.

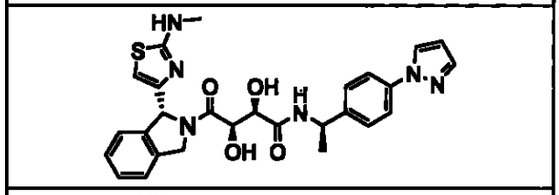
En una realización más preferida, el compuesto se selecciona del grupo 1113 que consiste en:

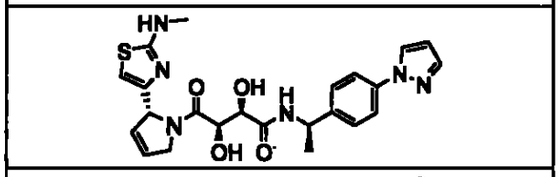


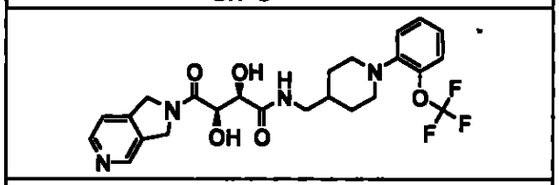


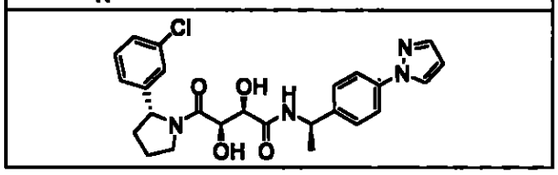


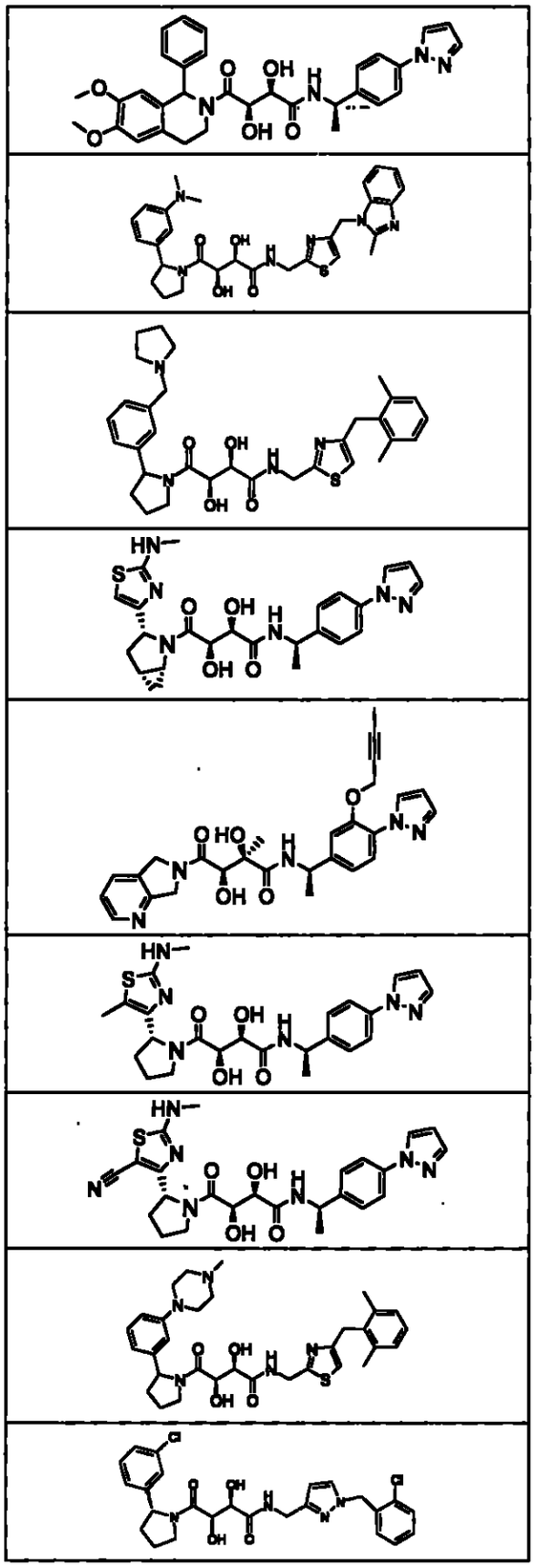


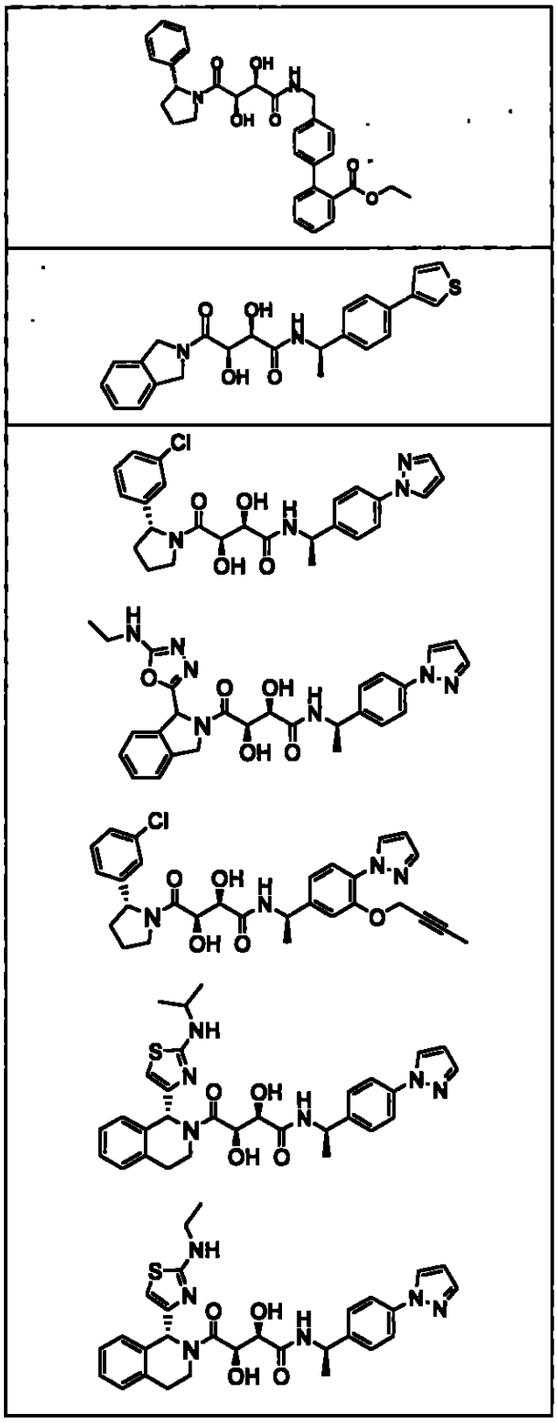


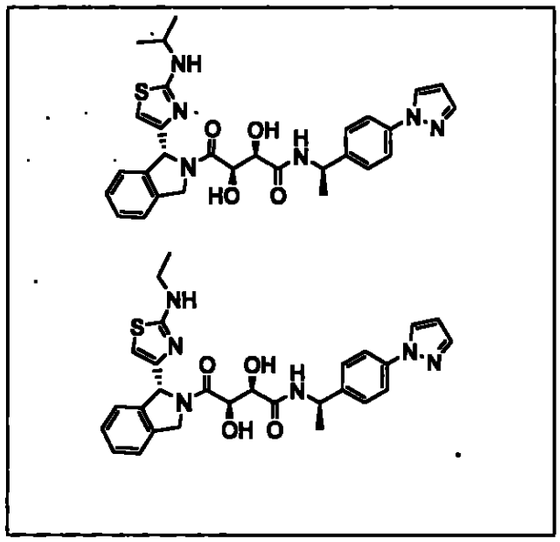












Los compuestos de mayor preferencia anteriores poseen valores de K_i para TACE menores de 5 nM.

En otro aspecto, la invención provee una composición farmacéutica para el tratamiento de trastornos asociados con TACE, TNF-α, MMP, ADAM o cualquier combinación de las mismas en un sujeto, que comprende administrar al sujeto que necesita tal tratamiento una cantidad terapéuticamente efectiva de un compuesto de fórmula 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

En otro aspecto, la invención provee un compuesto de fórmula 1 en forma purificada.

En otro aspecto, la invención provee un método para tratar una afección o enfermedad mediada por TACE, MMPs, TNF-α, agrecanasa (tal como agrecanasa 1 o agrecanasa 2), o cualquier combinación de las mismas en un sujeto, que comprende: administrar al sujeto que necesita tal tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de fórmula 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

En otro aspecto, la invención provee un método para tratar una afección o enfermedad seleccionada del grupo que consiste en artritis reumatoidea,

osteoartritis, periodontitis, gingivitis, úlcera de córnea, crecimiento de tumor sólido e invasión de tumor por parte de metástasis secundarias, glaucoma neovascular, enfermedad intestinal inflamatoria, esclerosis múltiple y psoriasis en un sujeto, que comprende: administrar al sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de fórmula 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

En otro aspecto, la invención provee un método para tratar una afección o enfermedad seleccionada del grupo que consiste en fiebre, afecciones cardiovasculares, hemorragia, coagulación, caquexia, anorexia, alcoholismo, respuesta de fase aguda, infección aguda, shock, reacción injerto versus huésped, enfermedad autoinmune e infección por VIH en un sujeto, que comprende administrar al sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de fórmula 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

En otro aspecto, la invención provee un método para tratar una afección o enfermedad seleccionada del grupo que consiste en shock séptico, shock hemodinámico, síndrome séptico, lesión de reperfusión pos isquémica, malaria, infección micobacteriana, meningitis, psoriasis, insuficiencia cardíaca congestiva, enfermedades fibróticas, caquexia, rechazo a injerto, cánceres tales como linfoma de células T cutáneas, enfermedades relacionadas con angiogénesis, enfermedades autoinmunes, enfermedades inflamatorias de la piel, enfermedades intestinales inflamatorias tales como enfermedad de Crohn y colitis, osteoartritis y artritis reumatoidea, espondilitis anquilosante, artritis psoriásica, enfermedad de Still en adultos, ureítis, granulomatosis de Wegener, enfermedad de Behcehe, síndrome de Sjogren, sarcoidosis, polimiositis, dermatomiositis, esclerosis múltiple, ciática, síndrome de dolor regional complejo, lesión por radiación, lesión alveolar hiperóxica, enfermedad periodontal, VIH, diabetes mellitus no-insulino

dependiente, lupus eritematoso sistémico, glaucoma, sarcoidosis, fibrosis pulmonar idiopática, displasia broncopulmonar, enfermedad retinal, esclerodermia; osteoporosis, isquemia renal, infarto de miocardio; accidente cerebrovascular; isquemia cerebral, nefritis, hepatitis, glomerulonefritis, aveolitis fibrosa criptogénica, psoriasis, rechazo a transplante, dermatitis atópica, vasculitis, alergia, rinitis alérgica estacional, obstrucción reversible de vías aéreas, síndrome de insuficiencia respiratoria de adultos, asma, enfermedad pulmonar obstructiva crónica (COPD) y bronquitis en un sujeto, que comprende administrar al sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de fórmula 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

En otro aspecto, la invención provee un método para el tratamiento de una afección o enfermedad asociada con COPD, que comprende: administrar al sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

En otro aspecto, la invención provee un método para el tratamiento de una afección o enfermedad asociada con artritis reumatoidea, que comprende: administrar al sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de fórmula 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

En otro aspecto, la invención provee un método para el tratamiento de una afección o enfermedad asociada con Enfermedad de Crohn, que comprende: administrar al sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de fórmula 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

En otro aspecto, la invención provee un método para el tratamiento de una afección o enfermedad asociada con psoriasis, que comprende: administrar al sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de fórmula 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

En otro aspecto, la invención provee un método para el tratamiento de una afección o enfermedad asociada con espondilitis anquilosante, que comprende: administrar al sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de fórmula 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

En otro aspecto, la invención provee un método para el tratamiento de una afección o enfermedad asociada con ciática, que comprende: administrar al sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de fórmula 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

En otro aspecto, la invención provee un método para el tratamiento de una afección o enfermedad asociada con síndrome de dolor regional complejo, que comprende: administrar al sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de fórmula 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

En otro aspecto, la invención provee un método para el tratamiento de una afección o enfermedad asociada con artritis psoriásica, que comprende: administrar al sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de fórmula 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

En otro aspecto, la invención provee un método para el tratamiento de una afección o enfermedad asociada con esclerosis múltiple, que comprende:

administrar al sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de fórmula 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo, en combinación con un compuesto seleccionado del grupo que consiste en Avonex®, Betaseron, Copaxone u otros compuestos indicados para el tratamiento de la esclerosis múltiple.

Adicionalmente, un compuesto de la presente invención se puede co-administrar o usar en combinación con fármacos anti-reumáticos que modifican la enfermedad (DMARDS) tal como metotrexato, azatioprina, leflunomida, pencilinamina, sales de oro, micofenolato mofetil, ciclofosfamida y otros fármacos similares. También se pueden co-administrar con o usar en combinación con NSAIDS tales como piroxicam, naproxeno, indometacina, ibuprofeno y similares; inhibidores selectivos de COX-2 tales como Vioxx® y Celebrex®; inmunosupresores tales como esteroides, ciclosporina, Tacrolimus, rapamicina y similares; modificadores de respuesta biológica (BRMs) tales como Enbrel®, Remicade®, antagonistas de IL-1, anti-CD40, anti-CD28, IL-10, moléculas anti-adhesión y similares; y otros agentes anti-inflamatorios tales como inhibidores de quinasa p38, inhibidores de PDE4, otros inhibidores de TACE químicamente diferentes, antagonistas de receptores de quimiocinas, Talidomida y otros inhibidores micromoleculares de la producción de citoquinas pro-inflamatorias.

También, un compuesto de la presente invención se puede co-administrar o usar en combinación con un antagonista de H1 para el tratamiento de la rinitis alérgica estacional y/o asma. Antagonistas de H1 adecuados pueden ser, por ejemplo, Claritin®, Clarinex®, Allegra®, o Zyrtec®.

En otro aspecto, la invención provee un método para tratar una afección o enfermedad mediada por TACE, MMPs, TNF-α, agrecanasa, o cualquier combinación de las mismas, en un sujeto, que comprende: administrar al sujeto

que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de fórmula 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo en combinación con una cantidad terapéuticamente efectiva de al menos un medicamento seleccionado del grupo que consiste en fármacos anti-reumáticos modificadores de la enfermedad (DMARDS), NSAIDs, inhibidores de COX-2, inhibidores de COX-1, inmunosupresores, modificadores de respuesta biológica (BRMs), agentes anti-inflamatorios y antagonistas de H1.

En otro aspecto, la invención provee un método para tratar una afección o enfermedad seleccionada del grupo que consiste en artritis reumatoidea, osteoartritis, periodontitis, gingivitis, úlcera de córnea, crecimiento de tumores sólidos e invasión tumoral por parte de metástasis secundarias, neovascular glaucoma, enfermedad intestinal inflamatoria, esclerosis múltiple y psoriasis en un sujeto, que comprende: administrar al sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo en combinación con una cantidad terapéuticamente efectiva de al menos un medicamento seleccionado del grupo que consiste en DMARDS, NSAIDs, inhibidores de COX-2, inhibidores de COX-1, inmunosupresores, BRMs, agentes anti-inflamatorios y antagonistas de H1.

En otro aspecto, la invención provee un método para tratar una afección o enfermedad seleccionada del grupo que consiste en shock séptico, shock hemodinámico, síndrome séptico, lesión de reperfusión pos isquémica, malaria, infección micobacteriana, meningitis, psoriasis, insuficiencia cardíaca congestivo, enfermedades fibrosas, caquexia, rechazo a injerto, cánceres tal como linfoma de células T cutáneas, enfermedades relacionadas con la angiogénesis, enfermedades autoinmunes, enfermedades inflamatorias de la piel, enfermedades intestinales inflamatorias tales como enfermedad de Crohn y colitis, osteoartritis y

artritis reumatoidea, espondilitis anquilosante, artritis psoriásica, enfermedad de Still en adultos, ureítis, granulomatosis de Wegener, enfermedad de Behcehe, síndrome de Sjogren, sarcoidosis, polomiositis, dermatomiositis, esclerosis múltiple, ciática, síndrome de dolor regional complejo, lesión por radiación, lesión hiperóxica alveolar, enfermedad periodontal, VIH, diabetes mellitus no-insulino dependiente, lupus eritematosa sistémica, glaucoma, sarcoidosis, fibrosis pulmonar idiopática, displasia broncopulmonar, enfermedad retinal, escleroderma, osteoporosis, isquemia renal, infarto de miocardio, accidente cerebrovascular, isquemia cerebral, nefritis, hepatitis, glomerulonefritis, aveolitis fibrosante criptogénica, psoriasis, rechazo a injerto, dermatitis atópica, vasculitis, alergia, rinitis alérgica estacional, obstrucción reversible de vías respiratorias, síndrome de deficiencia respiratoria de adultos, asma, enfermedad pulmonar obstructiva crónica (COPD) y bronquitis en un sujeto, que comprende administrar al sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo en combinación con una cantidad terapéuticamente efectiva de al menos un medicamento seleccionado del grupo que consiste en DMARDS, NSAIDs, inhibidores de COX-2, inhibidores de COX-1, inmunosupresores, BRMs, agentes anti-inflamatorios y antagonistas de H1.

En otro aspecto, la invención provee un método para tratar la AR que comprende administrar un compuesto de fórmula I en combinación con un compuesto seleccionado de la clase que consiste en un inhibidor de COX-2, por ejemplo Celebrex® or Vioxx®; un inhibidor de COX-1, por ejemplo Feldene®; un inmunosupresor, por ejemplo metotrexato o ciclosporina; un esteroide, por ej. β-metasona; y un compuesto anti-TNF-α, por ej. Enbrel® or Remicade®; un inhibidor de PDE IV, u otras clase de compuestos indicados para el tratamiento de la AR.

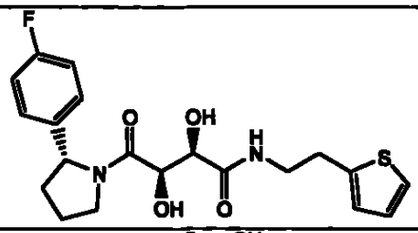
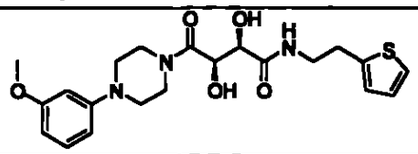
En otro aspecto, la invención provee un método para tratar esclerosis múltiple que comprende administrar un compuesto de fórmula I en combinación con un compuesto seleccionado del grupo que consiste en Avonex®, Betaseron, Copaxone u otros compuestos indicados para el tratamiento de la esclerosis múltiple.

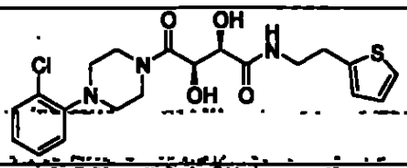
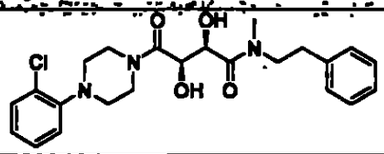
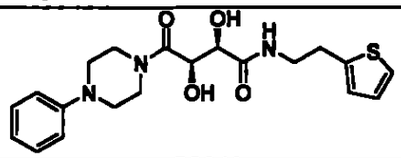
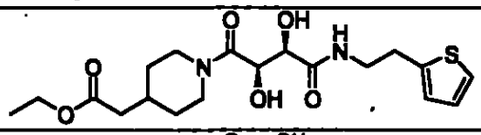
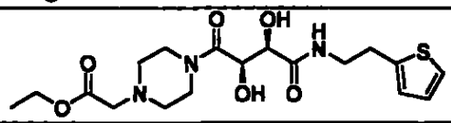
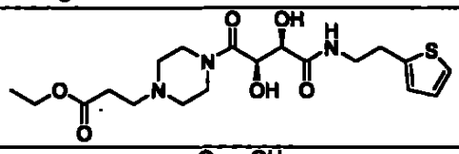
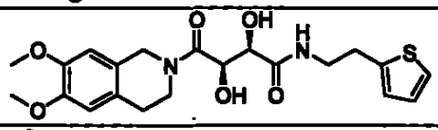
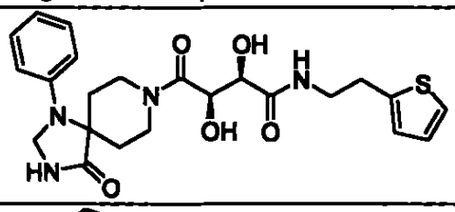
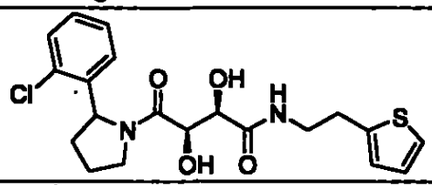
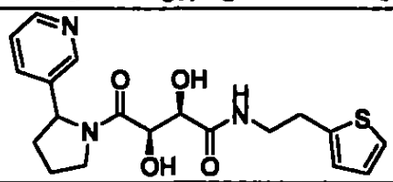
La actividad de TACE se determina mediante un ensayo cinético que mide el grado de incremento de intensidad fluorescente generada por la ruptura catalizada por TACE de un sustrato peptídico desactivado internamente (SPDL-3). Se usa en el ensayo el dominio catalítico purificado de TACE humano recombinante (rhTACEc, Residuo 215 a 477 con dos mutaciones (S266A y N452Q) y una cola de 6xHis). Se purifica a partir del sistema de expresión de baculovirus/células Hi5 usando cromatografía de afinidad. El sustrato SPDL-3 es un péptido desactivado internamente (MCA-Pro-Leu-Ala-Gln-Ala-Val-Arg-Ser-Ser-Ser-Dpa-Arg-NH2), con su secuencia derivada del sitio de ruptura de pro-TNFα. MCA es (7-metoxicumarin-4-il)acetilo. Dpa es N-3-(2,4-dinitrofenil)-L-2,3-diaminopropionilo.

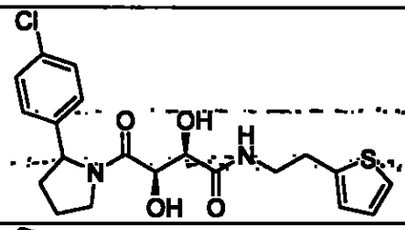
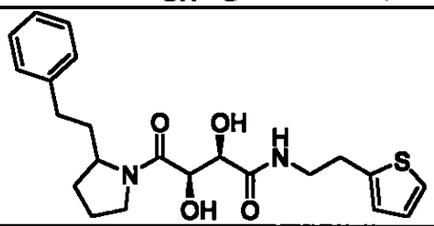
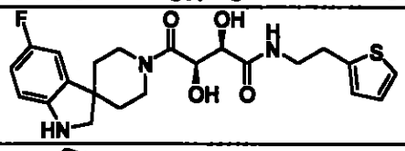
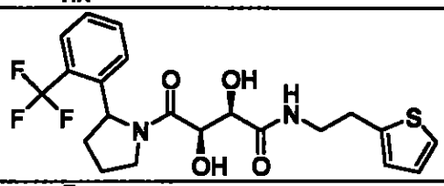
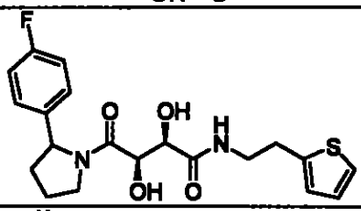
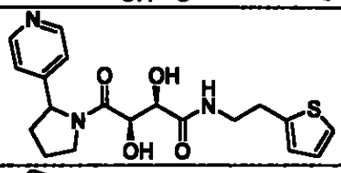
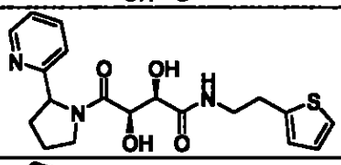
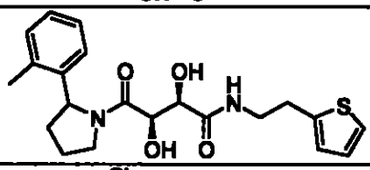
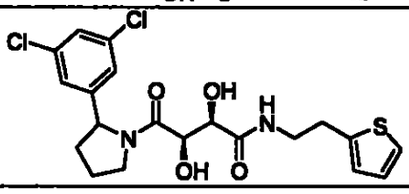
Una mezcla de ensayo de 50 µl contiene HEPES 20 mM, pH 7,3, $CaCl_2$ 5 mM, $ZnCl_2$ 100 µM, 2% de DMSO, 0,04% de metilcelulosa, SPDL-3 30 µM, rhTACEc 70 pM y un compuesto de prueba. RhTACEc se pre-incuba con el compuesto de prueba durante 90 min. a 25°C. La reacción se inicia por adición del sustrato. La intensidad fluorescente (excitación a 320 nm, emisión a 405 nm) se midió cada 45 segundos durante 30 min. usando un fluoroespectrómetro (GEMINI XS, Molecular Devices). La velocidad de reacción enzimática se muestra como unidades por Segundo. El efecto de un compuesto de prueba se muestra como % de actividad de TACE en ausencia del compuesto.

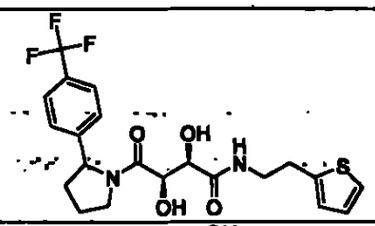
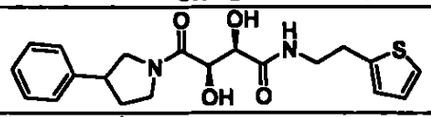
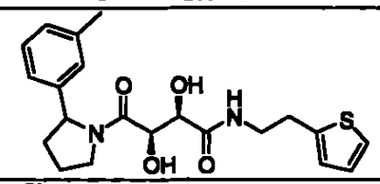
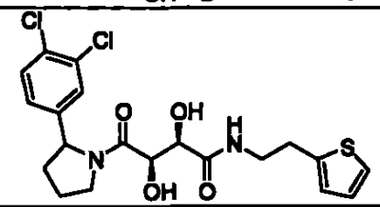
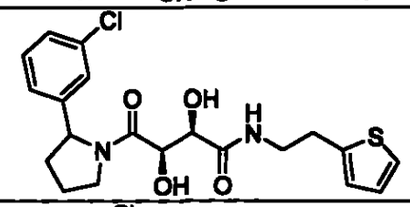
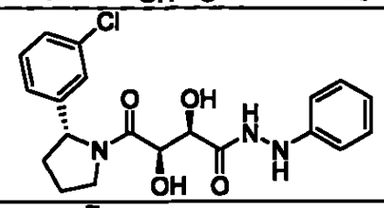
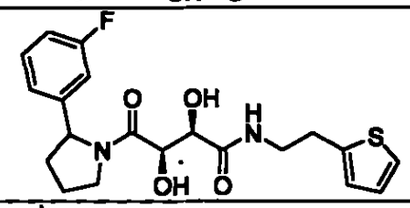
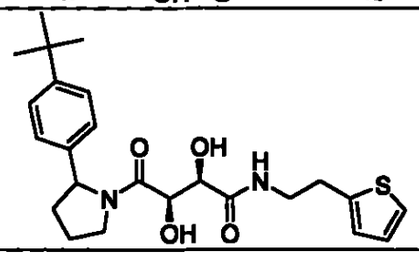
Las actividades inhibidoras de TACE para compuestos representativos se muestran en la siguiente tabla. Los valores de K_i mayores de 1000 nM (1 µM) se

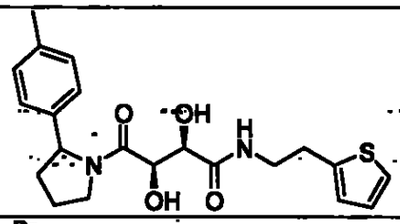
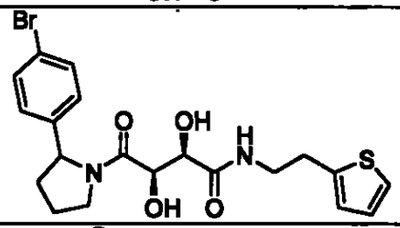
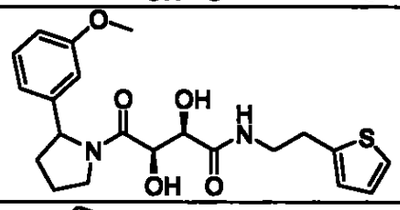
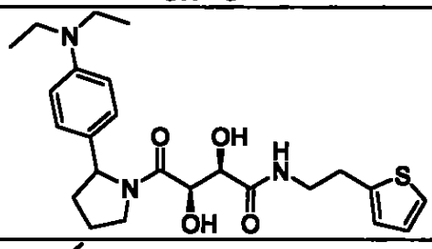
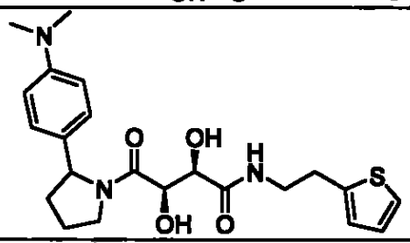
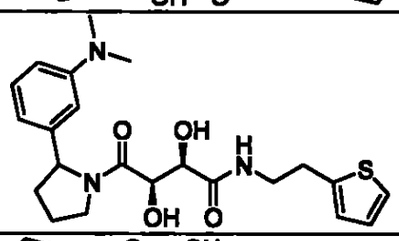
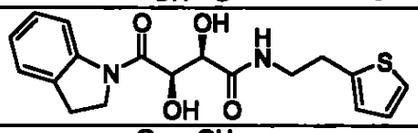
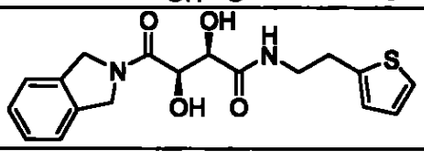
denominan de clase D. Los valores de K_i entre 100 nM (0,1 μM) y 1000 nM (1 μM) se denominan de clase C. Los valores de K_i entre 20 nM (0.02 μM) y 100 nM (0.1 μM) se denominan de clase B. Los valores de K_i menores de 20 nM (0,02 μM) se denominan de clase A.

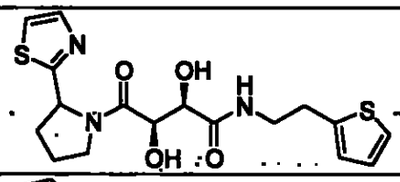
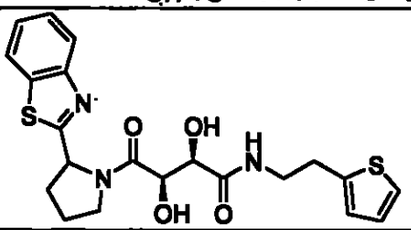
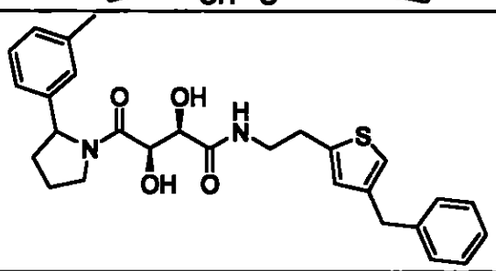
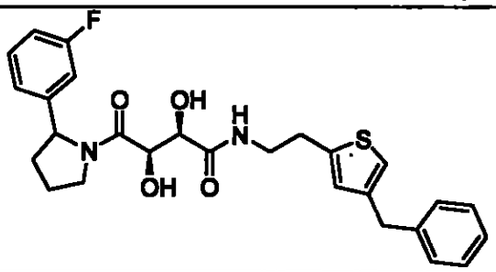
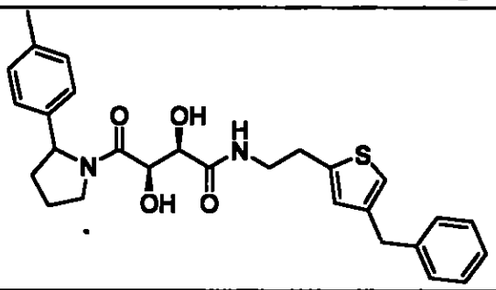
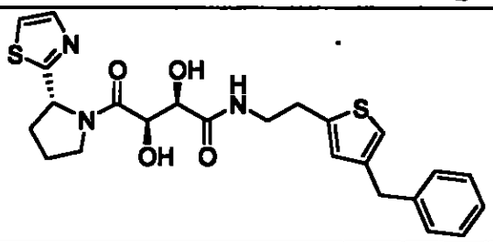
Compuesto #	Estructura	K_i (nM)
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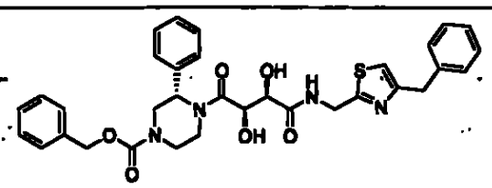
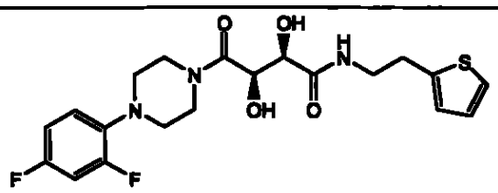
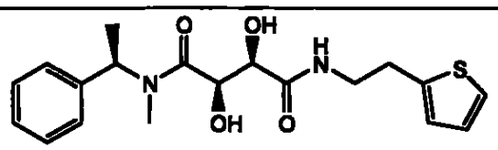
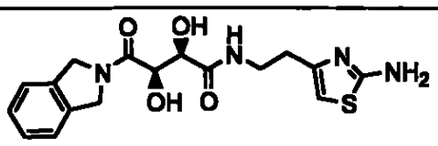
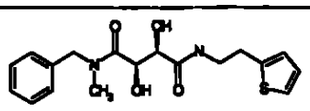
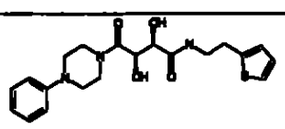
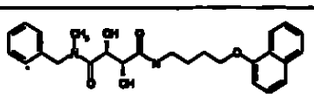
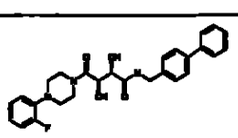
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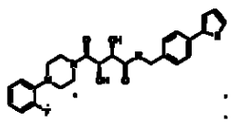
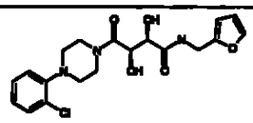
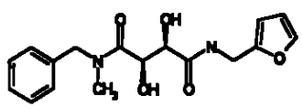
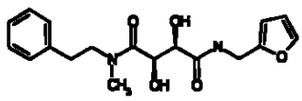
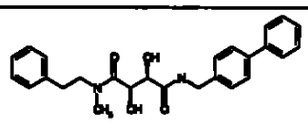
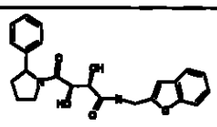
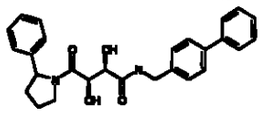
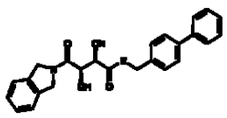
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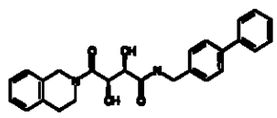
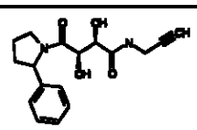
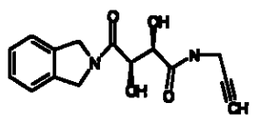
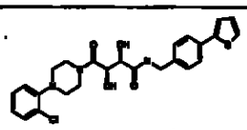
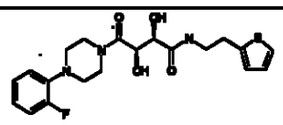
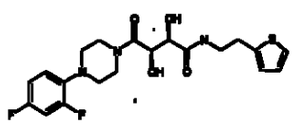
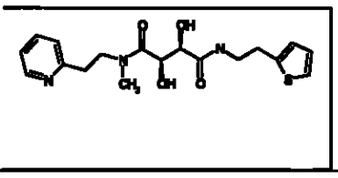
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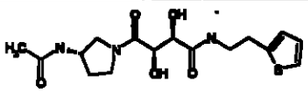
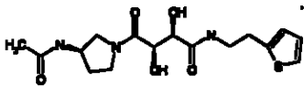
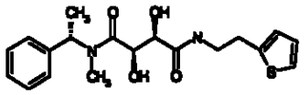
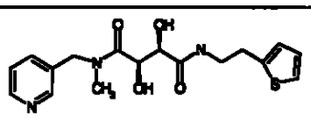
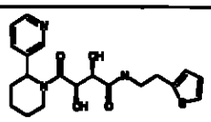
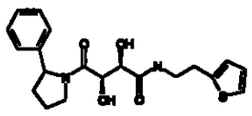
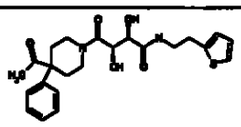
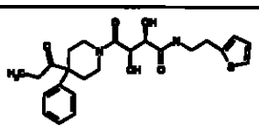
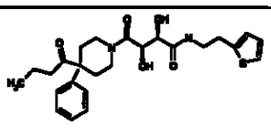
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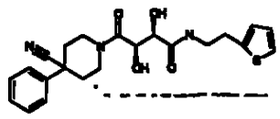
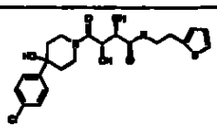
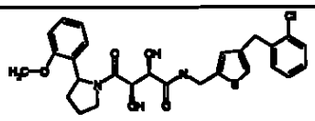
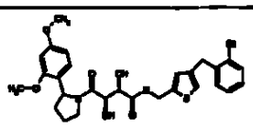
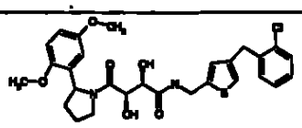
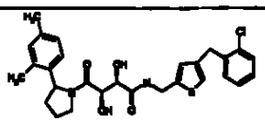
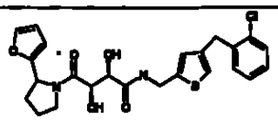
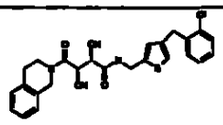
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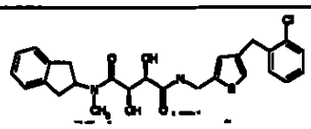
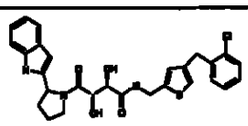
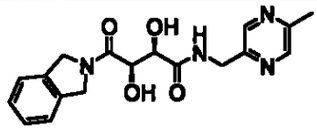
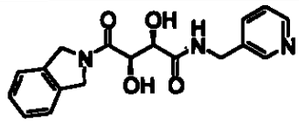
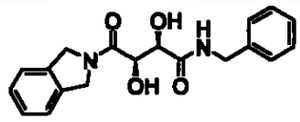
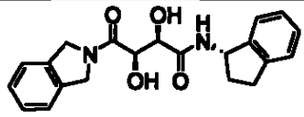
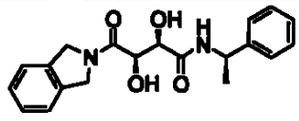
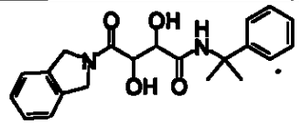
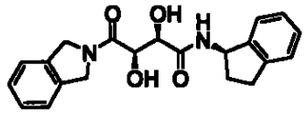
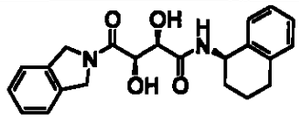
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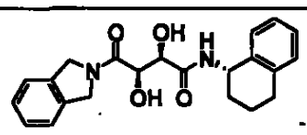
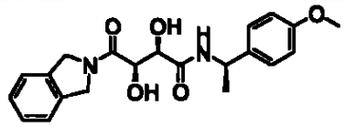
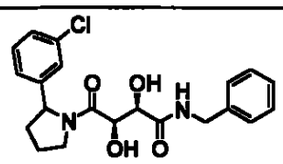
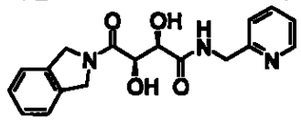
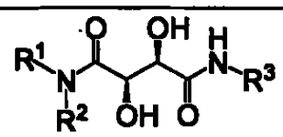
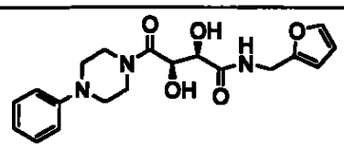
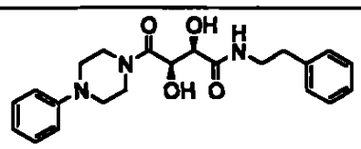
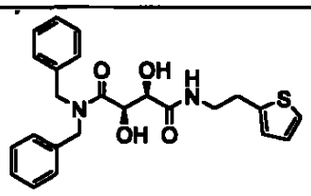
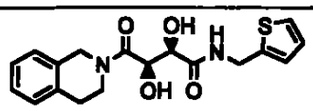
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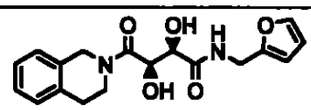
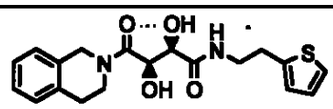
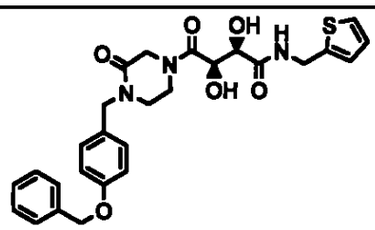
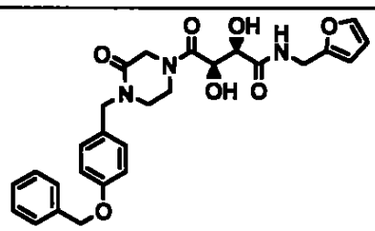
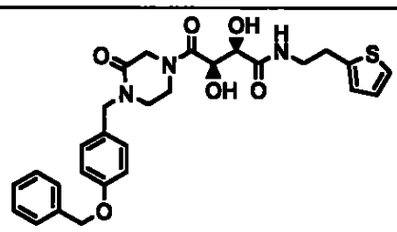
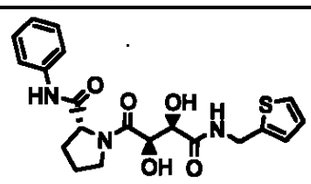
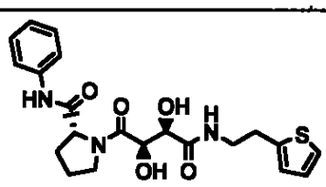
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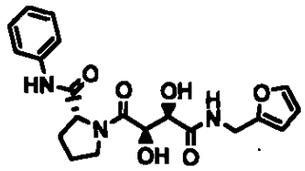
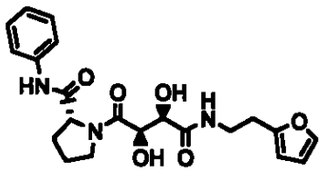
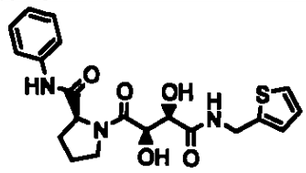
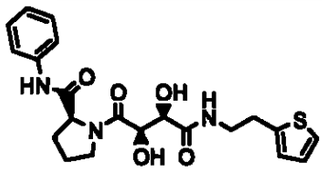
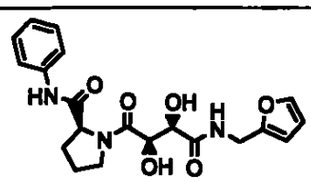
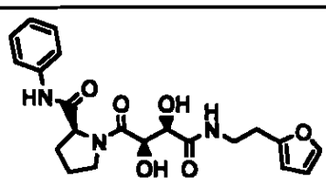
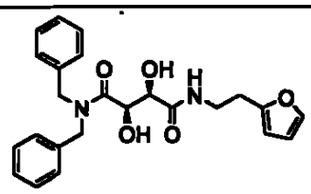
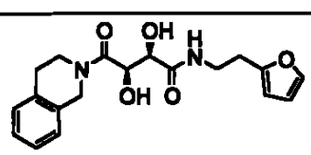
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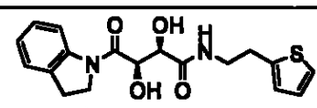
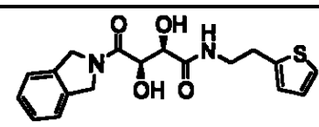
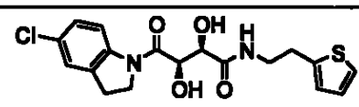
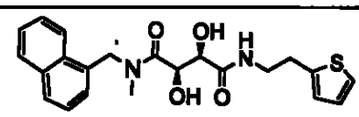
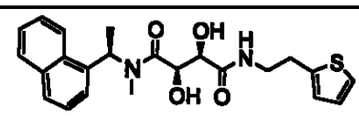
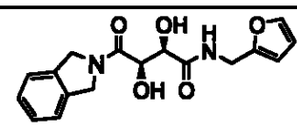
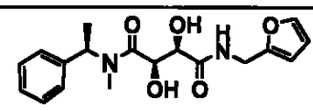
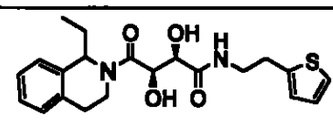
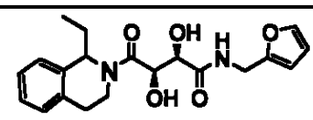
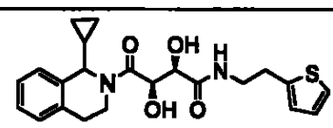
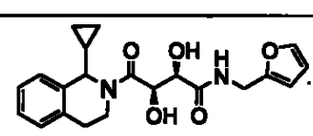
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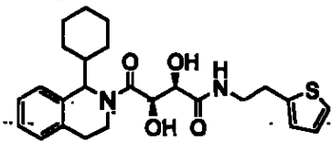
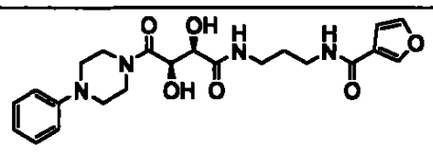
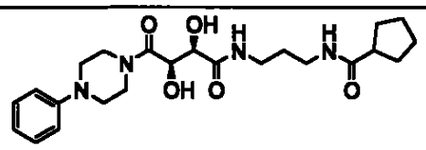
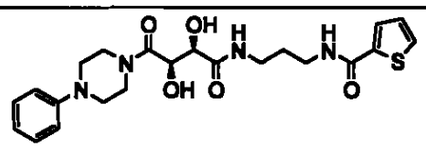
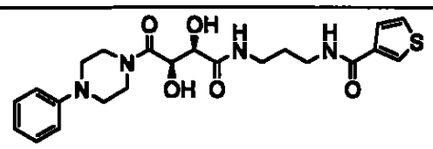
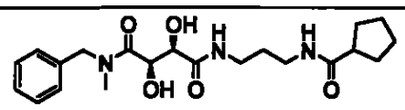
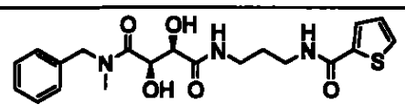
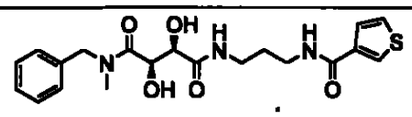
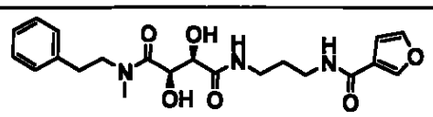
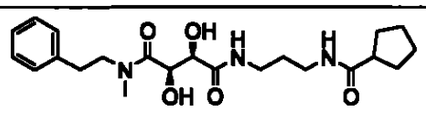
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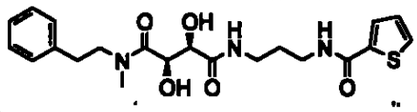
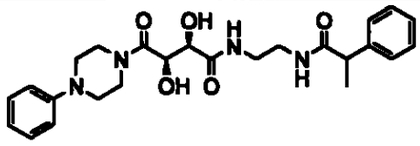
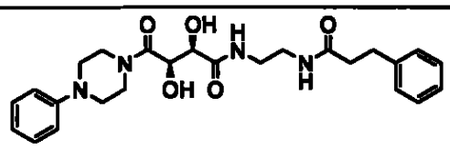
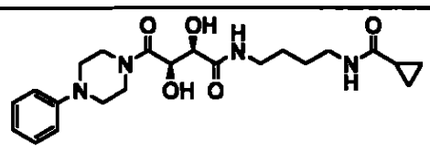
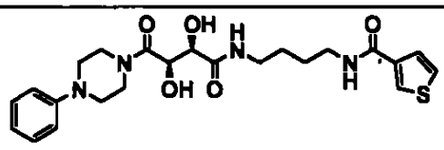
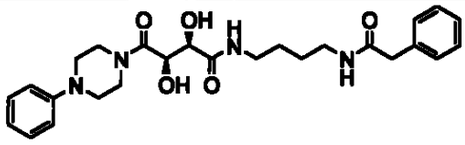
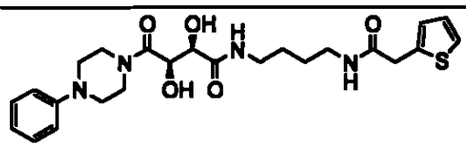
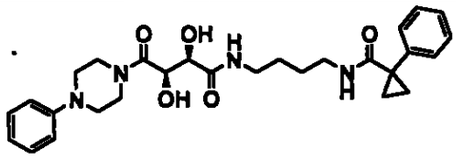
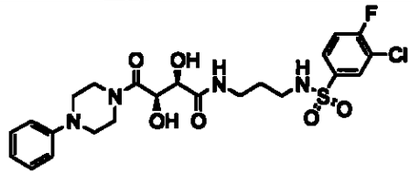
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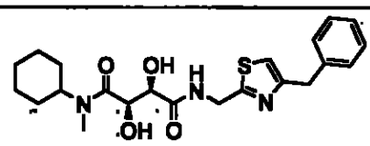
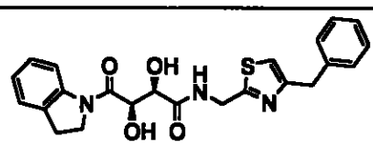
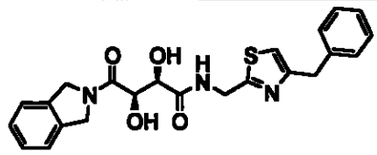
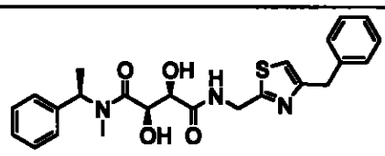
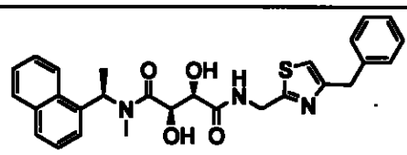
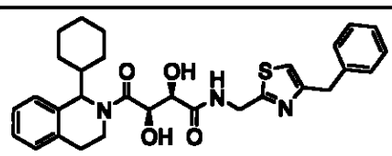
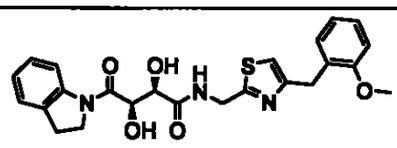
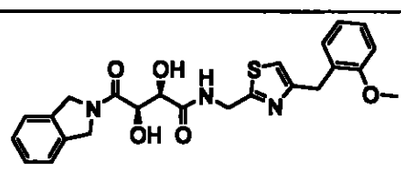
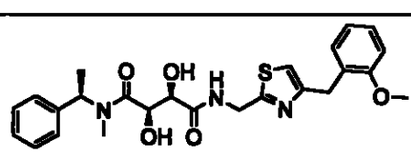
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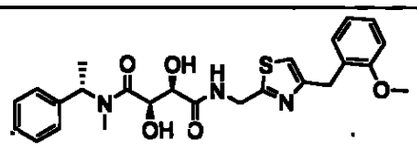
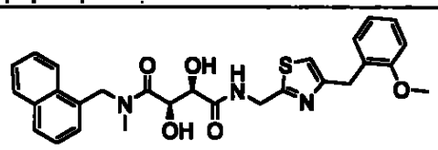
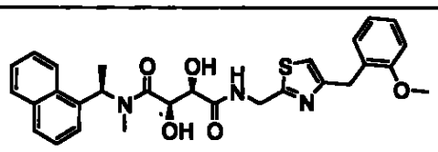
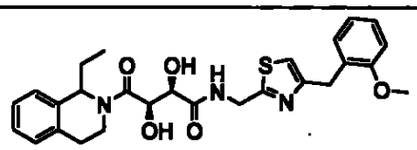
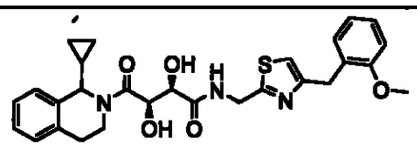
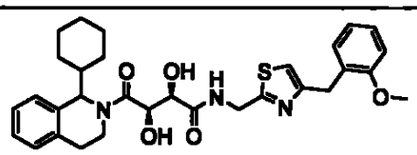
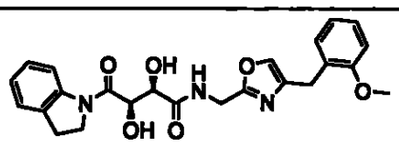
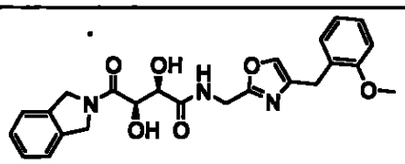
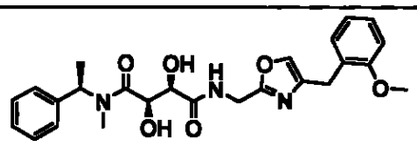
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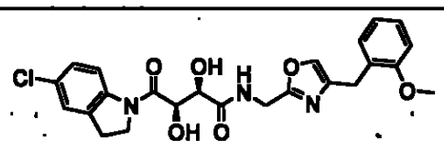
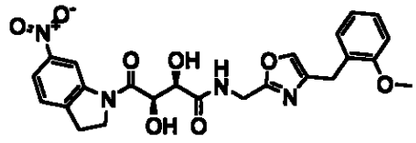
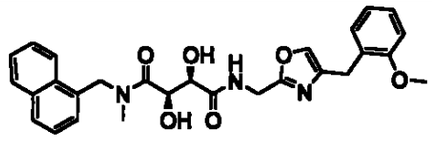
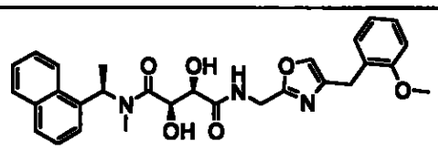
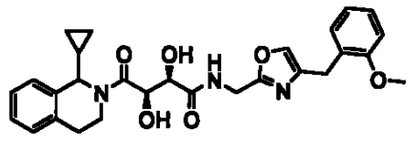
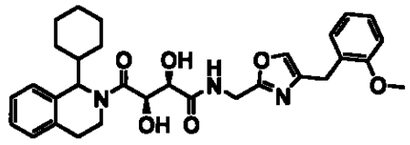
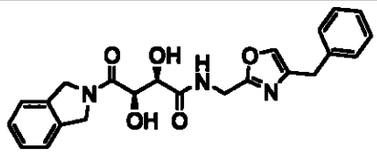
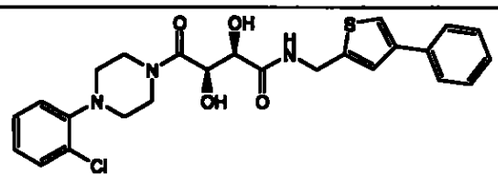
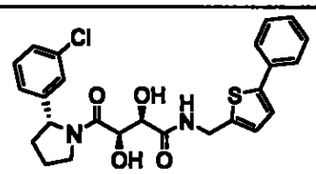
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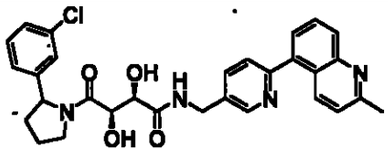
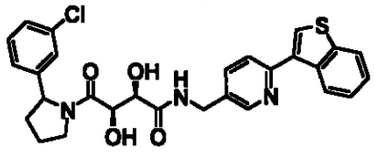
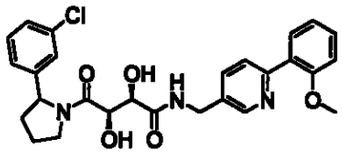
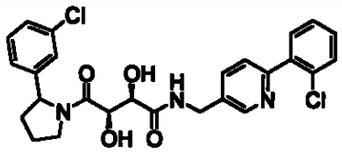
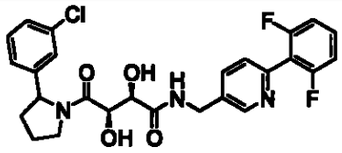
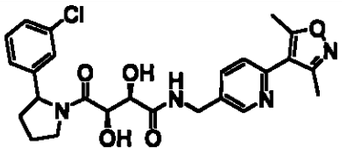
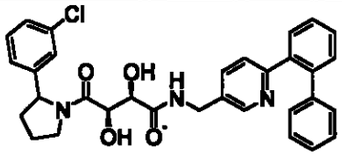
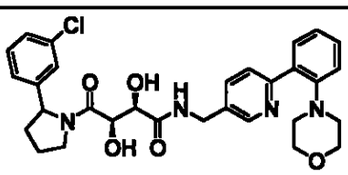
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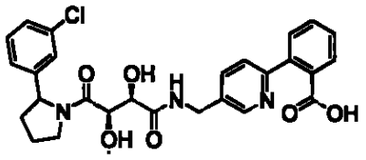
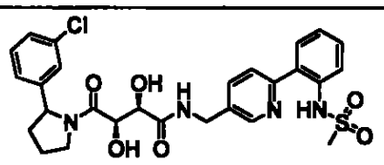
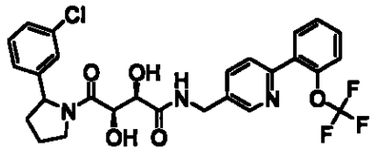
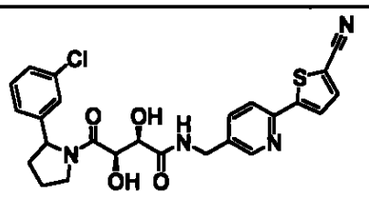
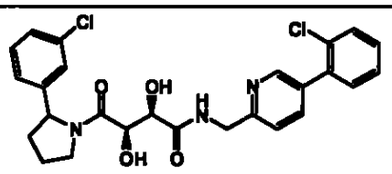
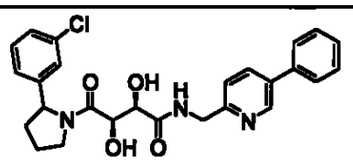
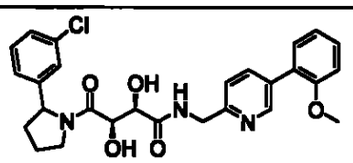
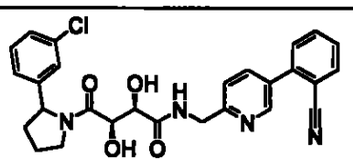
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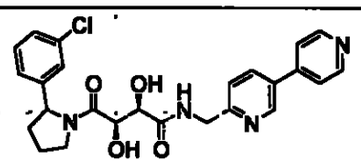
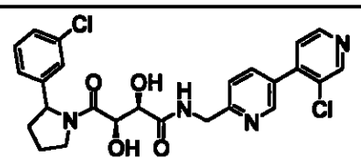
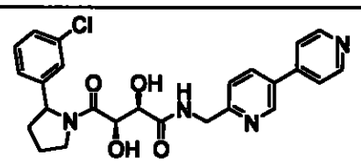
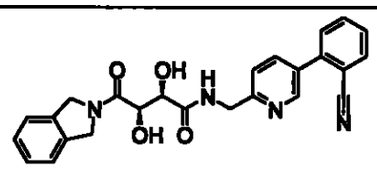
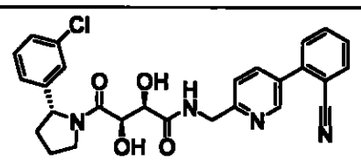
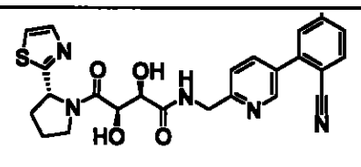
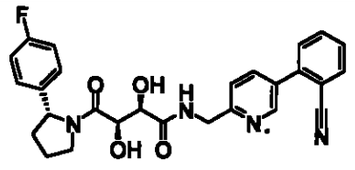
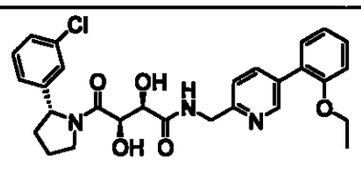
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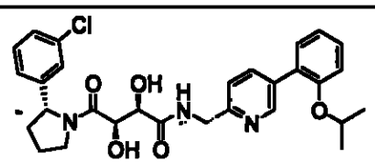
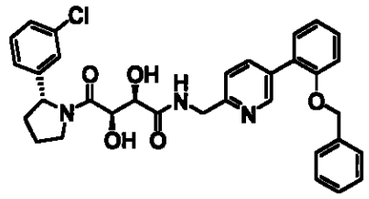
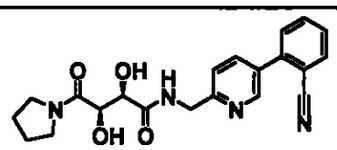
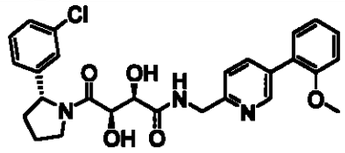
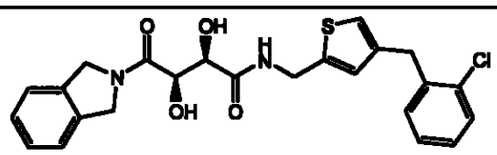
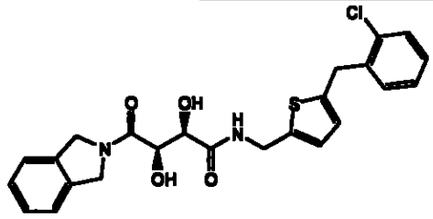
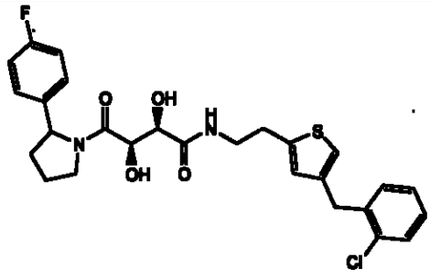
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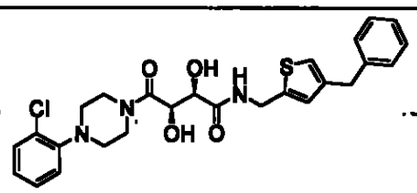
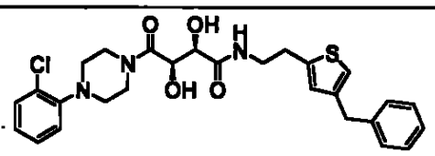
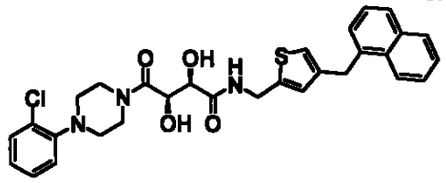
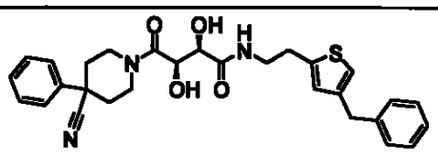
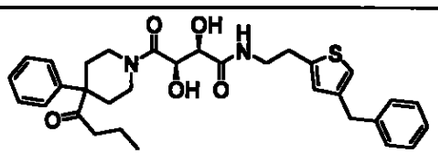
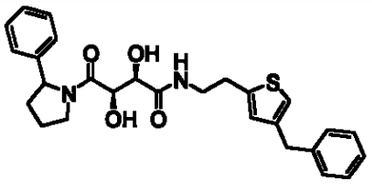
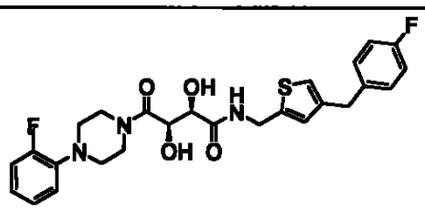
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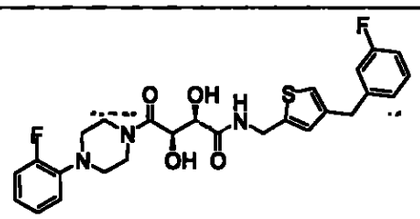
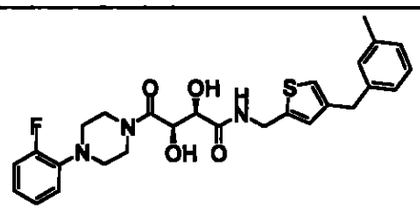
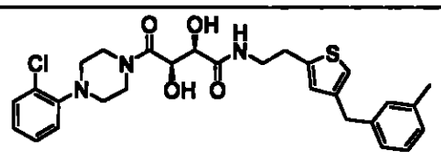
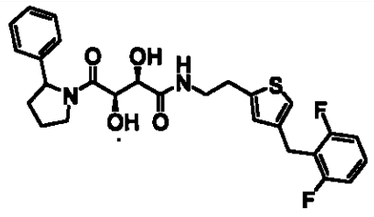
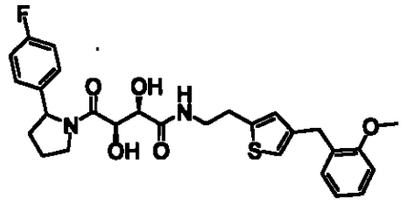
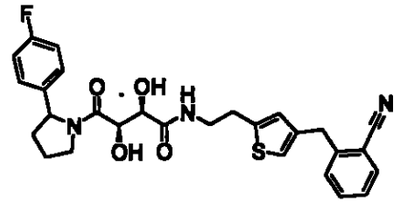
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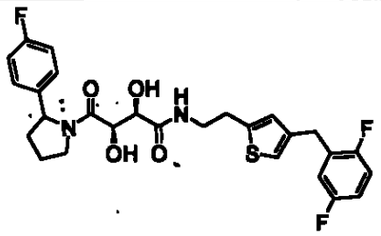
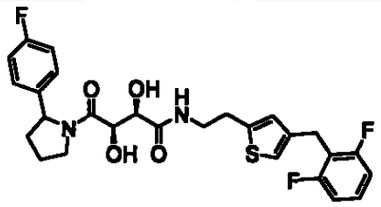
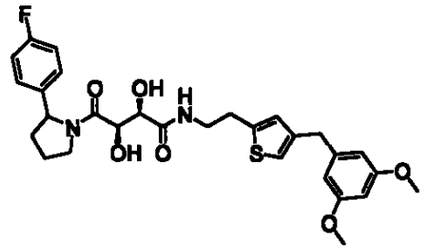
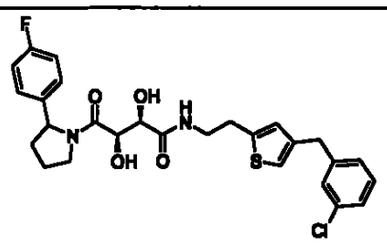
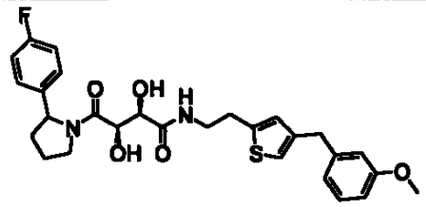
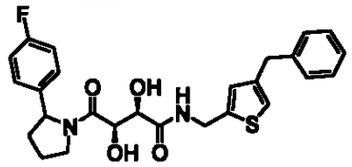
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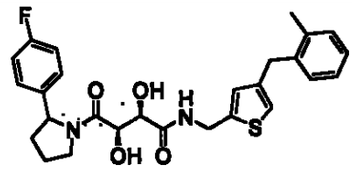
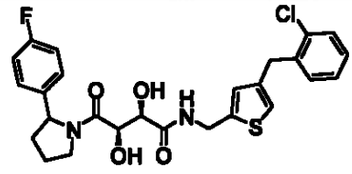
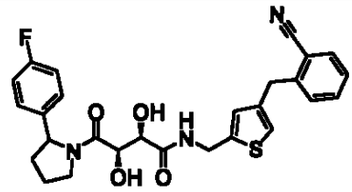
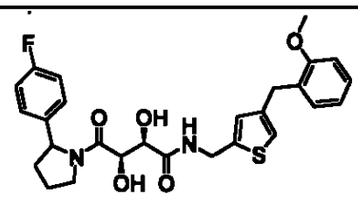
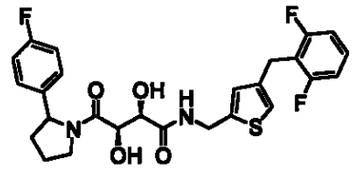
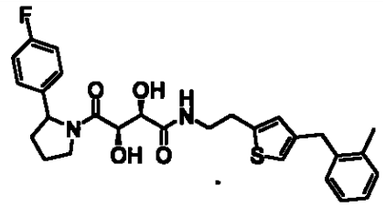
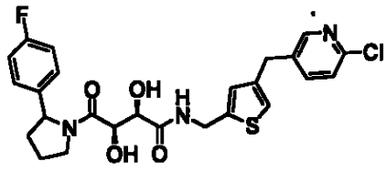
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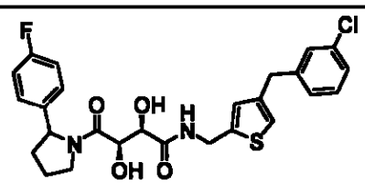
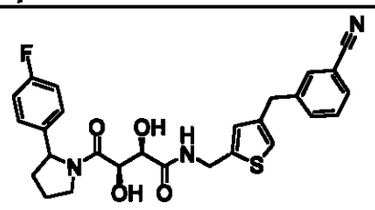
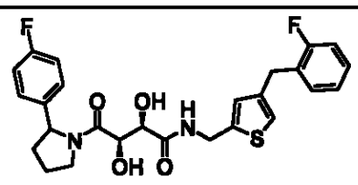
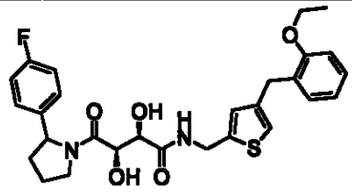
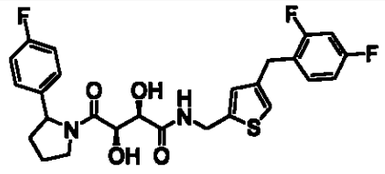
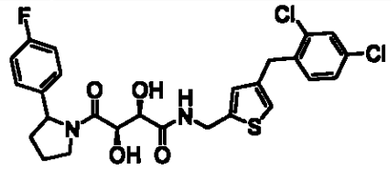
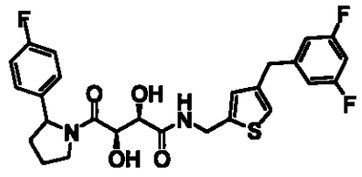
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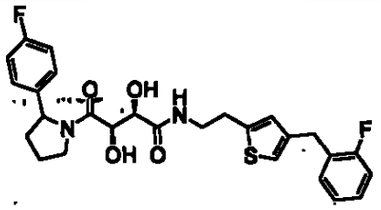
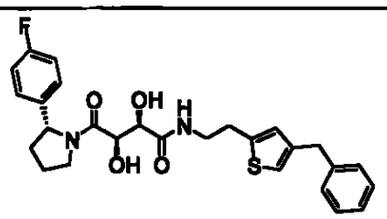
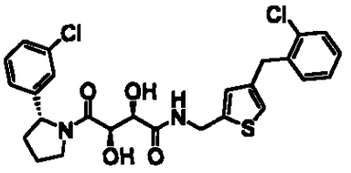
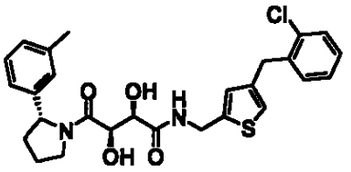
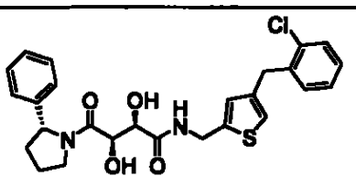
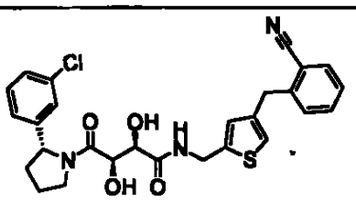
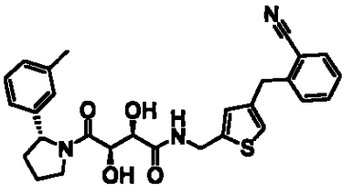
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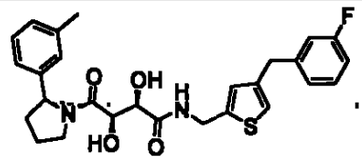
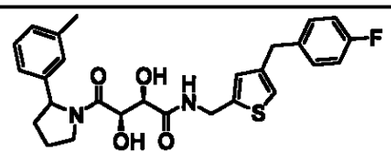
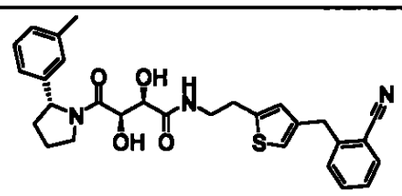
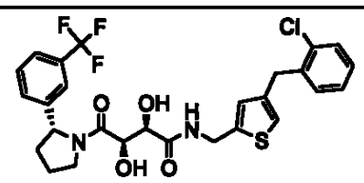
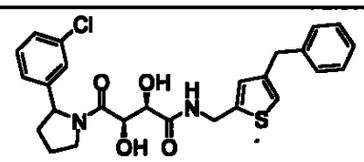
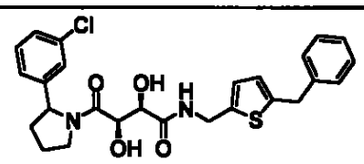
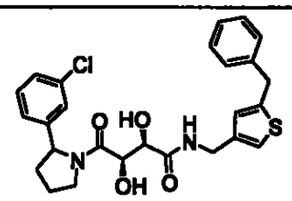
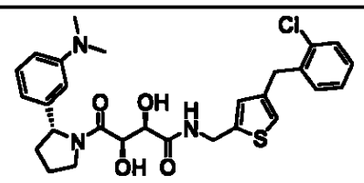
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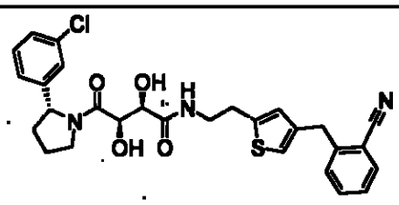
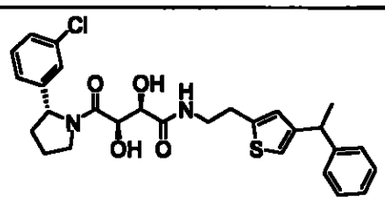
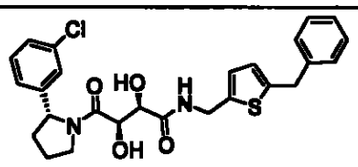
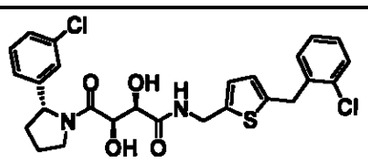
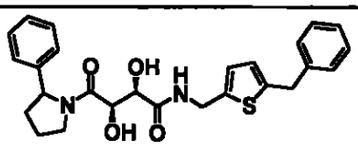
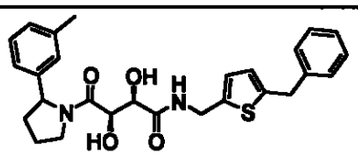
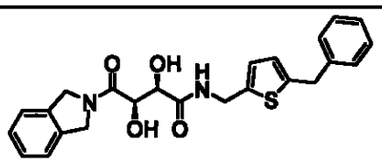
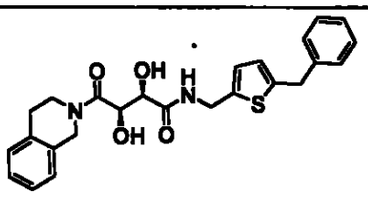
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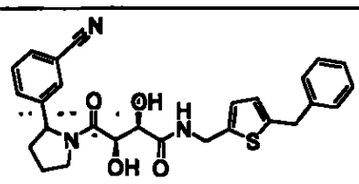
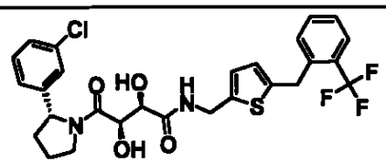
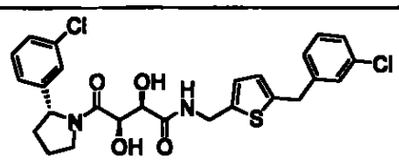
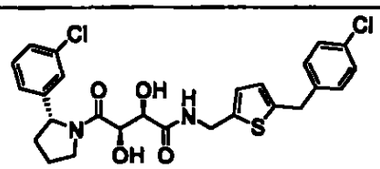
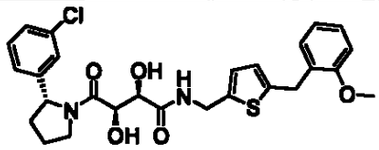
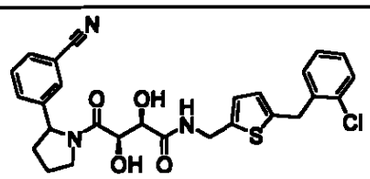
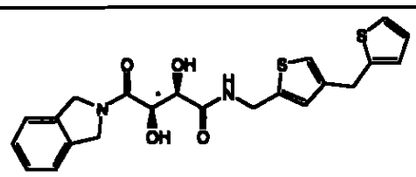
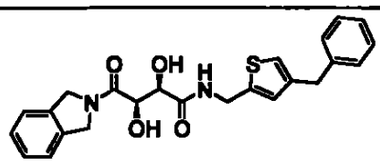
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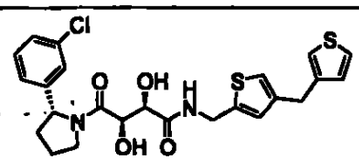
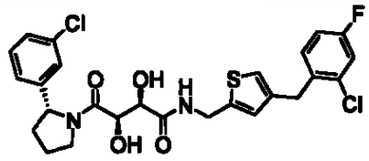
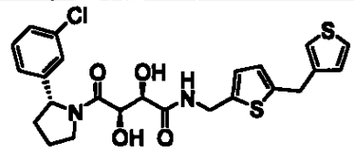
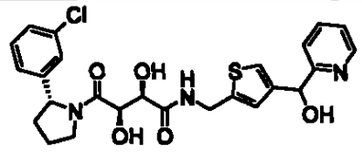
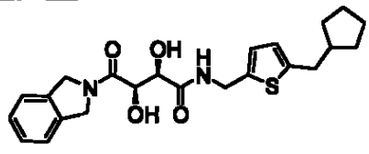
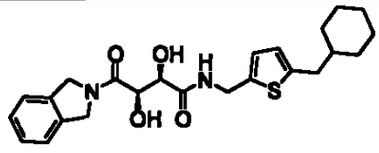
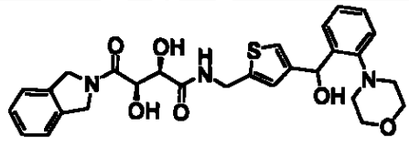
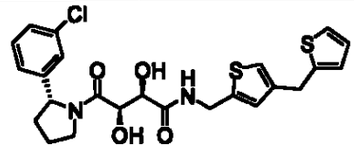
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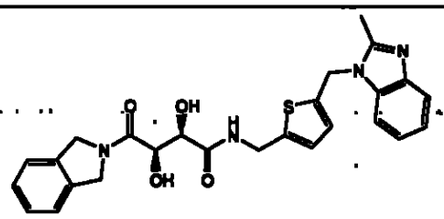
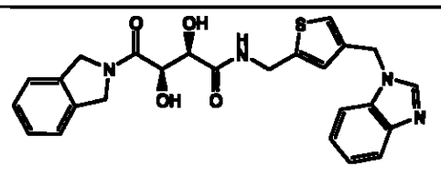
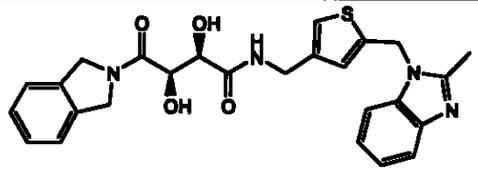
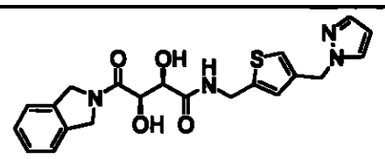
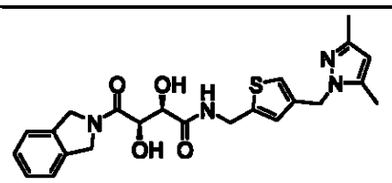
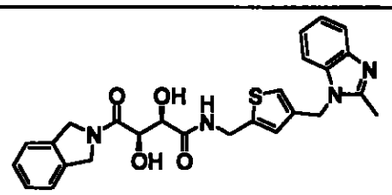
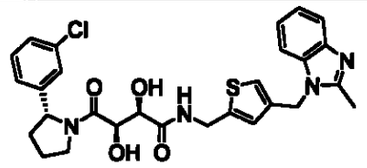
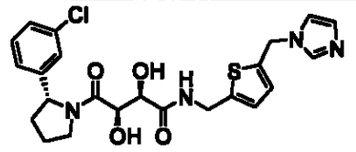
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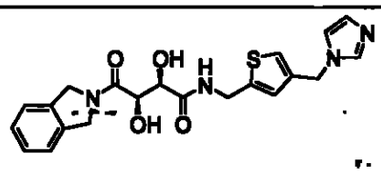
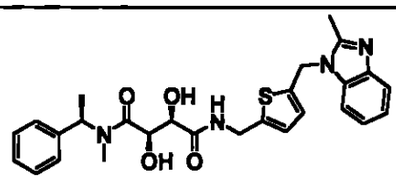
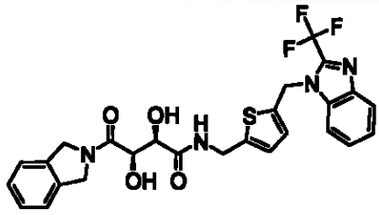
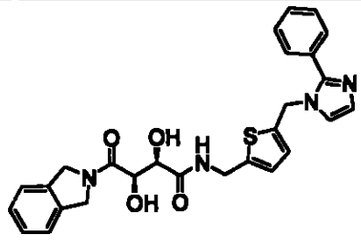
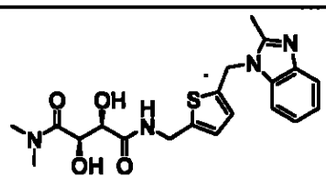
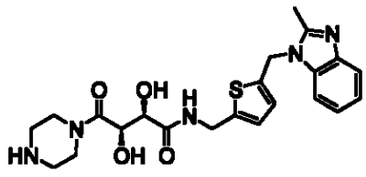
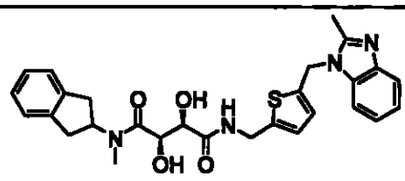
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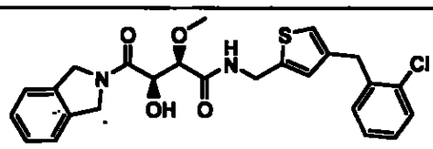
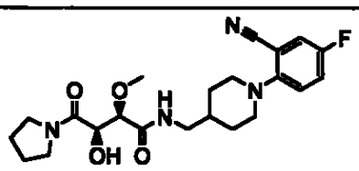
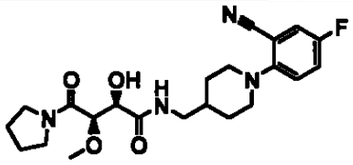
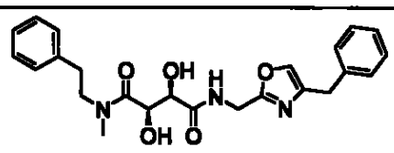
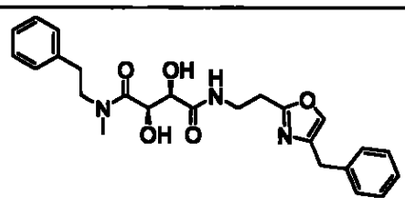
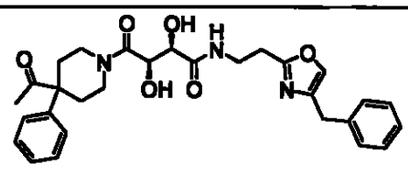
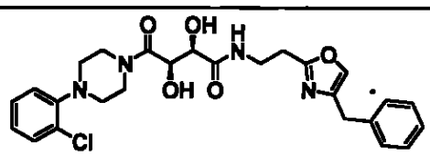
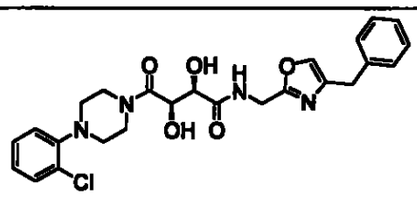
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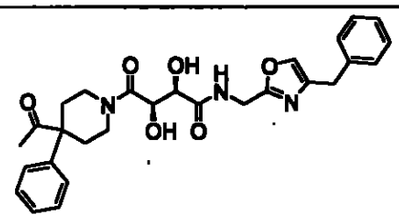
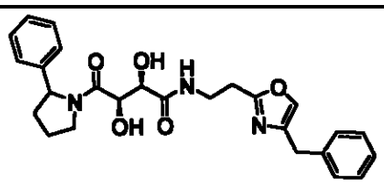
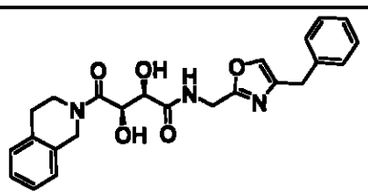
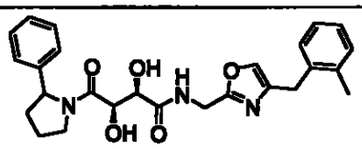
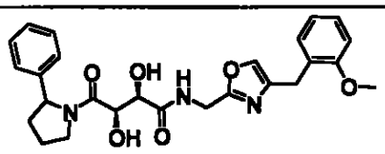
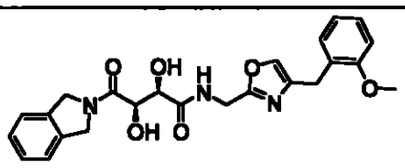
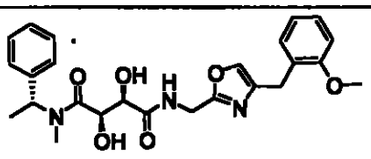
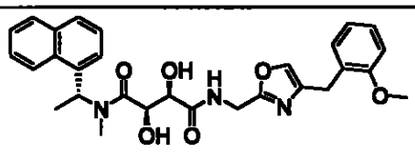
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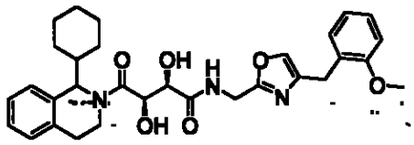
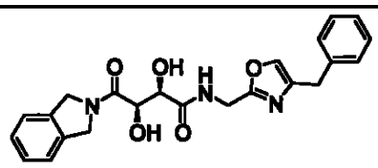
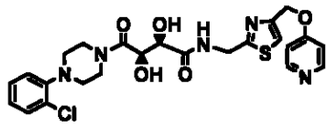
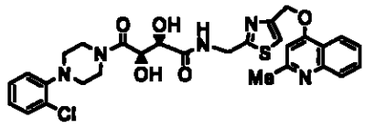
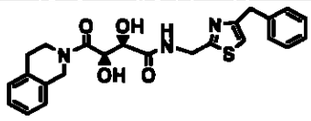
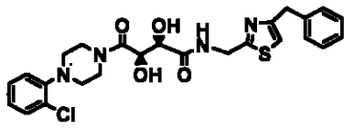
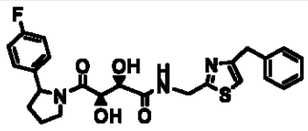
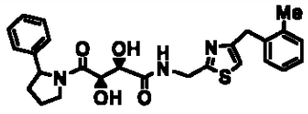
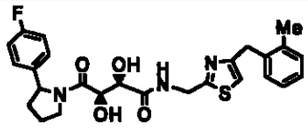
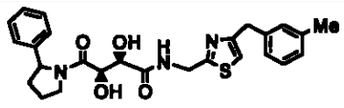
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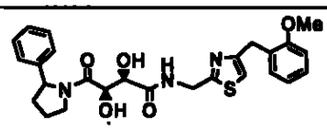
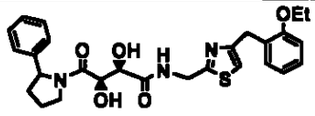
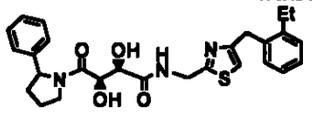
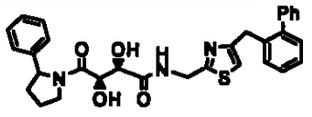
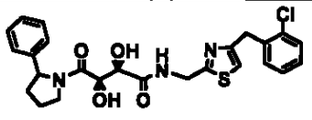
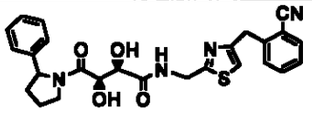
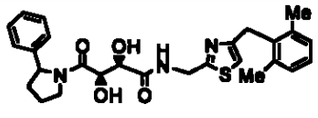
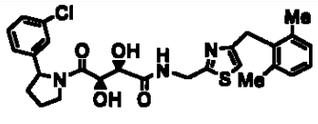
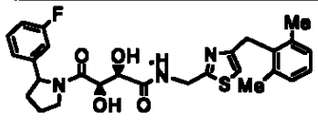
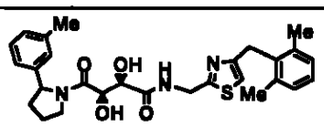
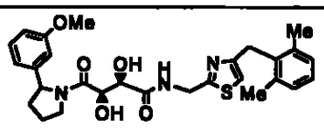
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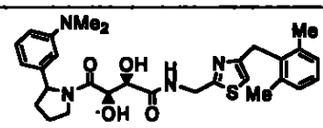
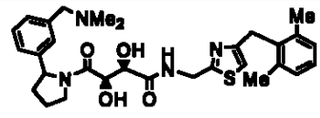
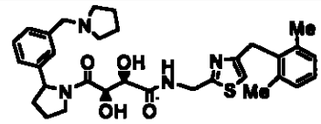
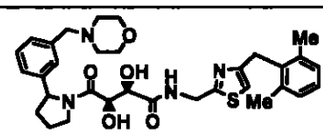
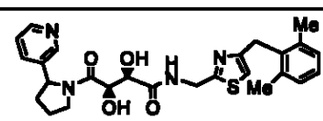
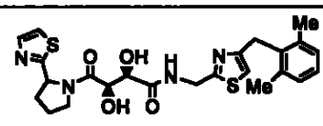
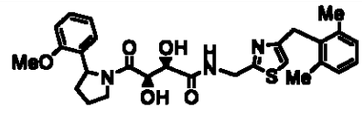
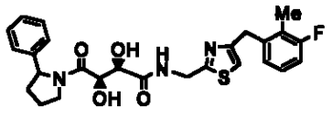
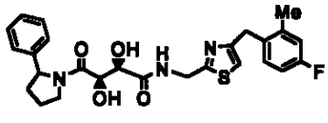
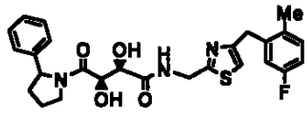
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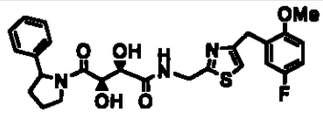
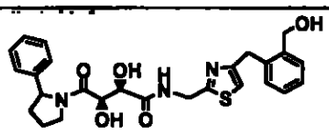
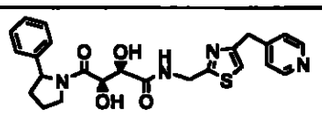
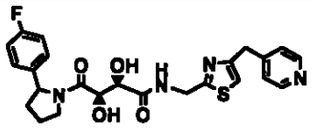
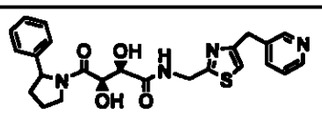
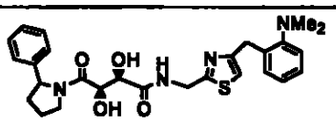
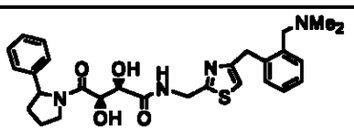
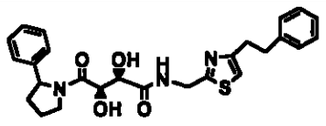
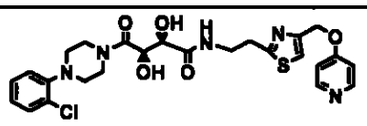
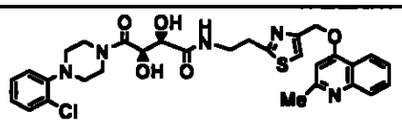
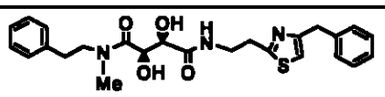
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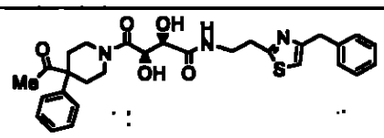
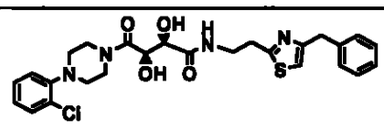
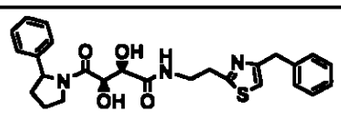
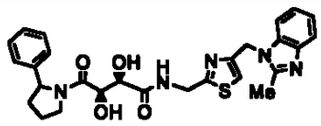
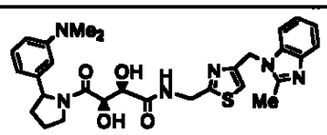
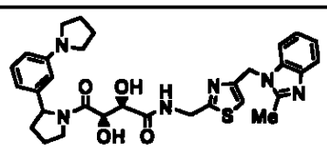
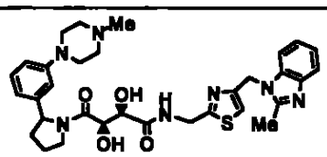
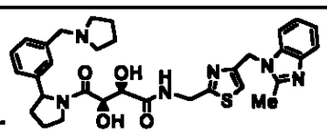
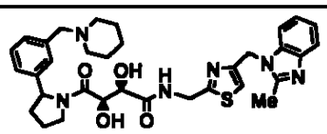
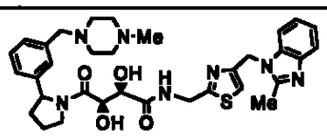
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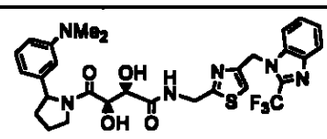
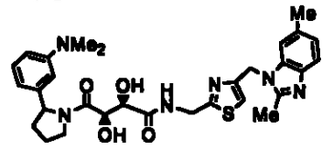
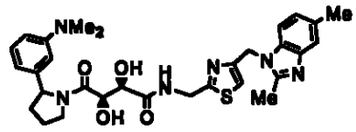
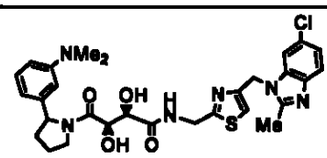
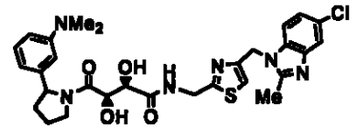
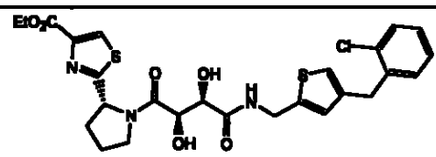
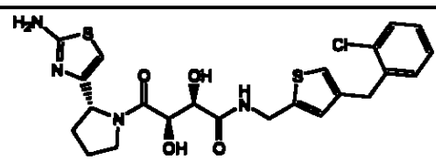
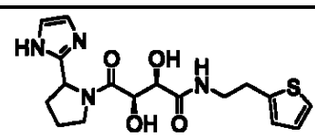
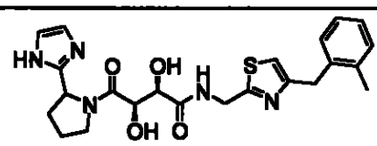
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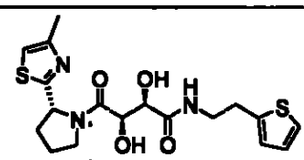
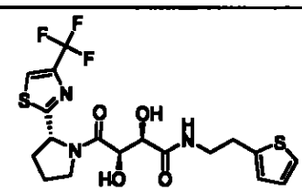
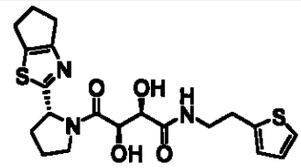
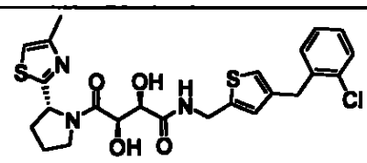
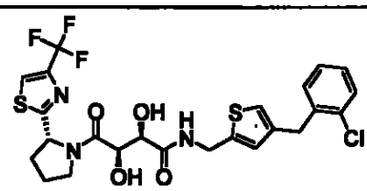
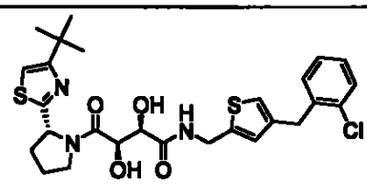
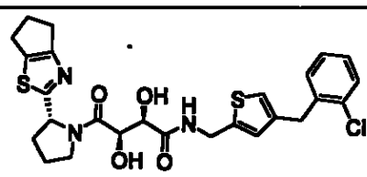
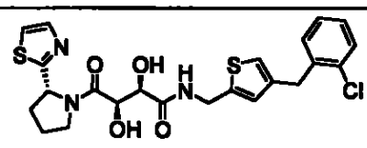
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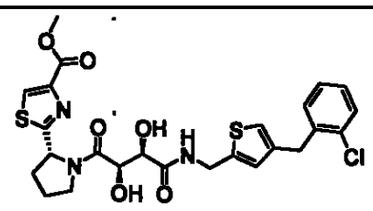
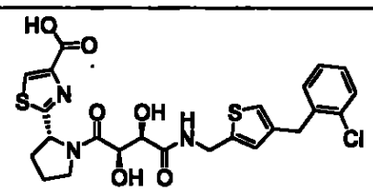
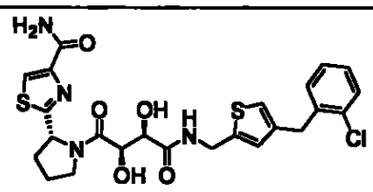
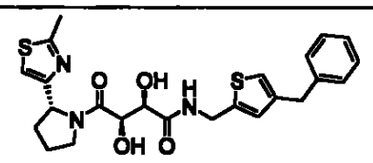
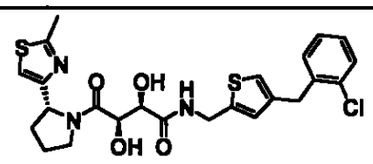
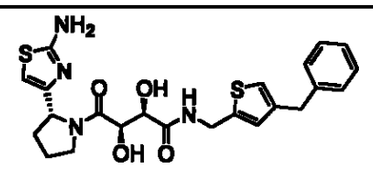
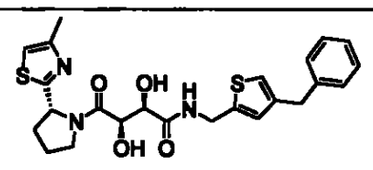
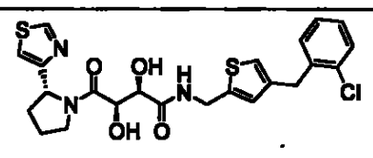
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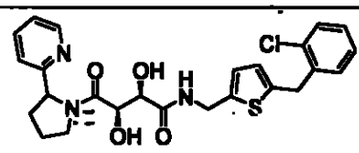
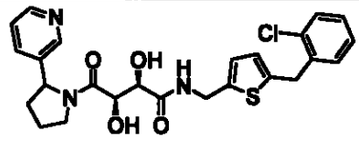
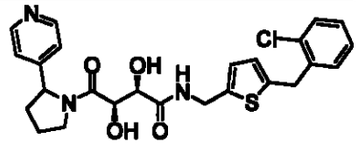
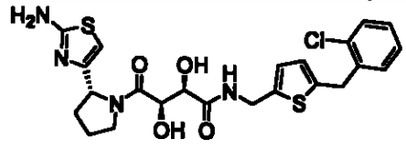
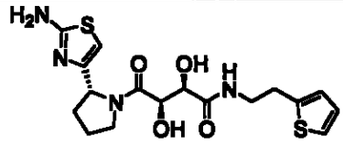
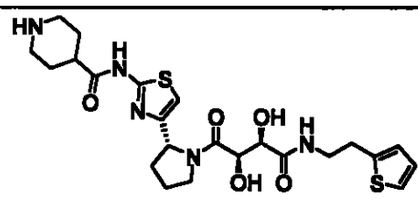
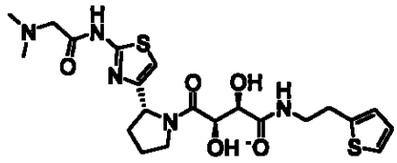
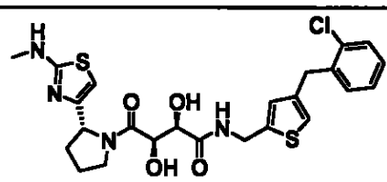
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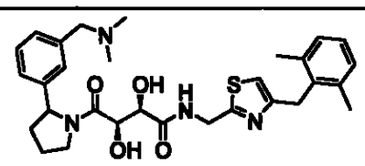
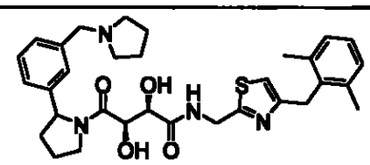
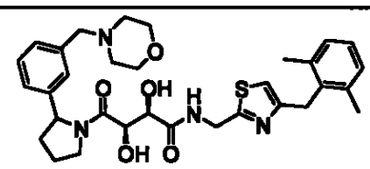
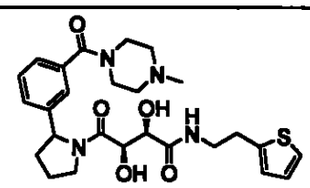
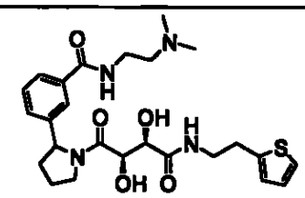
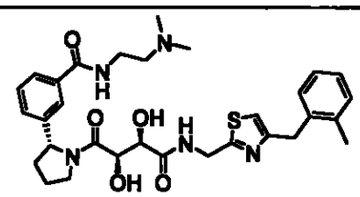
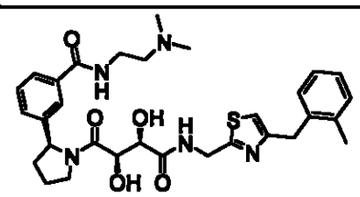
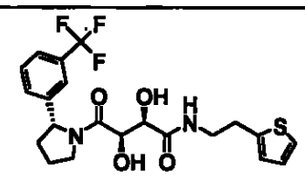
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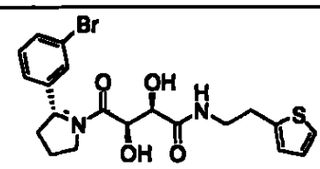
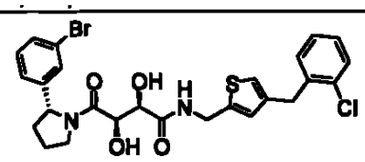
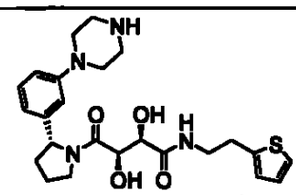
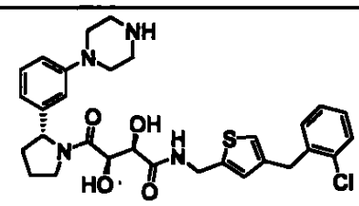
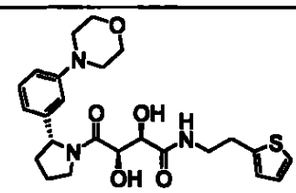
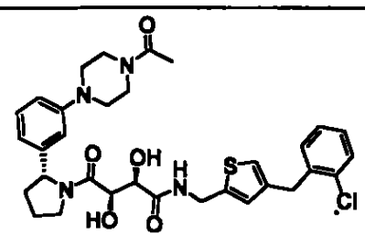
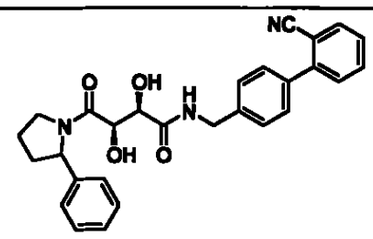
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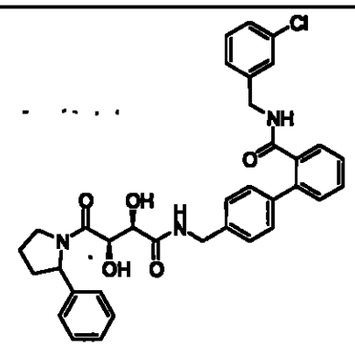
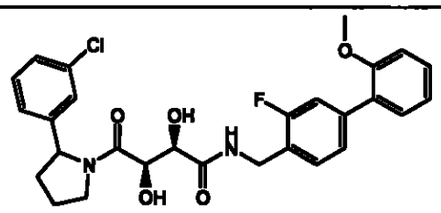
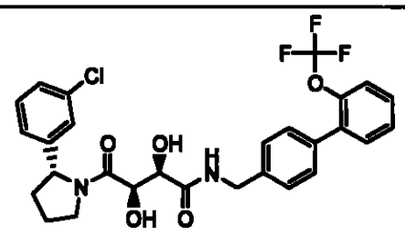
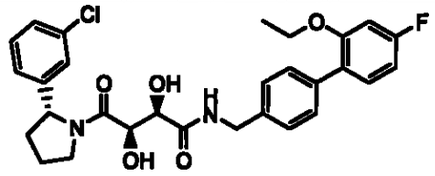
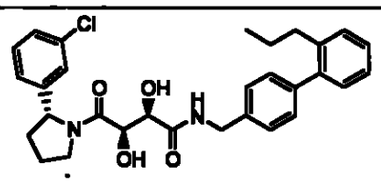
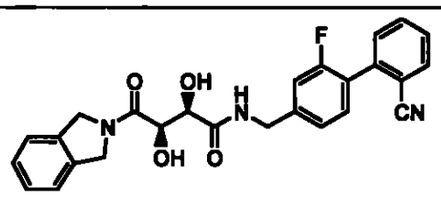
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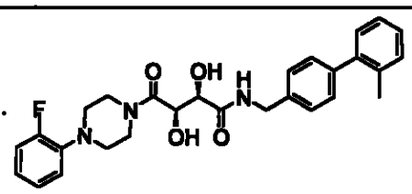
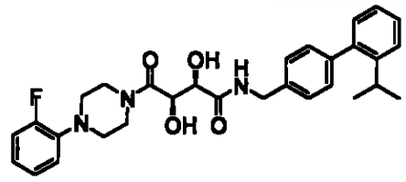
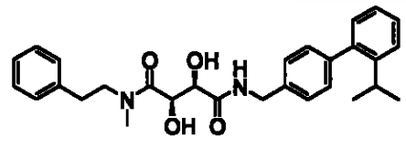
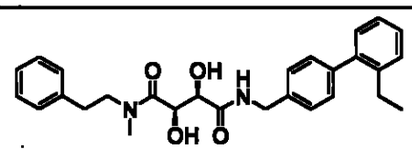
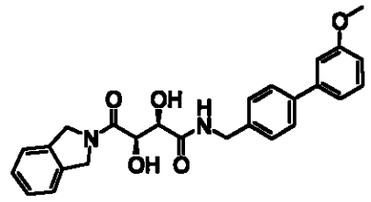
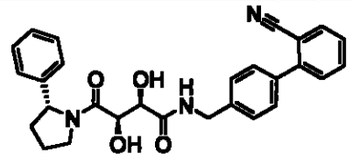
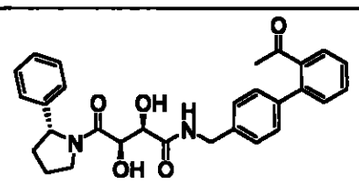
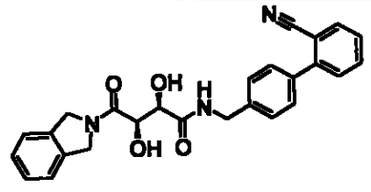
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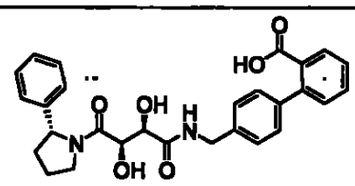
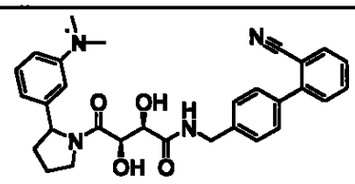
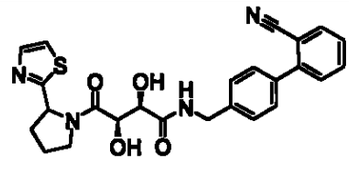
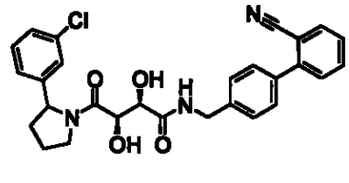
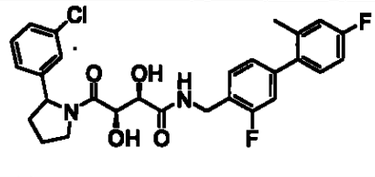
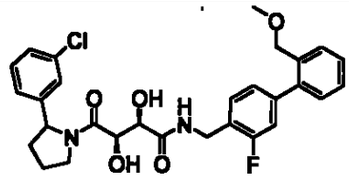
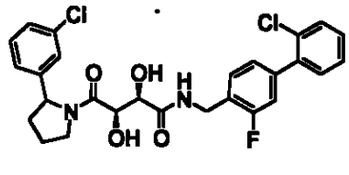
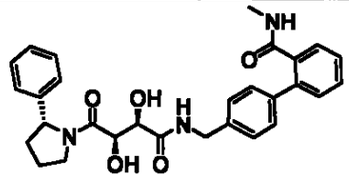
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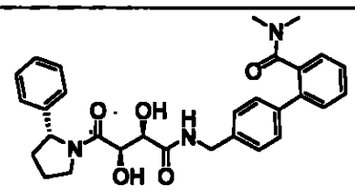
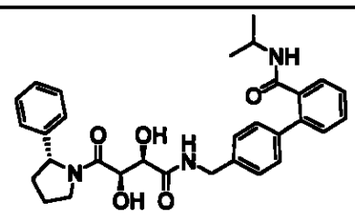
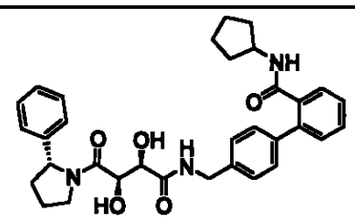
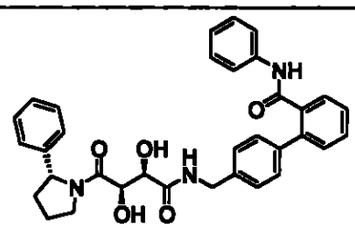
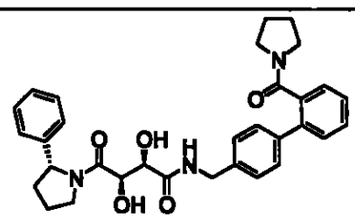
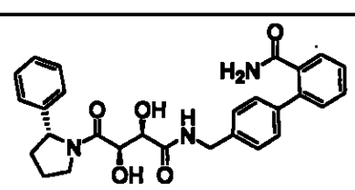
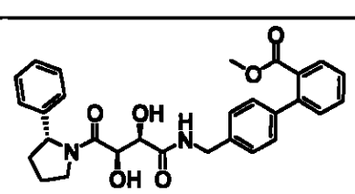
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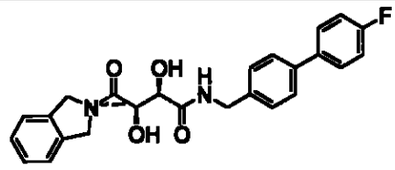
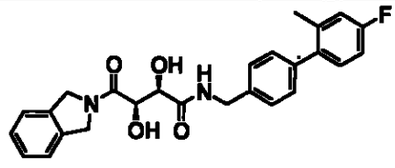
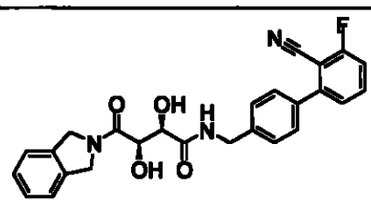
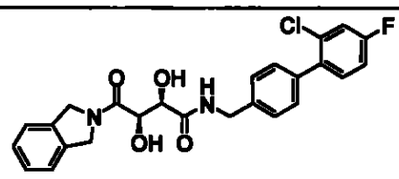
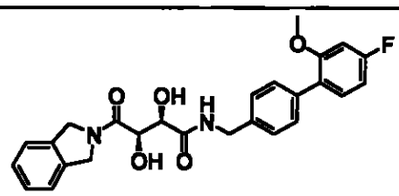
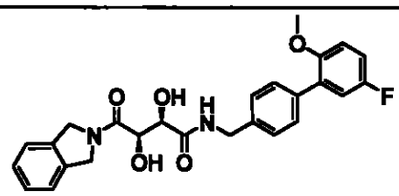
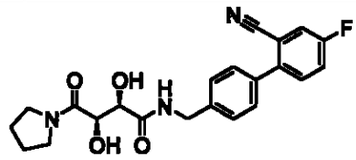
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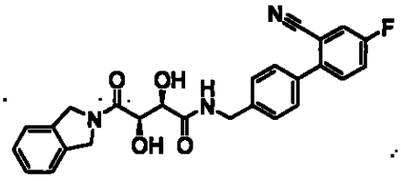
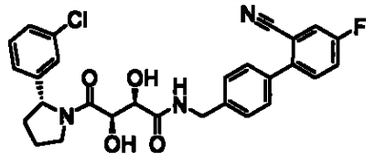
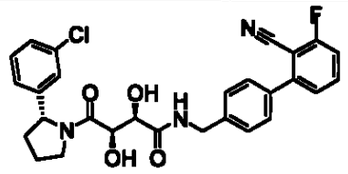
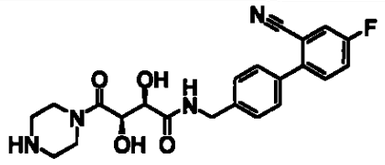
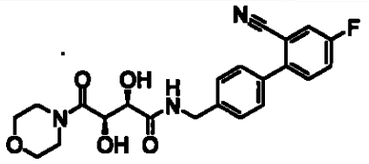
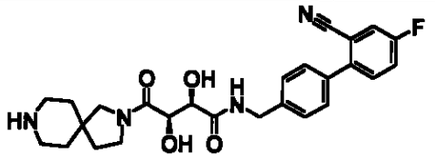
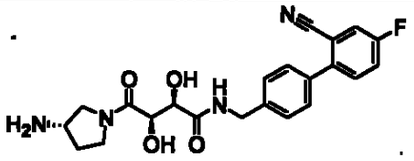
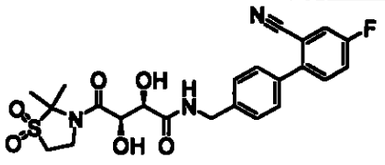
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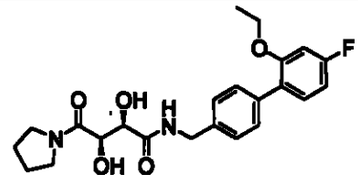
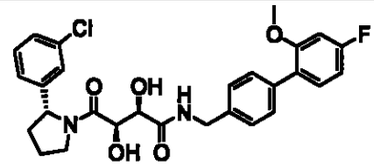
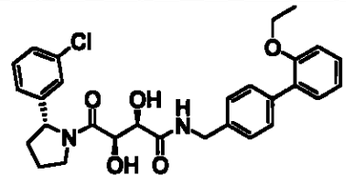
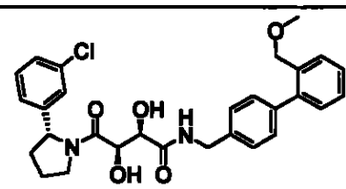
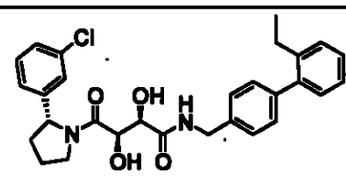
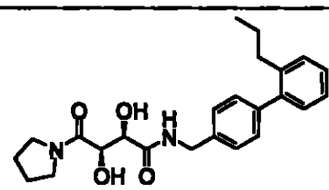
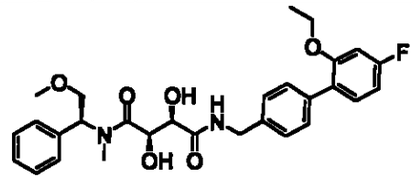
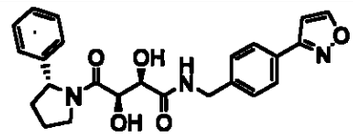
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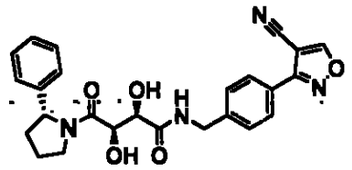
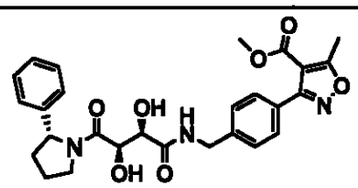
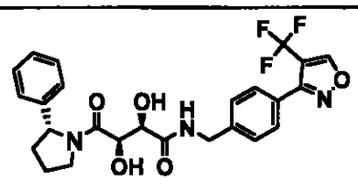
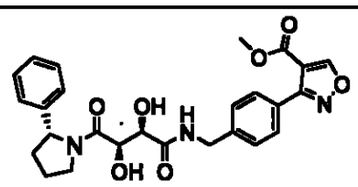
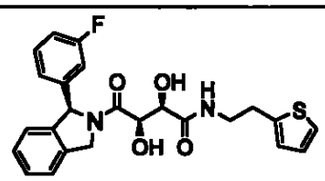
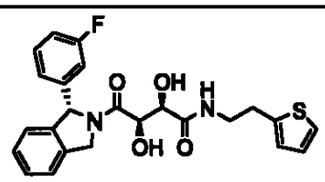
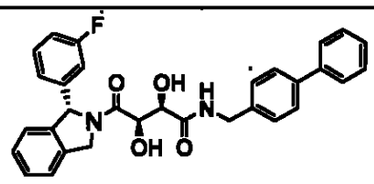
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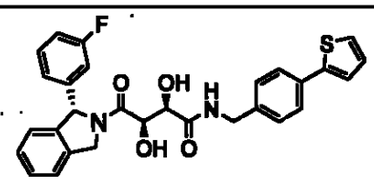
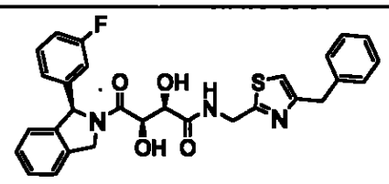
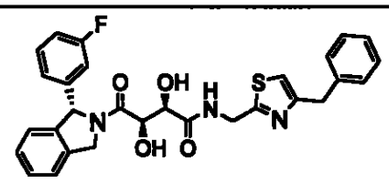
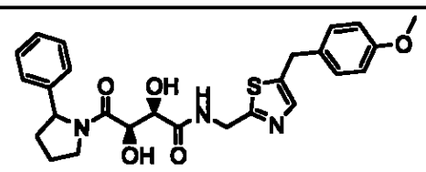
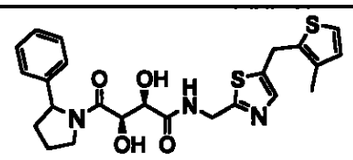
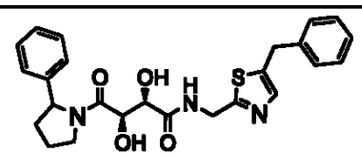
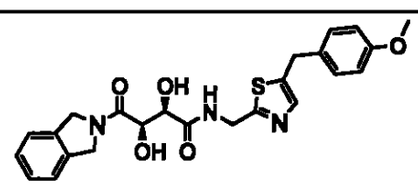
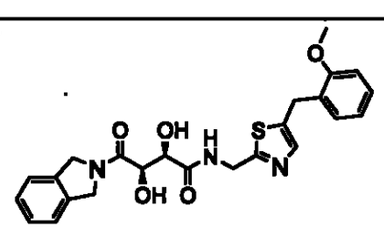
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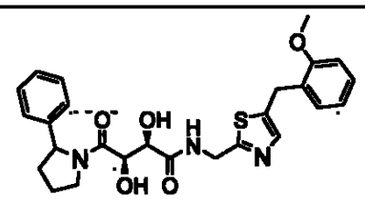
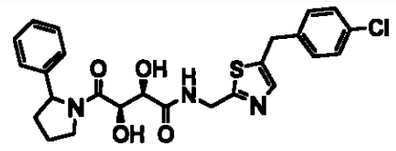
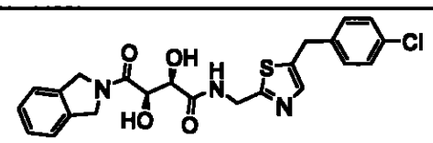
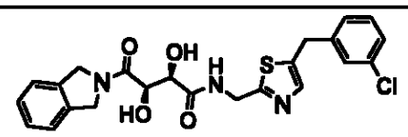
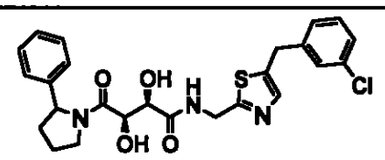
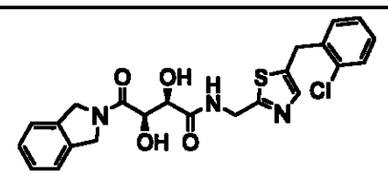
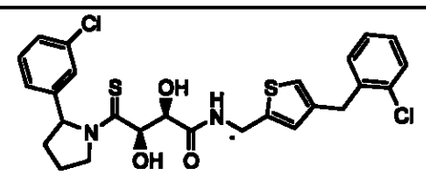
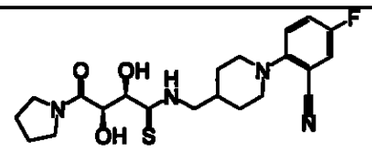
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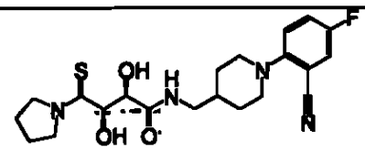
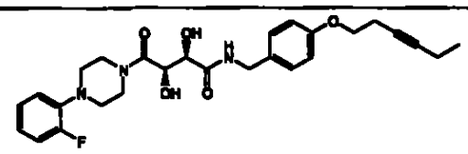
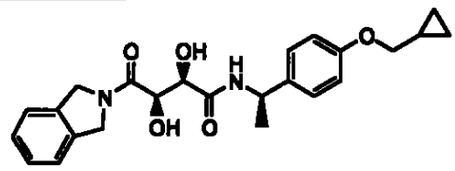
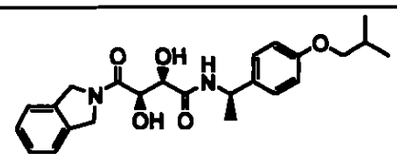
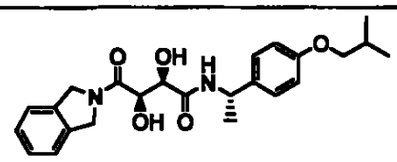
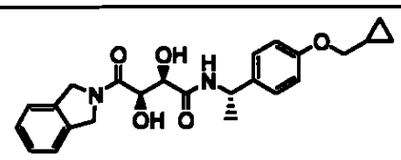
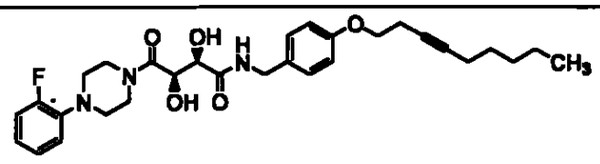
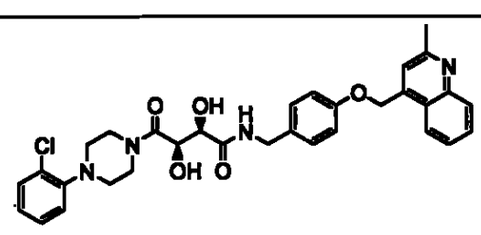
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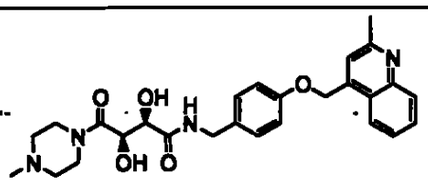
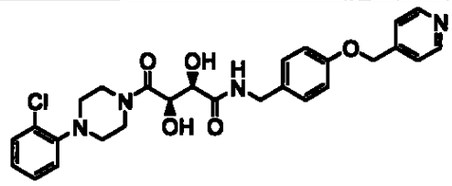
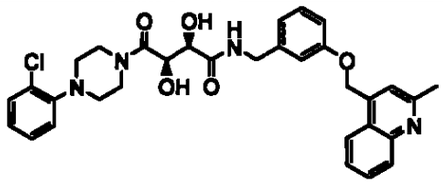
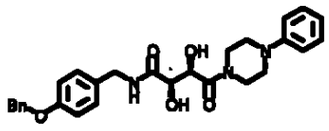
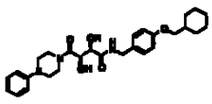
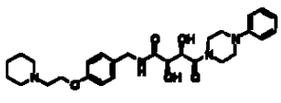
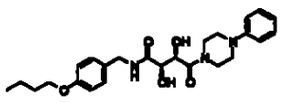
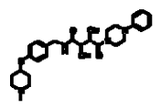
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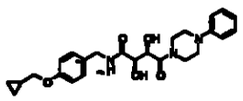
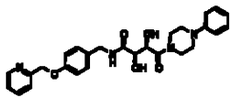
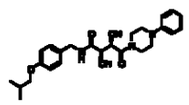
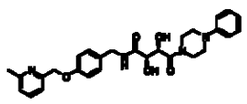
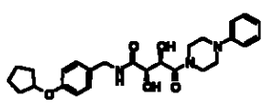
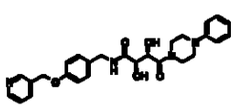
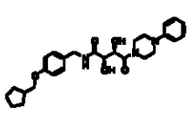
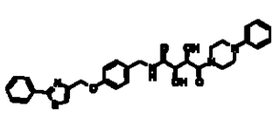
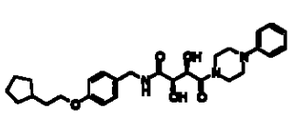
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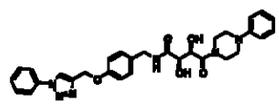
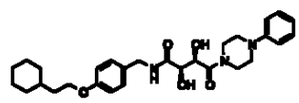
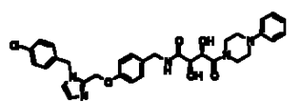
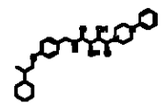
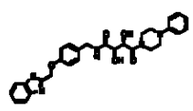
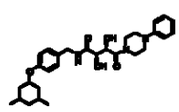
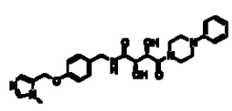
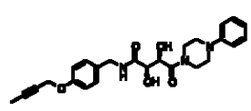
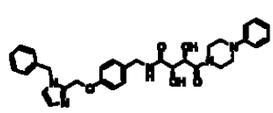
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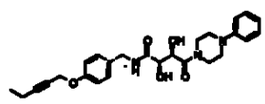
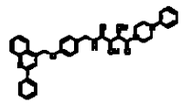
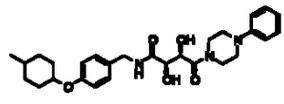
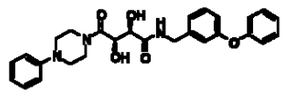
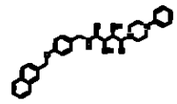
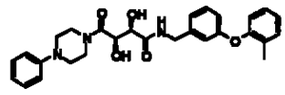
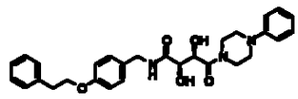
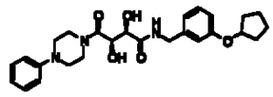
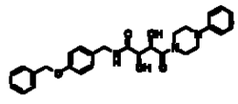
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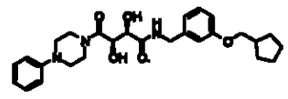
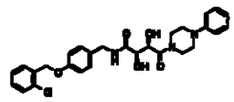
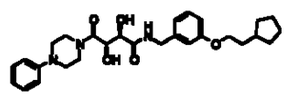
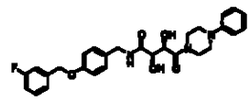
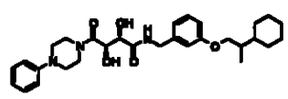
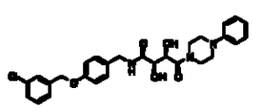
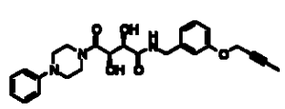
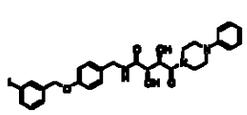
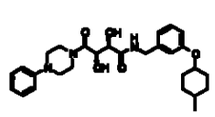
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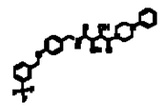
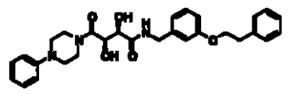
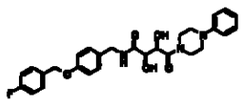
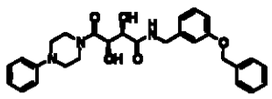
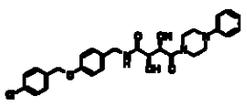
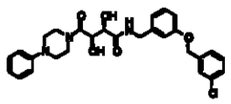
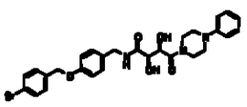
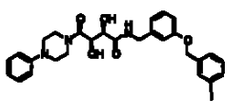
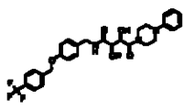
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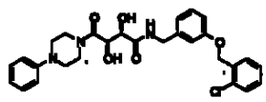
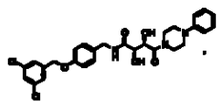
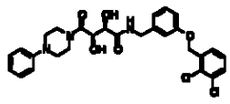
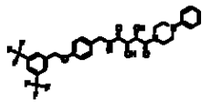
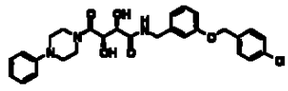
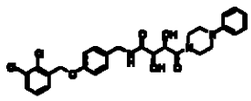
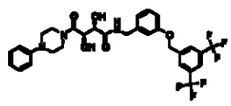
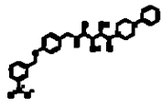
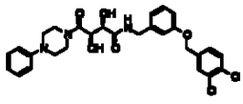
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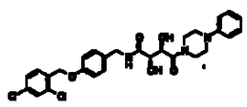
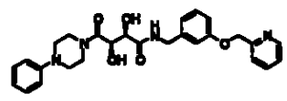
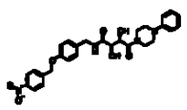
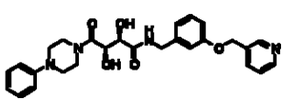
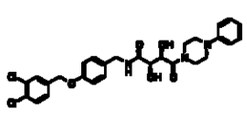
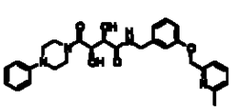
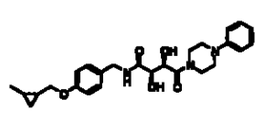
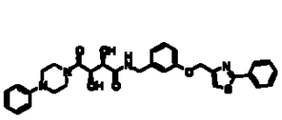
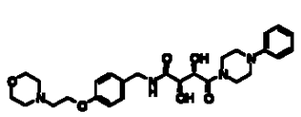
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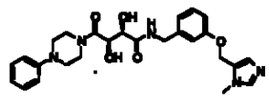
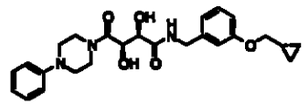
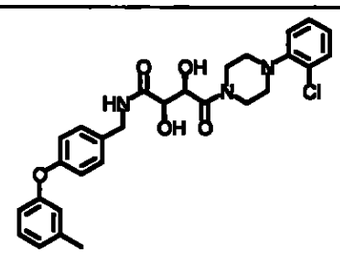
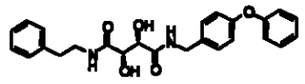
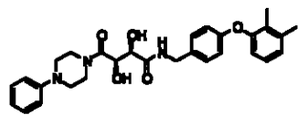
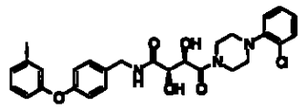
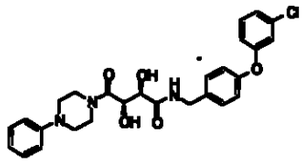
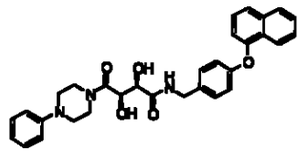
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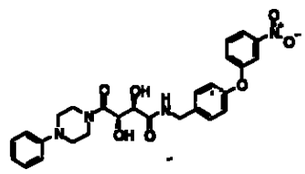
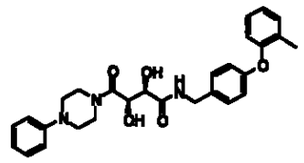
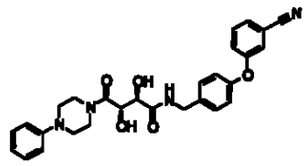
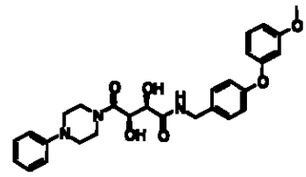
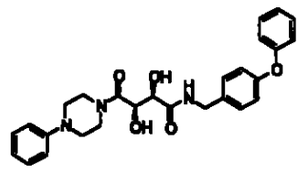
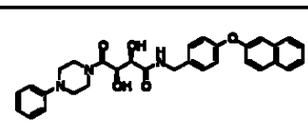
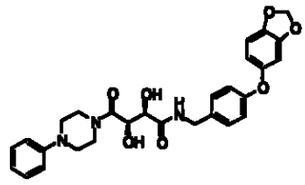
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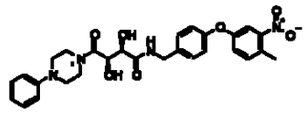
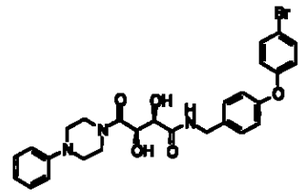
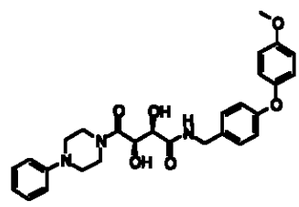
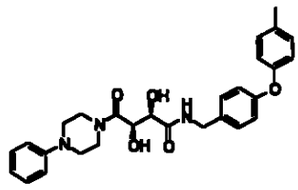
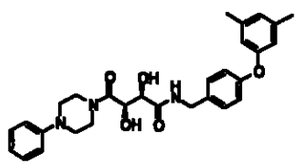
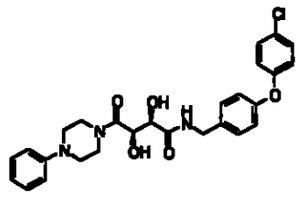
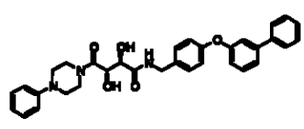
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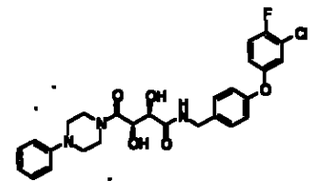
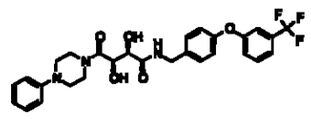
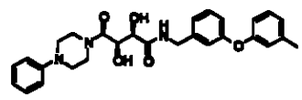
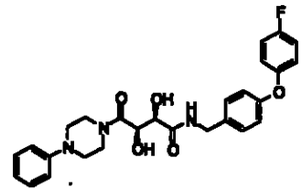
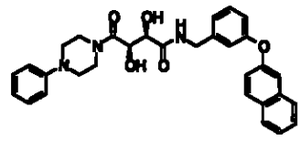
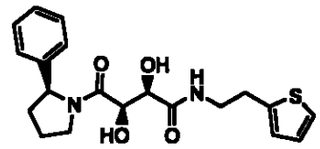
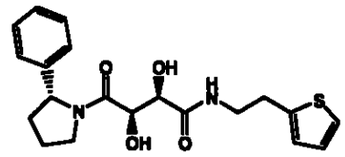
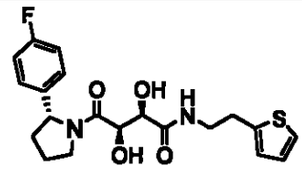
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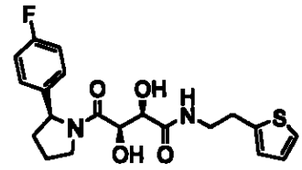
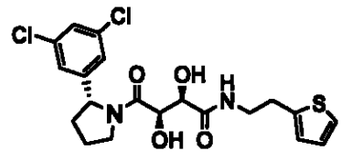
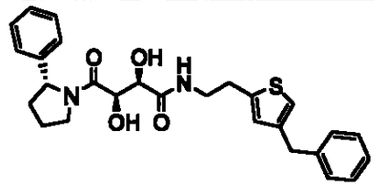
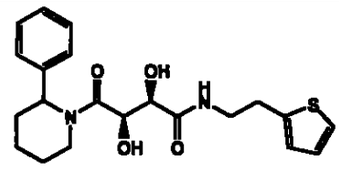
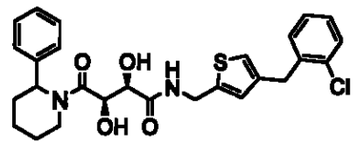
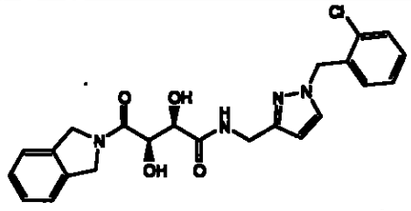
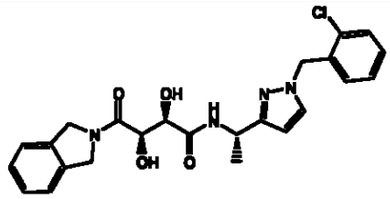
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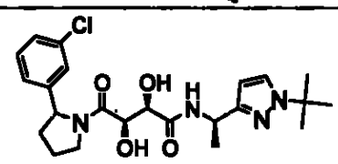
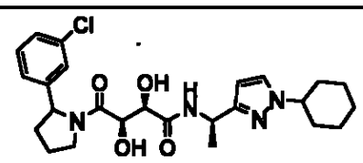
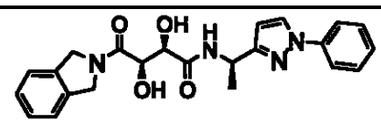
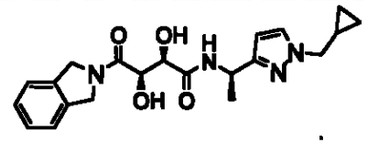
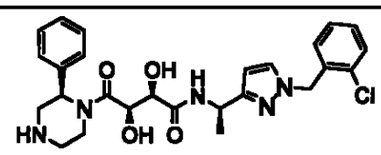
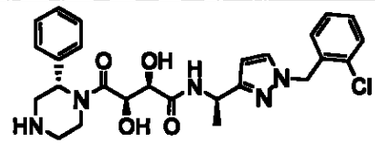
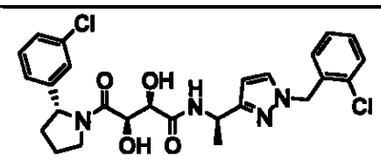
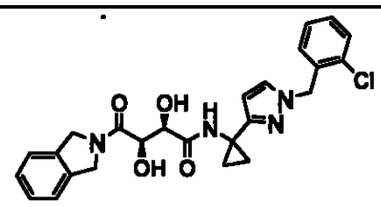
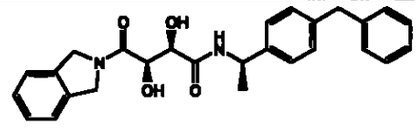
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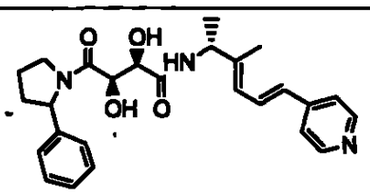
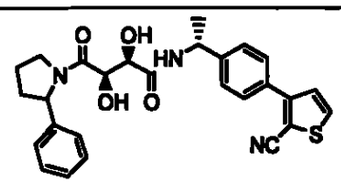
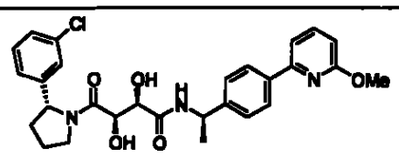
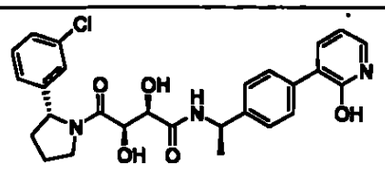
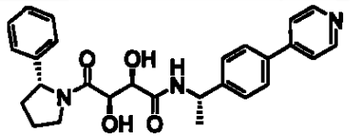
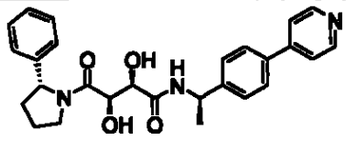
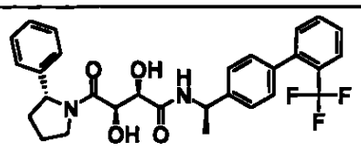
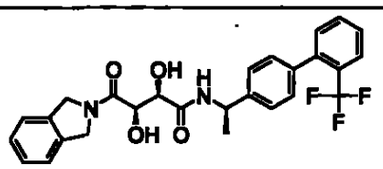
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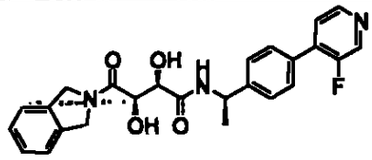
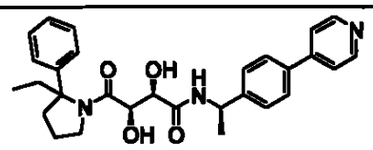
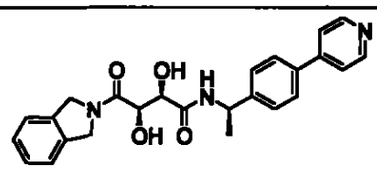
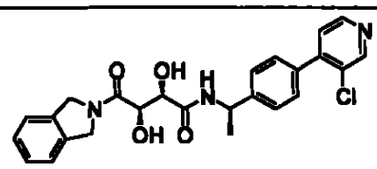
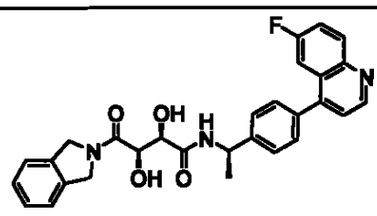
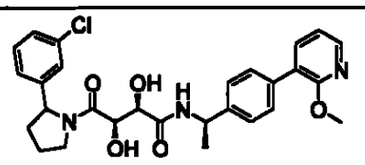
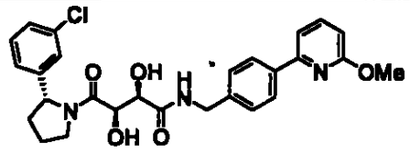
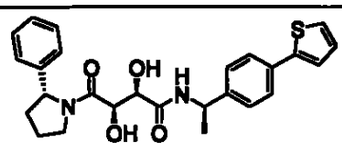
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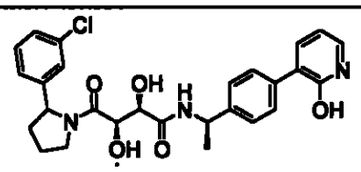
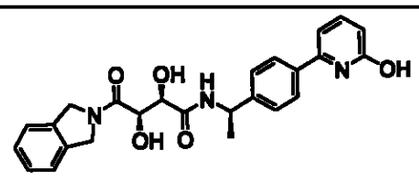
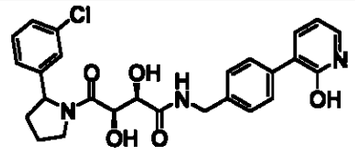
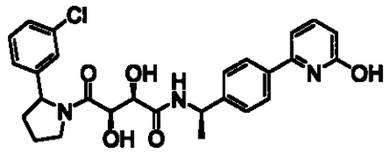
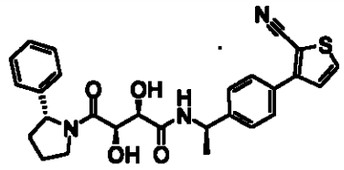
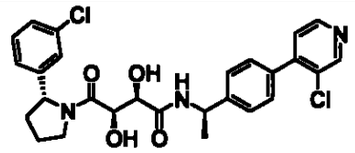
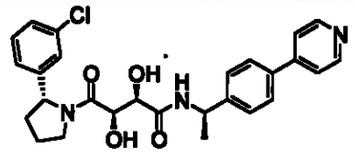
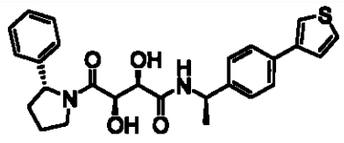
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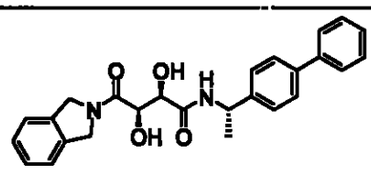
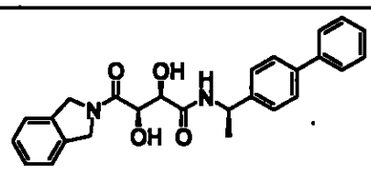
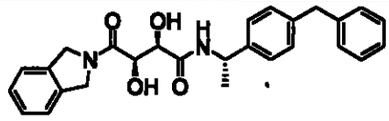
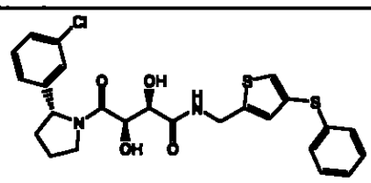
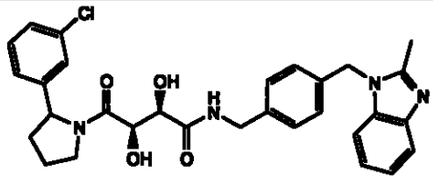
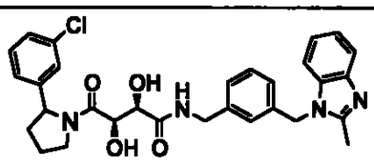
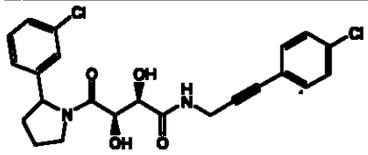
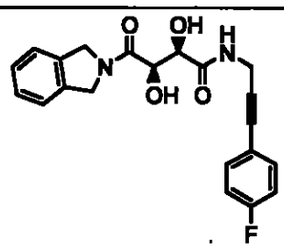
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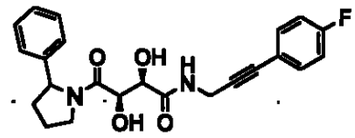
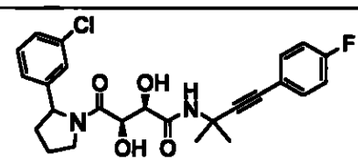
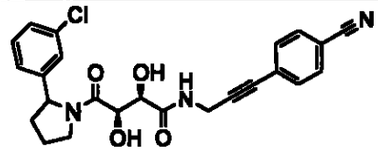
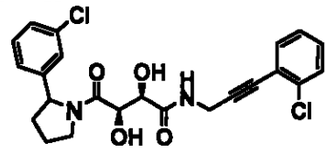
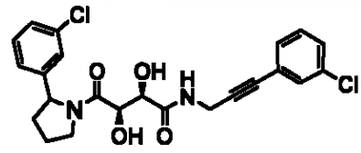
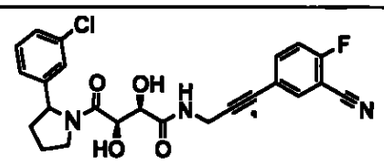
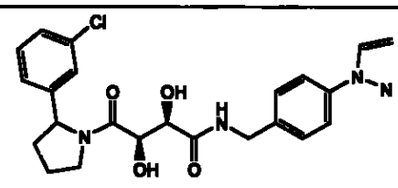
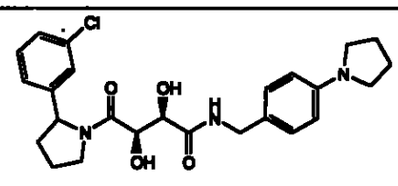
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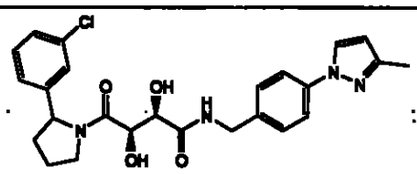
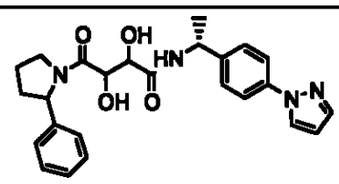
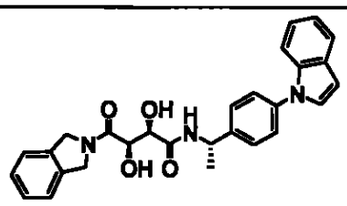
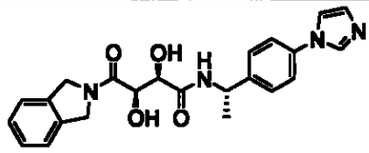
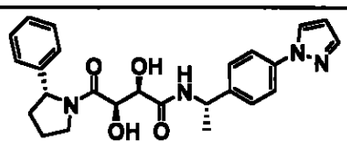
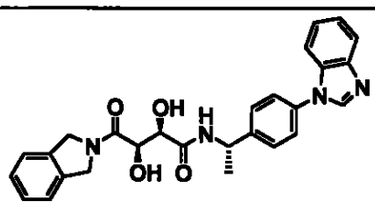
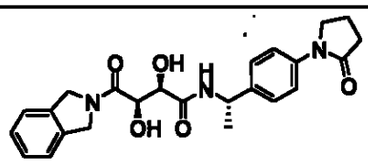
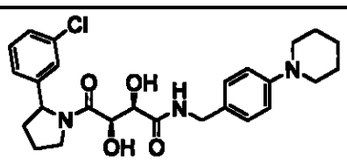
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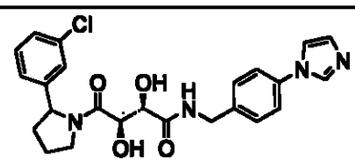
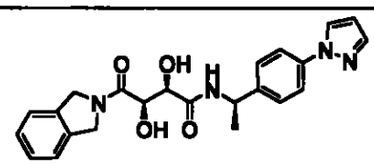
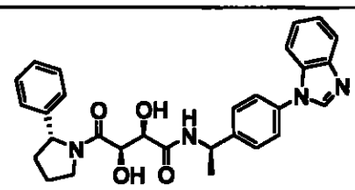
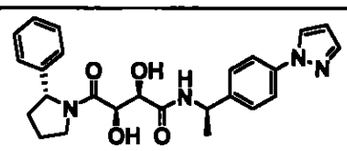
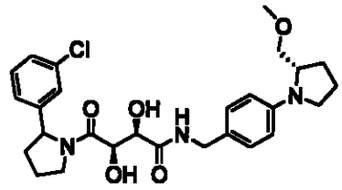
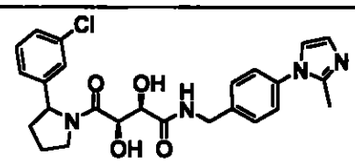
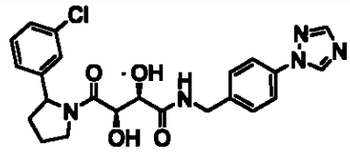
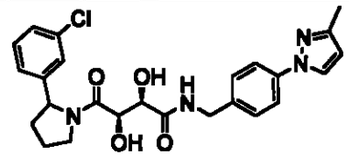
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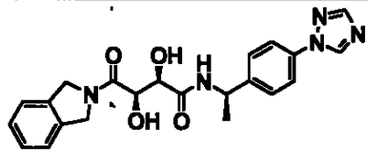
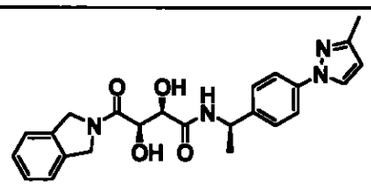
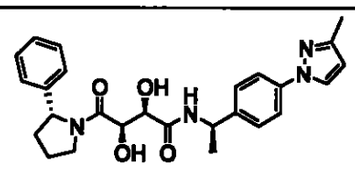
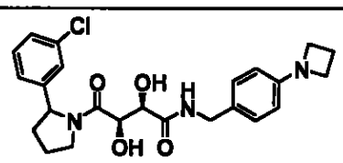
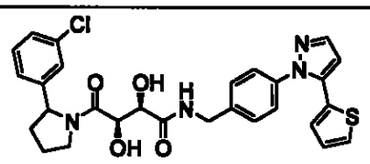
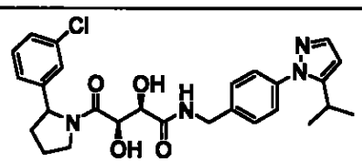
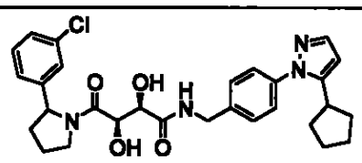
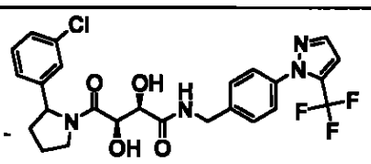
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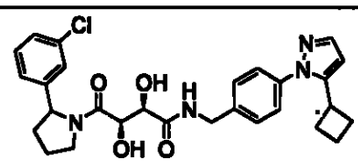
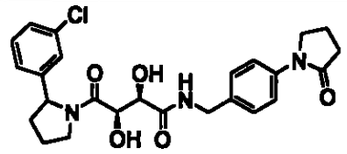
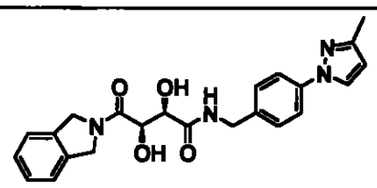
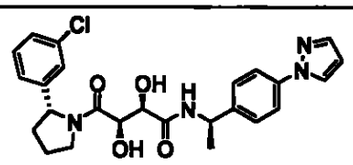
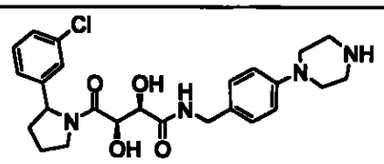
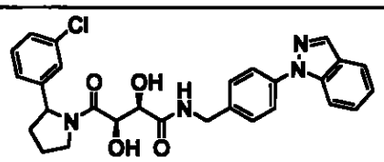
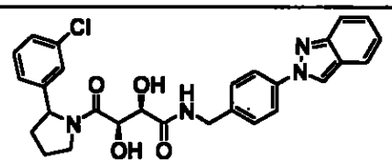
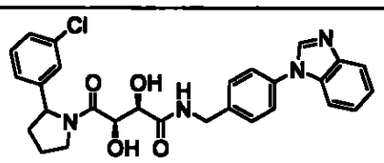
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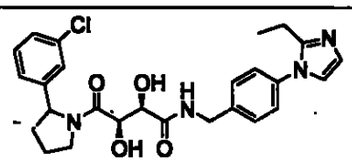
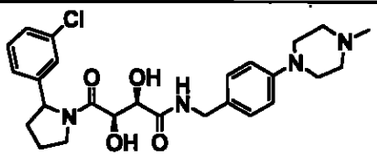
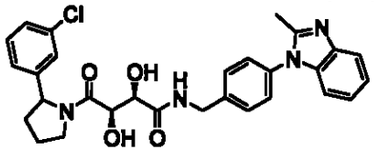
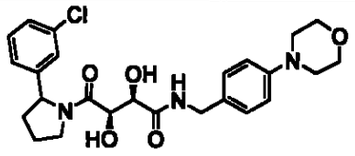
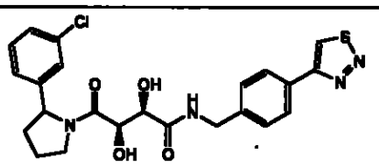
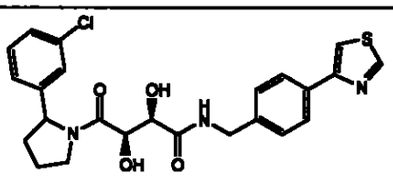
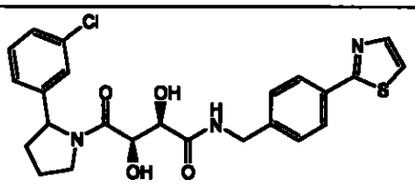
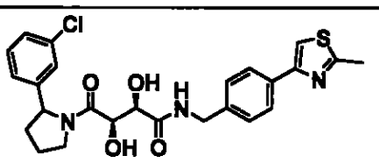
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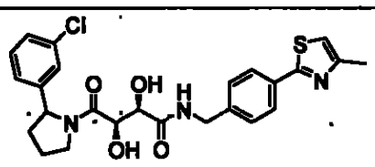
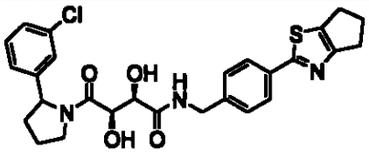
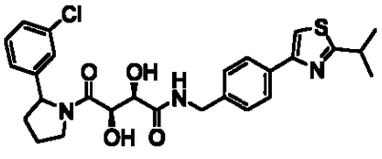
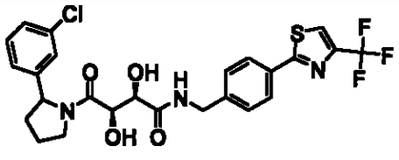
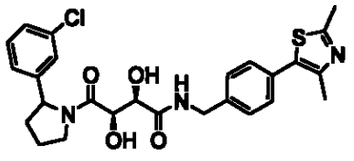
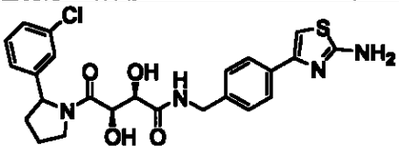
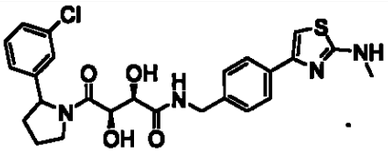
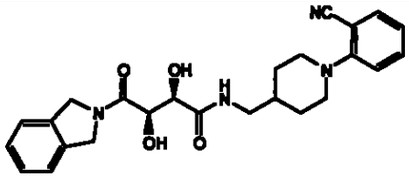
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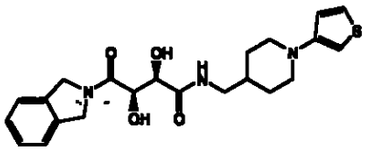
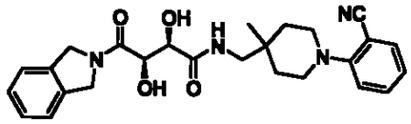
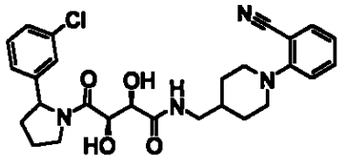
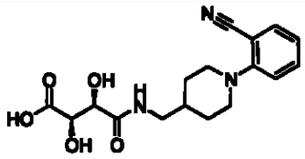
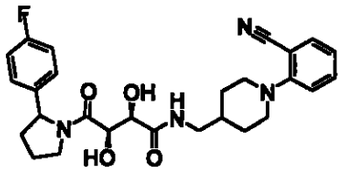
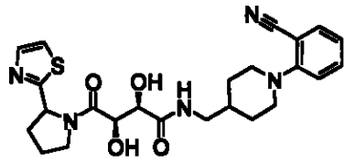
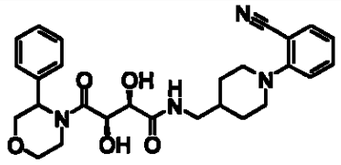
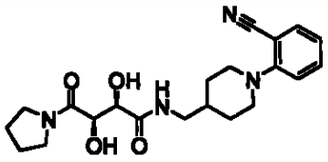
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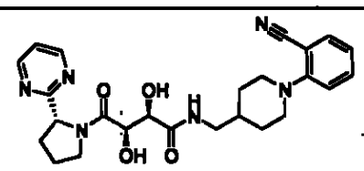
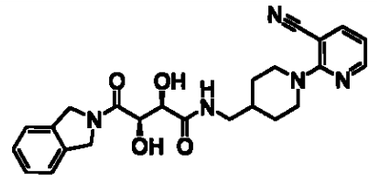
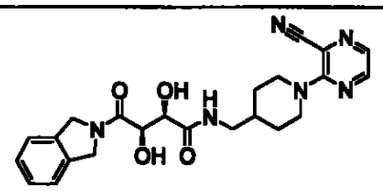
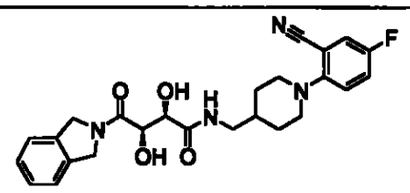
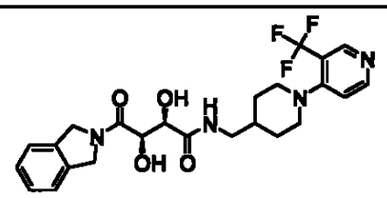
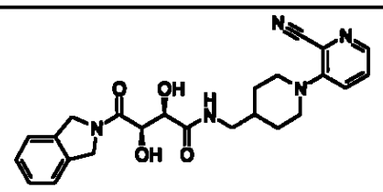
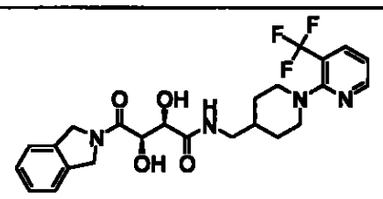
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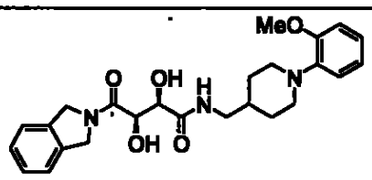
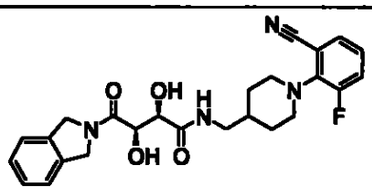
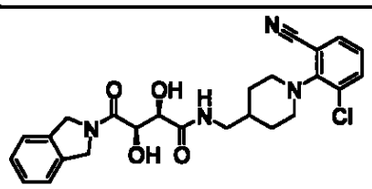
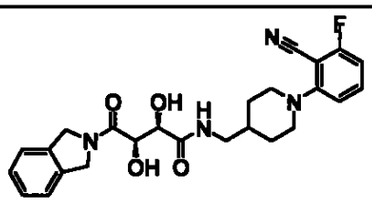
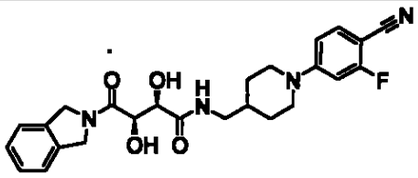
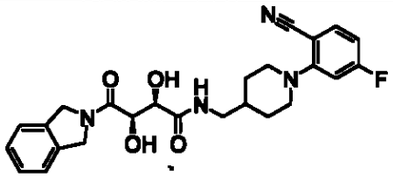
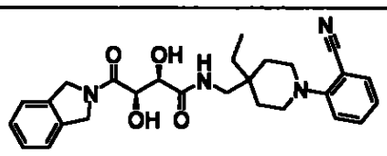
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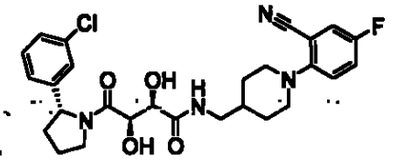
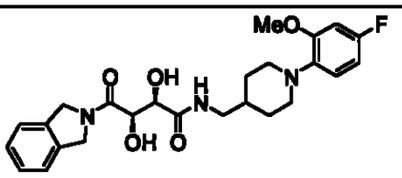
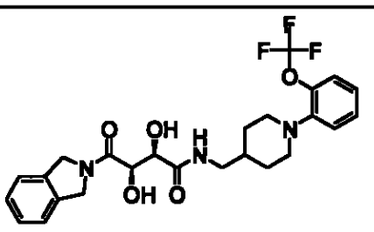
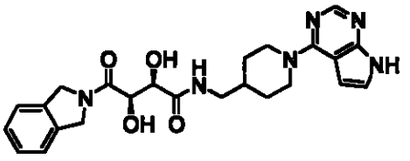
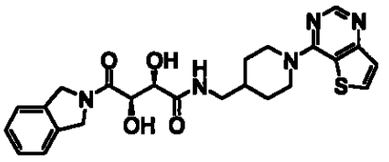
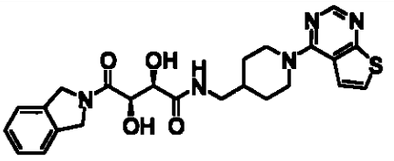
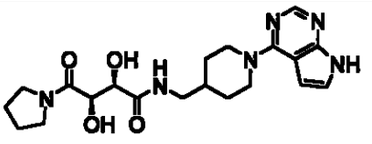
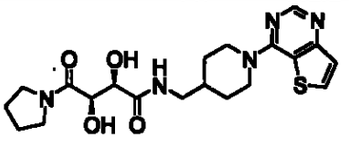
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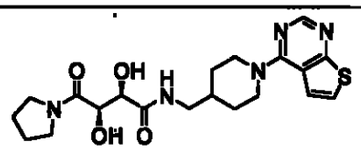
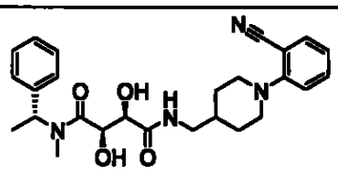
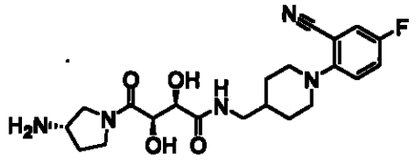
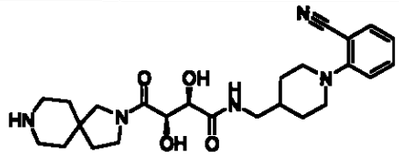
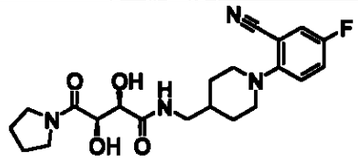
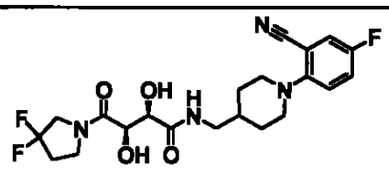
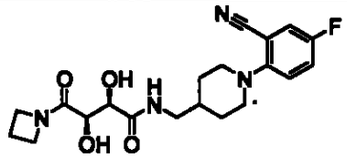
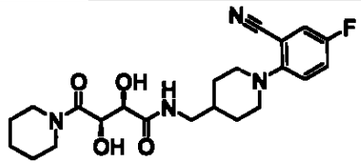
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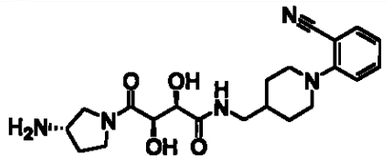
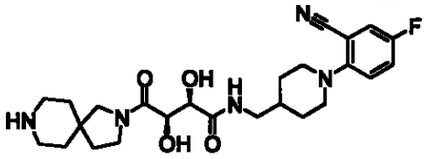
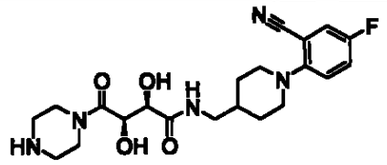
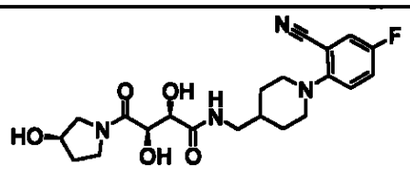
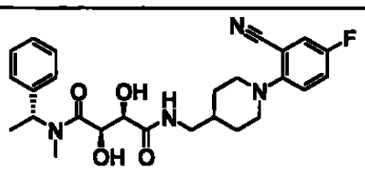
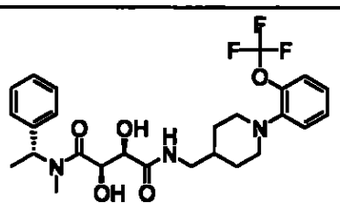
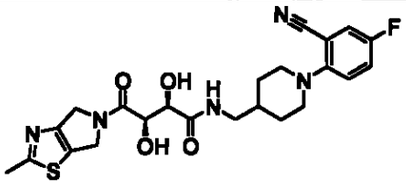
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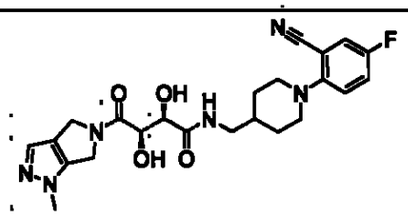
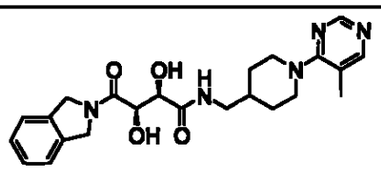
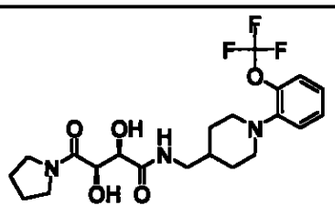
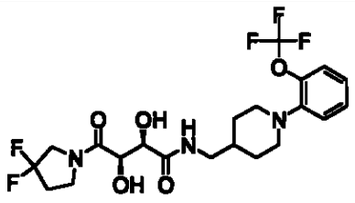
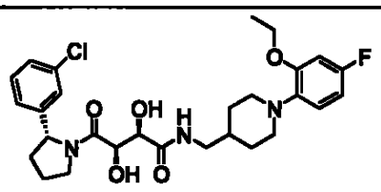
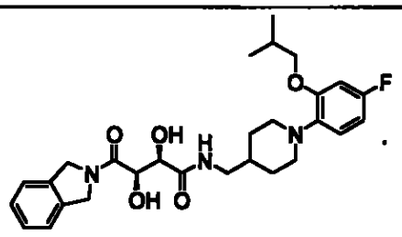
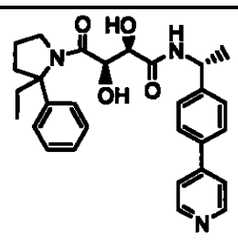
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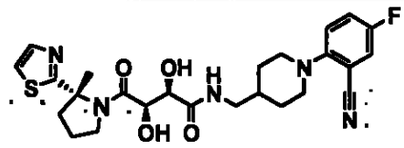
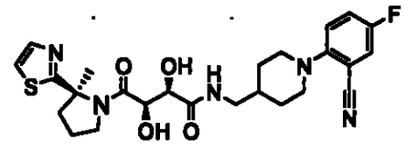
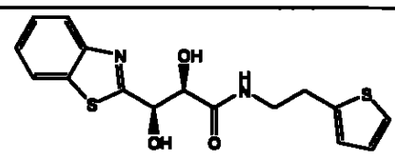
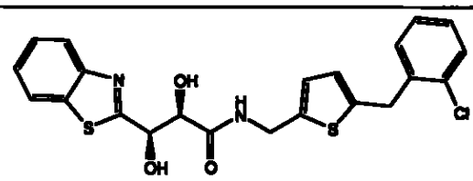
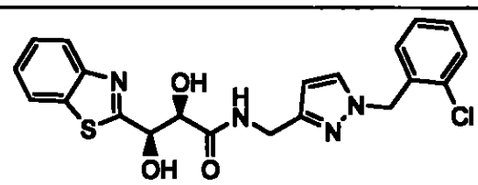
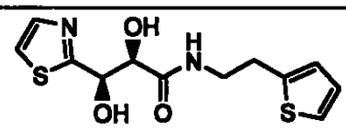
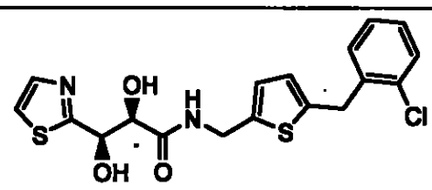
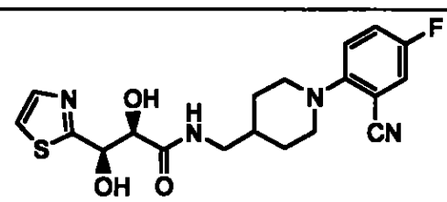
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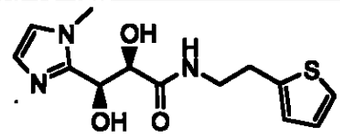
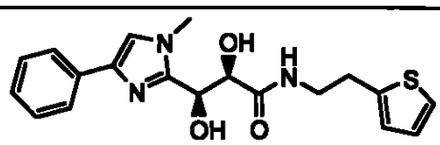
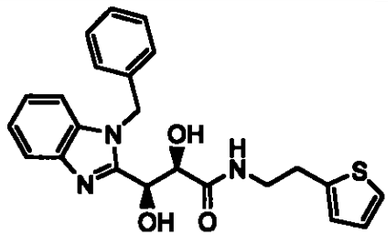
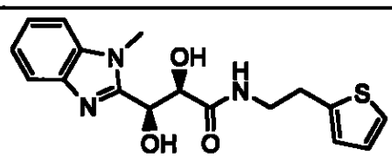
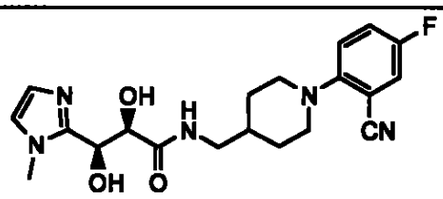
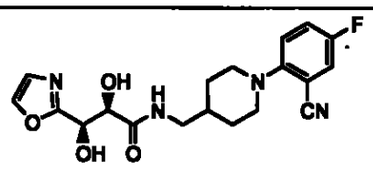
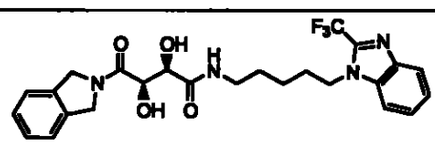
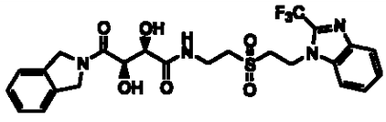
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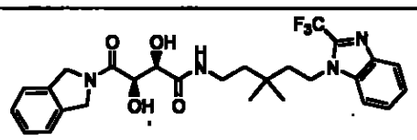
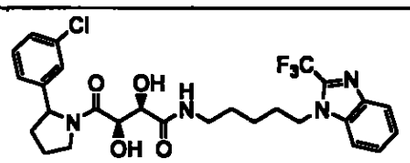
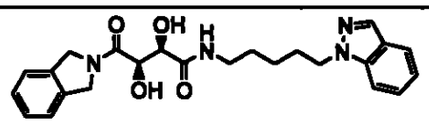
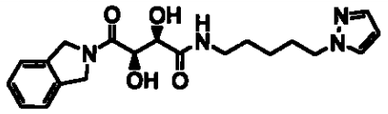
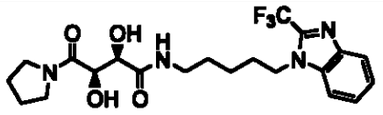
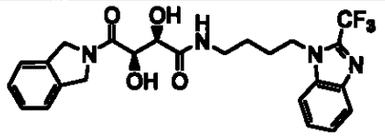
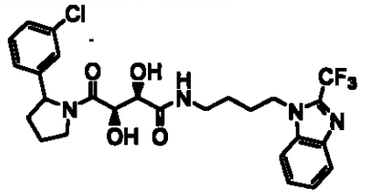
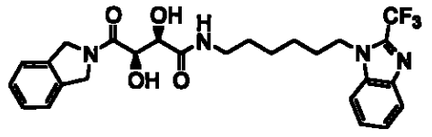
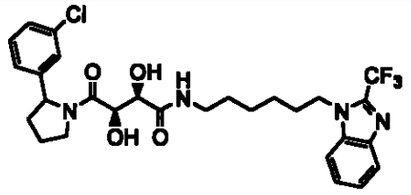
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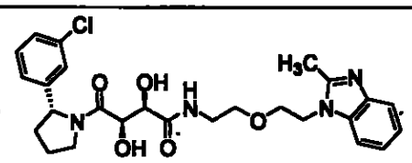
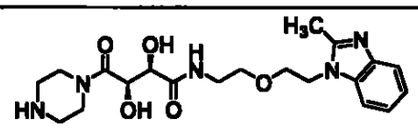
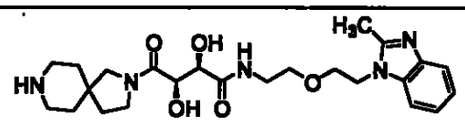
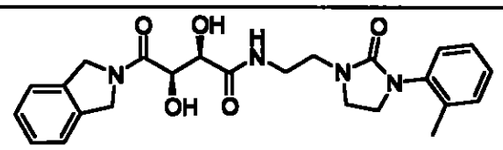
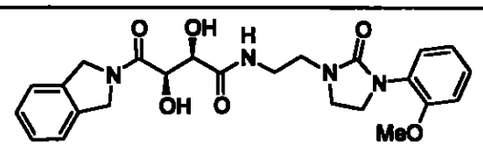
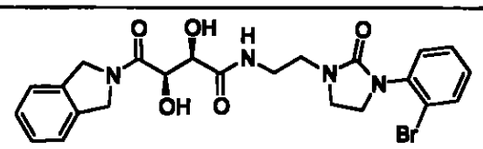
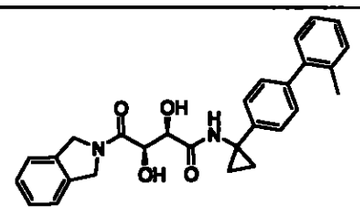
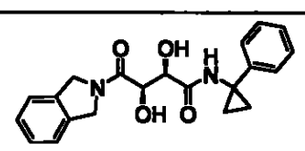
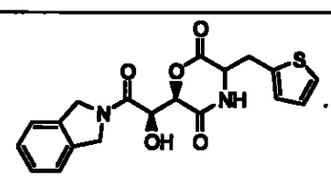
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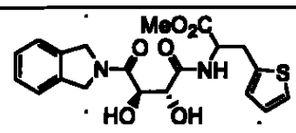
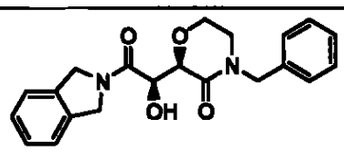
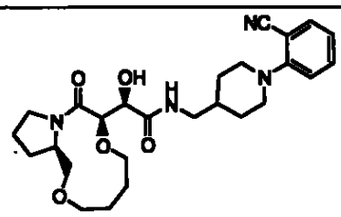
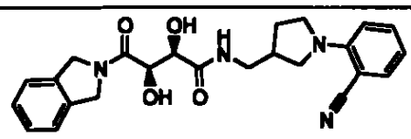
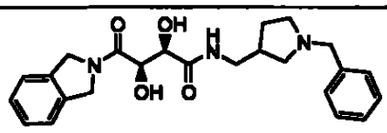
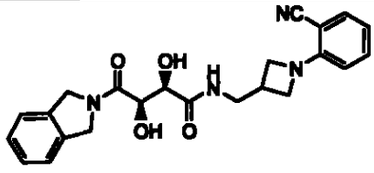
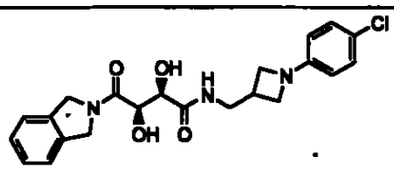
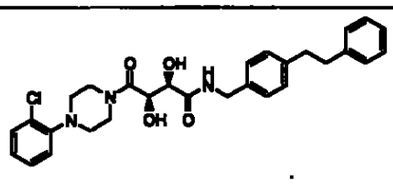
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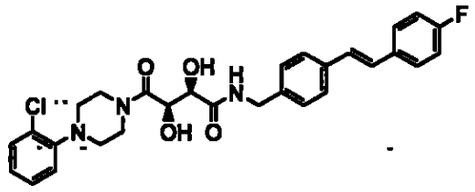
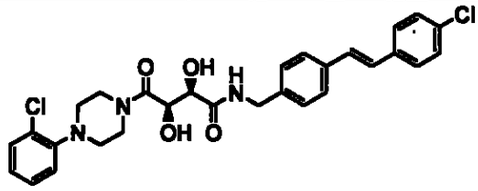
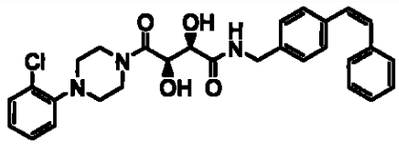
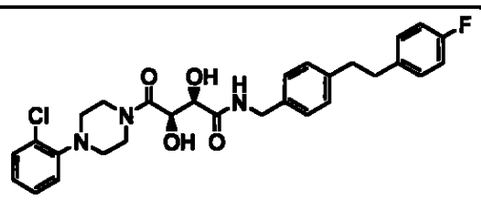
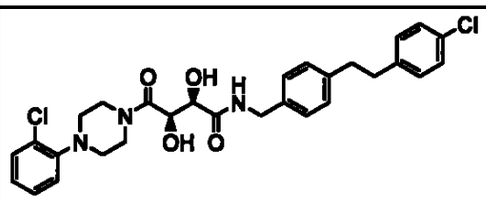
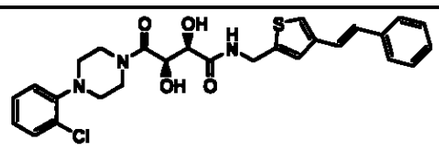
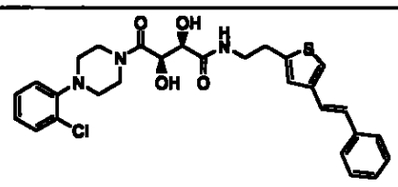
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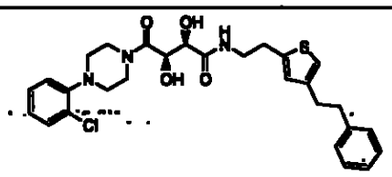
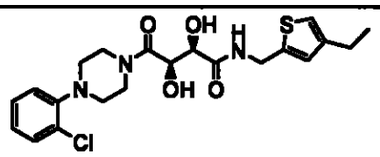
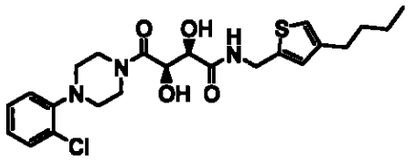
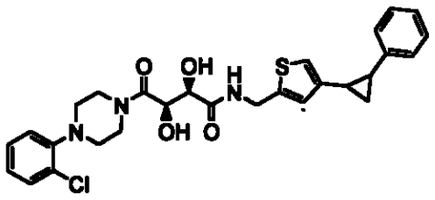
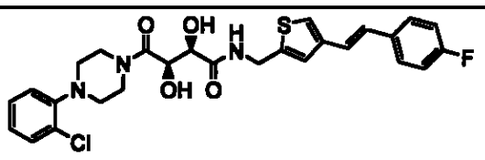
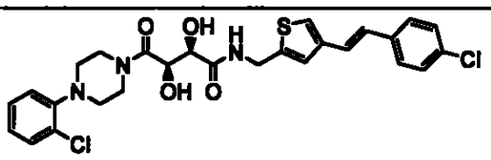
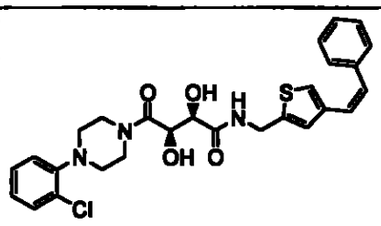
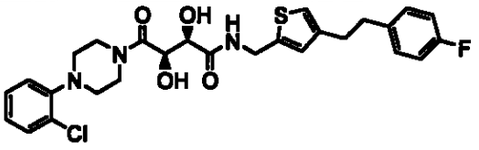
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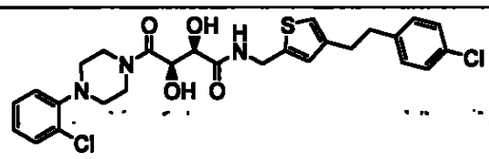
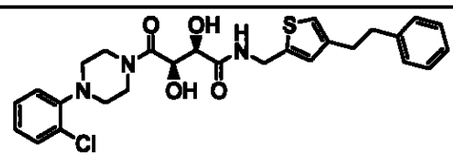
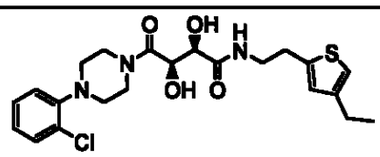
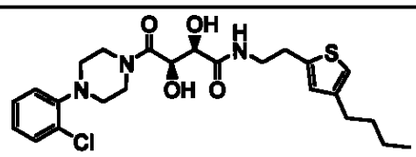
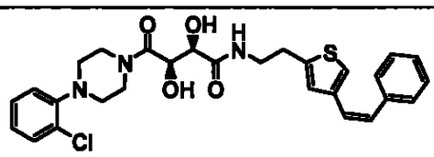
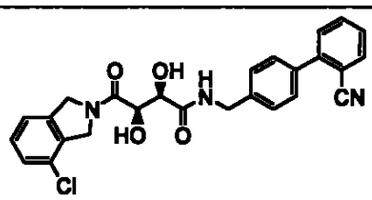
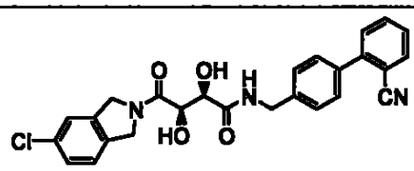
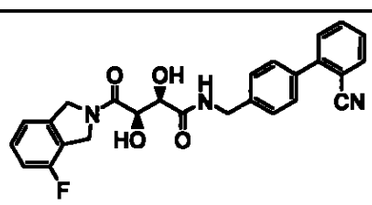
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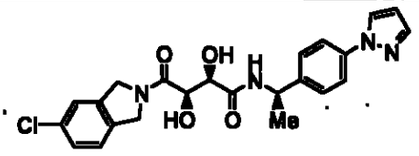
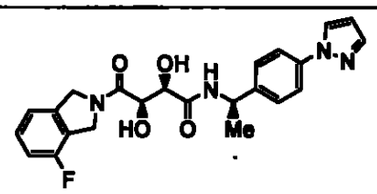
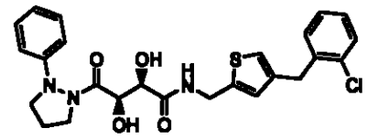
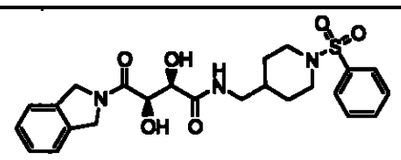
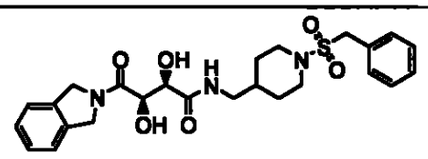
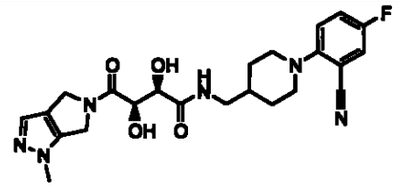
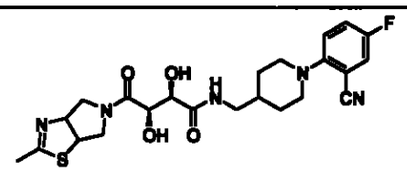
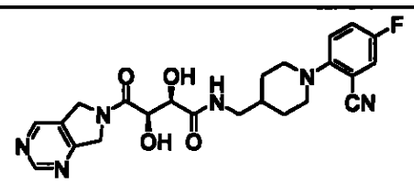
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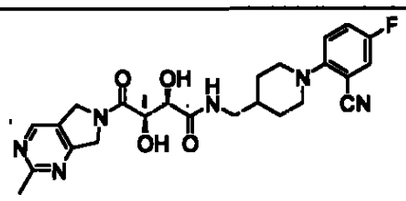
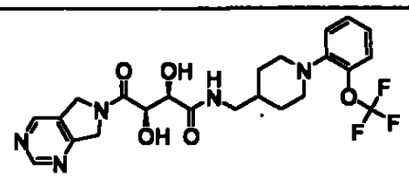
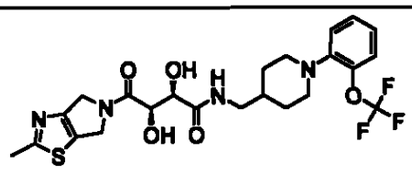
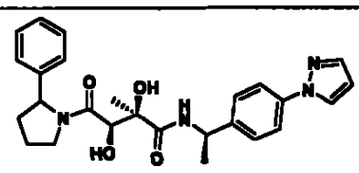
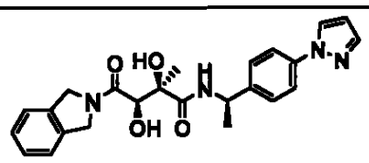
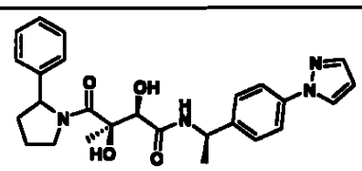
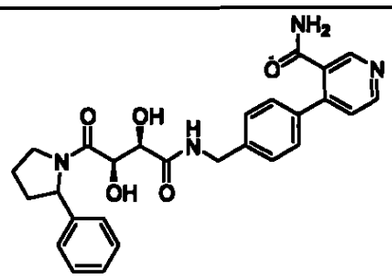
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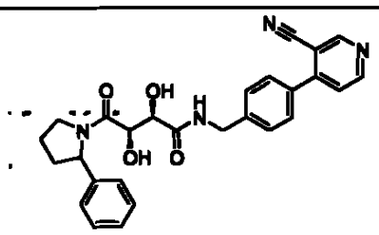
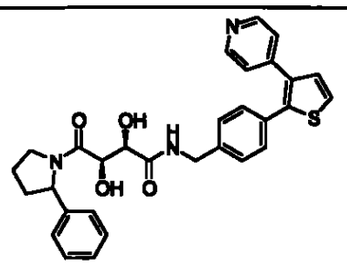
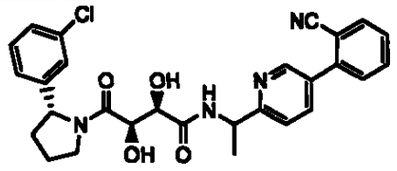
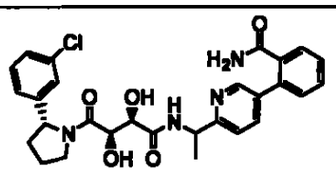
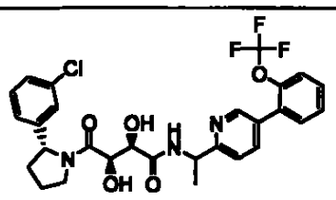
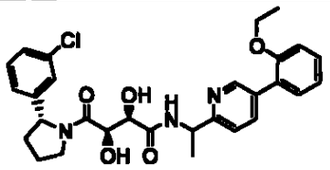
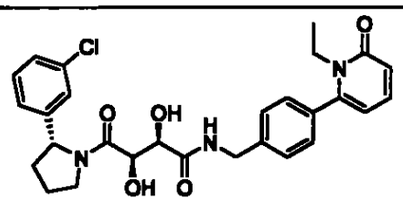
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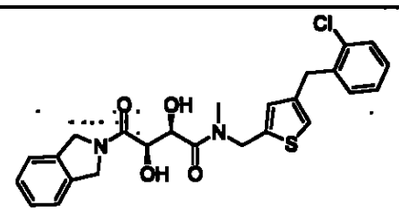
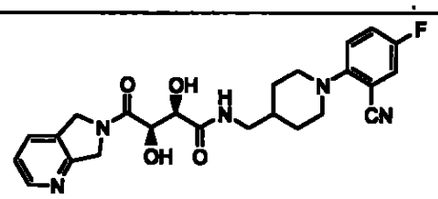
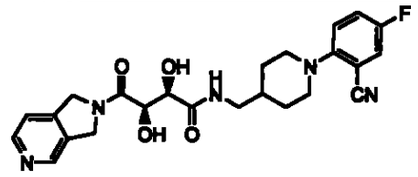
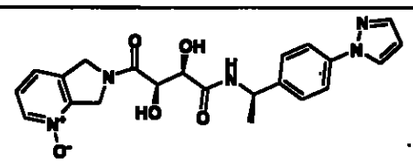
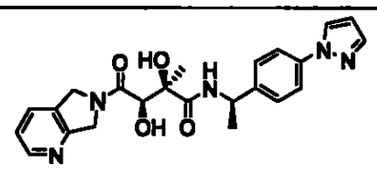
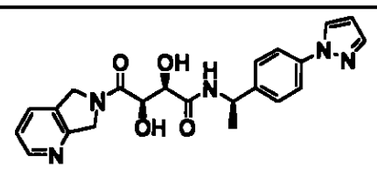
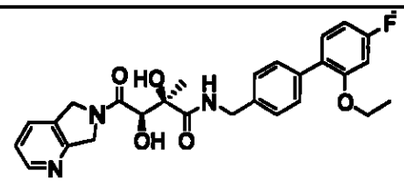
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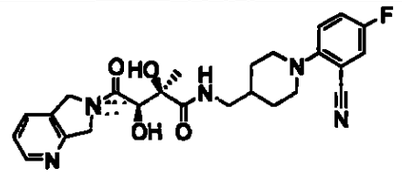
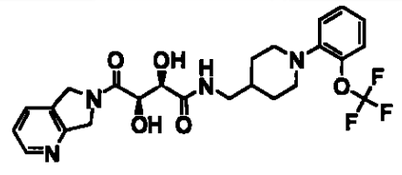
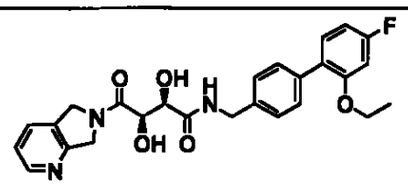
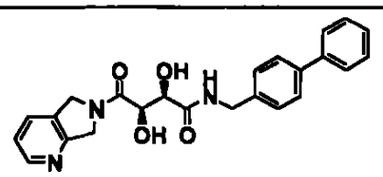
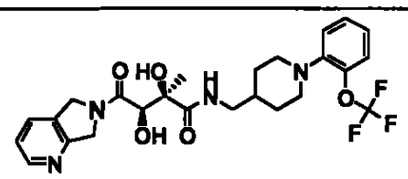
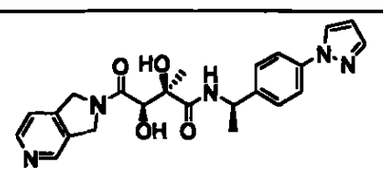
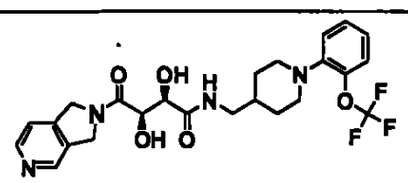
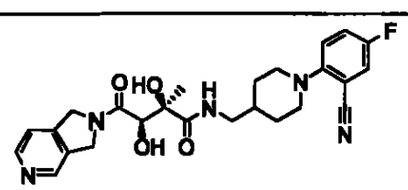
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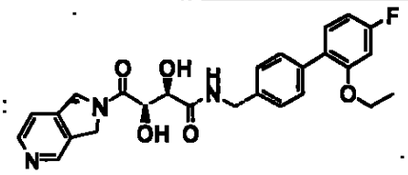
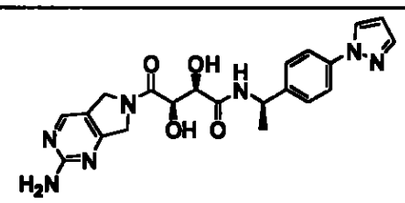
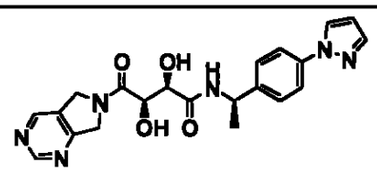
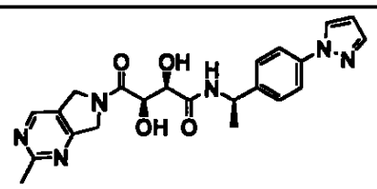
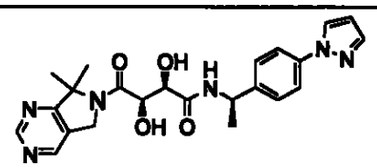
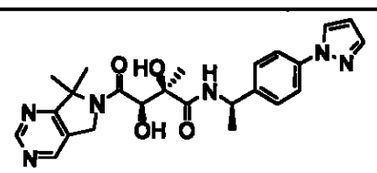
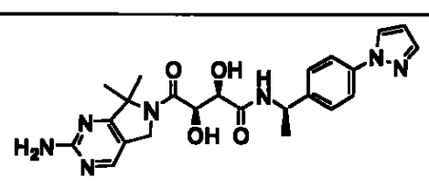
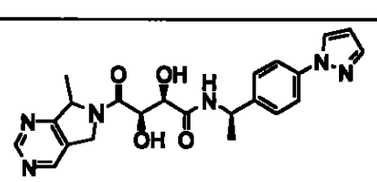
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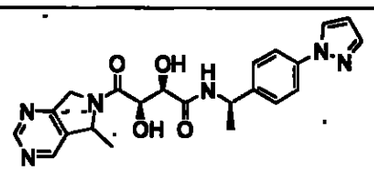
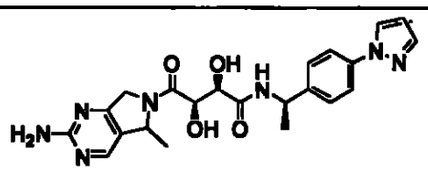
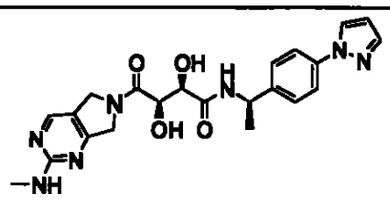
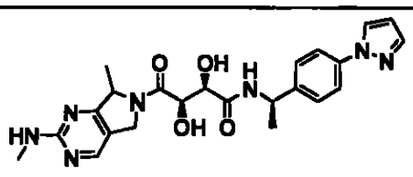
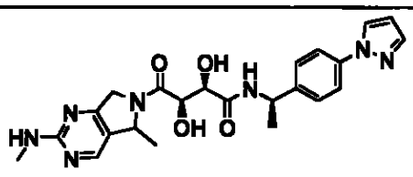
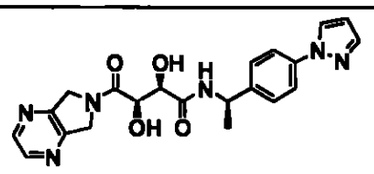
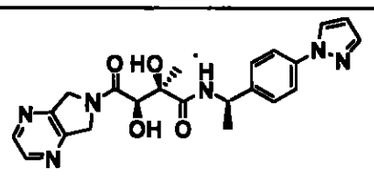
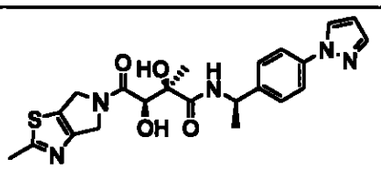
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1243A, B (diastereómeros)		
1243C		
1247A, B (diastereómeros) (?)		
1255		

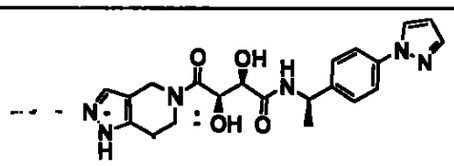
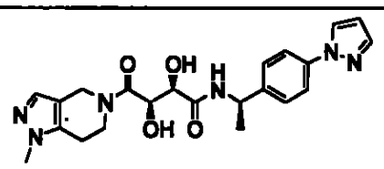
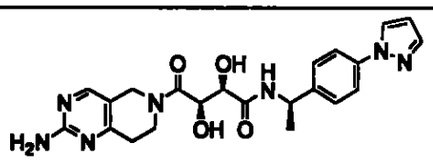
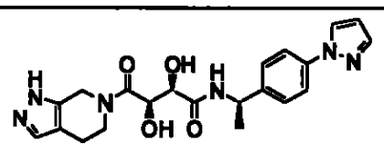
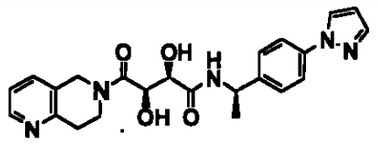
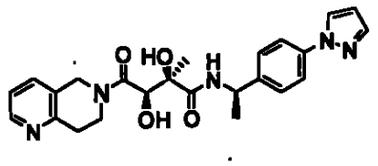
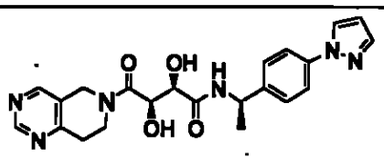
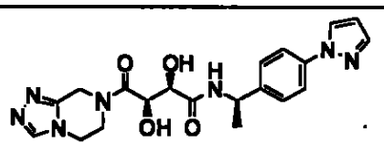
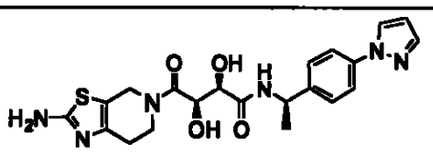
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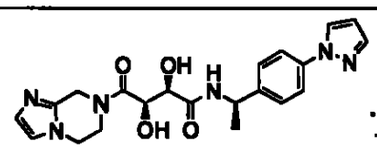
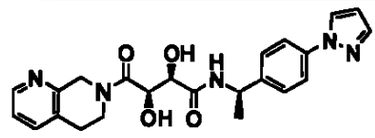
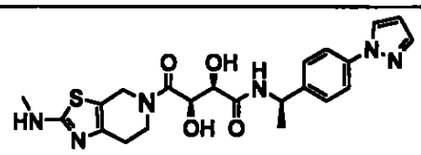
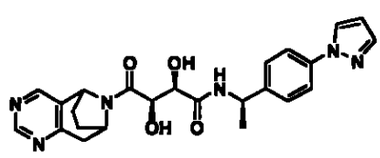
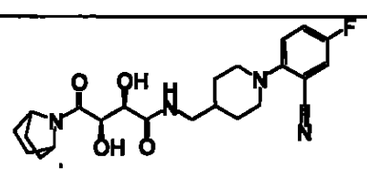
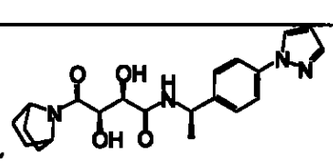
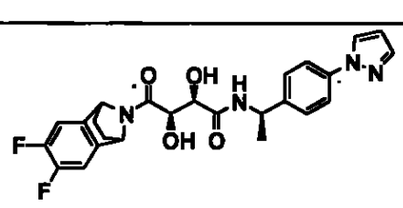
1280		
2003		B
2007		A
2030		B
2031		A
2032		A
2033		A

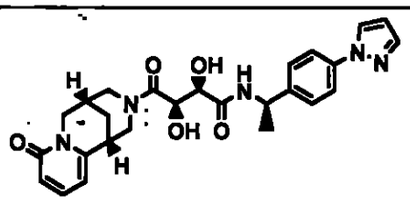
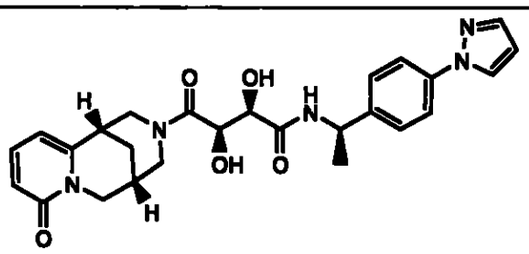
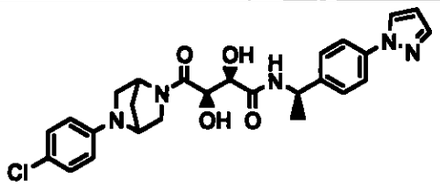
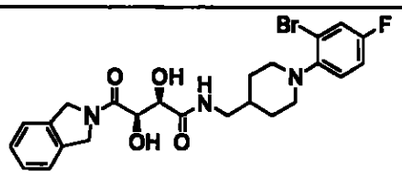
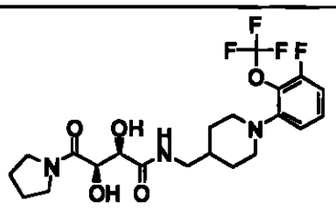
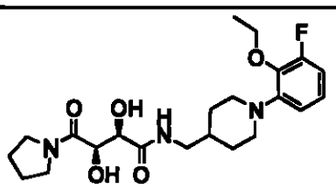
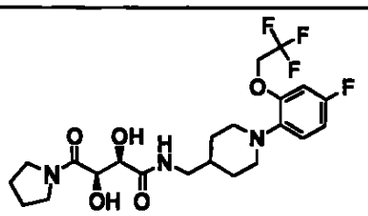
2034		B
2035		A
2036		A
2037		B
2038		B
2039		A
2040		A
2041		B

2042		A
2043		A
2044		A
2045		C
2046		C
2047		C
2048		B
2049		B

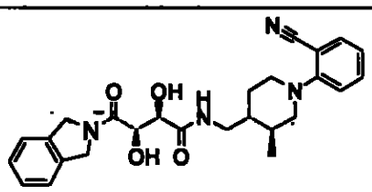
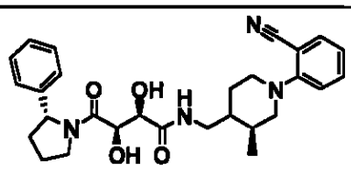
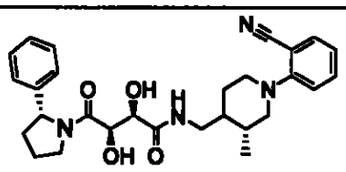
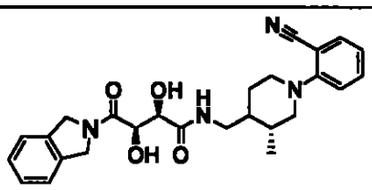
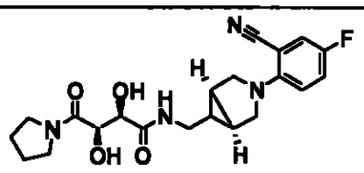
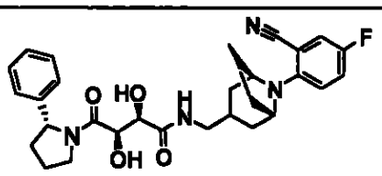
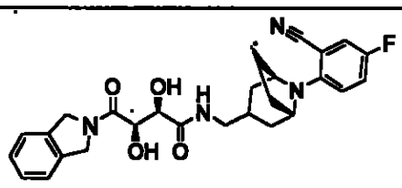
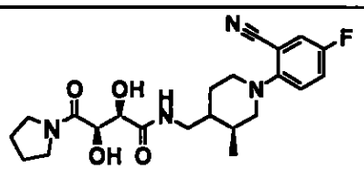
2050		B
2051		B
2052		A
2053		B
2054		A
2055		A
2056		A
2057		A

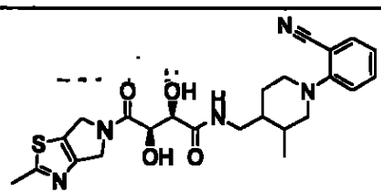
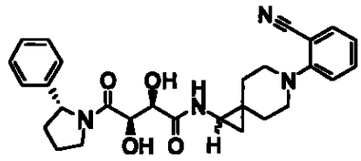
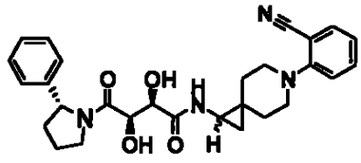
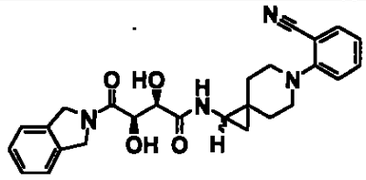
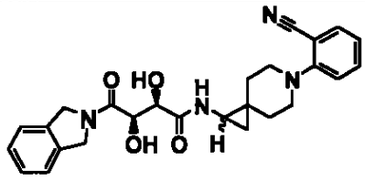
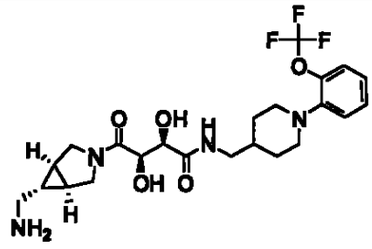
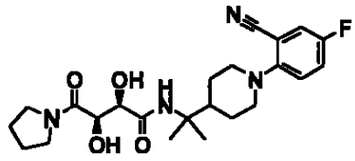
2073		B
2074		B
2075		B
2076		B
2077		B
2078		C
2079		C
2080		C
2081		A

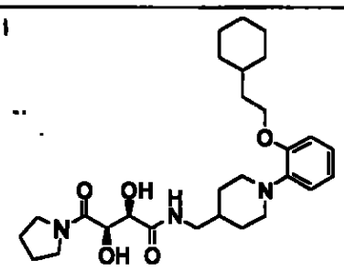
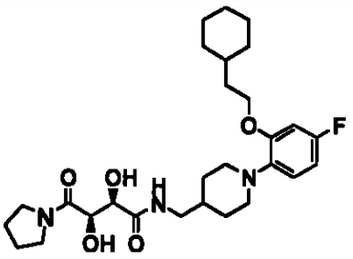
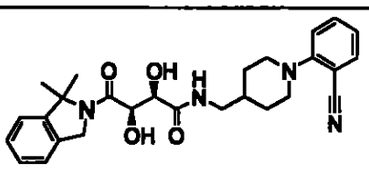
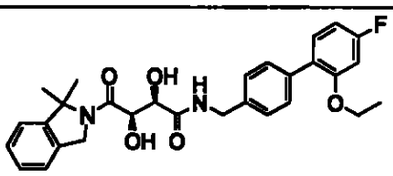
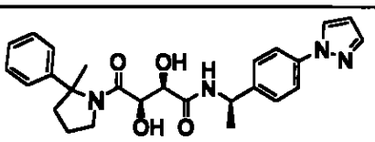
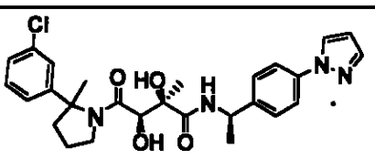
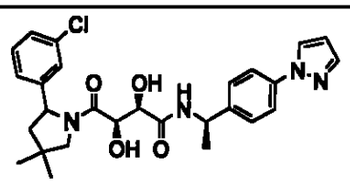
2082		C
2083		B
2084		B
2093		D
2094		D
2095		C
2096		C

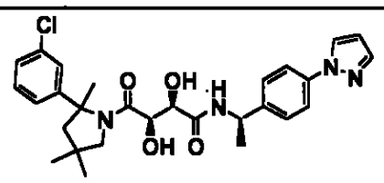
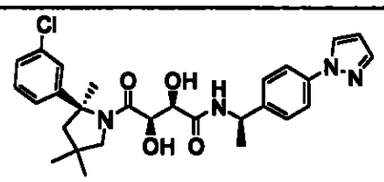
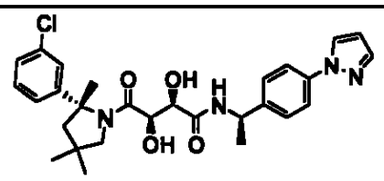
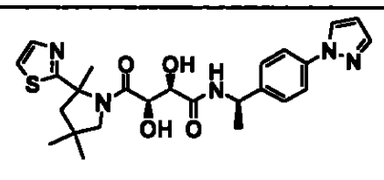
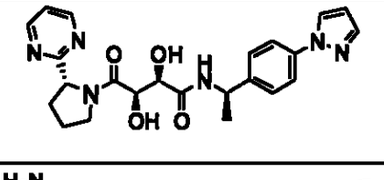
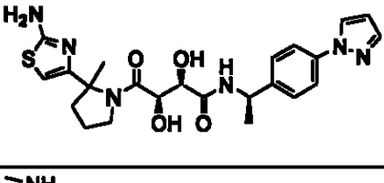
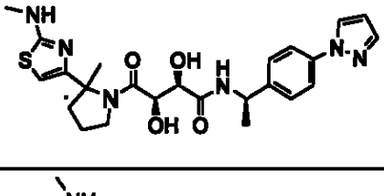
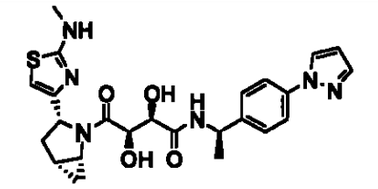
2097		C
2098		C
2099		C
2139		A
2140		D
2141		D
2142		B

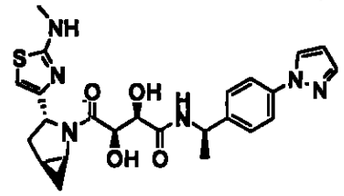
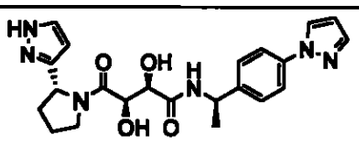
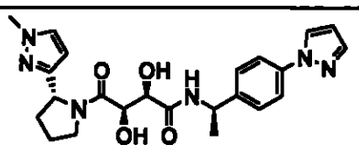
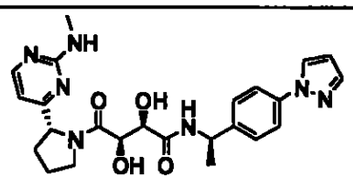
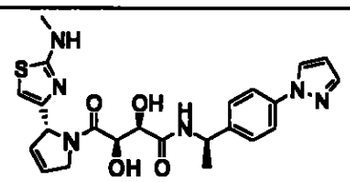
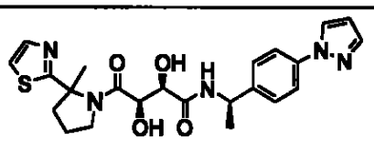
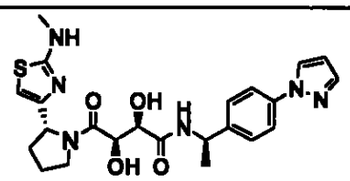
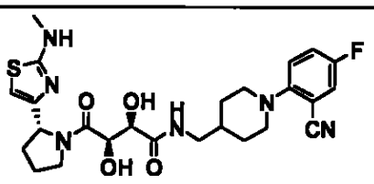
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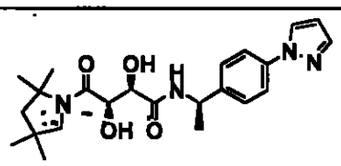
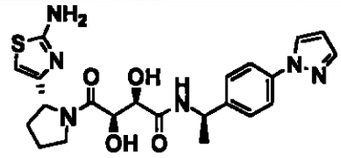
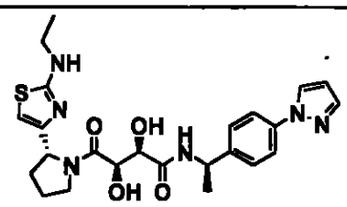
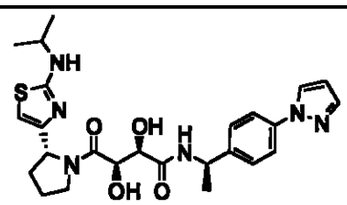
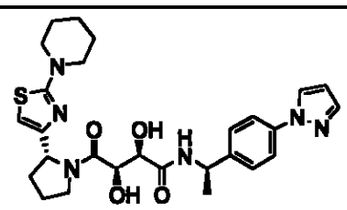
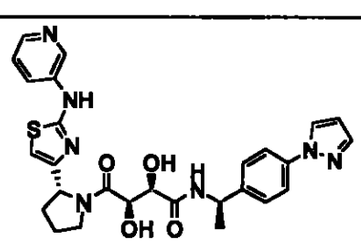
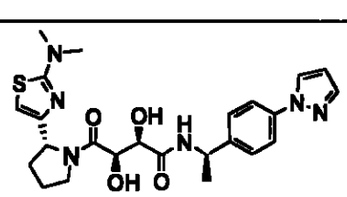
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2144		A
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2146		C
2147		C
2148		C
2149		C
2150		B

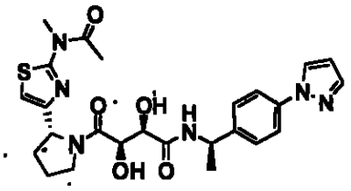
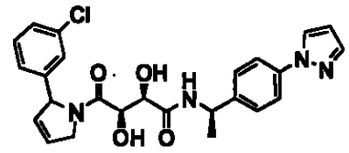
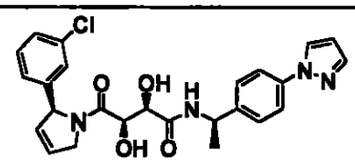
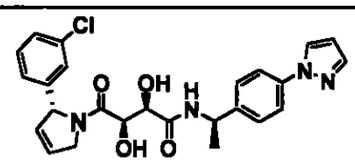
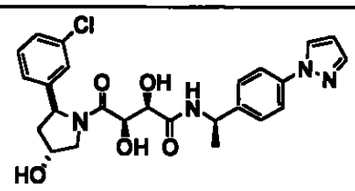
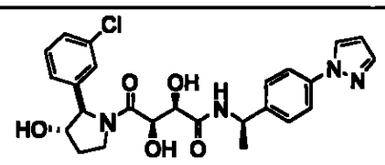
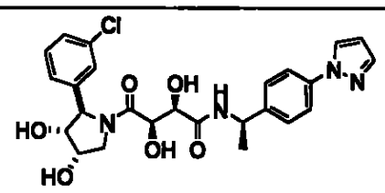
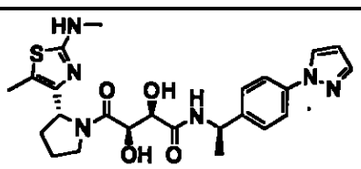
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2153		D
2154		D
2155		D
2156		B
2157		B

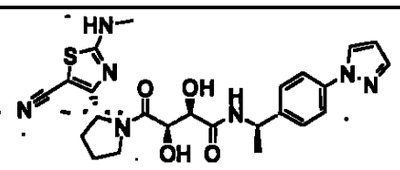
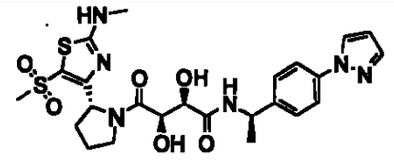
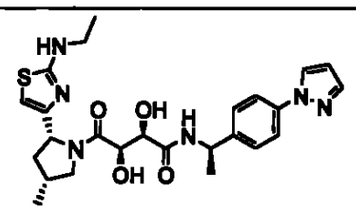
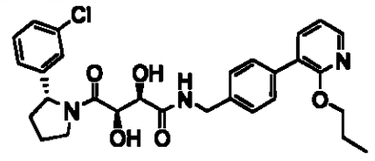
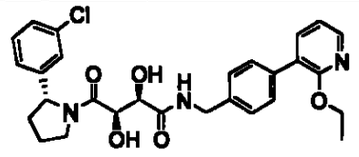
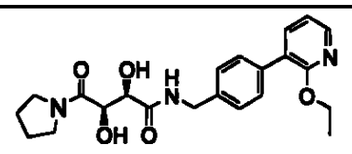
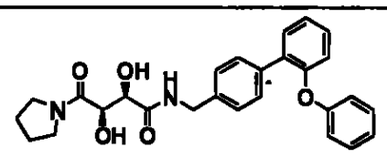
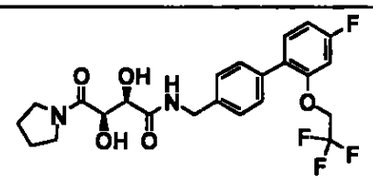
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2159		B
2233		A
2234		C
2235		A
2236		D
2237		C

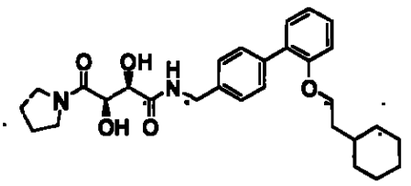
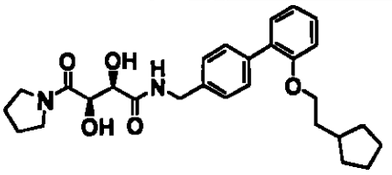
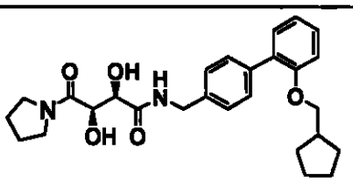
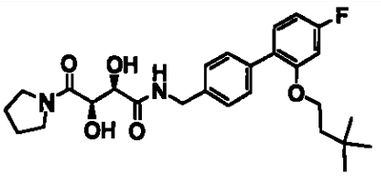
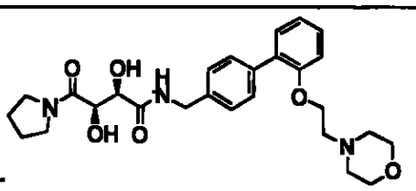
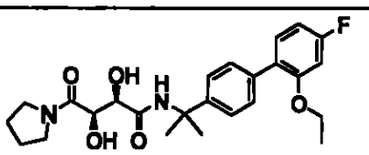
2238		B
2239		D
2240		B
2241		C
2242		A
2243		A
2244		A
2245		A

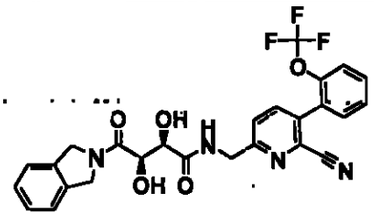
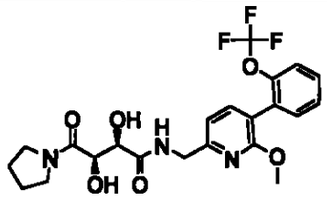
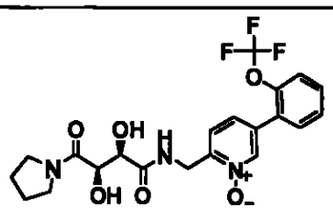
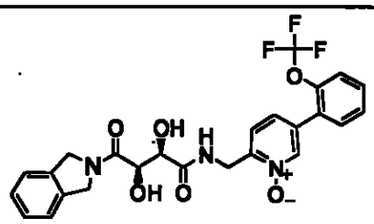
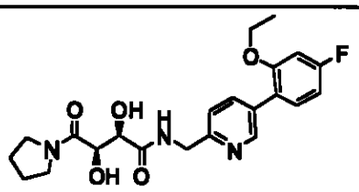
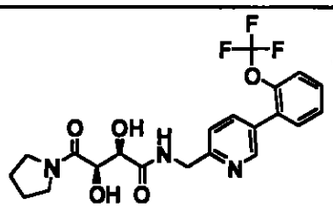
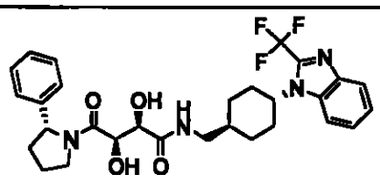
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2248		A
2249		A
2250		A
2251		A
2252		A
2253		A

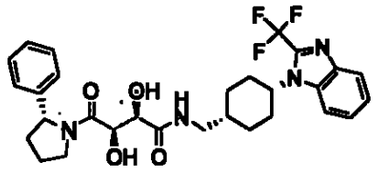
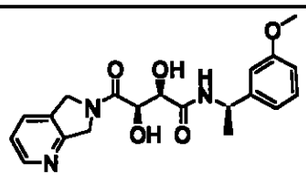
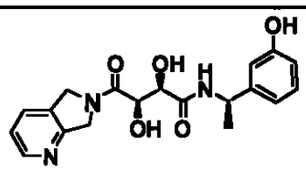
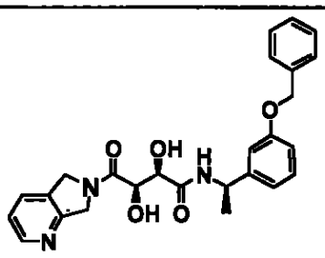
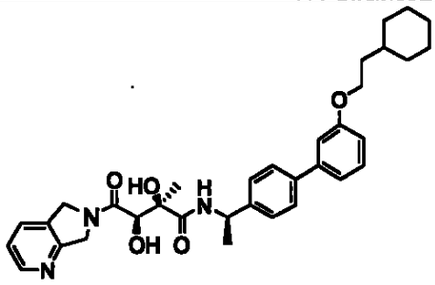
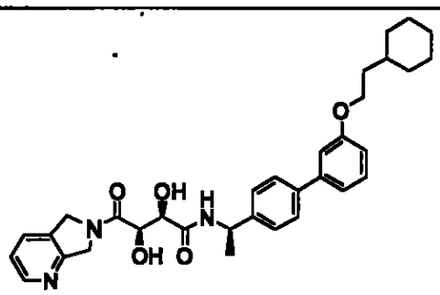
2254		C
2255		A
2256		A
2257		A
2258		B
2259		A
2260		B

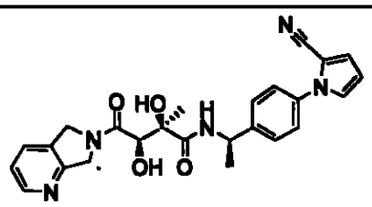
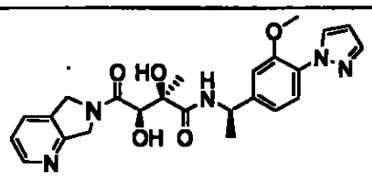
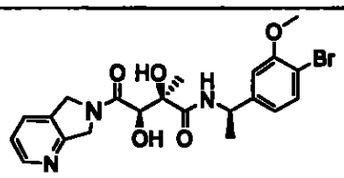
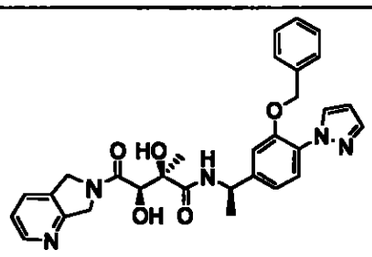
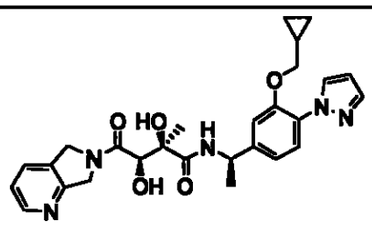
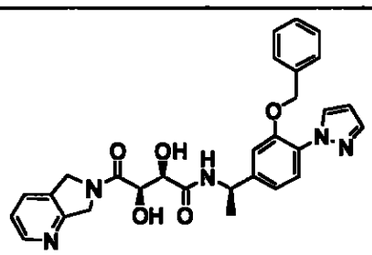
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2262		A
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2264		A
2265		A
2266		A
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2268		A

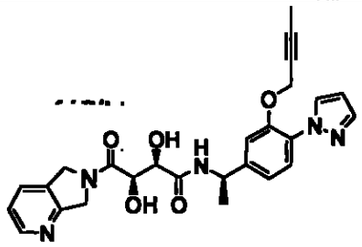
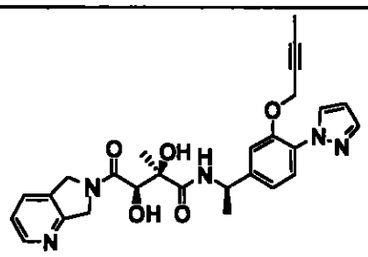
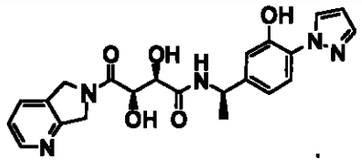
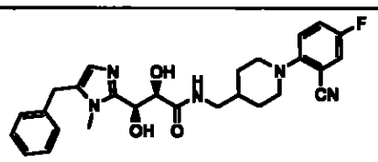
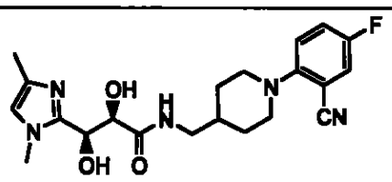
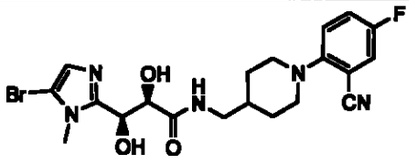
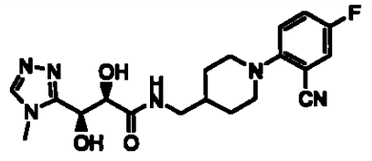
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2270		A
2271		A
2333		A
2334		A
2335		C
2336		C
2337		B

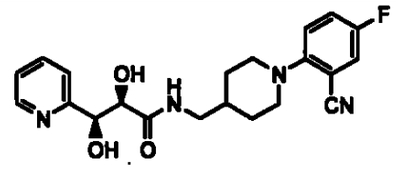
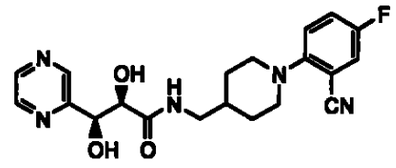
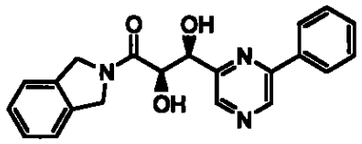
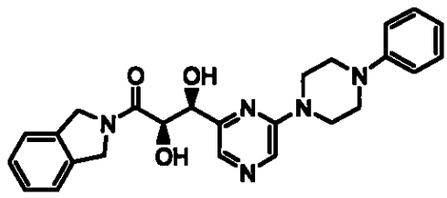
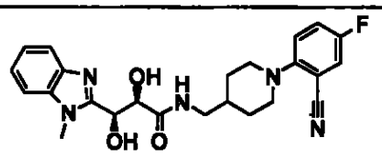
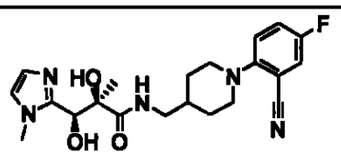
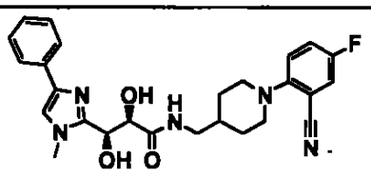
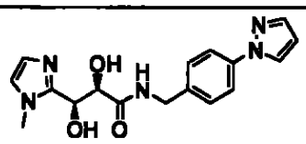
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2339		B
2340		B
2341		C
2342		C
2343		D
2344		D

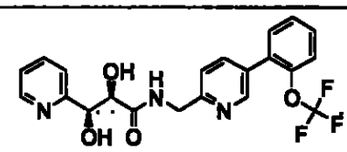
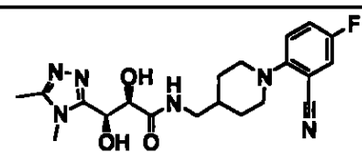
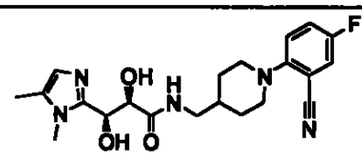
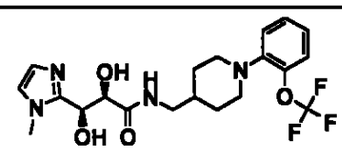
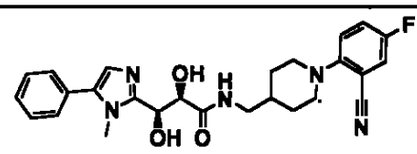
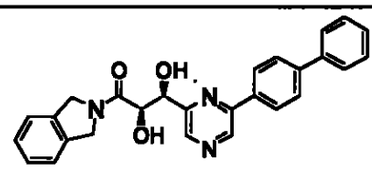
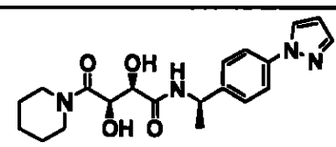
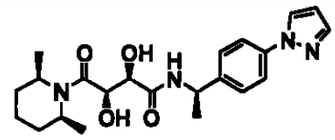
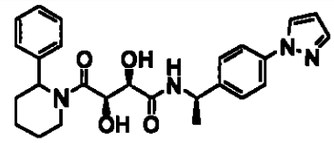
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2346		D
2347		D
2348		C
2349		A
2350		A
2351		A

2352		A
2306		D
2307		D
2308		D
2353A		C
2353B		B

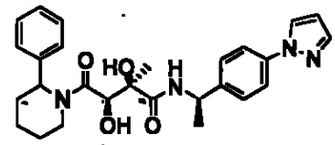
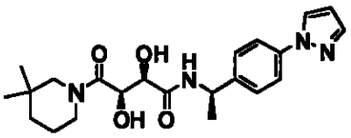
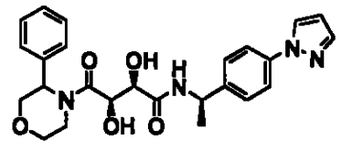
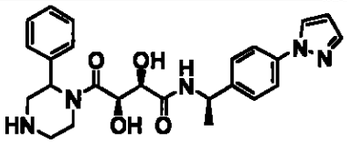
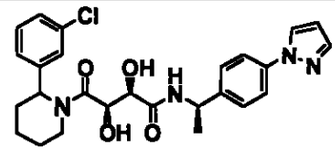
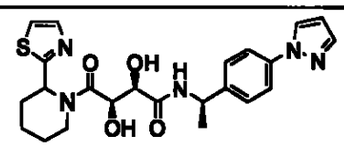
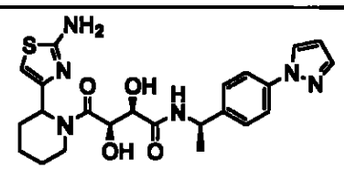
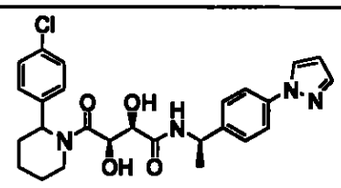
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2355		A
2356		D
2357		A
2358		C
2304		A

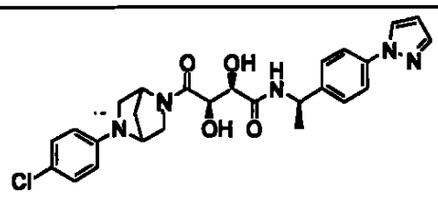
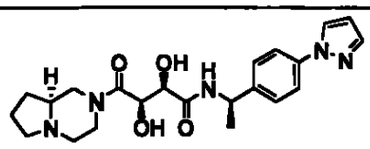
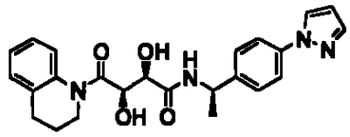
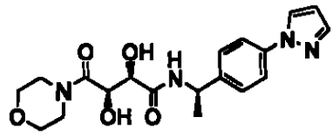
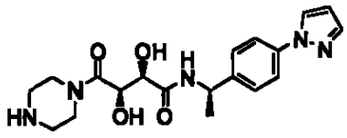
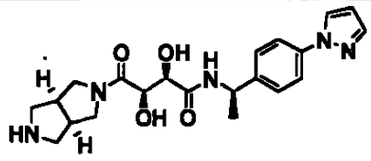
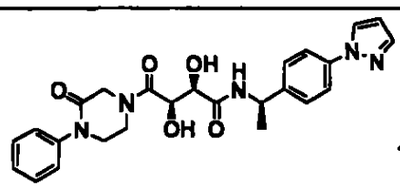
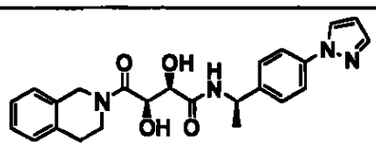
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2360		A
2305		A
2365		C
2369		
2372		D
2376		D

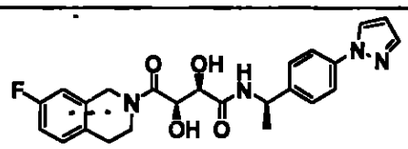
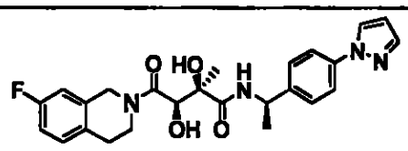
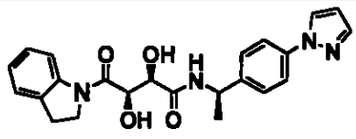
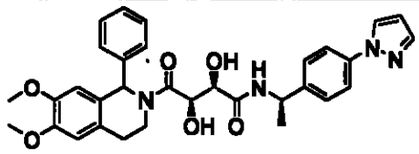
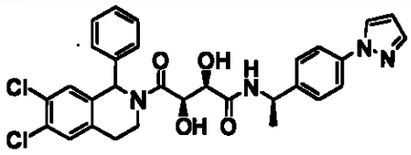
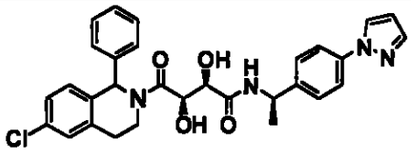
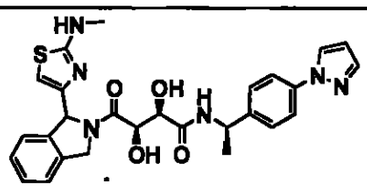
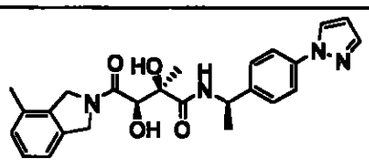
2382		D
2387		D
2391		D
2393		D
2394		D
2395		C
2396		D
2397		D

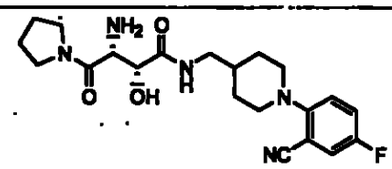
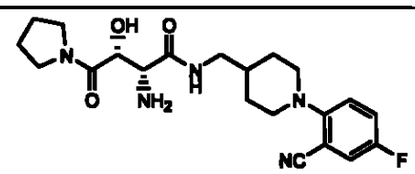
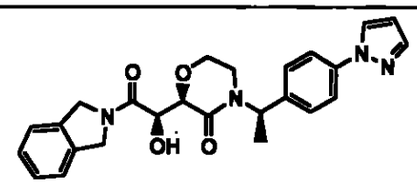
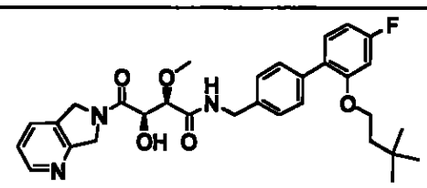
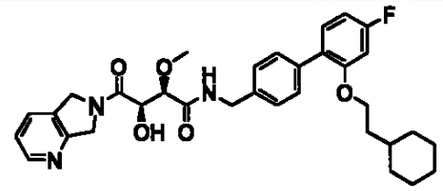
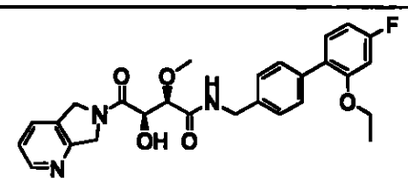
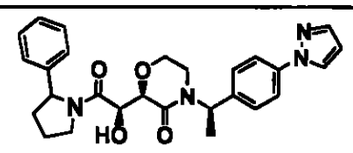
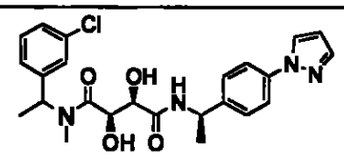
2398		D
2399		D
2400		C
2401		C
2402		D
2403		D
2408		B
2409		C
2410		A

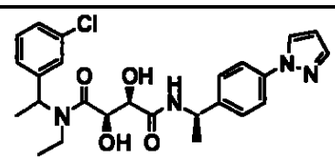
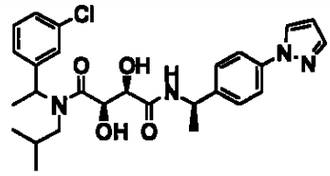
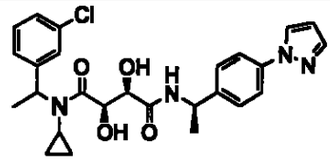
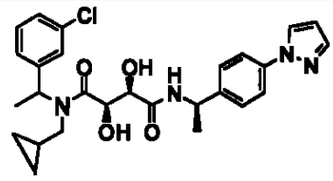
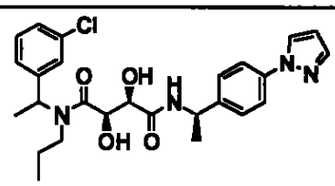
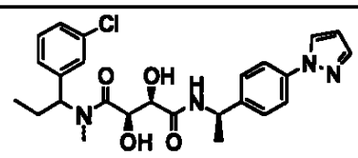
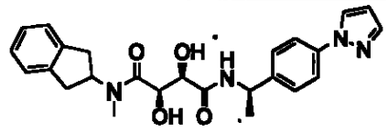
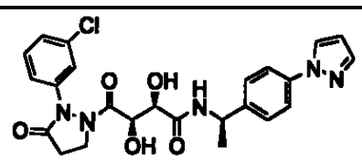
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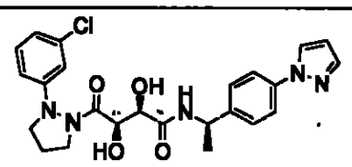
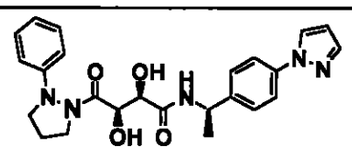
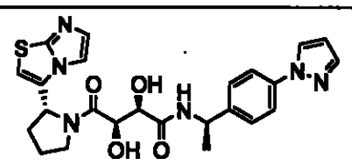
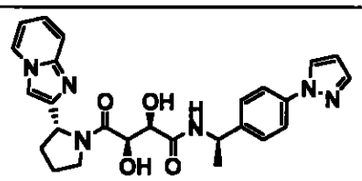
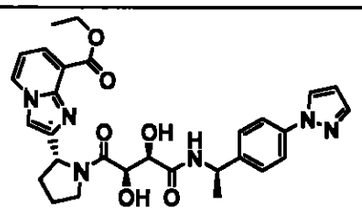
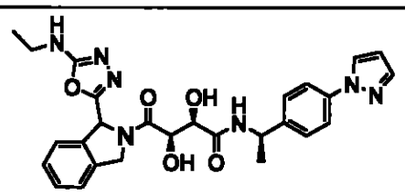
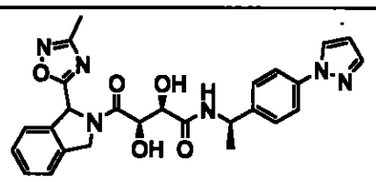
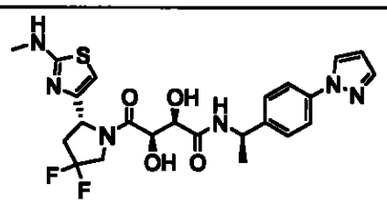
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2415		B
2416		B
2417		B
2418		B

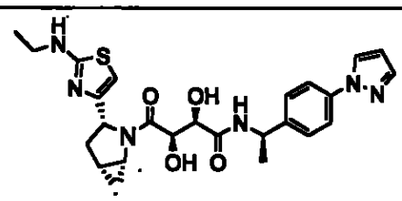
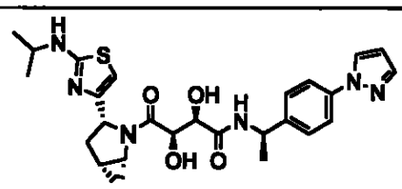
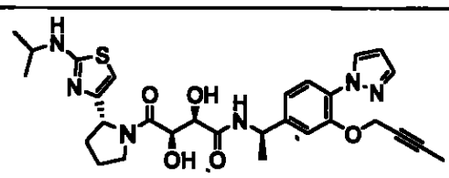
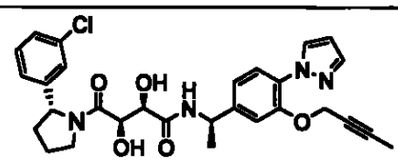
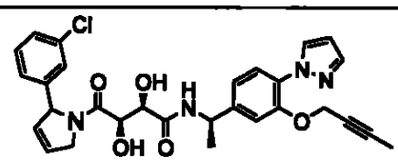
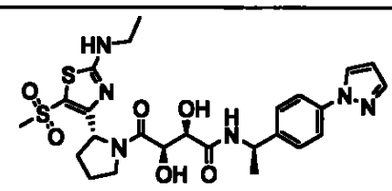
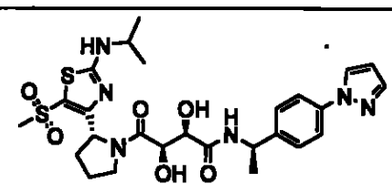
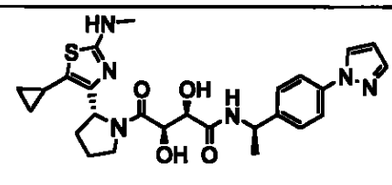
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2422		B
2423		C
2424		C
2425		C
2438		A

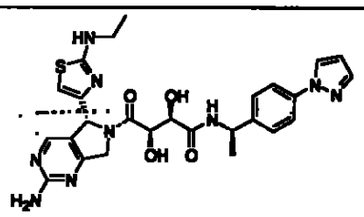
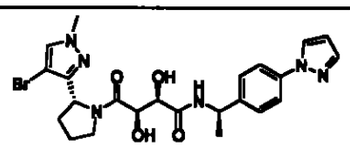
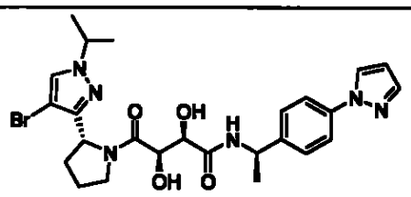
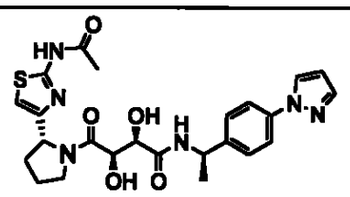
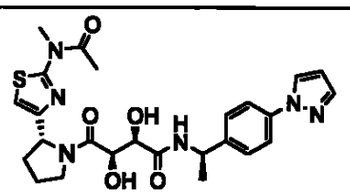
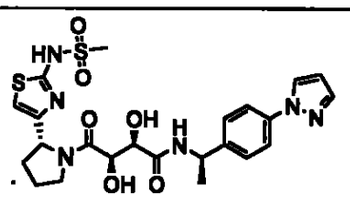
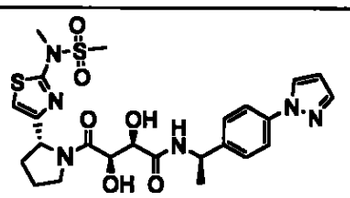
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2441		B
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2443		A
2444		A
2445		A
2446		B

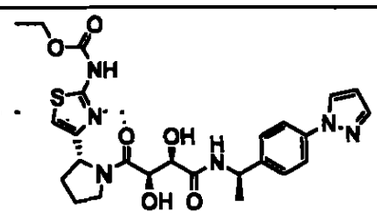
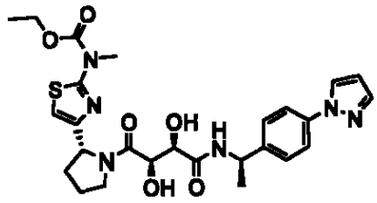
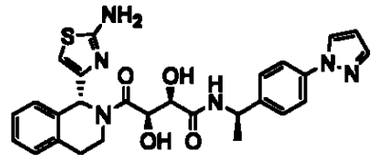
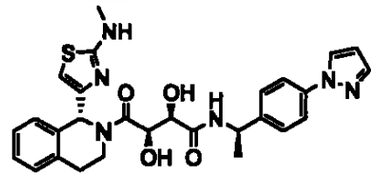
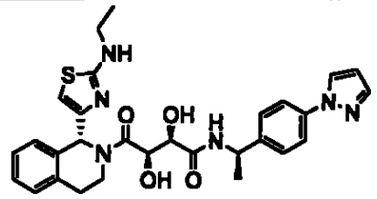
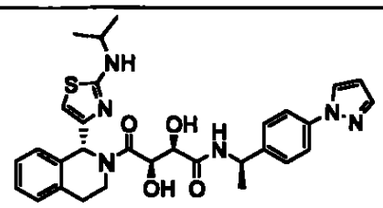
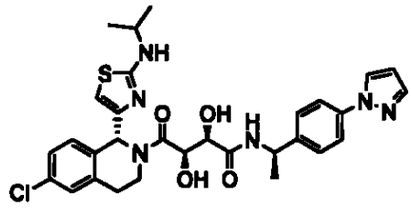
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2474		D
2475		B
2476		B
2477		C
2478		D
2480		B

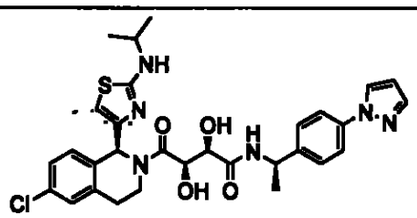
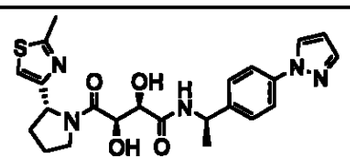
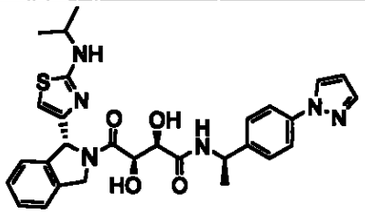
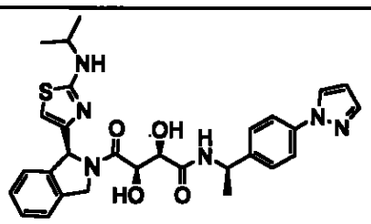
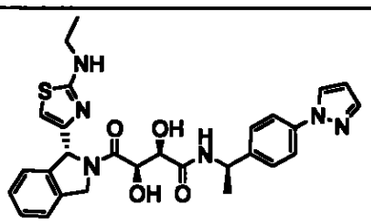
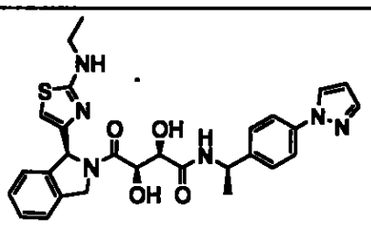
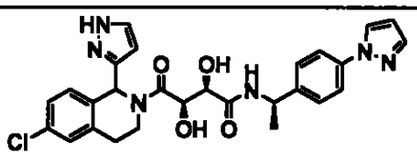
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2483		D
2485		D
2486		D
2487		B
2489		B
2494		C

2495		C
2496		C
2506		A
2507		A
2508		B
2527		A
2528		A
2567		A

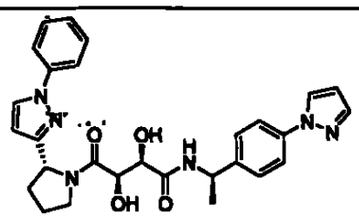
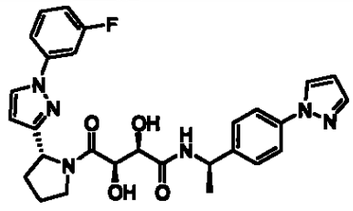
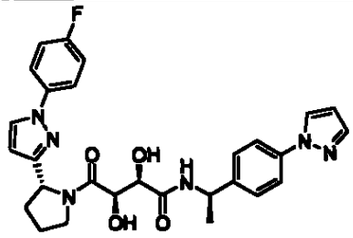
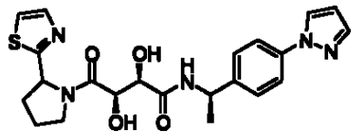
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2581		A
2582		A

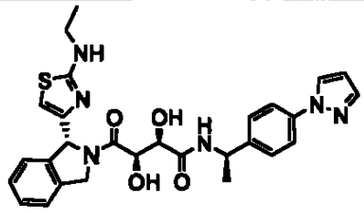
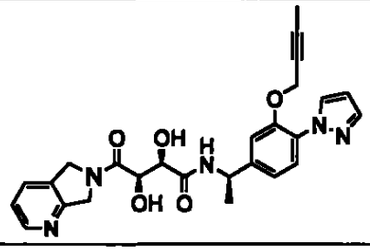
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2589		A

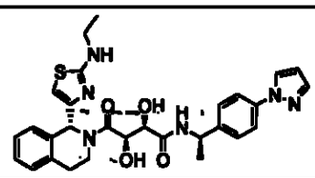
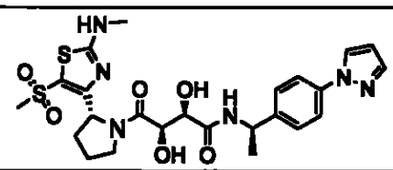
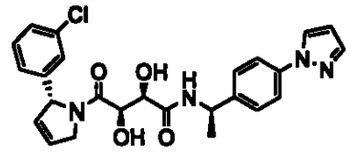
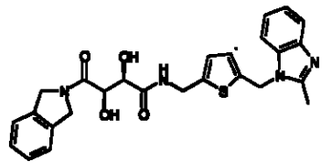
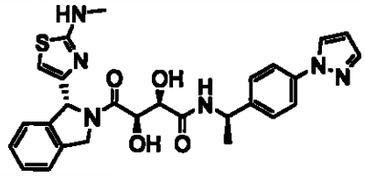
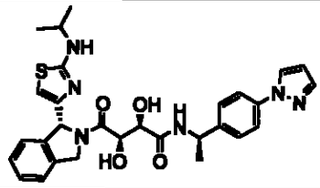
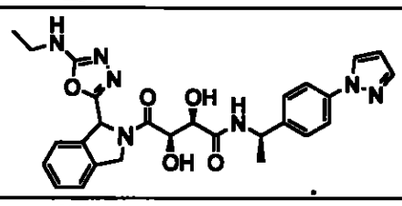
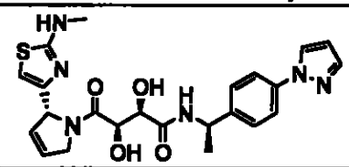
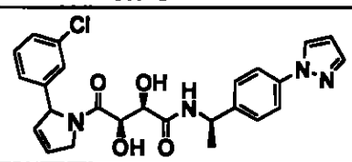
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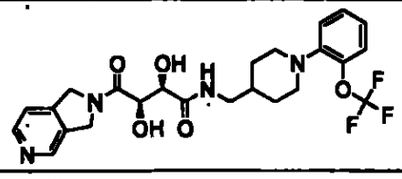
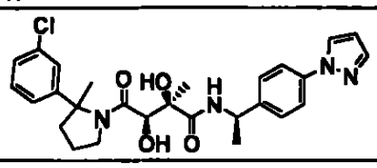
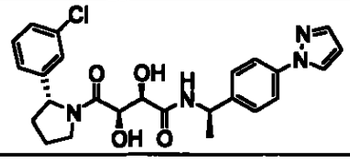
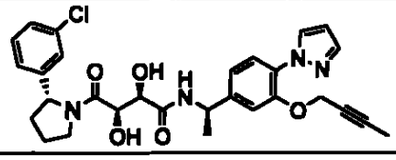
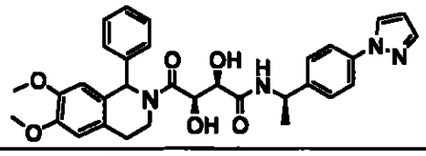
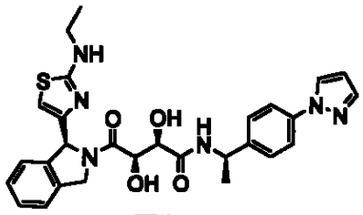
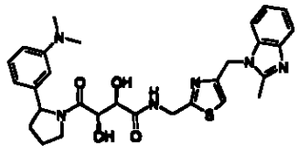
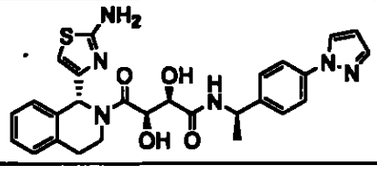
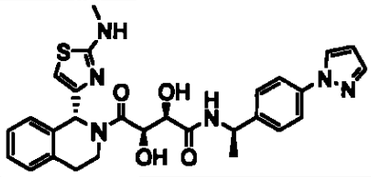
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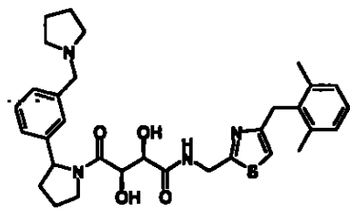
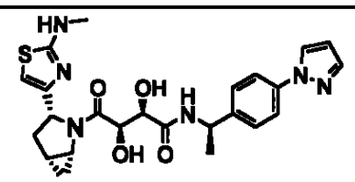
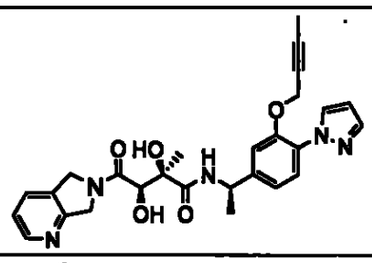
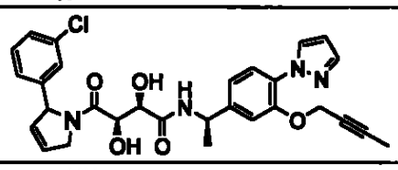
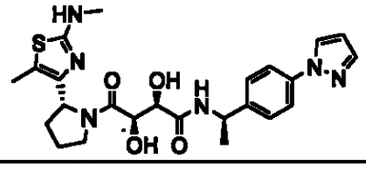
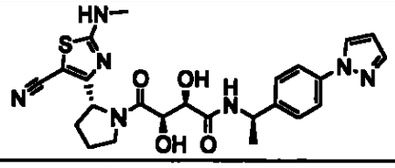
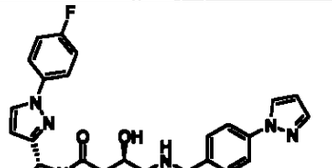
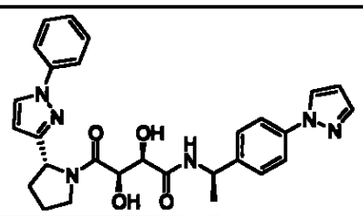
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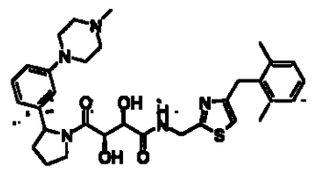
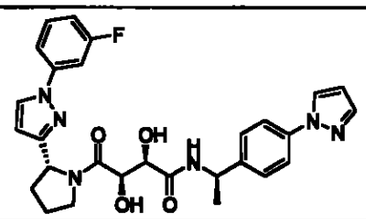
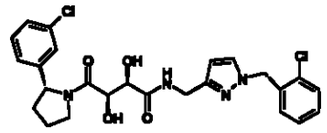
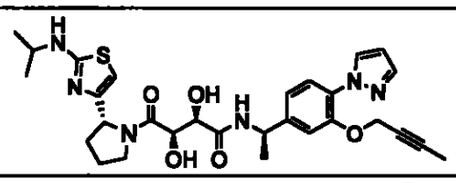
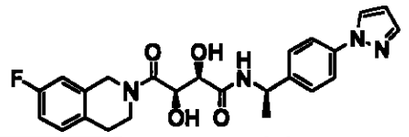
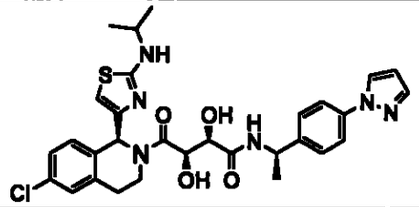
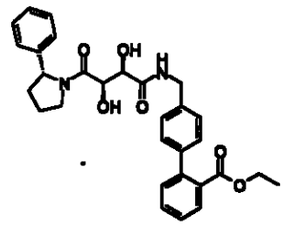
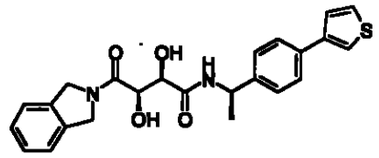
En la siguiente tabla se enumeran Ejemplos representativos de compuestos de la invención con sus respectivos valores de K_i :

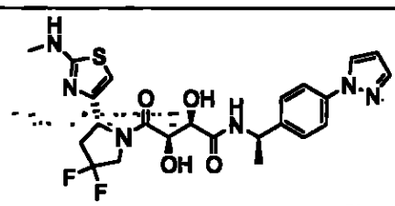
	Estructura	Ki (nM)
		0,16
		0,25

		0,3
		0,38
		0,49
		0,5
		0,5
		0,54
		0,56
		0,57
		0,6

		0,74
		0,75
		0,8
		0,85
		0,86
		0,89
Mezcla de diastereómeros		1
		1,1
		1,4

Un diastereómero		1,4
		1,4
		1,44
		1,54
		2
		2
		2,0
		2,3

Mezcla de diastereómeros		2,5
		2,7
		2,7
		2,9
		3,0
		3,3
		3,6
		3,8

		3,9

Las composiciones farmacéuticas que contienen el componente activo se pueden encontrar en una forma adecuada para uso oral, por ejemplo como comprimidos, pastillas, suspensiones acuosas o aceitosas, polvos dispersables o gránulos, emulsiones, cápsulas duras o blandas, o jarabes y elixires. Las composiciones destinadas a uso oral se pueden preparar de acuerdo con cualquier método conocido en la técnica para la fabricación de composiciones farmacéuticas y tales composiciones pueden contener uno o más agentes seleccionados del grupo que consiste en agentes edulcorantes, agentes saborizantes, agentes colorantes y agentes conservantes para proveer preparaciones elegantes y gustosas para uso farmacéutico. Los comprimidos contienen el componente activo en mezcla con excipientes aceptables para uso farmacéutico no tóxicos que son adecuados para la fabricación de comprimidos. Estos excipientes pueden ser, por ejemplo, diluyentes inertes, tales como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio o fosfato de sodio; agentes de granulación y desintegrantes, por ejemplo almidón de maíz, o ácido algínico; agentes aglutinantes, por ejemplo, almidón, gelatina o acacia, y agentes lubricantes, por ejemplo estearato de magnesio, ácido esteárico o talco. Los comprimidos puede no estar recubiertos o pueden estar cubiertos mediante técnicas conocidas para demorar la desintegración y absorción en el tracto gastrointestinal y proporcionando de esa manera una acción prolongada durante un período más largo. Por ejemplo, se puede emplear un material de demora de tiempo tal como monoestearato de glicerilo o diestearato de glicerilo. También pueden estar recubiertos mediante la técnica descripta en las Patentes

Estadounidenses Nos. 4.256.108; 4.166.452; y 4.265.874 para formar comprimidos terapéuticos osmóticos para la liberación controlada.

Las formulaciones para uso oral también se pueden presentar como cápsulas duras de gelatina donde los componentes activos se mezclan con un diluyente inerte sólido, por ejemplo, carbonato de calcio, fosfato de calcio o caolín, o cápsulas blandas de gelatina donde en componente activo se mezcla con agua o un medio de aceite, por ejemplo, aceite de maní, parafina líquida o aceite de oliva.

Las suspensiones acuosas contienen el material activo en mezcla con excipientes adecuados par ala fabricación de suspensiones acuosas. Tales excipientes son agentes en suspensión, por ejemplo, carboximetilcelulosa de sodio, metilcelulosa, hidroxipropilmetil-celulosa, alginato de sodio, polivinil-pirrolidona, goma tragacanto y goma acacia; agentes dispersantes o humectantes pueden ser fosfátidos de origen natural, por ejemplo lecitina, o productos de condensación de un óxido de alquileno con ácidos grasos, por ejemplo estearato de polioxietileno, o productos de condensación del óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilen-oxicetanol, o productos de condensación del óxido de etileno con ésteres parciales que derivan de ácidos grasos y un hexitol tal como monooleato de polioxietilen sorbitol, o productos de condensación del óxido de etileno con ésteres parciales que derivan de ácidos grasos y anhídridos de hexitol, por ejemplo, monooleato de polietilén sorbitano. Las suspensiones acuosas también pueden contener uno o más conservantes, por ejemplo, , p-hidroxibenzoato de etilo o n-propilo, uno o más agentes colorantes, uno o más agentes saborizantes y uno o más agentes edulcorantes, tales como sacarosa, sacarina o aspartamo.

Las suspensiones aceitosas también se pueden formular mediante la suspensión del componente activo en un aceite vegetal, por ejemplo, aceite de

araquis, aceite de oliva, aceite de sésamo o aceite de coco, o en aceite mineral tal como parafina líquida. Las suspensiones aceitosas pueden contener un agente espesante, por ejemplo, cera de abeja, parafina dura o alcohol cetílico. Se pueden agregar agentes edulcorantes tales como aquellos expuestos anteriormente, y agentes saborizantes para proporcionar una preparación oral gustosa. Estas composiciones se pueden preservar mediante la adición de un anti-oxidante tal como ácido ascórbico.

Los polvos y gránulos dispersables adecuados para la preparación de una suspensión acuosa mediante la adición de agua proporcionan el componente activo en mezcla con un agente dispersante o humectante, agente de suspensión y uno o más conservantes. Se ejemplifican agentes dispersantes o humectantes adecuados y agentes de suspensión mediante aquellos ya mencionados anteriormente. También se pueden encontrar presentes excipientes adicionales, por ejemplo agentes edulcorantes, saborizantes y colorantes.

Las composiciones farmacéuticas de la invención también pueden encontrarse en forma de una emulsión de aceite en agua. La fase aceitosa puede ser un aceite vegetal, por ejemplo, aceite de oliva o aceite de araquis, o un aceite mineral, por ejemplo, parafina líquida o mezclas de estas. Los agentes emulsionantes adecuados pueden ser fosfátidos de origen natural, por ejemplo, granos de soja, lecitina, y ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, monooleato de sorbitano y productos de condensación de dichos ésteres parciales con óxido de etileno, por ej. monooleato de polioxietilén sorbitano. Las emulsiones también pueden contener agentes edulcorantes o saborizantes.

Se pueden formular jaleas y elíxires con agentes edulcorantes, por ejemplo, glicerol, propilenglicol, sorbitol o sacarosa. Tales formulaciones también

pueden contener un emoliente, un conservante y agentes saborizantes y colorantes.

Las composiciones farmacéuticas se pueden encontrar en forma de suspensión estéril inyectable acuosa u oleaginosa. Esta suspensión se puede formular de acuerdo con la técnica conocida usando aquellos agentes dispersantes o humectantes adecuados que se mencionaron anteriormente. La preparación estéril inyectable también puede ser una solución o suspensión estéril inyectable en un diluyente o solvente no tóxico aceptable para uso parenteral, por ej. una solución en 1,3-butanodiol. Entre los vehículos y solventes aceptables que se pueden usar se encuentran agua, solución de Ringer y solución isotónica de cloruro de sodio. Además, los aceites fijos estériles se emplean de manera convencional como un solvente o medio de suspensión. Con este fin, se puede emplear cualquier aceite fijo suave incluyendo mono- o diglicéridos sintéticos. Además, se pueden usar ácidos grasos tales como ácido oleico en la preparación de inyectables.

Los compuestos de la invención también se pueden administrar en forma de supositorios para administración rectal del fármaco. Las composiciones se pueden preparar mediante la mezcla del fármaco con un excipiente no irritante adecuado que es sólido en temperaturas comunes pero líquido a temperatura rectal y que, por lo tanto, se fusionará en el recto para liberar el fármaco. Tales materiales son manteca de cacao y glicoles de polietileno.

Para el uso tópico, se emplean cremas, ungüentos, jaleas, soluciones o suspensiones, etc. que contienen el compuesto de la invención. (a los fines de la presente invención, la aplicación tópica incluirá enjuagues bucales y gárgaras).

Los compuestos para la presente invención se pueden administrar de forma intranasal mediante el uso tópico de vehículos intranasales adecuados, o mediante rutas transdérmicas, usando aquellas formas de parches de piel

transdérmica conocidos para aquellos de experiencia común en la técnica. Para ser administrados en forma de un sistema de entrega transdérmica, la administración de dosificación será, obviamente, continua en lugar de intermitente a través del régimen de dosificación. Los compuestos de la presente invención también se pueden entregar como un supositorio empleando bases tales como manteca de cacao, gelatina glicerinada, aceites vegetales hidrogenados, mezclas de polietilenglicoles de diversos pesos moleculares y ésteres de ácidos grasos de polietilenglicol.

El régimen de dosificación usando los compuestos de la presente invención se selecciona de acuerdo con una diversidad de factores incluyendo tipo, especie, peso, sexo y condición médica del paciente; la severidad de la condición a tratar; la vía de administración; la función renal y hepática del paciente; y el compuesto particular del mismo empleado. Un médico o veterinario de experiencia ordinaria en la técnica puede determinar fácilmente y prescribir la cantidad efectiva del fármaco que se requiere para prevenir, contrarrestar, detener o invertir el progreso de la condición. La precisión óptima en el logro de l concentración del fármaco dentro del rango que provee eficacia sin toxicidad requiere un régimen basado en la cinética de la disponibilidad del fármaco para sitios blanco. Esto comprende una consideración de la distribución, equilibrio y eliminación de un fármaco. Preferentemente, las dosis del compuesto de fórmula I útil en el método de la presente invención oscilan de 0,01 a 1000 mg por día. Más preferentemente, las dosificaciones oscilan de 0,1 a 1000 mg/día. Más preferentemente, las dosificaciones oscilan de 0,1 a 500 mg/día. Para la administración oral, las composiciones se proveen preferentemente en forma de comprimidos que contienen de 0,01 a 1000 miligramos del componente activo, en especial 0,01, 0,05, 0,1, 0,5, 1,0, 2,5, 5,0, 10,0, 15,0, 25,0, 50,0, 100 y 500 miligramos del componente activo para la regulación sintomática de la dosificación para el

paciente a tratar. Se provee comúnmente una cantidad efectiva del fármaco a un nivel de dosificación de alrededor de 0,0002 mg/kg a alrededor de 50 mg/kg de peso corporal por día. El rango es más en especial de alrededor de 0,001 mg/kg a 1 mg/kg de peso corporal por día.

De manera ventajosa, el agente activo de la presente invención se puede administrar en una dosis diaria simple, o la dosificación diaria total se puede administrar en dosis divididas de dos, tres o cuatro veces al día.

La cantidad de componente activo que se pueden combinar con los materiales de vehículo para producir formas de dosificación simples variarán dependiendo del huésped tratado u del modo particular de administración.

Se entenderá, no obstante, que el nivel de dosis específico para cualquier paciente en particular dependerá de una variedad de factores incluyendo edad, peso corporal, salud general, sexo, dieta, tiempo de administración, vía de administración, velocidad de excreción, combinación de fármacos y la gravedad de la enfermedad particular que se somete a terapia.

Los compuestos de la invención se pueden producir mediante procesos conocidos para aquellos con experiencia en la técnica y según se muestra en los siguientes esquemas de reacción y en las preparaciones y ejemplos que se describen a continuación.

Ejemplos

Se usan las siguientes abreviaturas en los procedimientos y esquemas:

ACN	Acetonitrilo
AcOH	Ácido acético
ADDP	1,1[1]-(Azodicarbonil)dipiperidina
Anh.	Anhidro
Aq	acuoso
BOC	ter-butoxicarbonilo

°C	grados Celsius
CBZCl	cloroformiato de bencilo
CDI	Carbodiimida
DBU	1,8-Diazabiciclo[5.4.0]undec-7-eno
DCC	Diciclohexilcarbodiimida
DCM	diclorometano
DEAD	azodicarboxilato de dietilo
(DHQ)2PHAL	diéter de Hidroquinina 1,4-ftalazindiilo
DIAD	Diisopropilazodicarboxilato
DIEA	Diisopropiletilamina
DMA	N,N-Dimetilacetamida
DMAP	4-Dimetilaminopiridina
DME	Dimetoxietano
DMF	Dimetilformamida
DMFDMA	N,N-Dimetilformamida dimetilacetal
DMPU	1,3-Dimetil-3,4,5,6-tetrahidro-2(1h)-pirimidinona
DMSO	Dimetilsulfóxido
EDC	clorhidrato de 1-(3-Dimetilaminopropil)-3-etilcarbodiimida
EI	Ionización de Electrones
Eq	Equivalentes
EtOAc	Acetato de etilo
EtOH	Etanol
g	gramos
h.	horas
^1H	protón
HATU	Hexafluorofosfato de N,N,N',N'-tetrametil-O-(7-azabenzotriazol-1-il)uronio

Hex	hexanos.
HOBt	1-Hidroxibenzotriazol
HPLC	Cromatografía líquida de alta presión
LAH	Hidruro de litio y aluminio
LDA	Litio diisopropilamida
M	Molar
mCPBA	ácido *meta*-cloroperoxibenzoico
Me	Metilo
MeCN	Acetonitrilo
MeOH	Metanol
min	Minutos
mg	Miligramos
MHz	Megahertz
ml	Mililitro
MS	Espectroscopía de masa
NMM	N-Metilmorfolina
NMP	1-metil-2-pirrolidona
ON	Hasta el día siguiente
$Pd(^tBu_3P)_2$	Bis-(tri-*ter*-butilfosfina)paladio
$Pd(TPP)_4$	Tetrakis-(trifenilfosfina)paladio
$Pd(Oac)_2$	Acetato de Paladio(II)
$PdCl_2(TPP)_2$	Cloruro de Bis-(trifenilfosfina)paladio(II)
$PdCl_2$(ddppf)	dicloruro de dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio(ii)
$Pd_2(dba)_3$	Tris(dibencillidenacetona)dipaladio(0)
PyBrOP	hexafluorofosfato de bromo-tris-pirrolidino-fosfonio
Pyr	Piridina

TA	Temperatura ambiente
SiO_2	Cromatografía de gel de sílice 60
sgc	Cromatografíade gel de sílice 60
tBOC	ter-butoxicarbonilo
TACE	enzima de conversión de TNF-alfa
TEA	Trietilamina
TFA	Ácido trifluoroacético
THF	Tetrahidrofurano
TLC	Cromatografía en capa delgada
TPP	Trifenilfosfina
t_R	Tiempo de retención

Los espectros de RMN se adquirieron en un Espectrómetro Mercuryplus 400 MHz RMN (Varian), usando CDCl3 o DMSO-d6 como solventes. Los datos de LC-MS se obtuvieron usando un Agilent 1100 Serie LC/MSD (cuadripolar, API-ES (Electroaspersión de Interfaz de Presión Atmosférica) con un voltaje capilar configurado para 3500 V y funcionando en modo positivo. Los tiempos de retención de HPLC analítico reportado (LC/MS) se obtuvieron usando una columna C18 de fase reversa (150 x 4,6 mm) con un gradiente de 5 o 10 minutos de 0,1% de ácido trifluoroacético en agua para acetonitrilo:agua 95:5 con un caudal de flujo de 3 ml/min.

La purificación mediante cromatografía de fase reversa se logró usando una columna C18 de fase reversa con un gradiente de 0,1% de ácido trifluoroacético en agua para 95:5 acetonitrilo:agua con un caudal de flujo de 20 ml/min. Las muestras se recolectaron usando un UV (Gilson, 254 nm) o señal de espectro de masa (Agilent 1100 Serie LC/MSD modelo SL).

Se logró una cromatografía en gel de sílice de fase normal en un instrumento Biotage usando un sistema Quad UV (P/N 07052) usando columnas KP-SIL 32-63 um, 60Å con cartuchos flash 12+M o 25+M.

Los compuestos de fórmula (I) se pueden producir mediante procesos conocidos para aquellos con experiencia en la técnica y según se muestra en los siguientes esquemas de reacción y en las preparaciones y ejemplos descriptos a continuación. No se debe considerar que estas preparaciones y ejemplos limitan el alcance de la invención de la revelación. Rutas de mecanismos alternativos y estructuras análogas pueden ser evidentes para aquellos con experiencia en la técnica. Algunos de los compuestos preparados mediante estos procesos se enumeran en la Tabla 1. Todos los tipos de formas isoméricas de los compuestos son considerados dentro del alcance de la presente invención.

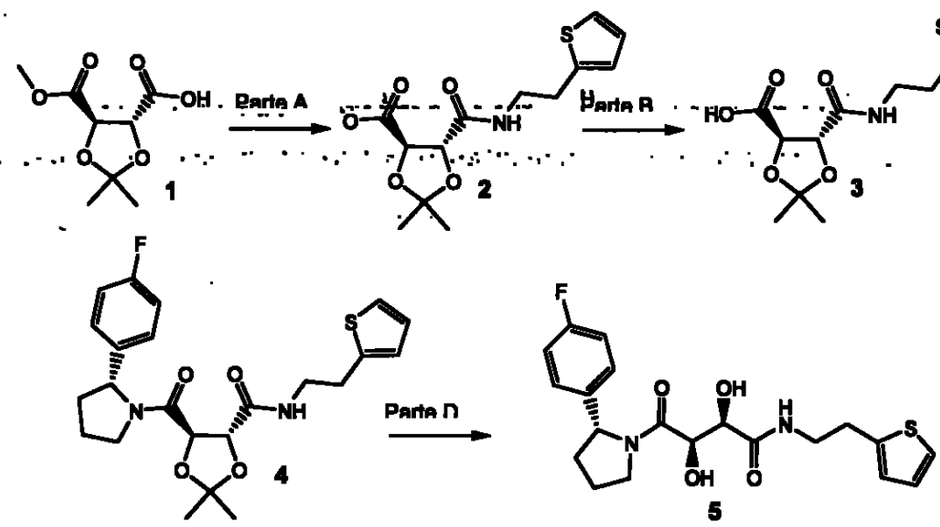
Ejemplo 1: Síntesis General de inhibidores derivados de tartrato

Existen dos rutas generales para la síntesis de diamidas de tartrato a partir de aminas. El primero (Ejemplo 1) usa un intermediario monoácido/monoéster protegido por acetonida preparado a partir del dimetil éster de acetonida disponible comercialmente usando un procedimiento de la literatura (*J. Am. Chem. Soc.* **1978**, *100*, 4865-4872). En general, de los Ejemplos generales 1 o 2 se podrían usar indistintamente, aunque se descubrió que el Ejemplo 2 es de mayor preferencia para compuestos que contuvieran grupos funcionales que fueran inestables con respecto a las condiciones ácidas de desprotección (tal como **113**).

Una variedad de reactivos de acoplamiento de enlace de amida fueron aceptables, incluyendo HATU, CDI, EDC, DCC/HOBt, PyBrOP, CDI soportado en polímero con HOBt, carbodiimida sostenida en polímero, y EDC soportada en polímero (PS-EDC) con HOBt.

Estos reactivos de acoplamiento se podrían usar con una variedad de bases, incluyendo trietilamina (TEA), diisopropiletilamina (DIEA), N-metil morfolina, piridina, dimetilaminopiridina (DMAP) e imidazol. En algunos casos, las aminas en exceso en los pasos de acoplamiento de péptidos se eliminaron usando extracción líquido/líquido o resinas secuestrantes poliméricas tales como las de isocianato soportada en polímero (PS-NCO) y/o ácido tósico soportada en polímero (MP-TsOH). Los ácidos sin reaccionar se podrían eliminar usando resina de carbonato MP o resinas de polímeros que contienen grupos funcionales básicos tales como trisamina (es decir, PS-trisamina), amberlita o morfolina. Los acoplamientos de péptidos se llevaron a cabo en una diversidad de solventes, incluyendo DMF, THF, dioxano, acetonitrilo, NMP y DCM. Estos solventes también se pueden combinar en varias proporciones para optimizar las condiciones de la reacción. Una ruta menos preferida pero viable usando intermediarios de éster de pentafluorofenilo (PFP) también se pueden usar para preparar mono- o diamidas; los solventes preferidos para este enfoque deberían incluir THF. Se pueden encontrar estrategias generales de acoplamiento de péptidos, incluyendo enfoques basados en PFP, en Bodanszky & Bodanszky, *The Practice of Peptide Synthesis, second edition, Springer-Verlag, 1994.*

La ruptura (saponificación) del metil éster del intermediario se podría lograr en una variedad de condiciones conocidas; incluyendo: un leve exceso (1,1-3 equivalentes) de una base, KOH en metanol, LiOH en THF/agua, LiOH en metanol/agua, y NaOH/THF/MeOH/agua. La eliminación del grupo protector acetonida se podría producir usando una variedad de condiciones ácidas, incluyendo combinaciones de TFA:agua (tal como 80:20).



Parte A:

Se agregó un monometil éster del ácido 2,2-dimetil-[1,3]dioxolan-4R,5R-dicarboxílico (1) (Musich, J.A.; Rapoport, H.; *J. Am. Chem. Soc.* **1978**, *100*, 4865-4872) (500 mg, 2,45 mmol) en DMF (5 ml) 2-tiofenetilamina (316 µl, 2,70 mmol), DIEA (0,94 ml, 5,4 mmol) y HATU (989 mg, 2,60 mmol). La mezcla de reacción se agitó hasta el día siguiente y el DMF se eliminó in vacuo. El residuo se disolvió en EtOAc, se lavó con agua, solución de bicarbonato saturado, HCl 0,1 N, y salmuera. La capa orgánica se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 10% de EtOAc/DCM) dio 2 como un aceite (491 mg, 64%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,17 (dd, 1H , J = 1,2, 5,2 Hz), 6,95 (dd, 1H, J = 2,1, 5,2 Hz), 6,84 (d, 1H, J = 2,4 Hz), 6,66 (bs, 1H, NH), 4,72 (ABq, 2H, J = 13,2 Hz), 3,84 (s, 3H), 3,65 (m, 1H), 3,57 (m, 1H), 3,09 (t, 2H, J = 6,4 Hz), 1,47 (s, 3H), 1,40 (s, 3H); HPLC-MS t_R = 1,63 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{14}H_{19}NO_5S$ 313,1, LCMS observada m/z 314,2 (M+H).

Parte B:

A 2 (869 mg, 2,77 mmol) en THF (10 ml) se agregó LiOH 1,0 M (3 ml, 3 mmol) y la reacción se agitó hasta el día siguiente a temperatura ambiente. La

mezcla de reacción se diluyó con agua (10 ml) y el THF se eliminó in vacuo. La capa acuosa básica se extrajo con éter dietilo y el enjuague de éter se desechó. La capa acuosa se acidó con HCl 1,0 N y se extrajo con dietil éter. Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se concentraron para dar **3** como un sólido amarillo (443 mg, 53%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21 (dd, 1H, J = 1,2, 5,2 Hz), 6,97 (dd, 1H, J = 3,6, 5,2 Hz), 6,90 (bs, 1H, NH), 6,86 (d, 1H, J = 3,2 Hz), 4,48 (ABq, 2H, J = 9,2 Hz), 3,76 (m, 1H), 3,60 (m, 1H), 3,15 (m, 2H), 1,53 (s, 3H), 1,41 (s, 3H); HPLC-MS t_R = 1,34 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{13}H_{17}NO_5S$ 299,1, LCMS observada m/z 300,1 (M+H).

Parte C:

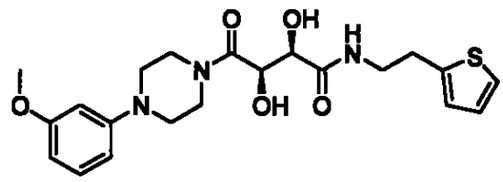
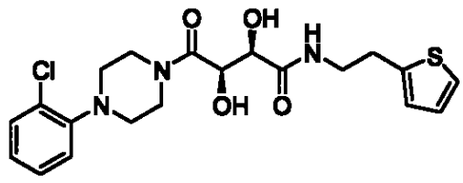
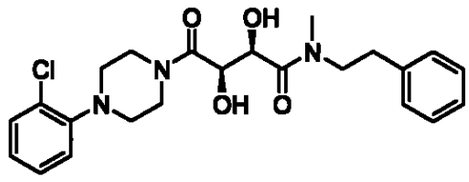
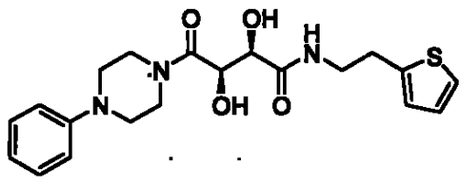
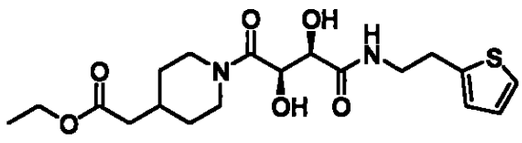
A **3** (150 mg, 0,5 mmol) en DMF (2 ml) se agregó 2-(4-fluoro-fenil)-pirrolidina racémica (99 mg, 0,6 mmol), DIEA (261 µl, 1,5 mmol), y HATU (228 mg, 0,6 mmol) y la mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. El DMF se eliminó in vacuo y el residuo se disolvió en acetato de etilo. La capa orgánica se lavó con NaOH 0,1 N, HCl 0,1 N, agua, y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 10% a 50% de EtOAc/DCM) dio un aceite (220 mg, 99%). Los diastereómeros se resolvieron (según se describió en Ejemplo 18) mediante HPLC de fase reversa para dar el isómero deseado **4** (78 mg, 35%) después de la liofilización. HPLC-MS t_R = 1,93 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{23}H_{27}FN_2O_4S$ 446,2, LCMS observada m/z 447,3 (M+H).

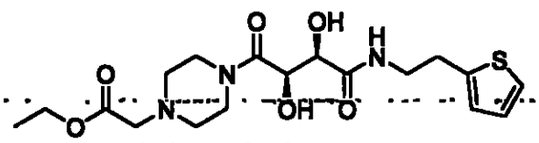
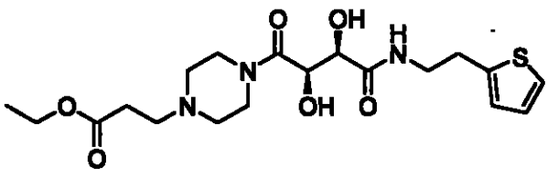
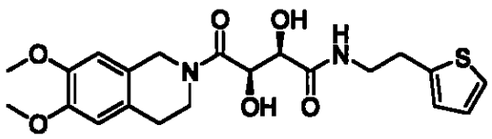
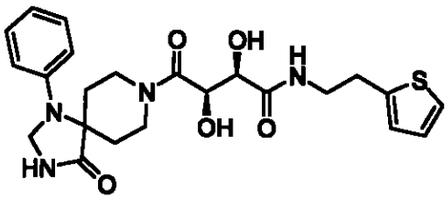
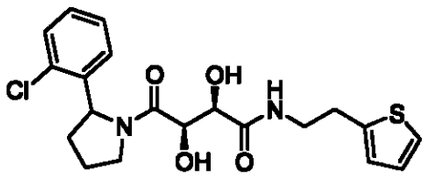
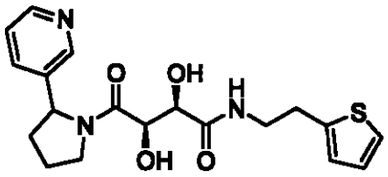
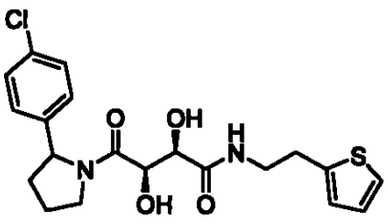
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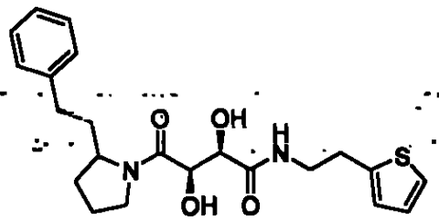
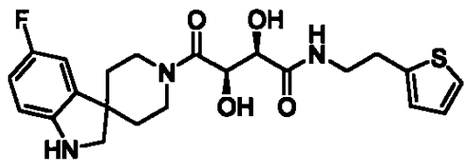
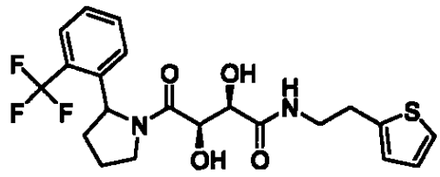
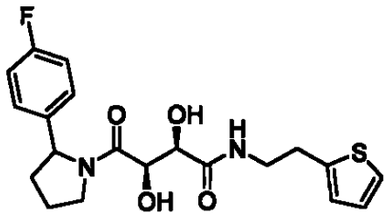
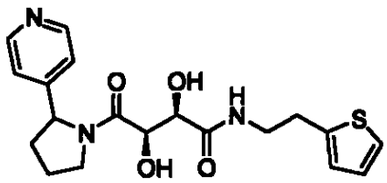
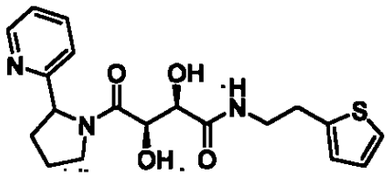
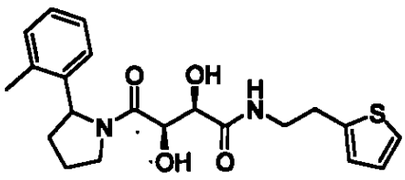
Se disolvió Compuesto **4** (78 mg, 0,17 mmol) en TFA:agua 90:10 (5 ml) y se agitó durante 4 horas a temperatura ambiente. La mezcla de reacción se desactivó con 1:1 ACN:agua (10 ml) y se concentró. El residuo se redisolvió en 1:1 ACN:agua (10 ml) y se concentró. La liofilización dio **5** como sólido blanco (62 mg, 87%). ^{1}H RMN (400 MHz, $CDCl_3$) mezcla de rotámeros δ 7,16- 6,8 (m, 8H),

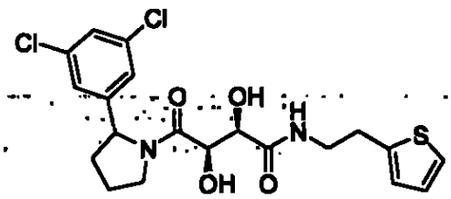
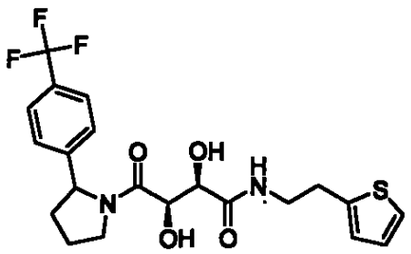
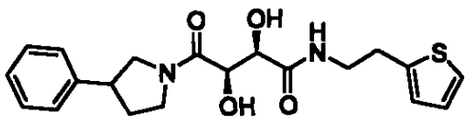
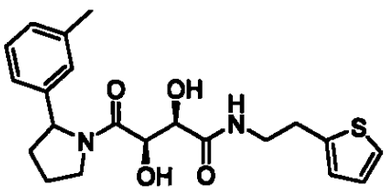
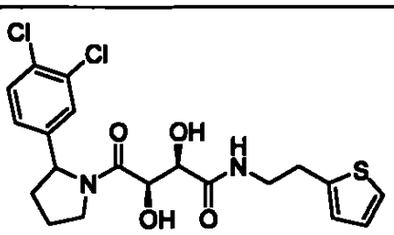
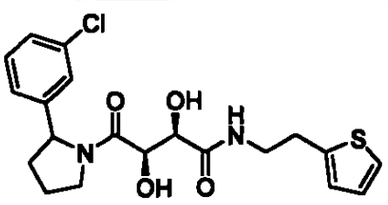
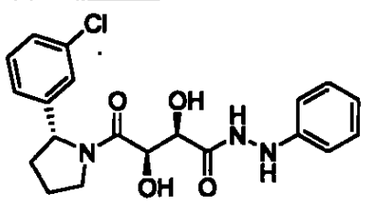
5,23-5,11 (m, 1H), 4,85 (m, 1H), 4,40-4,15 (m, 1H), 3,90-3,48 (m, 6H), 3,00 (m, 2H), 2,33 (m, 1H), 2,05-1,83 (m, 3H); HPLC-MS. t_R = 1,50 min. ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{20}H_{23}FN_2O_4S$ 406,1, LCMS observada m/z 407,2 (M+H). 1218

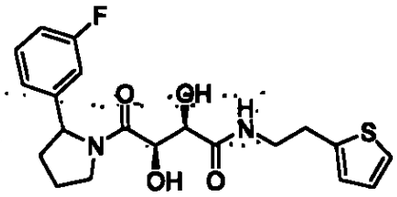
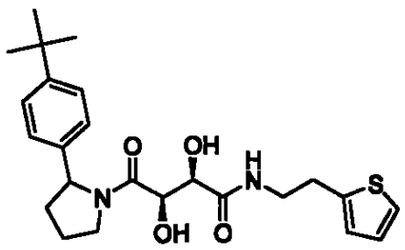
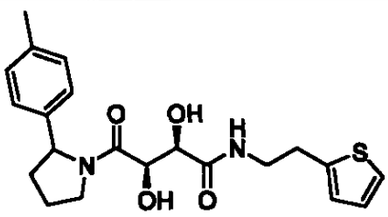
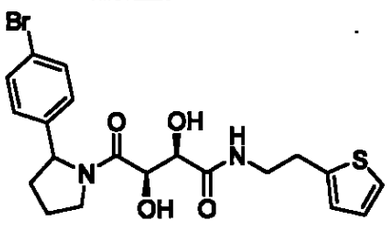
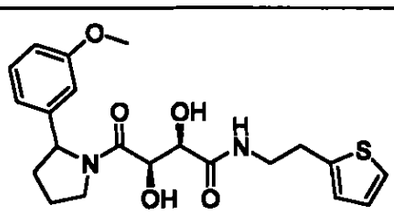
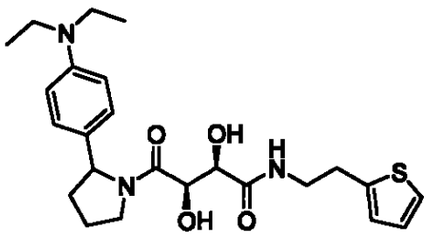
La siguiente tabla contiene compuestos sintetizados usando los procedimientos anteriores.

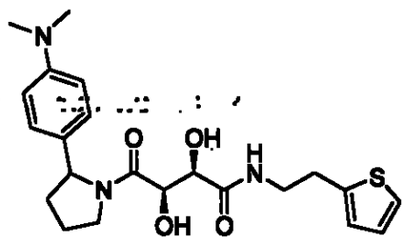
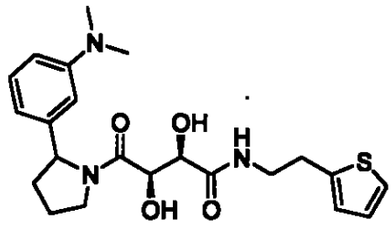
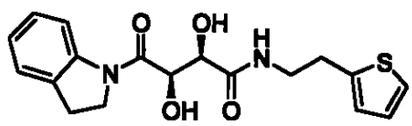
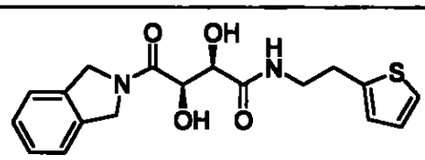
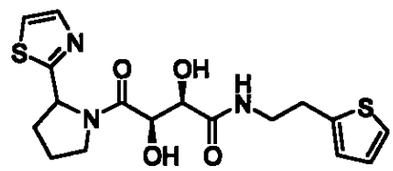
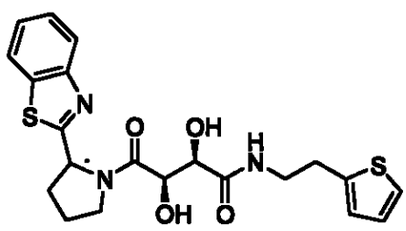
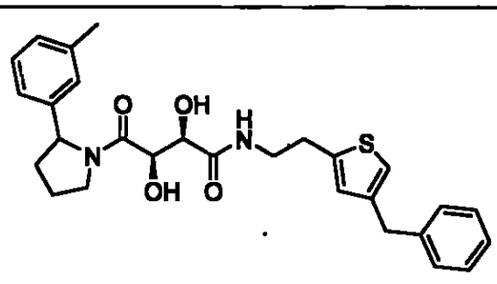
Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
6		433,2	434,1
7A		437,1	438,0
7B		445,2	446,1
8		403,2	404,1
9		412,2	413,2

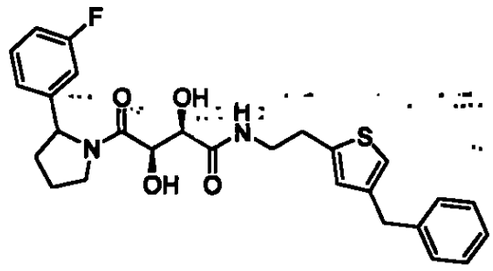
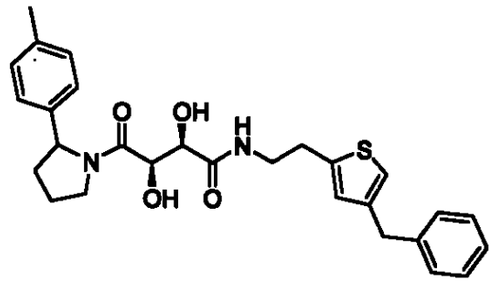
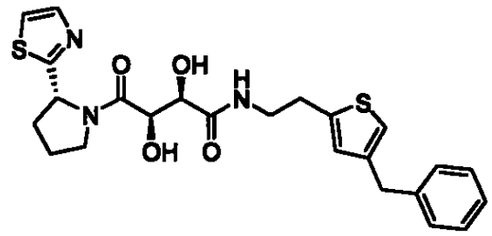
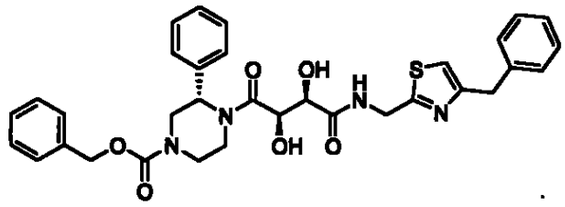
10		413,2	414,0
11		427,2	428,2
12		434,2	435,1
13		472,2	473,2
14		422,1	423,4
15		389,1	390,1
16		422,1	423,3

17		416,2	417,2
18		447,2	448,1
19		456,1	457,1
20		406,1	407,2
21		389,1	390,1
22		389,1	390,1
23		402,2	403,1

24		456,1	457,0
25		456,1	457,1
26		388,2	389,2
27		402,2	403,1
28		456,1	457,0
29A		422,1	423,1
29B		403,1	404,1

30		406,1	407,2
31		444,2	445,3
32		402,2	403,1
33		466,1	467,0
34		418,2	419,2
35		459,2	460,3

36		431,2	432,2
37		431,2	432,2
38		360,1	361,1
39		360,1	361,1
40		395,1	396,1
41		445,1	446,2
42		492,2	493,1

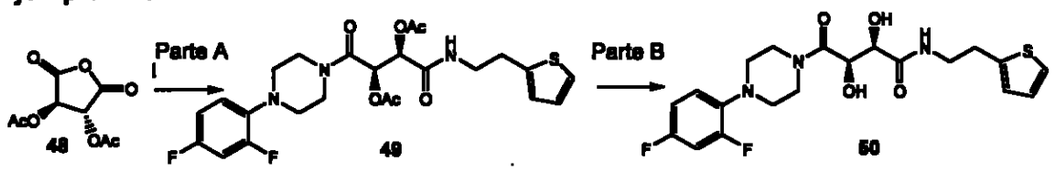
43		496,2	497,2
44		492,2	493,1
46		485,1	486,1
47		614,2	615,0

Ejemplo 2: Vía del anhidrido para inhibidores con estructura de diamida de tartrato

Una segunda vía general para compuestos con grupo diamida partiendo de un intermediario anhidro se delinea a continuación en el Ejemplo 2. El anhídrido (+)-diacetil –L-tartárico **(48)** es un artículo comercial y reacciona fácilmente con una variedad de aminas para generar un intermediario monoácido/monoamida. El solvente preferido para la apertura del anillo es DCM; aunque DMF, THF o dioxano también pueden ser compatibles. El siguiente paso de acoplamiento de

péptidos procede en una variedad de condiciones estándar provistas por el ejemplo 1. Los grupos acetato se pueden eliminar usando una variedad de condiciones incluyendo hidrazina/metanol, NaOMe en metanol, amoníaco/metanol, hidróxido de litio/THF/agua (saponificación), carbonato de potasio en metanol, o carbonato de MP. En algunas ocasiones, el conjunto de condiciones preferidas para la síntesis paralela es usar el carbonato de MP. También se observó que uno o ambos grupos protectores de acetato se pueden escindir durante transformaciones sintéticas relacionadas con nucleófilos, reactivos básicos, calentamiento en solventes próticos o exposición a reactivos organometálicos.

Ejemplo 2A:



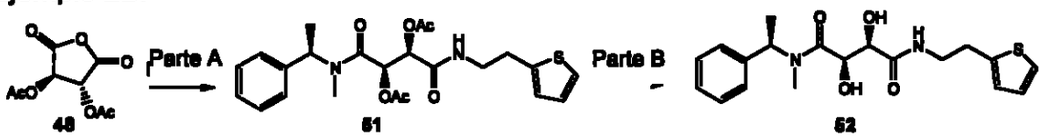
Parte A:

A 48 (26 mg, 0,1 mmol) en DMF (1 ml) se agregó 2,4-difluorofenilpiperazina (20 mg, 0,1 mmol). La mezcla de reacción se agitó durante 1,5 horas. A la mezcla bruta se agregó 2-tiofenetilamina (14 µl, 0,12 mmol), DIEA (38 µl, 0,22 mmol) y HATU (42 mg, 0,11 mmol). La reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se vertió en agua y se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con NaOH 0,1 N, HCl 0,1 N, y salmuera; se secaron sobre sulfato de sodio y se concentraron in vacuo para dar 49 como un aceite (49 mg, 94%). HPLC-MS t_R = 2,10 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{24}H_{27}F_2N_3O_6S$ 523,2, LCMS observada m/z 524,4 (M+H); pureza > 95% (ELSD).

Parte B:

A **49** (49 mg, 0,09 mmol) en MeOH (2 ml) se agregó hidrazina anhidra (5 µl, 0,16 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se concentró in vacuo y se secó en freezer para dar **50** como un polvo blanco (40 mg, 100%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,17 (d, 1H, J = 5,2 Hz), 6,96 (m, 2H), 6,85 (m, 4H), 4,87 (s, 1H), 4,24 (s, 1H), 3,90 (m, 2H), 3,72 (m, 2H), 3,60 (m, 4H), 3,08 (m, 4H); HPLC-MS t_R = 1,85 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{20}H_{23}F_2N_3O_4S$ 439,1, LCMS observada m/z 440,2 (M+H).

Ejemplo 2B:



Parte A:

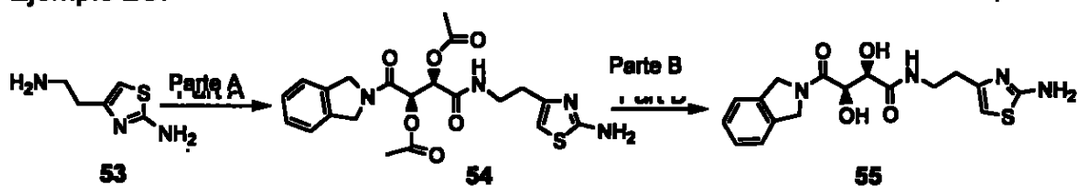
A **48** (26 mg, 0,1 mmol) en DMF (1 ml) se agregó N-metil-(1*R*-fenil-etil)-amina (15 µl, 0,1 mmol). La mezcla de reacción se agitó durante 1 hora. A la mezcla bruta se agregó 2-tiofenetilamina (47 µl, 0,4 mmol), HOBt (27 mg, 0,2 mmol), Resina carbodiimida de PS (312 mg, 0,4 mmol). A la mezcla de reacción se agregó resina PS-TsOH (0,6 mmol) y resina de carbonato de MP (0,4 mmol). La reacción se asentó hasta el día siguiente, se filtró y se concentró. Compuesto **51** se usó sin purificación adicional. HPLC-MS t_R = 1,82 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{23}H_{28}N_2O_6S$ 460,2, LCMS observada m/z 461,1 (M+H).

Parte B:

A **51** en MeOH (2 ml) se agregó hidrazina anhidra (5 µl, 0,16 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se concentró in vacuo, se purificó mediante HPLC prep. de fase reversa y se secó en freezer para dar **52** como un polvo blanco (6,7 mg, 18% overall). ^{1}H RMN (400 MHz, $CDCl_3$) rotómero principal δ 7,40- 7,25 (m, 6H), 7,16 (d, 1H, J = 4,8 Hz), 6,95 (app. t, 1H, J = 4,8 Hz), 6,87 (bs, 1H, NH), 5,96 (q, 1H, J

= 7,2 Hz), 4,91 (d, 1H, J = 1,2 Hz), 4,22 (d, 1H, J = 1,2 Hz), 3,60 (m, 2H), 3,08 (m, 2H), 2,79 (s, 3H), 1,56 (d, 3H, J = 5,7Hz); HPLC-MS t_R = 3,80 min (UV$_{254\text{-}nm}$, 10 min); masa calculada para la fórmula $C_{19}H_{24}N_2O_4S$ 376,2; LCMS observada m/z: 377,2 (M+H).

Ejemplo 2C:



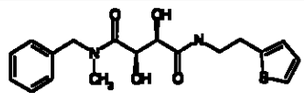
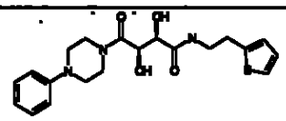
53 54 55

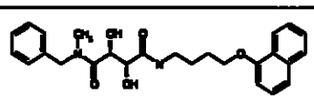
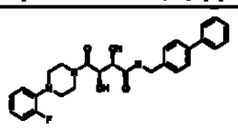
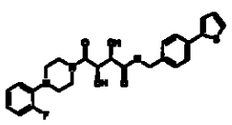
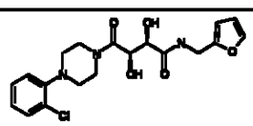
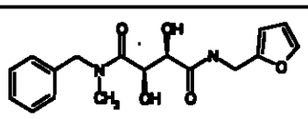
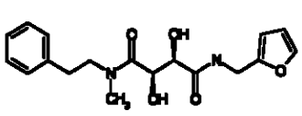
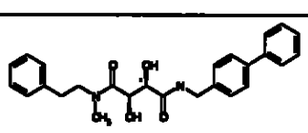
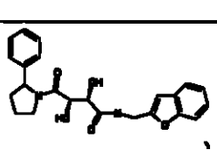
Se preparó el compuesto **53** de acuerdo con el procedimiento descripto por D. Miller et al (*J. Med. Chem.* **1999**, 42, 2287).

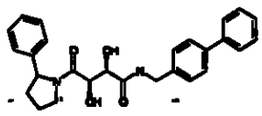
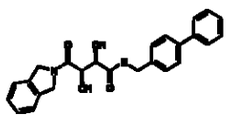
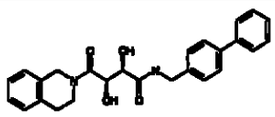
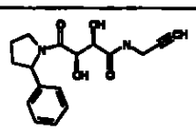
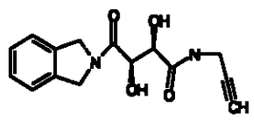
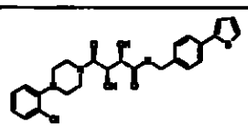
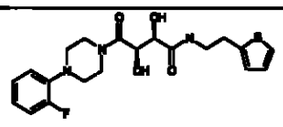
Partes A & B:

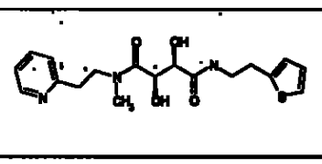
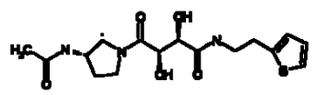
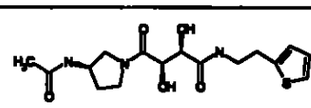
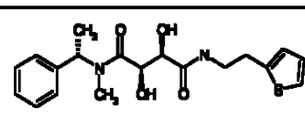
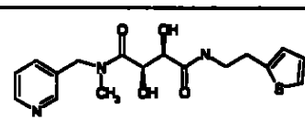
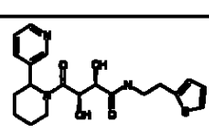
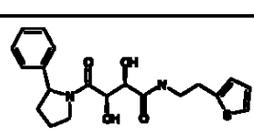
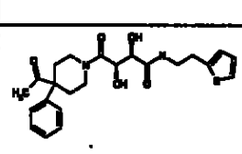
Se preparó el compuesto **55** usando procedimientos similares a aquellos descriptos en el Ejemplo 14, Partes D & E.

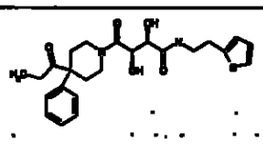
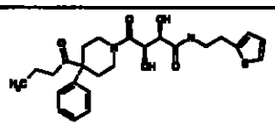
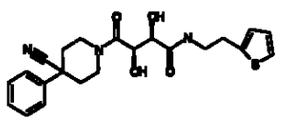
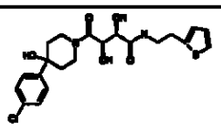
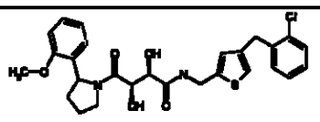
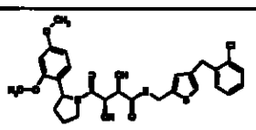
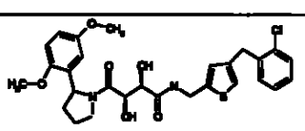
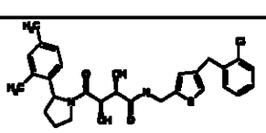
Datos para **54**: ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,51-7,25 (m, 6H), 6,22 (s, 1H), 5,75-5,67 (m, 2H), 5,36 (s, 2H), 5,28-4,61 (m, 4H), 3,69-3,40 (m, 2H), 2,74 (s, 1H), 2,24 (s, 3H), 2,18 (s, 3H). Datos para **55**: ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,54-7,26 (m, 6H), 6,24 (s, 1H), 5,22-5,02 (m, 2H), 4,94-4,82 (m, 3H) 4,42 (s, 1H), 3,72-3,50 (m, 2H), 2,92-2,76 (m, 2H) MS (EI) m/z M+H Obs. 377,1

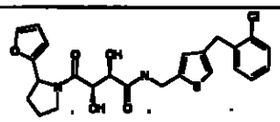
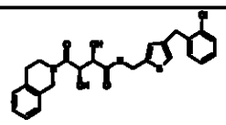
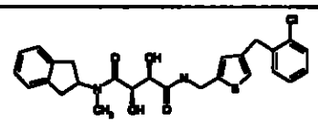
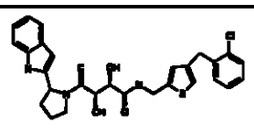
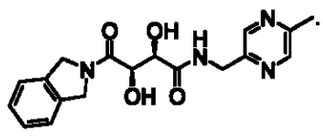
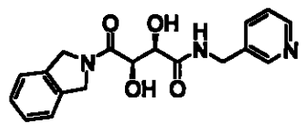
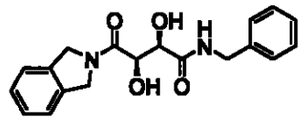
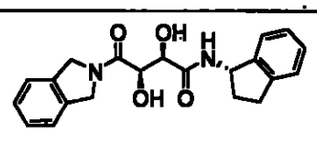
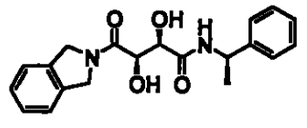
Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
56		362,1	363,1
57		403,2	404,1

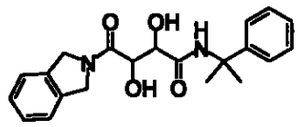
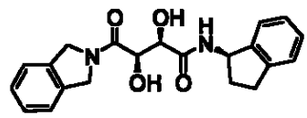
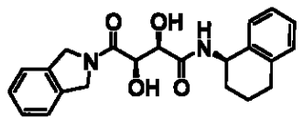
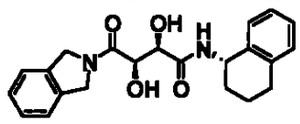
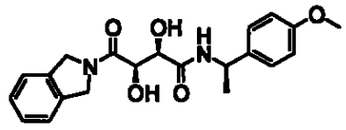
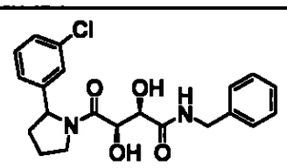
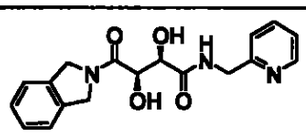
58		450,2	451,1
59		477,2	478,2
60		483,2	484,2
61		407,1	408,1
62		332,1	333,1
63		346,15	347,2
64		432,2	433,2
65		408,2	409,2

66		444,2	445,1
67		416,2	417,1
68		430,2	431,1
69		316,1	317,1
70		288,1	289,1
71		499,1	500,1
72		421,2	422,1
73		439,1	440,2

74		377,1	378,1
75		369,1	370,1
76		369,1	370,1
77		376,2	377,10
78		363,1	364,1
79		403,2	404,2
80		388,2	389,2
81		444,2	445,1

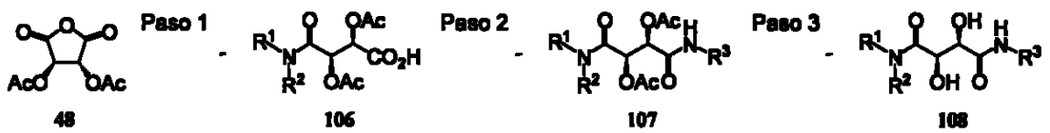
82		458,2	459,1
83		472,2	473,2
84		427,2	428,2
85		452,1	453,1
86		528,2	529,2
87		558,2	559,2
88		558,2	559,2
89		526,2	527,2

90		488,1	489,1
91		484,1	485,0
92		498,1	499,1
93		537,2	538,2
94		356,2	357,2
95		341,1	342,1
96		340,1	341,1
97		366,16	367,1
98		354,16	355,1

99		**368,17**	**369,1**
100		**366,16**	**367,1**
101		**380,17**	**381,2**
102		**380,2**	**381,2**
103		**384,2**	**385,1**
104		**402,1**	**403,1**
105		**341,1**	**342,1**

Ejemplo 2D:

Método A



Método A, Paso 1:

Se preparó Compuesto **106** (R1 = R2 = CH_2Ph) de **48** siguiendo el procedimiento descripto en el Ejemplo 4A, Parte C.

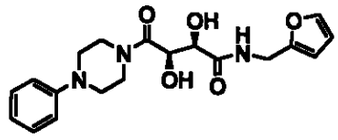
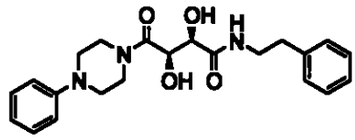
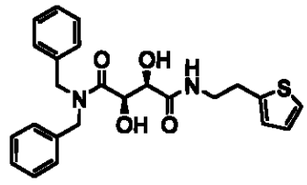
Método A, Paso 2:

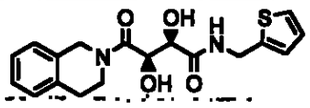
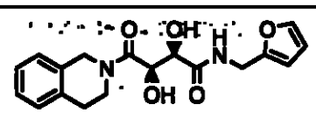
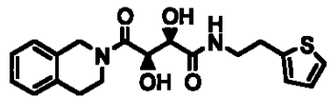
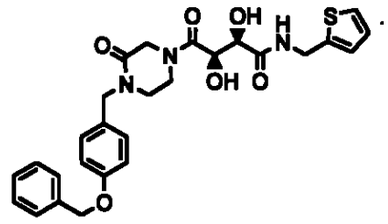
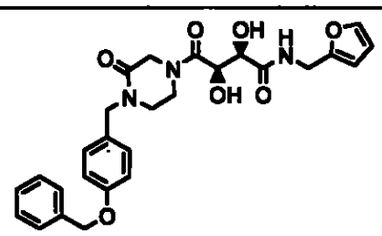
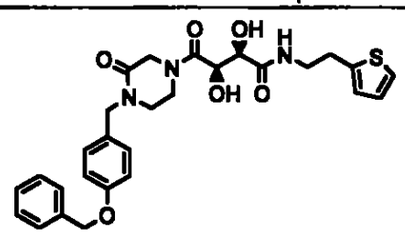
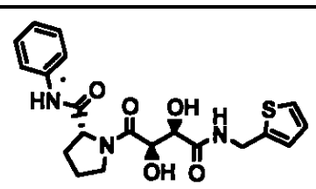
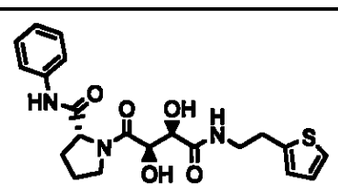
A una solución de THF/MeCN (1:1, 0,5 ml) de resina de EDC de poliestireno (57 mg, 3 eq) en un cartucho fritado de 6 ml se agregó una solución de THF/MeCN (1:1) de **106** (0,028 mmol), una solución de THF de HOBT (0,3 ml, 1,5 eq) y una solución de THF/MeCN 1M (1:1) de 2-furanetilamina (0,056 ml, 2 eq). El cartucho se tapó y se dejó agitar a 25°C durante 20 h. Se agregó resina de poliestireno isocianato (57 mg, 3 eq) y poliestireno trisamina (39 mg, 6 eq) seguidos por 0,5 ml de THF y la mezcla se agitó durante 6 h. La suspensión se filtró y el filtrado se concentró para dar **107** (R1 = R2 = CH_2Ph, R3 = $CH_2CH_2(C_4H_4O)$.

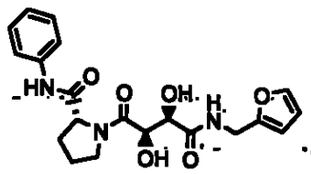
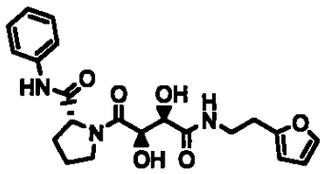
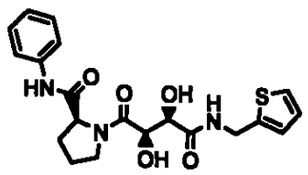
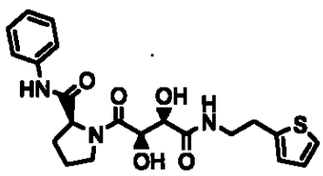
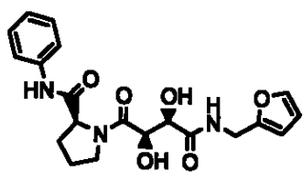
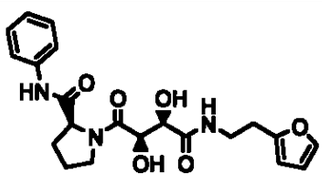
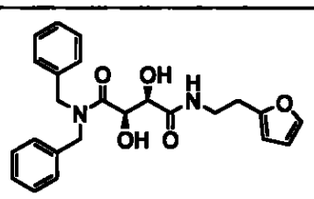
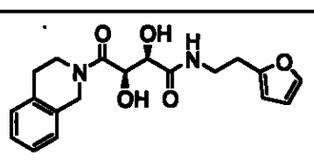
Método A, Paso 3:

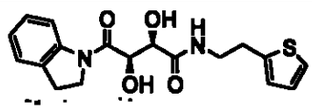
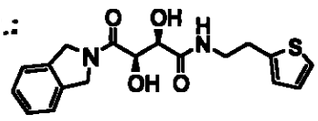
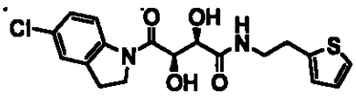
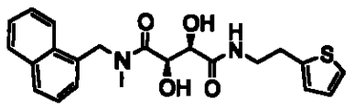
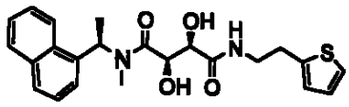
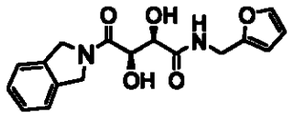
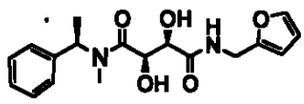
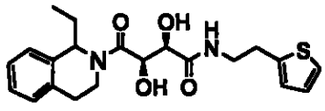
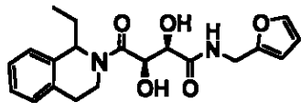
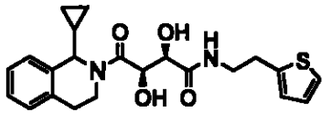
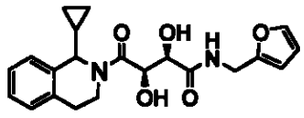
Se trató Compuesto **107** con una solución 2N de NH_3 en MeOH (3 ml) durante 1,5 h. El solvente se removió entonces in vacuo para dar **108** (R1 = R2 = CH_2Ph, R3 = $CH_2CH_2(C_4H_4O)$.

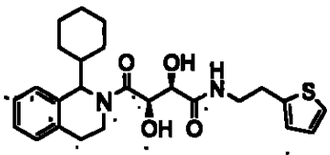
Ejemplo 2D Tabla A

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
109		373,2	374,2
110		397,2	398,2
111		438,2	439,1

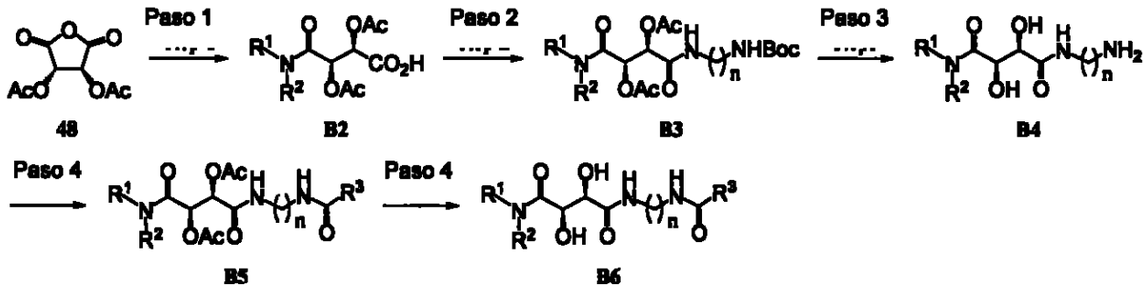
112		**360,1**	**361,1**
113		**344,1**	**345,1**
114		**374,1**	**375,1**
115		**523,2**	**524,1**
116		**507,2**	**508,1**
117		**537,2**	**538,1**
118A		**417,1**	**418,1**
118B		**431,2**	**432,2**

119		401,2	402,1
120		415,2	416,1
121		417,1	418,1
122		431,2	432,2
123		401,2	402,1
124		415,2	416,1
108		422,2	423,1
125		358,2	359,1

38		360,1	361,2
39		360,1	361,2
126		394,1	395,2
127		412,2	413,2
128		426,2	427,2
129		330,1	331,2
130		346,2	347,2
131		402,2	403,1
132		372,2	373,1
133		414,2	415,1
134		384,2	385,1

135		456,2	457,1

Método B



Método B, Paso 1:

Se preparó Compuesto **B2** (R^1 = CH_2Ph, R^2 = CH_3) a partir de **48** siguiendo el procedimiento descripto en el Ejemplo 4A Parte C.

Método B, Paso 2:

A una solución de DMF (40 ml) de **B2** (2,0 g, 5,93 mmol), HOBT (880 mg, 6,52 mmol), y N-Boc-1,3-propilendiamina (1,14 g, 6,52 mmol) se agregó EDCI (1,48 g, 7,61 mmol) a 25 °C bajo N_2. Después de agitar durante 20 h, 1N HCl se agregó, los productos se extrajeron con acetato de etilo (3X), se combinaron, luego se lavaron con $NaHCO_3$ sat., agua (3x), y se secaron sobre $MgSO_4$. Los productos luego se filtraron y se concentró in vacuo para dar **B3** (R^1 = CH_2Ph, R^2 = CH_3, n = 3).

Método B, Paso 3:

A una solución de MeCN (30 ml) de **B3** (1,18 g, 2,4 mmol) a 25°C se agregó 20 ml de una solución 4N de HCl en dioxano. La solución se tapó y se agitó 25 °C durante 2,5 h. El solvente se removió entonces in vacuo. El producto se disolvió entonces en 45 ml de THF/MeCN/DMF (4:4:1) y se agregó resina de poliestireno NEt_2 (4,5 g, 14,4 mmol). Después de agitar durante 1,5 h, la solución se filtró y la

resina se lavó con THF:MeCN (1:1). El filtrados se diluyeron entonces a 120 ml con THF/MeCN adicional (1:1) y **B4** (R^1 = CH_2Ph, R^2 = CH_3, n = 3) se usó en la preparación de la siguiente biblioteca:

Método B, Paso 4:

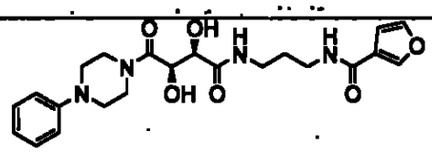
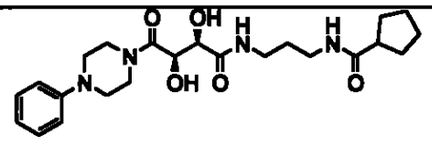
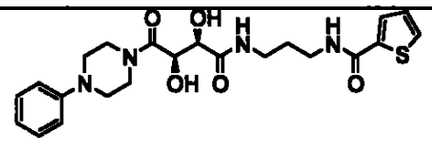
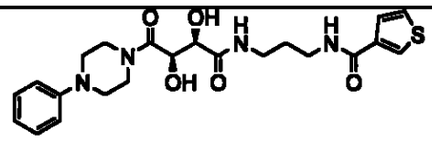
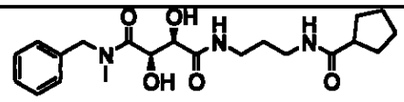
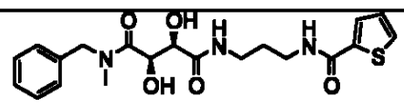
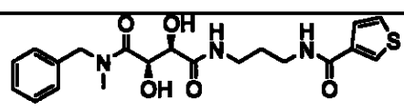
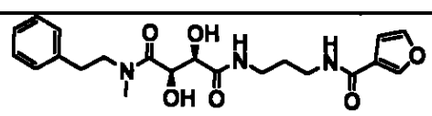
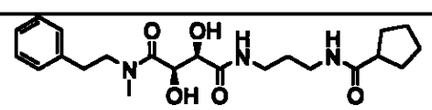
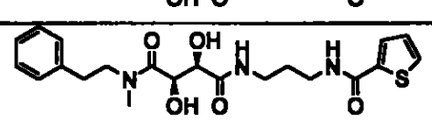
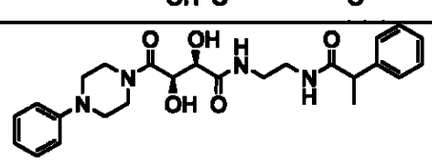
Se agregó resina EDC de poliestireno (30mg, 0,045 mmol) a 96 pocillos de una placa de microtitulación de pocillos profundos seguida de solución madre de MeCN/THF/DMF (6:6:1) (1 ml) de **B4** (0,015 mmol) y HOBT (0,0225 mmol). Luego, se agregaron soluciones madre 1M de cada uno de los ácidos individuales (R^1-96COOH) (0,023 ml, 0,021 mmol) a los pocillos, que luego se selló y se agitó a 25 °C durante 20h. Las soluciones se filtraron a través de una frita de polipropileno en una 2da. placa de microtitulación que contiene resina de poliestireno isocianato (3 equivalentes, 0,045 mmol) y resina de poliestireno trisamina (6 equivalentes, 0,09 mmol). Una vez lavada la placa superior con MeCN (0,5 ml), se retiró la placa, se selló la placa de microtitulación inferior y se agitó a 25 °C durante 16h. Luego, las soluciones se filtraron a través de una frita de polipropileno en una placa de recolección de 96 pocillos. Las pocillos de la placa superior se lavaron entonces con MeCN (0,5 ml), y la placa se removió. Luego, las soluciones resultantes en la recolección se transfirieron a viales y los solventes se eliminaron in vacuo mediante SpeedVac para dar amidas **B5**.

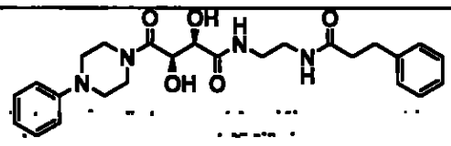
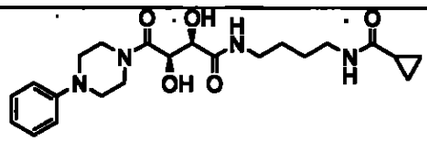
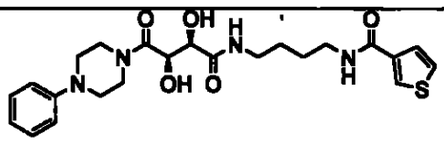
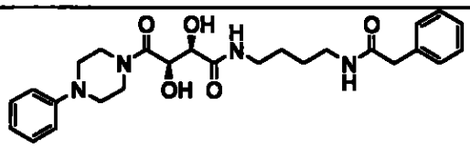
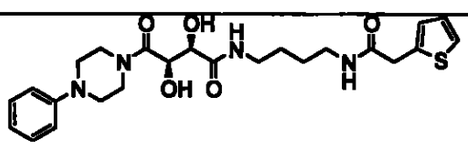
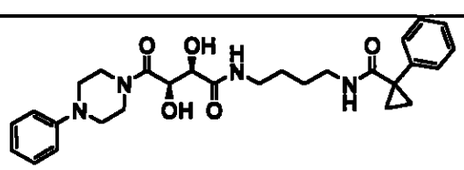
Método B, Paso 5:

Se prepararon compuestos **B6** a partir de **B5** siguiendo el procedimiento descripto en Método A, Paso 3 (ver arriba).

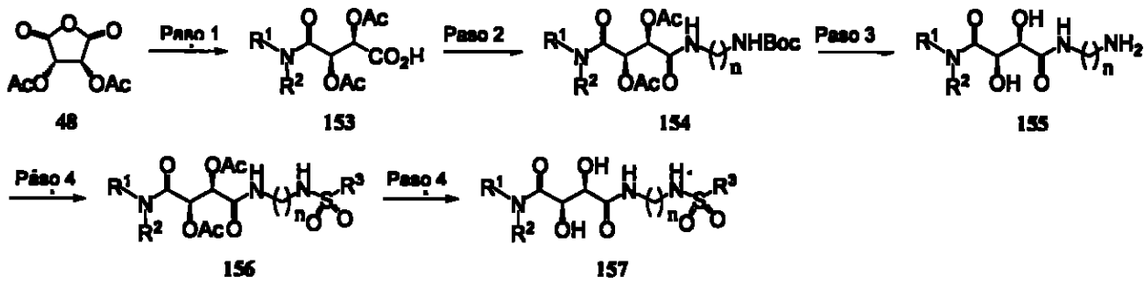
1340
1300

Ejemplo 2D Tabla B

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
136		444,2	445,2
137		446,3	447,3
138		460,2	461,3
139		460,2	461,3
140		405,2	406,2
141		419,2	420,2
142		419,2	420,2
143		417,2	418,2
144		419,2	420,2
145		433,2	434,2
146		468,2	469,3

147		468,2	469,3
148		432,2	433,2
149		474,2	475,3
150		482,3	483,3
151		488,2	489,3
152		508,3	509,3

Método C



Método C, Paso 1:

Se preparó Compuesto **153** (R^1R^2N = 4-fenilpiperazina) a partir de **48** siguiendo el procedimiento descripto en Método B, Paso 1 (ver arriba).

Método C, Paso 2:

Se preparó Compuesto **154** (R^1R^2N = 4-fenilpiperazina, n = 3) a partir de **153** siguiendo el procedimiento descripto en Método B, Paso 2 (ver arriba).

Método C, Paso 3:

Se preparó el compuesto **155** (R^1R^2N = 4-fenilpiperazina, n = 3) a partir de **154** siguiendo el procedimiento descripto en Método B, Paso 3 (ver arriba) y se usó en la preparación de la siguiente biblioteca:

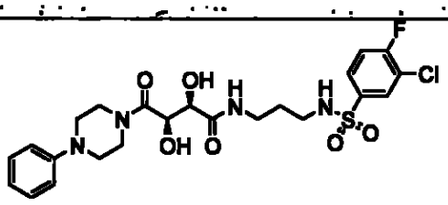
Método C, Paso 4:

Se agregó resina de poliestireno DIEA (30mg, 0,045 mmol) a 72-pocillos de una placa de microtitulación de polipropileno de pocillo profundo seguida de una solución madre de MeCN/THF/DMF (6:6:1) (1 ml) de **155** (0,015 mmol). Luego, se agregaron soluciones madre 1M de cada uno de los cloruros de sulfonilo individuales (R^1-72SO_2Cl) (0,023 ml, 0,021 mmol) a los pocillos, que luego se sellaron y se agitaron a 25 °C durante 20h. Las soluciones se filtraron a través de una frita de polipropileno en una segunda placa de microtitulación que contenía resina de poliestireno isocianato (3 equivalentes, 0,045 mmol) y resina de poliestireno trisamina (6 equivalentes, 0,09 mmol). Una vez lavada la placa superior con MeCN (0,5 ml), se retiró la placa, la placa de microtitulación inferior se selló y se agitó a 25 °C durante 16h. Luego, las soluciones se filtraron a través de una frita de polipropileno en una placa de recolección de 96 pocillos. Los pocillos de la placa superior se lavaron luego con MeCN (0,5 ml), y se retiró la placa. Luego, las soluciones resultantes en la placa de recolección se transfirieron a viales y los solventes se eliminaron in vacuo mediante un SpeedVac para dar las sulfonamidas **156.**

Método C, Paso 5:

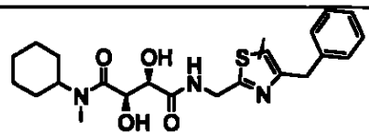
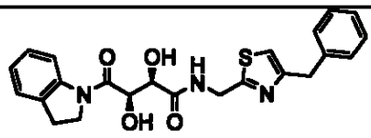
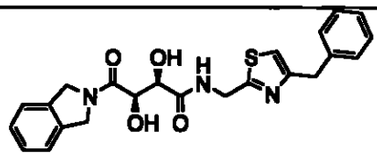
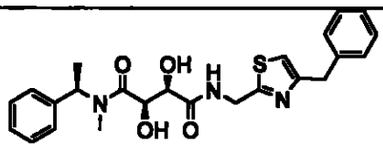
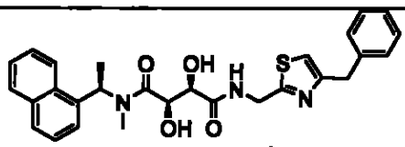
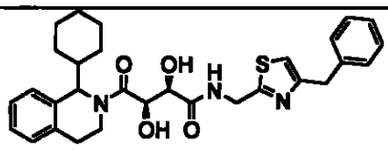
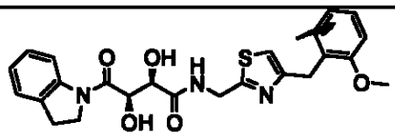
Se prepararon compuestos **157** a partir de **156** siguiendo el procedimiento descripto en Método A, Paso 3 (ver arriba).

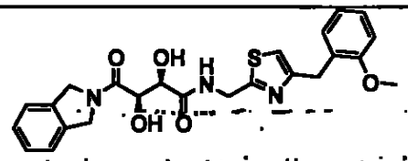
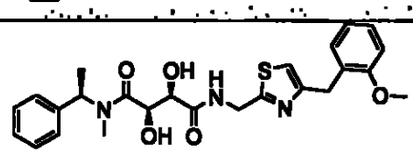
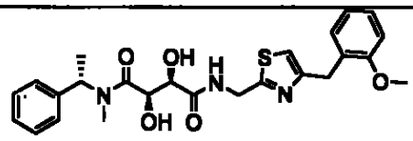
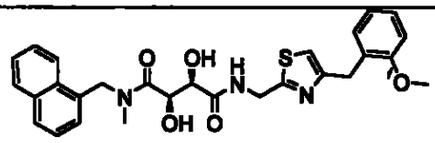
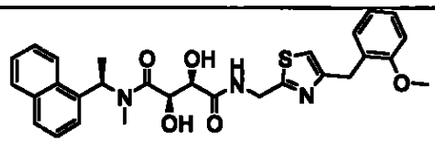
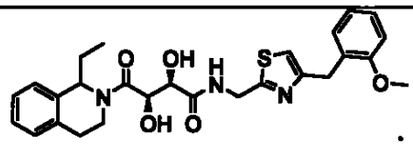
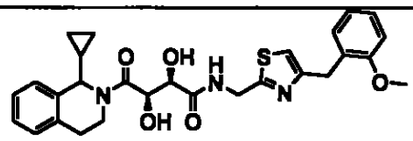
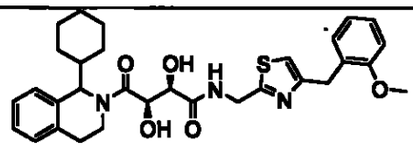
Ejemplo 2D Tabla C

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
157		542,2	543,3

Estos compuestos se prepararon usando el Método A:

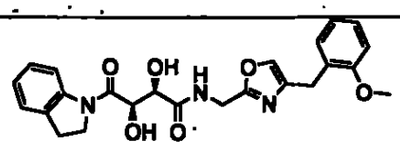
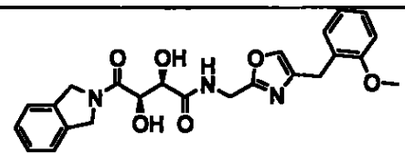
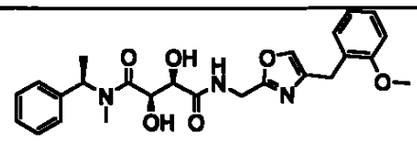
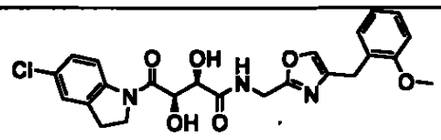
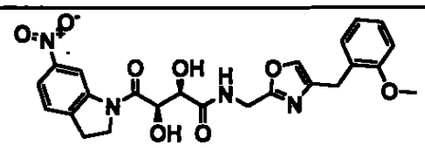
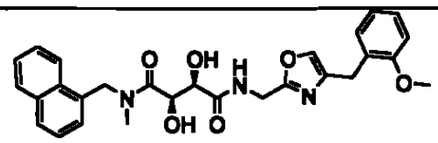
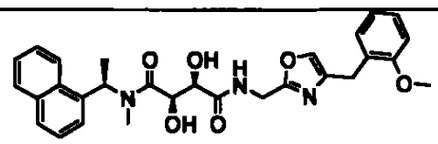
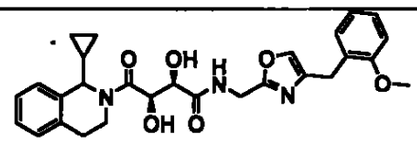
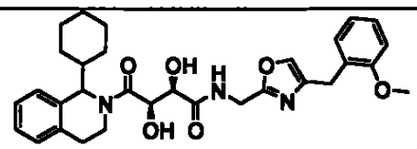
Ejemplo 2D Tabla D

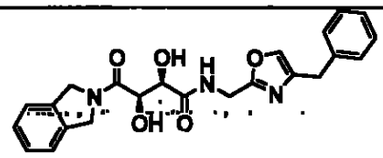
Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
158		431,2	432,2
159		437,1	438,2
160		437,1	438,2
161		453,2	454,3
162		503,2	504,3
163		533,2	534,2
164		467,2	468,3

165		467,2	468,3
166		483,2	484,3
167		483,2	484,3
168		519,2	520,3
169		533,2	534,3
170		509,2	510,3
171		521,2	522,3
172		563,2	564,3

Estos compuestos se prepararon usando el Método A:

Ejemplo 2D Tabla E

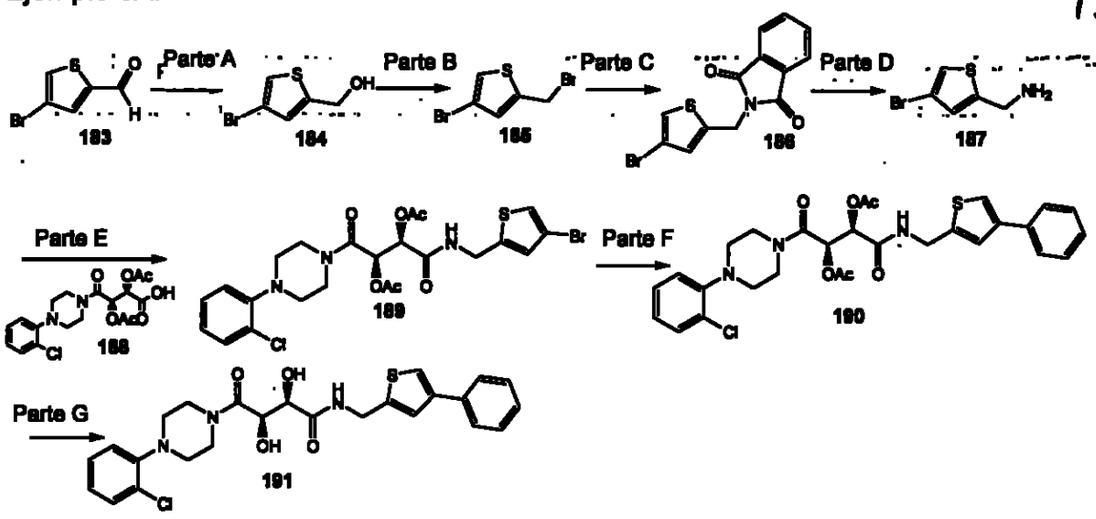
Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
173		451,2	452,3
174		451,2	452,3
175		467,2	468,3
176		485,1	486,3
177		496,2	497,3
178		503,2	504,3
179		517,2	518,3
180		505,2	506,3
181		547,3	548,3

182		421,2	422,2

Ejemplo 3: Compuestos con heteroaril biarilo

Un precursor del compuesto se puede preparar de manera que se facilite la síntesis de análogos directos. Ejemplos de esquemas para la síntesis de biarilos se enumeran a continuación. Se sabe que los haluros de arilo y "pseudo haluros" (es decir, triflatos) reaccionan con ácidos borónicos en una gama de condiciones establecidas (*Top. Curr. Chem.* **2002**, *219*, 12-49). Se conocen una diversidad de bases para esta reacción en la literatura, incluyendo carbonato de sodio, carbonato de potasio, carbonato de cesio, t-butóxido de potasio, t-butóxido de sodio, TEA, DIEA, fluoruro de potasio, y fosfato de potasio. Para la mayoría de las aplicaciones se prefirió el fosfato de potasio y dio producciones aceptables y quimioselectividad. También se usó una cantidad de solventes en la literatura para las reacciones de Suzuki, incluyendo THF, dioxano, NMP, DMF, DME, DMA, tolueno y agua. En general, descubrimos que los solventes preferidos son THF o dioxano. Los solventes también se pueden mezclar en varias porciones para mejorar la reactividad y/o quimioselectividad. Las fuentes de paladio para esta reacción también son numerosas, incluyendo $Pd(TPP)_4$, $Pd(OAc)_2$, $PdCl_2(TPP)_2$, $PdCl_2(dppf)$, $Pd_2(dba)_3$. En general, se descubrió que $PdCl_2(dppf)$ es una fuente preferida de paladio.

Ejemplo 3A:



Parte A:

A una solución helada en metanol (100 ml) de 4-bromo-tiofen-2-carbaldehído **(183)** (90%, 11,1 g, 58,1 mmol, 1,00 equiv) se agregó borohidruro de sodio en porciones (2,20 g, 58,1 mmol, 1,00 equiv) durante aproximadamente 10 minutos. El baño de enfriamiento se retiró y la solución de reacción se dejó reposar 30 min. La reacción se desactivó a ta mediante la adición de acetona (hasta que cesó la evolución del gas), se concentró, y se dividió entre acetato de etilo y HCl 0,1 N. La fase orgánica se lavó con agua, salmuera, se secó (sulfato de sodio), se filtró y luego se concentró para dar **184** como un aceite naranja (10,5 g, 95%) que se usó sin purificación adicional. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,18 (s, 1H), 6,93 (s, 1H), 4,81 (s, 2H).

Parte B:

A **184** (4,38 g, 22,7 mmol) en tolueno (25 ml) se agregó tribromuro de fósforo (2,36 ml, 25 mmol). La mezcla de reacción se calentó en un baño de aceite 90 °C durante 15 minutos. Después de enfriar a temperatura ambiente la mezcla de reacción se vertió sobre hielo y se extrajo con acetato de etilo. La capa orgánica combinada se lavó con agua (2x), solución saturada de bicarbonato de

sodio (1x) y solución de cloruro de sodio saturado, se secaron sobre sulfato de magnesio y se concentró para dar **185** as un aceite marrón claro (5,51 g, 95%). El material se usó sin purificación adicional.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21 (s, 1H), 7,03 (s, 1H), 4,66 (s, 2H).

Parte C:

A **185** (5,51 g, 21,5 mmol) en DMF (20 ml) se agregó ftalimida (3,80 g, 25,8 mmol) y carbonato de cesio (7,72 g, 23,7 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se filtró y el filtrado se concentró. El residuo se disolvió en acetato de etilo y agua. La capa orgánica se separó, se lavó con solución de cloruro de sodio saturado, se secó sobre sulfato de sodio y se concentró para dar un sólido marrón. La recristalización a partir de ~30 % de acetato de etilo/hexanos dio **186** como un sólido durazno (6,38 g, 2 gotas, 92%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,86 (m, 2H), 7,72 (m, 2H), 7,11 (s, 1H), 7,07 (s, 1H), 4,97 (s, 2H). HPLC-MS t_R = 2,02 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{13}H_8BrNO_2S$ 321,0, LCMS observada m/z 322,0 (M+H).

Parte D:

Una suspensión de **186** (5,76 g, 17,8 mmol) e hidrato de hidrazina (3,5 ml, 72 mmol) en etanol (50 ml) se calentó a reflujo. La suspensión se aclaró al calentarla antes que se formase una precipitado espeso. La mezcla de reacción se calentó durante 1 hora y se enfrió. El precipitado blanco se quebró mediante la adición de etanol (50 ml) y la sonicación de la mezcla. El precipitado se eliminó mediante filtración y los sólidos se lavaron cuidadosamente con etanol y acetato de etilo. El filtrado se concentró in vacuo. El residuo se disolvió en acetato de etilo y agua. Las capas se separaron. La capa orgánica se lavó con solución de cloruro de sodio saturado, se secó sobre sulfato de sodio y se concentró para dar **187** como un aceite naranja amarronado (2,66 g, 78%). ^{1}H RMN (400 MHz,

$CDCl_3$) δ 7,10 (s, 1H), 6,84 (s, 1H), 4,04 (s, 2H). HPLC-MS t_R = 0,58 min (UV_{254} nm); Masa calculada para la fórmula C_6H_6BrNS 190,9, LCMS observada m/z 192,0(M+H).

Parte E:

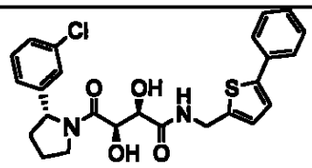
Siguiendo el procedimiento descripto en el Ejemplo 1 parte A: a **188** (preparado según se describió en Ejemplo 4 Parte C de anhídrido (+)-diacetil-L-tartárico (48) y 2-clorofenilpiperazina) (916 mg, 2,22 mmol) en DMF (5 ml) se agregó **187** (502 mg, 2,61 mmol), DIEA (850 µl, 4,88 mmol) y HATU (928 mg, 2,44 mmol). La purificación mediante cromatografía en columna (SiO_2, 20% a 50% de EtOAc/DCM) dio **189** como una espuma blancuzca (652 mg, 50%). ^1H RMN (400 MHz, $CDCl_3$) δ 7,37 (dd, 1H, J = 1,2, 7,6 Hz), 7,25 (dt, 1H, J = 1,2, 7,6 Hz), 7,14 (d, 1H, J = 1,2 Hz), 7,03 (m, 2H), 6,92 (d, 1H, J = 1,2 Hz), 6,74 (m, 1H, NH), 5,92 (d, 1H, J = 3,6 Hz), 5,70 (d, 1H, J = 4,0 Hz), 4,73 (dd, 1H, J = 6,4, 15,2 Hz), 4,50 (dd, 1H, J = 5,6, 15,6 Hz), 3,83 (m, 3H), 3,65 (m, 1H), 3,20 – 3,00 (m, 4H), 2,21 (s, 3H), 2,11 (s, 3H); Masa calculada para la fórmula $C_{23}H_{25}BrClN_3O_6S$ 585,0, LCMS observada m/z 586,1 (M+H).

Parte F:

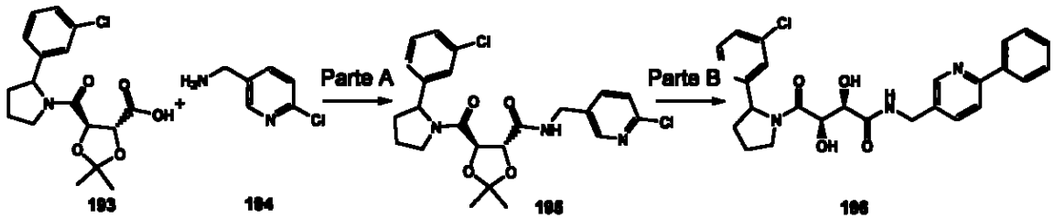
A **189** (59 mg, 0,1 mmol), se agregó ácido fenil borónico (13 mg, 0,11 mmol), fosfato de potasio (42 mg, 0,2 mmol), y $PdCl_2$(dppf) (4 mg, 0,005 mmol) dioxano (2 ml). La mezcla de reacción se saturó con argón y se calentó a 80 °C hasta el día siguiente. La mezcla de reacción se enfrió, se vertió en agua y se extrajo con EtOAc. Los orgánicos combinados se lavaron con salmuera, se secaron sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 20% de EtOAc/DCM) dio **190** como una espuma blancuzca (36 mg, 58%, 94% pureza). HPLC-MS t_R = 5,61 min ($UV_{254\ nm}$, 10 min.); masa calculada para la fórmula $C_{29}H_{30}ClN_3O_6S$ 583,2, LCMS observada m/z 584,2 (M+H).

Parte G:

A **190** (36 mg, 0,062 mmol) en metanol se agregó metóxido de sodio 0,5 M en metanol (6 µl, 0,003 mmol). La mezcla de reacción se agitó durante 1,5 horas a temperatura ambiente, se desactivó con HCl 0,1 N y se concentró. La purificación mediante LC prep. de fase reversa dio **191** como un sólido blanco (3,2 mg, 10%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,55 (dd, 2H, J = 1,2, 8,4 Hz), 7,40 a 7,20 (m, 9H), 7,09 (m, 1H, NH), 4,91 (d, 1H, J = 2,4 Hz), 4,70 (m, 2H), 4,33 (d, 1H, J = 2,0 Hz), 4,00 (m, 2H), 3,85 (m, 2H), 3,20 (m, 4H); HPLC-MS t_R = 1,94 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{25}H_{28}ClN_3O_4S$ 499,1, LCMS observada m/z 500,2 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
192		484,1	485,0

Ejemplo 3B: 3-Piridil-Biarilo



Parte A:

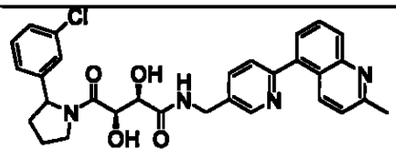
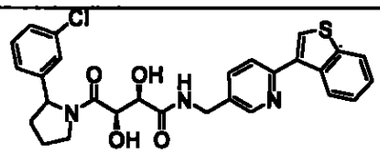
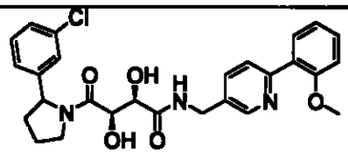
A **193** (preparado según se describió en Ejemplo 1) (1,5 g, 4,24 mmol) en DMF (10 ml) se agregó **194** (0,725 g, 5,09 mmol) y HATU (1,94 g, 5,09 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo, se lavó con bicarbonato de sodio saturado y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 80% de acetato de etilo/hexanos) dio **195** como un aceite incoloro (1,73 g, 86%). HPLC-MS t_R = 1,92

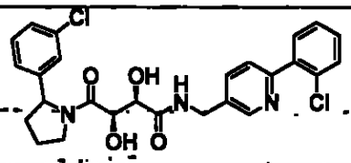
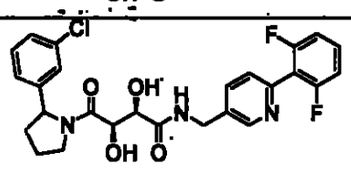
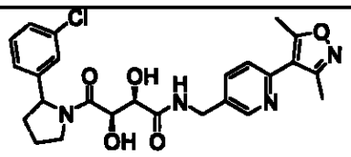
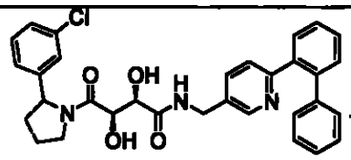
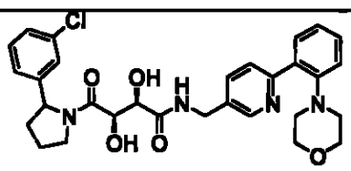
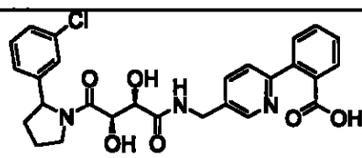
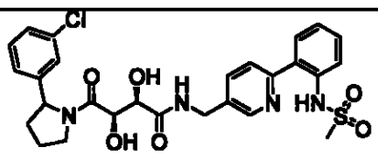
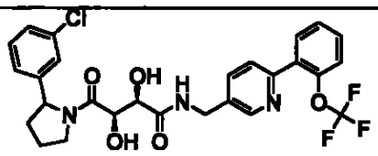
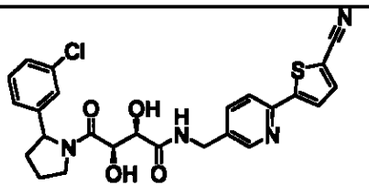
y 1,97 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{23}H_{25}Cl_2N_3O_4$ 477,1, LCMS observada m/z 478,1 (M+H).

Parte B:

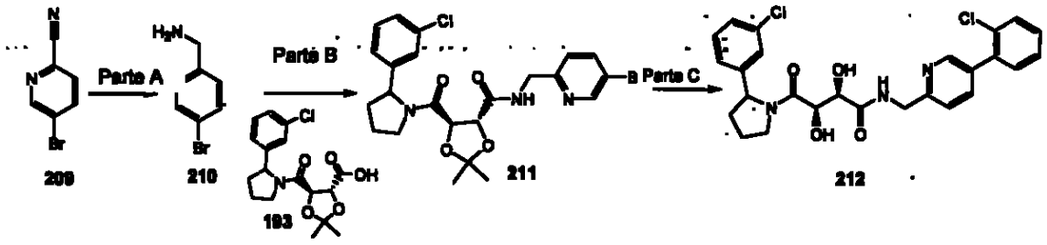
Paso 1: A ácido fenil borónico (10 mg, 0,084 mmol), fosfato de potasio (36 mg, 0,168 mmol) y $PdCl_2$(dppf) (3,1 mg, 10 mol%) bajo argón en un vial de 4-ml se agregó **195** (20 mg, 0,042 mmol) en dioxano (0,5 ml). La mezcla de reacción se calentó a 100 °C durante 16 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se diluyó con acetato de etilo y se filtró a través de Celite. El filtrado se concentró. HPLC-MS t_R = 2,01 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{29}H_{30}ClN_3O_4$ 519,2, LCMS observada m/z 520,2 (M+H).

Paso 2: El material bruto del Paso 1 se disolvió en TFA:agua 80:20 (1 ml) a 0 °C y se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se desactivó con agua:acetonitrilo 1:1 (2 ml) y se concentró. La purificación mediante LC prep. de fase reversa dio **196** como un sólido después de la liofilización. HPLC-MS t_R = 3,54 min ($UV_{254\ nm}$, 10 min); Masa calculada para la fórmula $C_{26}H_{26}ClN_3O_4$ 479,2, LCMS observada m/z 480,2 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
197		544,2	454,2
198		535,1	536,2
199		509,2	510,1

200		513,1	514,2
201		515,1	516,2
202		498,2	499,2
203		555,2	556,2
204		564,2	565,2
205		523,2	524,2
206		572,2	573,2
207		563,1	564,2
208		510,0	511,1

Ejemplo 3C: 2-Piridil-Biarilo



Parte A:

A 5-bromo-piridin-2-carbonitrilo **(209)** (1,0 g, 5,46 mmol) en tetrahidrofurano (10 ml) a –78°C se agregó hidruro de litio aluminio (1,0 M, 13,66 ml, 13,66 mmol). La reacción se agitó durante 2 horas a –78°C. La mezcla se desactivó a –78 °C con THF:agua 10:1. La mezcla se calentó hasta temperatura ambiente, se diluyó con acetato de etilo y se agitó con hidróxido de sodio 1,0 N durante 10 minutos. La mezcla de reacción se filtró a través de Celite y las capas se separaron. La capa orgánica se lavó con hidróxido de sodio 1,0 N y salmuera, se secó sobre sulfato de sodio y se concentró para dar **210** como un aceite (600 mg). El material se usó sin purificación adicional.

Parte B:

A **193** (1,13 g, 3,2 mmol) en DMF (10 ml) se agregó **210** (0,600 g, 3,2 mmol) y HATU (1,34 g, 3,52 mmol). La mezcla de reacción se agitó durante 5 horas a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo, se lavó con bicarbonato de sodio saturado y salmuera, se secó sobre sulfato de sodio y se concentró para dar **211** como un aceite (380 mg). HPLC-MS t_R = 2,00 y 2,05 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{23}H_{25}BrClN_3O_4$ 521,1, LCMS observada m/z 522,1 (M+H).

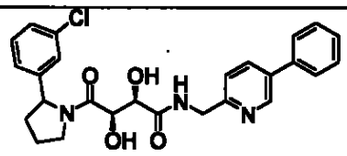
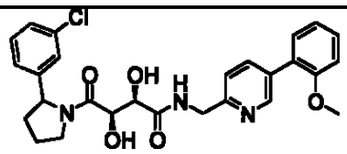
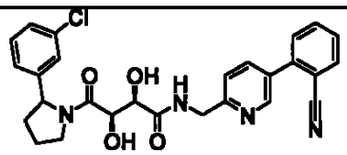
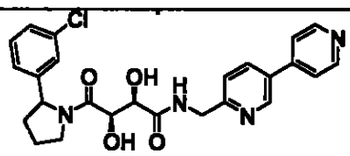
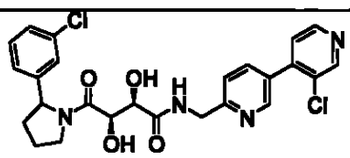
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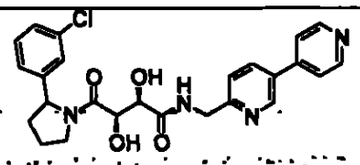
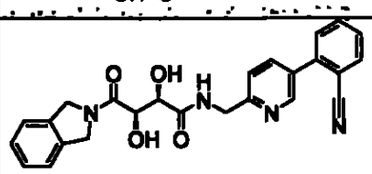
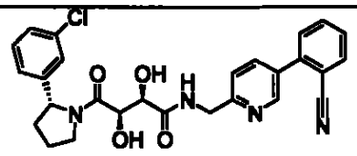
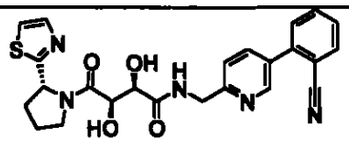
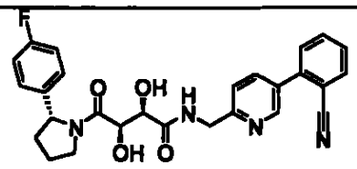
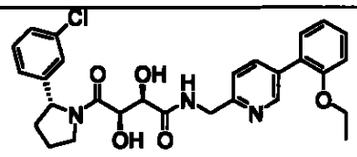
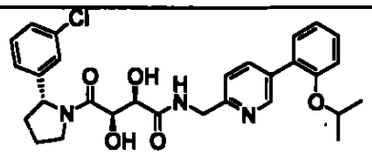
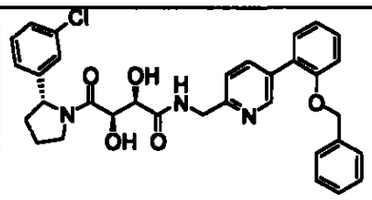
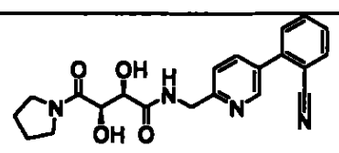
Paso 1: A 2-cloroácido fenil borónico (24 mg, 0,152 mmol), fosfato de potasio (65 mg, 0,306 mmol) y $PdCl_2$(dppf) (3,1 mg, 5 mol%) bajo argón en un vial de 4 ml se

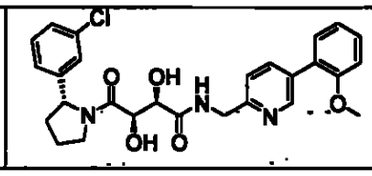
agregó **211** (40 mg, 0,076 mmol) en dioxano (0,5 ml). La mezcla de reacción se calentó a 100 °C durante 16 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se diluyó con acetato de etilo y se filtró a través de Celite. El filtrado se concentró.

Paso 2: El material bruto del Paso 1 se disolvió en 80:20 TFA:agua (1 ml) a 0 °C y se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se desactivó con agua:acetonitrilo 1:1 (2 ml) y se concentró. La purificación mediante LC prep. de fase reversa dio **212** como un sólido después de la liofilización. HPLC-MS t_R = 4,10 y 4,13 min ($UV_{254\ nm}$, 10 min); Masa calculada para la fórmula $C_{26}H_{25}Cl_2N_3O_4$ 513,2, LCMS observada m/z 514,2 (M+H).

Los siguientes compuestos se prepararon usando los procedimientos anteriores

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
213		479,2	480,1
214		509,2	510,1
215		504,2	505,1
216		480,2	481,1
217		514,1	515,0

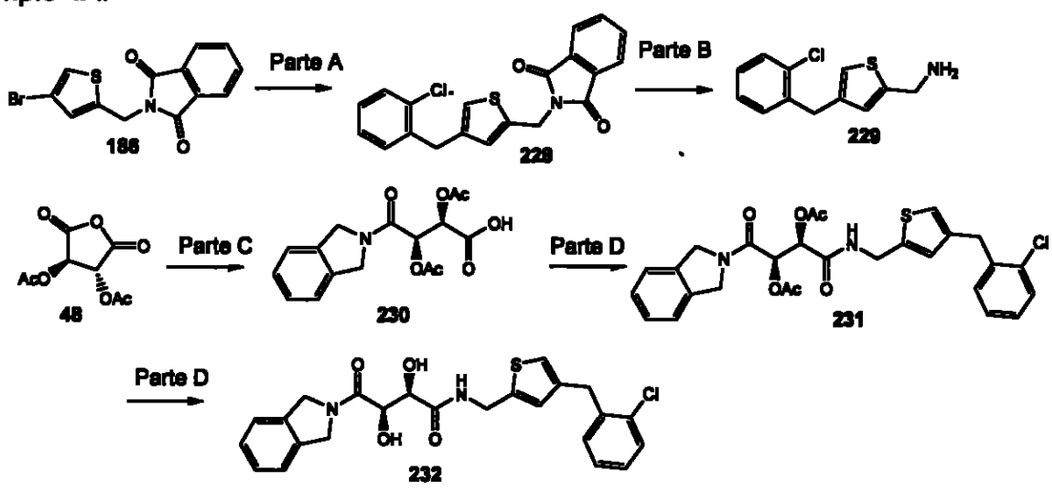
218		481,2	482,2
219		442,2	443,2
220		504,2	505,1
221		477,2	478,1
222		488,2	489,1
223		523,2	524,2
224		537,2	538,2
225		585,2	586,2
226		394,2	395,2

227		509,2	510,1

Ejemplo 4: Compuestos con grupo tiofen-bencilo

Los acoplamientos del tipo Negishi mediados por PD fueron una vía eficiente para generar un conjunto de compuestos relevantes para esta serie donde Ar era un anillo de fenilo. Mientras que se conoce un rango de fuentes de paladio, descubrimos que se prefirió $Pd(P^tBu_3)_2$. La reacción se puede correr en una diversidad de sistemas de solventes, incluyendo, dioxano, THF, o DMA. Un método preferido utilizó el solvente del reactivo de cinc, que se encontraba disponible de típicamente como una solución madre de THF. La eliminación del grupo t-BOC se puede completar usando una variedad de condiciones ácidas incluyendo TFA/agua, HCl en metanol, y HCl en dioxano; la totalidad de las cuales procedió igualmente bien con la mayoría de los sustratos de la reacción. Las reacciones se concentraron típicamente y se secaron por congelamiento para dar sales de HCl o TFA. Las reacciones de Negishi procedieron de manera comparable, y en muchos casos, mejor, cuando la amina estaba protegida por una ftalamida. El grupo protector de ftalamida se podría eliminar por medio de calentar etanol que contiene hidrato de hidrazina.

Ejemplo 4A:



Parte A:

A **186** (3,47 g, 10,8 mmol) y bis-(tri-*ter*-butil-fosfina) paladio (0,28 g, 0,54 mmol) en una matraz bajo argón se agregó cloruro de 2-clorobencil cinc (0,5 M en THF, 54 ml, 27 mmol). La reacción se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se diluyó con EtOAc (200 ml) y se lavó con solución de cloruro de sodio saturado (100 ml), solución de bicarbonato (100 ml) y salmuera (100 ml). La capa orgánica se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 20% de EtOAc/Hex) dio **228** como un sólido blanco (3,59 g, 91%). ^1H RMN (400 MHz, $CDCl_3$) δ 7,85 (dd, 2H, J = 3,2, 5,6 Hz), 7,71 (dd, 2H, J = 3,2, 5,6 Hz), 7,36 (m, 1H), 7,17 (m, 3H), 6,99 (d, 1H, J = 1,0 Hz), 6,78 (d, 1H, J = 1,0 Hz), 4,95 (s, 2H), 4,00 (s, 2H).

Parte B:

A **228** (3,55 g, 9,72 mmol) suspendido en etanol (35 ml) se agregó monohidrato de hidrazina (1,9 ml, 38,9 mmol). La mezcla de reacción se calentó a reflujo durante 2 horas. Después del enfriamiento, los sólidos se eliminaron mediante filtración y se lavaron con etanol (100 ml) y acetato de etilo (50 ml). El filtrado se concentró y el residuo se disolvió en acetato de etilo (150 ml) y agua (100 ml). La capa orgánica se separó, se lavó con salmuera (100 ml), se secó sobre sulfato de sodio y se concentró para dar **229** como un aceite amarillo (2,54 g, 99%).

Parte C:

A **48** (2,16 mg, 10,0 mmol) en DCM (10 ml) se agregó isoindolina (1,13 ml, 10,0 mmol). La reacción se agitó a temperatura ambiente durante 2 horas. El solvente se eliminó in vacuo y el residuo se dividió entre acetato de etilo y HCl 1,0 N. La capa orgánica se separó, se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró para dar **230** como un sólido oscuro (3,35 g,

100%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 13,63 (bs, 1H), 7,38 – 7,28 (m, 4H), 5,01 (d, 1H, J = 13,2 Hz), 4,93 (d, 1H, J = 14,0 Hz), 4,71 (d, 1H, J = 16,4 Hz), 4,56 (d, 1H, J = 15,6 Hz), 2,12 (s, 3H), 2,07 (s, 3H); HPLC-MS t_R = 1,10 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{16}H_{17}NO_7$ 335,1, LCMS observada m/z 336,1 (M+H).

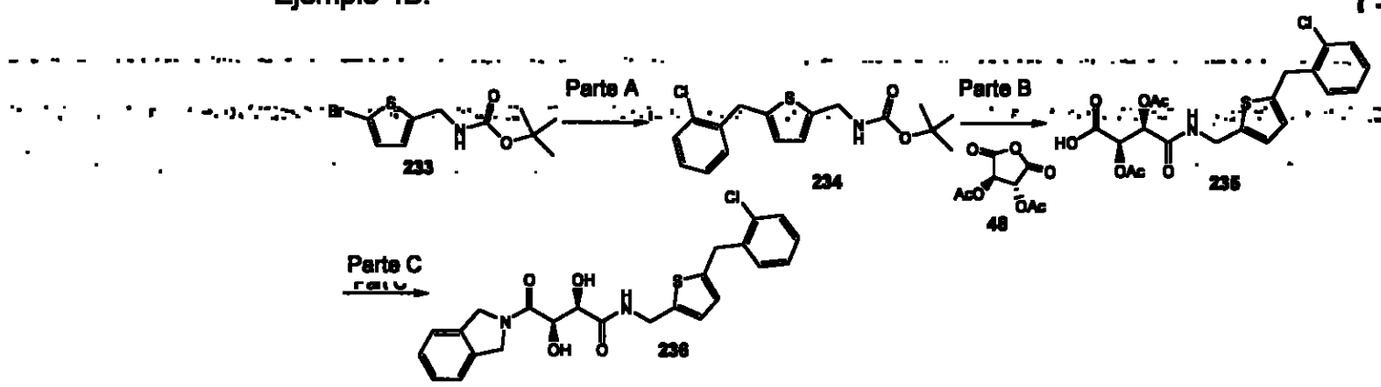
Parte D:

A **230** (18 mg, 0,053 mmol) en NMP (2 ml) se agregó **229** (19 mg, 0,08 mmol), DIEA (26 µl, 0,148 mmol) y HATU (30 mg, 0,08 mmol). La mezcla de reacción se agitó hasta el día siguiente. La mezcla de reacción se vertió en agua y se extrajo con acetato de etilo. La capa orgánica combinada se lavó con NaOH 0,1 N, HCl 0,1 N y salmuera, se secó sobre sulfato de sodio y se concentró para dar **231.**

Parte E:

A **231** (118 mg, 0,216 mmol) en metanol (3 ml) y DCM (3 ml) se agregó Resina de carbonato de MP (2,54 mmol/g, 85 mg). La reacción se agitó durante 3 horas, se filtró y se concentró para dar **232** como un sólido blanco (94 mg, 92%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,34 (t, 1H, J = 2,0 Hz) 7,79 (dd 1H, J = 0,8, 8,0 Hz), 7,64 (dt, 1H, J =1,6, 8,0 Hz), 7,47 (d, 1H, J = 7,6 Hz), 7,40 (dt, 1H, J = 0,8, 7,6 Hz), 7,35 – 7,27 (m, 4H), 6,97 (d, 1H, J = 1,6 Hz), 6,81 (d, 1H, J = 1,2 Hz), 5,67 (d, 1H, J = 6,4 Hz), 5,05 (d, 1H, J = 12,8 Hz), 4,97 (d, 1H, J = 8,0 Hz), 4,90 (d, 1H, J = 13,2 Hz), 4,75 (d, 1H, J = 13,2 Hz), 4,60 (m, 2H), 4,36 (m, 2H, J = 6,4, 15,2 Hz) 4,24 (dd, 1H, J = 3,2, 6,8 Hz); HPLC-MS t_R = 1,85 ($UV_{254\ nm}$); masa calculada para la fórmula $C_{24}H_{23}ClN_2O_4S$ 470,1, LCMS observada m/z 471,1.

Ejemplo 4B:



Parte A:

A **233** (4,00 g, 13,7 mmol) y bis-(tri-*ter*-butil-fosfina) paladio (0,28 g, 0,54 mmol) en una matraz bajo argón se agregó cloruro de 2-clorobencil cinc (0,5 M en THF, 69 ml, 34,5 mmol). La reacción se agitó a temperatura ambiente hasta el día siguiente. La mezcla de reacción se diluyó con EtOAc (200 ml) y se lavó con solución de cloruro de sodio saturado (100 ml), solución de bicarbonato (100 ml) y salmuera (100 ml). La capa orgánica se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 15% de EtOAc/Hex) dio **234** como un sólido blanco (4,5 g, 95%). ^1H RMN (400 MHz, $CDCl_3$) δ 7,36 (d, 1H J =3,6 Hz), 7,25 – 7,18 (m, 4H), 6,74 (s, 1H), 6,64 (d, 1H, J = 3,6 Hz), 4,40 (d, 2H, J = 5,2 Hz), 4,22 (s, 2H).

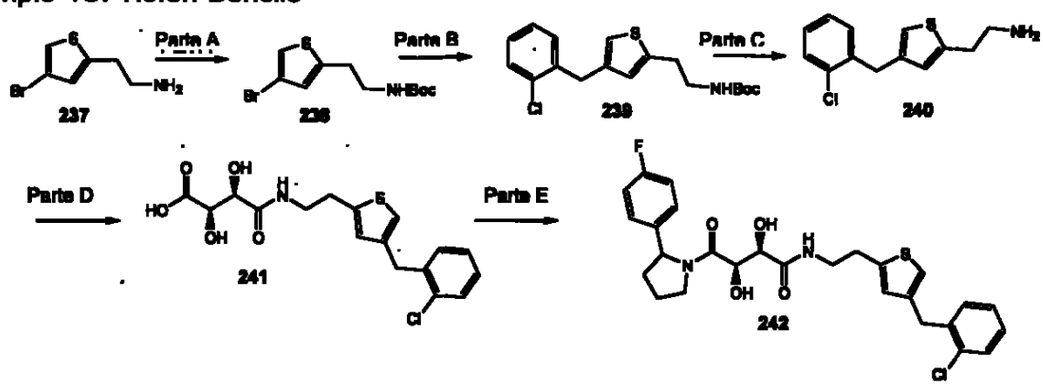
Parte B:

A **234** (450 mg, 1,34 mmol) se agregó HCl 4M en dioxano (1,5 ml) y la reacción se agitó durante 30 minutos. El dioxano se eliminó in vacuo. El residuo se disolvió en THF (10 ml) y se agregaron DIEA (500 µl, 2,68 mmol) y **48** (275 mg, 1,27 mmol). La reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo (60 ml) y se lavó con HCl 1,0 N. La capa orgánica se secó sobre sulfato de sodio y se concentró para dar **235** como una espuma amarilla (505 mg, 90%).

Parte C:

A 235 (40 mg, 0,09 mmol) en DMF (2 ml) se agregaron DIEA (50 µl, 0,29 mmol), isoindolina (14 mg, 0,12 mmol), y HATU (45 mg, 0,12 mmol). La mezcla de reacción se agitó durante 6 horas. La mezcla de reacción se diluyó con acetato de etilo (30 ml) y se lavó con NaOH 0,1 N, HCl 0,1 N y salmuera. La capa orgánica se secó sobre sulfato de sodio. El producto bruto se disolvió en metanol (3 ml) y carbonato de potasio (100 mg) in agua (1 ml) se agregó. Después de agitar durante 30 minutos, la mezcla de reacción se diluyó con acetato de etilo (20 ml) y se lavó con salmuera. La capa orgánica se secó sobre sulfato de sodio y se concentró. La purificación mediante LC prep. de fase reversa dio **236** como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,29 (t, 1H, J = 6,4 Hz) 7,42 (dd, 1H, J = 1,6, 7,8 Hz), 7,37 – 7,23 (m, 7H), 6,74 (d, 1H, J = 3,6 Hz), 6,65 (d, 1H, J = 3,2 Hz), 5,66 (d, 1H, J = 5,6 Hz), 5,04 (d, 1H, J = 14,8 Hz), 4,97 (bs, 1H), 4,89 (d, 1H, J = 15,2 Hz), 4,75 (d, 1H, J = 16,4 Hz), 4,60 (m, 2H), 4,38 (dd, 1H, J = 6,4, 15,2 Hz), 4,23 (bs, 1H), 4,15 (s, 2H); HPLC-MS t_R = 4,92 min ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{24}H_{23}ClN_2O_4S$ 470,1, LCMS observada m/z 471,1.

Ejemplo 4C: Tiofen-Bencilo



Se preparó el compuesto **237** de acuerdo con el procedimiento descripto por A. J. Hutchison et al (Patente europea 0323807 A2, Dic. 7, 1989)

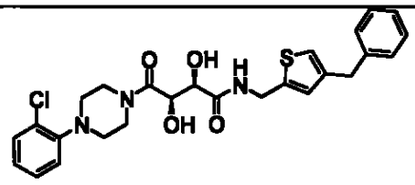
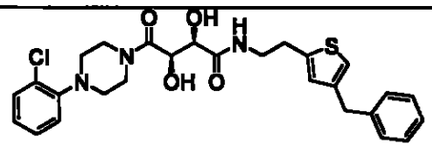
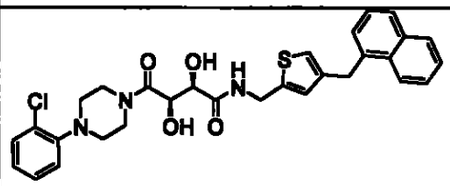
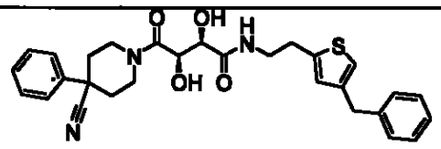
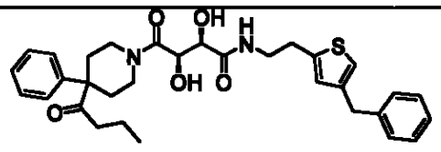
Partes A:

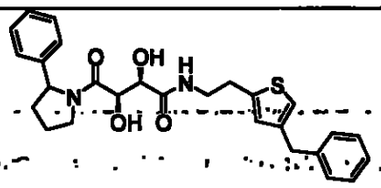
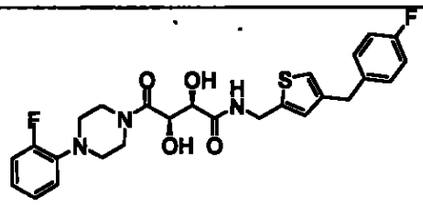
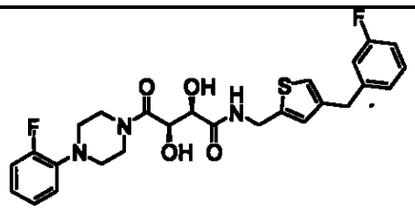
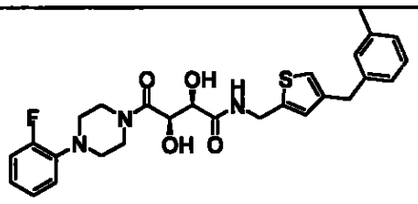
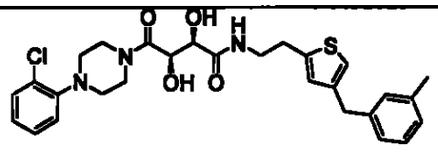
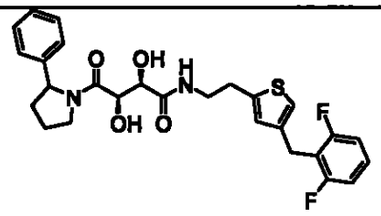
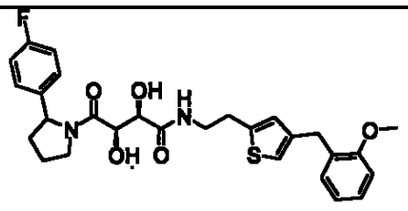
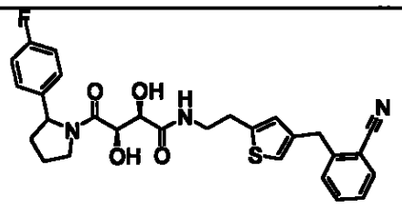
Se preparó el compuesto **238** mediante procedimientos similares a aquellos descriptos en el Ejemplo 5 Parte A.

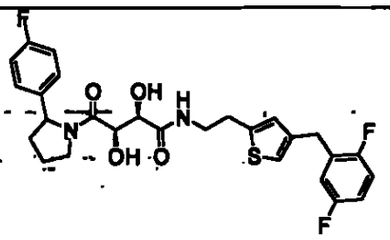
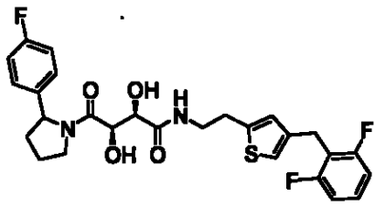
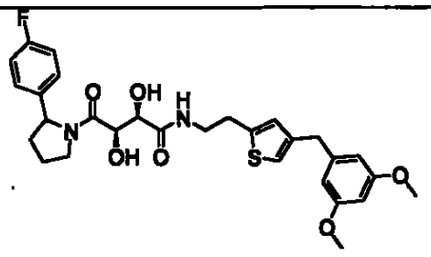
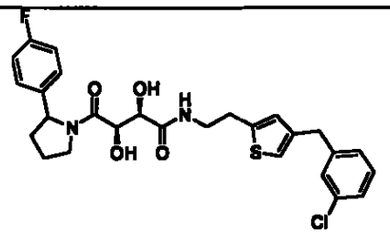
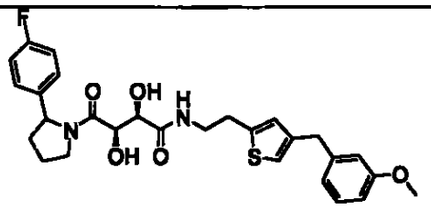
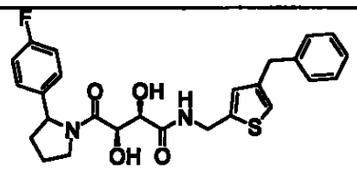
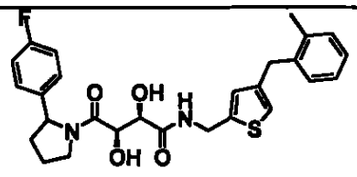
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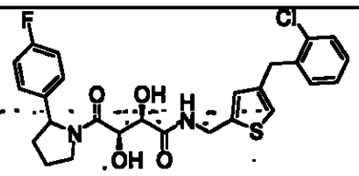
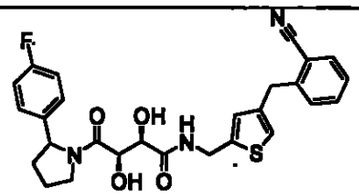
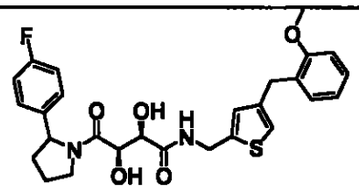
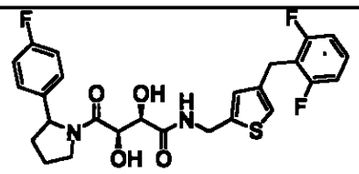
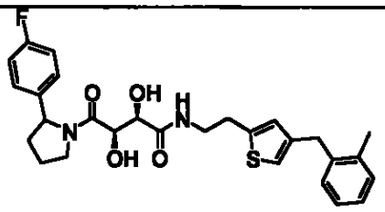
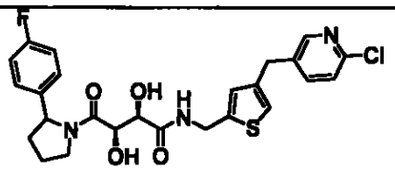
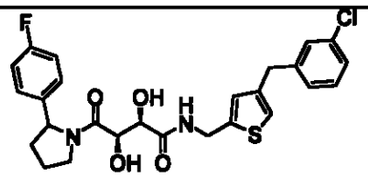
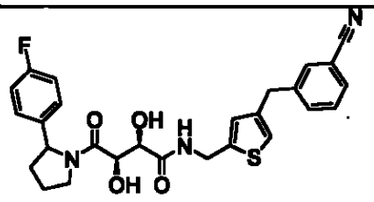
Se preparó Compuesto **242** mediante procedimientos similares a aquellos descriptos en el Ejemplo 4B Partes A a C. HPLC-MS t_R = 2,05 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{27}H_{28}ClFN_2O_4S$ 530,1, LCMS observada m/z 531,1 (M+H).

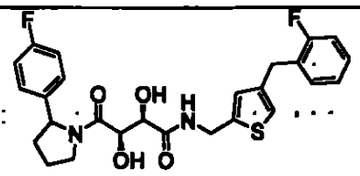
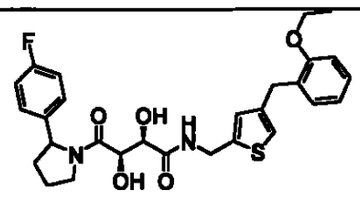
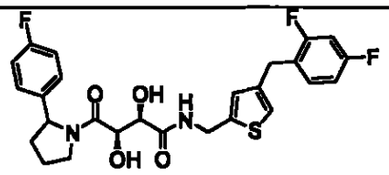
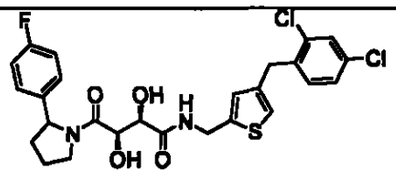
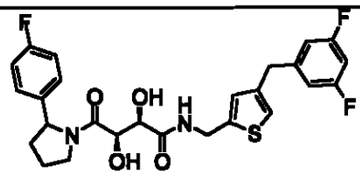
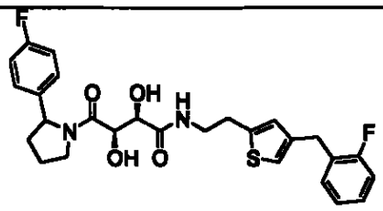
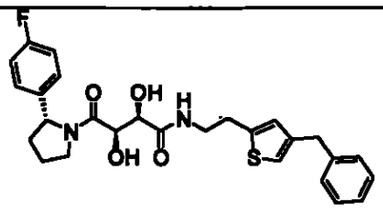
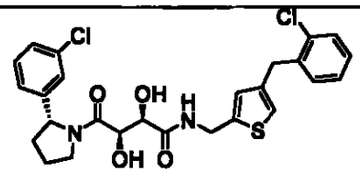
Los siguientes compuestos se prepararon mediante procedimientos descriptos en el Ejemplo 4A – 4C.

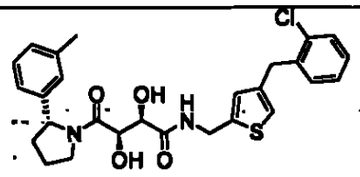
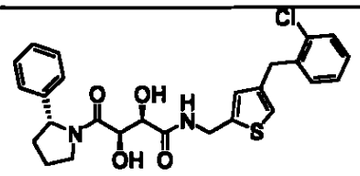
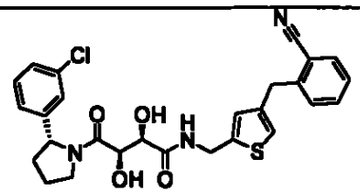
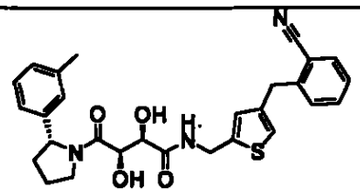
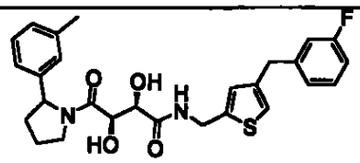
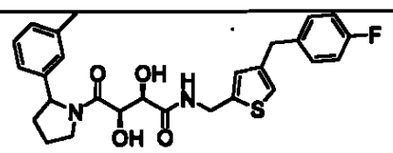
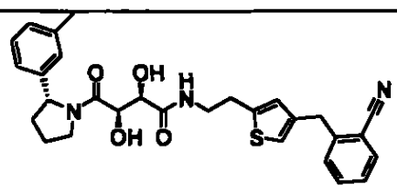
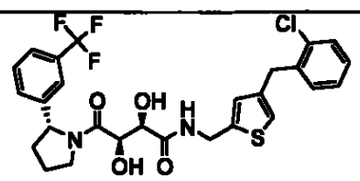
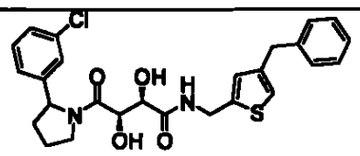
Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
243		513,2	514,2
244		527,2	528,1
245		563,2	564,2
246		517,2	518,2
247		562,3	563,2

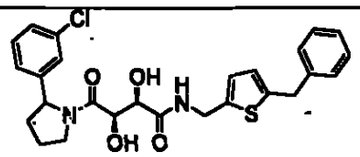
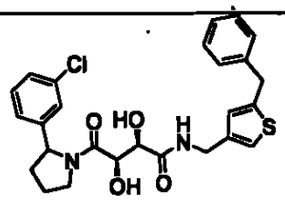
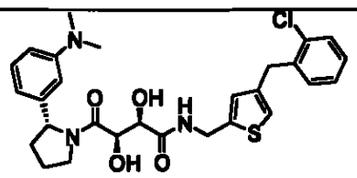
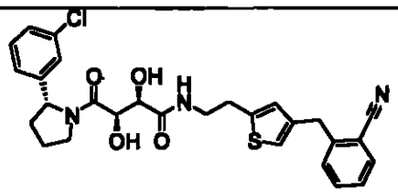
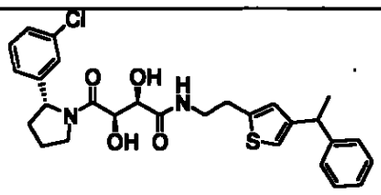
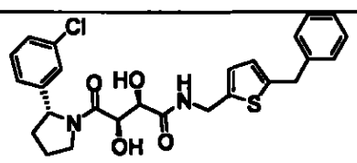
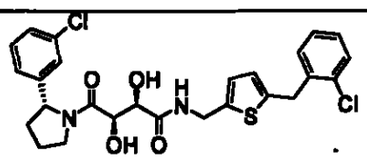
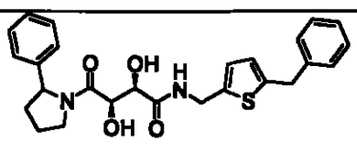
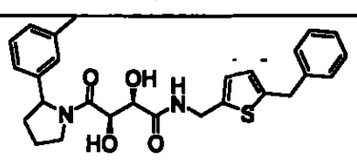
248		478,2	479,2
249		515,2	516,0
250		515,2	516,0
251		511,2	512,2
252		541,2	542,2
253		514,2	515,2
254		526,2	527,2
255		521,2	522,1

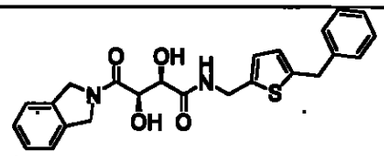
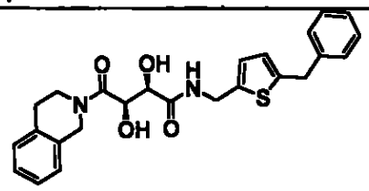
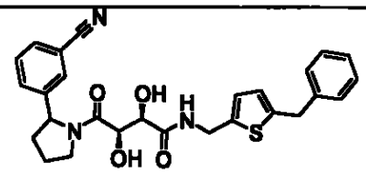
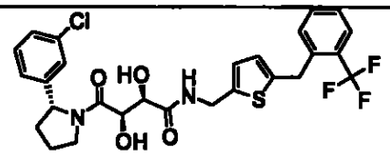
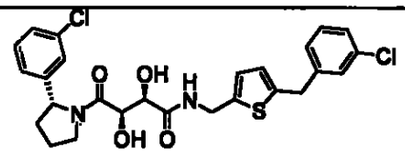
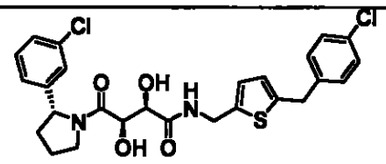
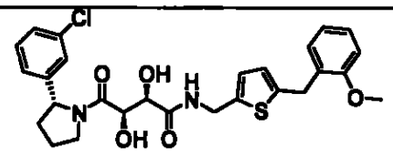
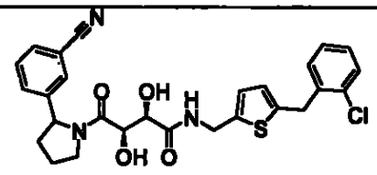
256		532,2	533,2
257		532,2	533,2
258		556,2	557,2
259		530,1	531,1
260		526,2	527,2
261		482,2	483,1
262		496,2	497,2

263		**516,1**	**517,2**
264		**507,2**	**508,1**
265		**512,2**	**513,2**
266		**518,2**	**519,1**
267		**510,2**	**511,1**
268		**517,1**	**518,0**
269		**516,1**	**517,2**
270		**507,2**	**508,1**

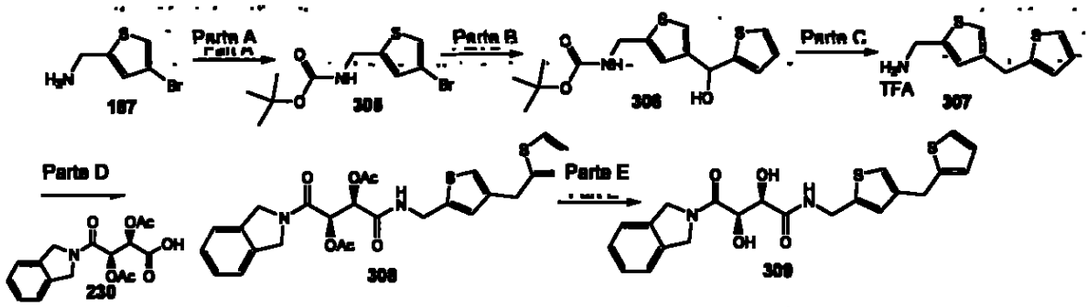
271		**500,2**	**501,1**
272		**526,2**	**527,2**
273		**518,2**	**519,1**
274		**550,1**	**551,0**
275		**518,2**	**519,1**
276		**514,2**	**515,2**
277		**496,2**	**497,1**
278		**532,1**	**533,0**

279		512,2	513,1
280		498,1	499,0
281		523,1	524,1
282		503,2	504,1
283		496,2	497,2
284		496,2	497,2
285		517,2	518,2
286		566,12	567,1
287		498,1	499,1

288		**498,1**	**499,1**
289		**498,1**	**499,1**
290		**541,2**	**542,2**
291		**537,2**	**538,2**
292		**526,2**	**527,0**
293		**498,1**	**499,1**
294		**532,1**	**533,0**
295		**464,2**	**465,1**
296		**478,2**	**479,2**

297		436,2	437,2
298		450,2	451,1
299		489,2	490,1
300		566,1	567,1
301		532,1	533,0
302		532,1	533,0
303		528,2	529,2
304		523,1	524,2

Ejemplo 5:



Parte A:

A una solución de **187** (2,68 g, 14,0 mmol) y piridina (2,26 ml, 28 mmol) en diclorometano (25 ml) se agregó dicarbonato de di-ter-butilo (3,21 g, 14,7 mmol). La mezcla se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se vertió en agua (25 ml) y las capas se separaron. La capa orgánica se lavó con HCl 1,0 N (20 ml), agua (20 ml), y solución de cloruro de sodio saturado (20 ml), se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, DCM) dio **305** como un sólido naranja claro (3,64 g, 89%). ^1H RMN (400 MHz, $CDCl_3$) δ 7,11 (s, 1H), 6,87 (s, 1H), 4,01 (bs, 1H), 4,44 (d, 2H, J = 6,0 Hz), 1,48 (s, 9H).

Parte B:

A *n*-butil litio (2,5 M, 0,31 ml, 0,78 mmol) en THF (2 ml) a –78 °C bajo argón se agregó **305** (100 mg, 0,34 mmol) en THF (1,5 ml) gota a gota. La mezcla de reacción se agitó durante 30 minutos a –78 °C. Luego, se agregó carbaldehído de 2-tiofeno (60 µl, 0,68 mmol). La mezcla de reacción se agitó durante 30 minutos a –78 °C. La mezcla de reacción se desactivó con solución de cloruro de sodio saturado y se calentó hasta temperatura ambiente. La mezcla se diluyó con acetato de etilo (10 ml) y las capas se separaron. La capa orgánica se lavó con agua y salmuera. Se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 20% de EtOAc/hexano) dio

306 (47 mg, 42%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,28 (m, 1H), 7,16 (s, 1H) 6,95 (m, 2H), 6,93 (s, 1H), 6,05 (s, 1H). 4,88 (bs, 1H), 4,43 (d, 2H, J = 5,6 Hz), 2,43 (bs, 1H), 1,48 (s, 9H).

Parte C:

A **306** (47 mg, 0,14 mmol) en DCM (2 ml) se agregó trietilsilano (0,2 ml). La mezcla se enfrió en un baño de hielo y se agregó TFA (0,2 ml). La mezcla se calentó hasta temperatura ambiente y se agitó hasta el día siguiente. Los solventes se eliminaron in vacuo y **307** se usó sin purificación adicional. ^{1}H RMN (400 MHz, CD_3OD) δ 7,20 (m, 2H), 7,09 (s, 1H) 6,90 (m, 1H), 6,86 (m, 1H), 4,26(s, 2H), 4,15 (s, 2H).

Parte D:

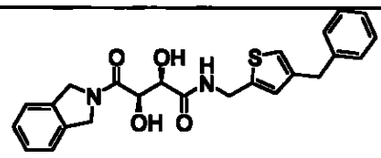
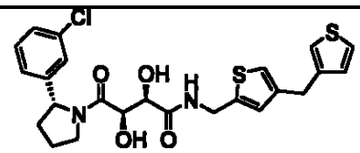
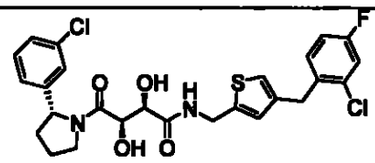
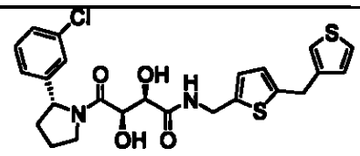
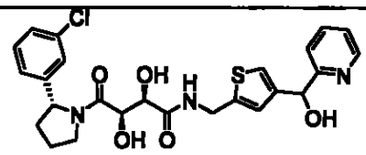
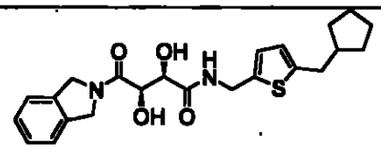
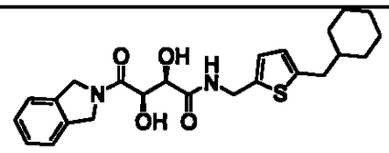
A **230** (19 mg, 0,06 mmol) en DMF (2 ml) se agregó **307** (18 mg, 0,06 mmol), DIEA (29 µl, 0,17 mmol) y HATU (28 mg, 0,07 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo (20 ml) y agua (20 ml). Las capas se separaron y la capa acuosa se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con sodio solución de bicarbonato y salmuera, se secaron sobre sulfato de sodio y se concentraron. Se usó Compuesto **308** sin purificación adicional. HPLC-MS t_R = 1,91 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{26}H_{26}N_2O_6S_2$ 526,1, LCMS observada m/z 269,9 (M+H).

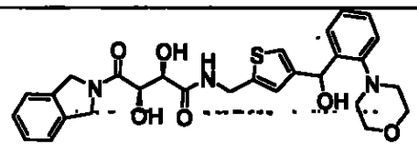
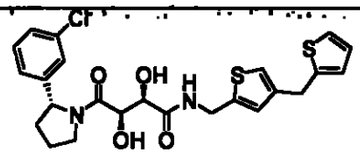
Parte E:

Se mezclaron Compuesto **308** y carbonato de potasio (20 mg) en metanol (2,5 ml) y agua (0,5 ml) y se agitaron durante 30 minutos. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante LC prep. de fase reversa dio **309** como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,33 (t, 1H, J = 5,6 Hz), 7,30 (m, 5H), 7,03 (s, 1H), 6,92 (s, 1H), 6,67 (s, 1H), 6,82 (s, 1H), 5,04 (d, 1H,

J = 14,0 Hz), 4,90 (d, 1H, J = 14,0 Hz), 4,75 (d, 1H, J = 16,0 Hz), 4,60 (m, 2H), 4,41 (dd, 1H, J = 6,8, 14,8 Hz), 4,33 (dd, 1H, J = 5,6, 14,4 Hz), 4,25 (s, 1H), 4,04 (s, 2H); HPLC-MS t_R = 4,45 min ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{22}H_{22}N_2O_4S_2$ 442,1, LCMS observada m/z 443,0 (M+H).

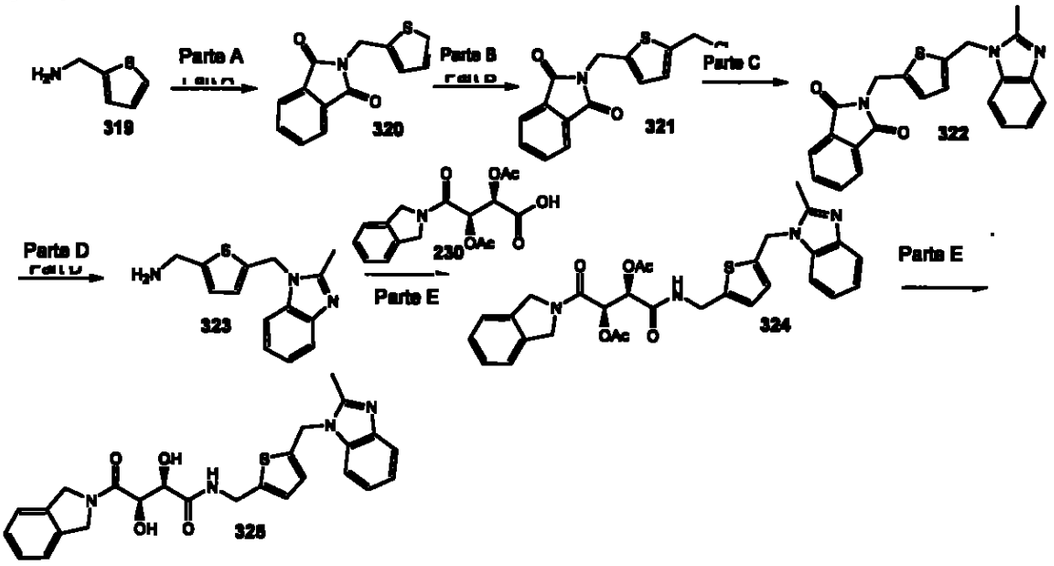
Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente. La Parte C no produjo la deshidratación para compuestos como **314** y **317**.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
310		436,2	437,3
311		504,1	505,1
312		550,1	551,0
313		504,1	505,1
314		515,1	516,1
315		428,2	429,1
316		442,2	443,0

317		537,2	538,0
318		504,09	505,0

Ejemplo 6

Ejemplo 6A:



Parte A:

Se agitó una mezcla de 2-(aminometil)tiofeno **(319)** (1,57 g, 13,8 mmol), ftalato de monometilo (2,75 g, 15,3 mmol), EDC (3,26 g, 16,6 mmol), HOBt (2,79 g, 20,7 mmol) y trietilamina (5 ml, 27,6 mmol) en DCM (40 ml) durante 12 horas. La mezcla de reacción se dividió entre acetato de etilo y agua. La capa acuosa se extrajo con acetato de etilo (2 x 50 ml). Las capas orgánicas combinadas se lavaron con HCl 1,0 N, solución de bicarbonato y salmuera, se secaron sobre sulfato de sodio y se concentraron. La recristalización de la mezcla a partir del acetato de etilo/hexanos dio **320** como un sólido (2,20 g, 67%). ^{1}H RMN (400

MHz, $CDCl_3$) δ 7,85 (m, 2H), 7,71 (m, 2H), 7,21 (m, 1H), 7,15 (m, 1H), 6,94 (m, 1H), 5,03 (s, 2H).

Parte B: (Feigel, M., Lugert, G., Heichert, C.; *Liebigs Ann. Chem.* 1987, 367)

A paraformaldehído (250 mg) en HCl (conc., 5 ml) se agregó cloruro de zinc 0,5 M en THF (1,7 ml, 0,85 mmol). A esta mezcla se agregó **320** (235 mg, 0,85 mmol) en porciones y luego dioxano (3 ml). La mezcla de reacción se agitó a 60 °C durante 45 minutos. La mezcla de reacción se enfrió y se diluyó con agua (50 ml) y acetato de etilo (50 ml). Las capas se separaron y la capa acuosa se extrajo con acetato de etilo (2 x 30 ml). Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se concentraron. La recristalización a partir de acetato de etilo / hexano dio **321** como un sólido (190 mg, 78%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,86 (dd, 2H, J = 3,2, 5,6 Hz), 7,72 (dd, 2H, J = 3,2, 5,6 Hz), 6,98 (d, 1H, J = 3,6 Hz), 6,90 (d, 1H, J = 3,6 Hz), 4,98 (s, 2H), 4,72 (s, 2H).

Parte C:

Se agitaron una mezcla **321** (190 mg, 0,65 mmol), 2-metilbenzoimidazol (112 mg, 0,85 mmol), yoduro de sodio (catalítico) y carbonato de cesio (275 mg, 0,85 mmol) en DMF (6 ml) hasta el día siguiente a temperatura ambiente. La mezcla de reacción se dividió entre acetato de etilo y agua. Las capas se separaron y la capa acuosa se extrajo con acetato de etilo (2 x 50 ml). Las capas orgánicas combinadas se lavaron con sodio solución de bicarbonato y salmuera, se secaron sobre sulfato de sodio y se concentraron. La recristalización a partir de acetato de etilo / hexano dio **322** (65 mg) y **322** contaminado con 2-metilbenzoimidazol (120 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,83 (dd, 2H, J = 3,2, 5,6 Hz), 7,70 (dd, 2H, J = 3,2, 5,6 Hz), 7,68 (m, 1H), 7,29 (m, 1H), 7,23 (m, 2H), 6,95 (d, 1H, J = 3,6 Hz), 6,70 (d, 1H, J = 3,6 Hz), 5,36 (s, 2H), 4,91 (s, 2H), 2,64 (s, 3H); HPLC-MS t_R = 1,14 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{22}H_{17}N_3O_2S$ 387,1, LCMS observada m/z 388,1 (M+H).

Parte D:

Se reflujaron el compuesto **322** (90 mg, 0,23 mmol) e hidrato de hidrazina (50 µl, 0,93 mmol) en etanol (10 ml) y DCM (5 ml) durante 1,5 horas. La mezcla de reacción se enfrió y se filtró. El filtrado se concentró y el producto bruto se usó sin purificación adicional.

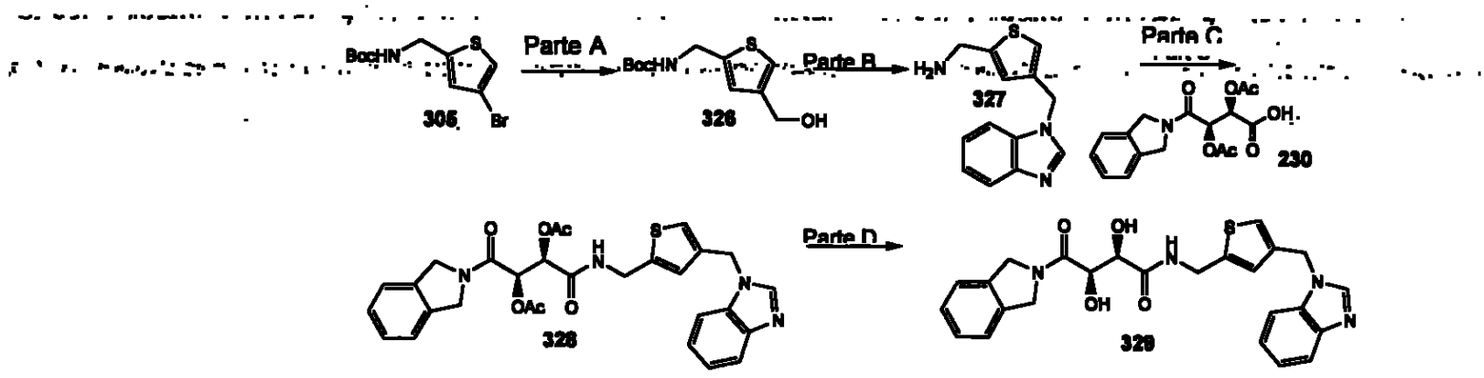
Parte E:

A **230** (83 mg, 0,24 mmol) en DMF (5 ml) se agregó **323** (82 mg, 0,32 mmol), DIEA (300 µl, 1,6 mmol) y HATU (135 mg, 0,36 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo (50 ml) y agua (50 ml). Las capas se separaron y la capa acuosa se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con sodio solución de bicarbonato y salmuera, se secaron sobre sulfato de sodio y se concentraron. El Compuesto **324** se usó sin purificación adicional. HPLC-MS t_R = 1,13 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{30}H_{30}N_4O_8S$ 574,2, LCMS observada m/z 575,1 (M+H).

Parte F:

Se mezclaron Compuesto **324** (~120 mg, 0,21 mmol) y carbonato de potasio (100 mg) en metanol (5 ml) y agua (1 ml). Después de 5 minutos, un sólido se precipitó y la reacción se agitó durante 30 minutos. El sólido se recolectó mediante filtración. La purificación mediante LC prep. de fase reversa dio **325** como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,35 (t, 1H, J = 6,0 Hz), 7,93 (d, 1H, J = 8,0 Hz), 7,73 (d, 1H, J = 6,8 Hz), 7,48 (m, 2H), 7,33 (m, 1H), 7,27 (m, 3H), 7,08 (d, 1H, J = 3;6 Hz), 6,82 (d, 1H, J = 3,6 Hz), 5,80 (s, 2H), 5,02 (d, 1H, J = 14,4 Hz), 4,86 (d, 1H, J = 15,2 Hz), 4,74 (d, 1H, J = 16,8 Hz), 4,58 (d, 1H, J = 16,4 Hz), 4,57 (s, 1H), 4,33 (m, 2H), 4,22 (s, 1H), 2,84 (s, 3H); HPLC-MS t_R = 2,74 min ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{26}H_{26}N_4O_4S$ 490,2, LCMS observada m/z 491,2 (M+H).

Ejemplo 6B:



Parte A:

A *n*-butil litio (2,5 M, 0,91 ml, 2,28 mmol) en THF (5 ml) a –78°C bajo argón se agregó **305** (300 mg, 1,03 mmol) en THF (5 ml) gota a gota. La mezcla de reacción se agitó durante 30 minutos a –78°C. Luego, se agregó dimetil formamida (151 mg, 2,06 mmol). La mezcla de reacción se agitó durante 30 minutos a –78 °C. La mezcla de reacción se desactivó con solución de cloruro de amonio saturado y se calentó hasta temperatura ambiente. La mezcla se diluyó con acetato de etilo (10 ml) y las capas se separaron. La capa orgánica se lavó con agua y salmuera. Se secó sobre sulfato de sodio y se concentró. El residuo se disolvió en metanol y se agregó borohidruro de sodio (156 mg, 4,12 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo y se lavó con HCl 0,1 N, água y salmuera. La capa orgánica se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 25% EtOAc/hexano) dio **326** (147 mg, 58%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,10 (s, 1H), 6,94 (s, 1H), 4,63 (s, 2H), 4,45 (d, 2H, J = 4,7 Hz), 1,48 (s, 9H).

Parte B:

A **326** (30 mg, 0,12 mmol) en THF (2 ml) se agregó benzimidazol (19 mg, 0,16 mmol), trifenilfosfina (42 mg, 0,16 mmol) y DIAD (32 mg, 0,16 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se concentró. El residuo se disolvió en diclorometano (2 ml) y se agregó TFA (0,5 ml). La mezcla de reacción se agitó durante 30 minutos y se concentró. El residuo se disolvió en dietil éter y se lavó dos veces con agua. La capa acuosa combinada se hizo DIEA básico y se extrajo con acetato de etilo. La capa orgánica combinada se lavó con salmuera, se secó y se concentró para dar **327** como una lámina (41 mg). El material se usó sin purificación adicional.

Parte C:

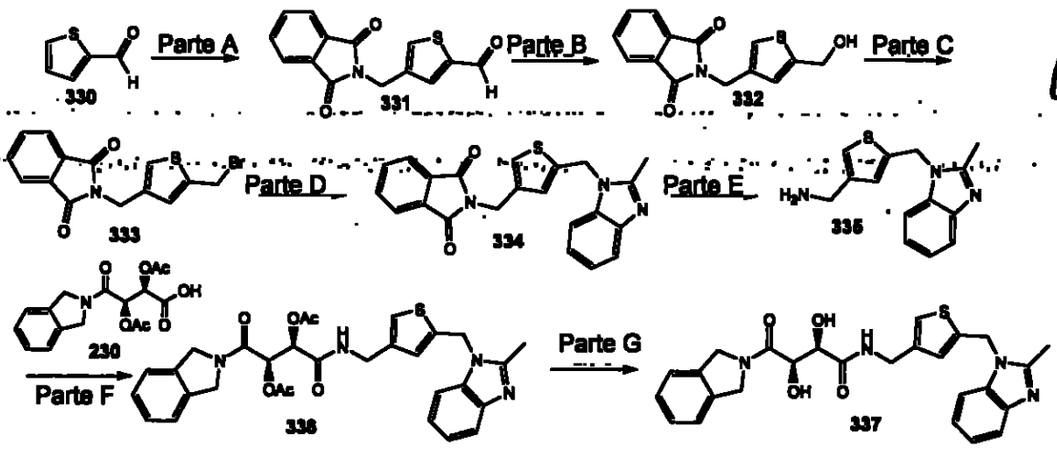
A **230** (20 mg, 0,06 mmol) en DMF (2 ml) se agregó **327** (19 mg, 0,08 mmol), DIEA (31 µl, 0,18 mmol), DMAP (1 mg) y HATU (30 mg, 0,08 mmol). La mezcla de reacción se agitó hasta el día siguiente. La mezcla se vertió en agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con NaOH 0,1 N, agua y salmuera, se secó sobre sulfato de sodio y se concentró. El compuesto **328** se usó sin purificación adicional.

Masa calculada para la fórmula $C_{29}H_{28}N_4O_6S$ 560,2. LCMS observada m/z 561,2 (M+H).

Parte D:

Se mezclaron compuesto **328** y carbonato de potasio (20 mg) en metanol (2,5 ml) y agua (0,5 ml) y se agitaron durante 30 minutos. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante LC prep de fase reversa dio **329** como un sólido blanco (8 mg). HPLC-MS t_R = 2,77 min ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{25}H_{24}N_4O_4S$ 476,2. LCMS observada m/z 477,1 (M+H).

Ejemplo 6C



Parte A:

Se disolvió N-(Hidroximetil)ftalamida (1,0 g, 5,6 mmol) en ácido tríflico 1% en ácido trifluoroacético (10 ml) a 0°C. A esta mezcla se agregó **330** (0,52 ml, 5,6 mmol). La mezcla de reacción se calentó hasta temperatura ambiente lentamente y se agitó hasta el día siguiente. La mezcla de reacción se vertió en ice agua (100 ml) y se extrajo con DCM. Las capas orgánicas combinadas se lavaron con solución de bicarbonato de sodio y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 30% EtOAc/Hex) dio **331** (619 mg, 41%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,85 (d, 1H, J = 1,6 Hz), 7,86 (m, 2H), 7,81 (d, 1H, J = 1,6 Hz), 7,76 (s, 1H), 7,73 (m, 2H), 4,87 (s, 2H).

Parte B:

Se disolvió compuesto **331** (315 mg, 1,16 mmol) en cloruro de metileno:metanol 1:1 (10 ml) y se enfrió en un baño de hielo. A esta solución se agregó borohidruro de sodio (11 mg, 0,29 mmol) y la reacción se agitó durante 30 minutos. Se agregó borohidruro de sodio adicional (3 mg, 0,08 mmol) y la reacción se agitó durante 30 minutos. La mezcla de reacción se diluyó con cloruro de metileno y se lavó con solución de cloruro de amonio saturado, agua y salmuera. La mezcla de reacción se secó sobre sulfato de sodio y se concentró

para dar **332** como un sólido blanco (310 mg, 98%). ^{1}H RMN (400 MHz, CD_3OD) δ 7,83 (m, 2H), 7,79 (m, 2H), 7,24 (s, 1H), 6,97 (s, 1H), 4,76 (s, 2H), 4,65 (s, 2H).

Parte C:

Se agitó una mezcla de **332** (97 mg, 0,36 mmol) y tribromuro de fósforo (34 µl, 0,39 mmol) en DCM (5 ml) durante 30 minutos a temperatura ambiente. La mezcla de reacción se vertió en ice agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución de bicarbonato de sodio y salmuera, se secaron sobre sulfato de sodio y se concentraron para dar **333** como un sólido blanco (104 mg, 87%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,85 (dd, 2H, J = 2,8, 5,2 Hz), 7,72 (dd, 2H, J = 2,8, 5,2 Hz), 7,32 (s, 1H), 7,15 (s, 1H), 4,77 (s, 2H), 4,66 (s, 2H).

Parte D:

Se agitó una mezcla de **333** (450 mg, 1,34 mmol), 2-metil-benzimidazol (355 mg, 2,69 mmol) y carbonato de cesio (875 mg, 2,69 mmol) en DMF (5 ml) hasta el día siguiente a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo y se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró. La recristalización a partir de acetato de etilo / hexanos dio **334** como un sólido blanco (252 mg, 49%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,84 (dd, 2H, J = 2,8, 5,2 Hz), 7,72 (dd, 2H, J = 2,8, 5,2 Hz), 7,68 (m, 1H), 7,23 (m, 3H), 7,19 (s, 1H), 7,05 (s, 1H), 5,38 (s, 2H), 4,75 (s, 2H), 2,66 (s, 3H).

Parte E:

Se reflujó una mezcla de **334** (225 mg, 0,58 mmol) e hidrato de hidrazina (113 µl, 2,32 mmol) in etanol (4 ml) durante 4 horas. La mezcla de reacción se enfrió y se filtró. El filtrado se concentró y el residuo se disolvió en acetato de etilo. La capa orgánica se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró para dar a **335** como sólido amarillo (148 mg, 99%).

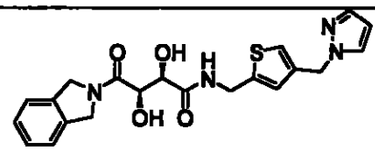
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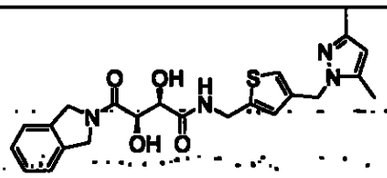
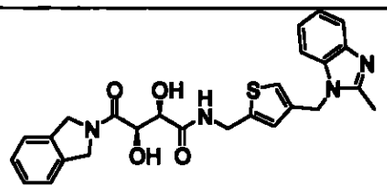
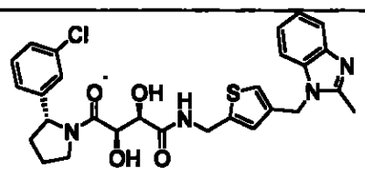
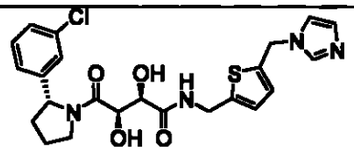
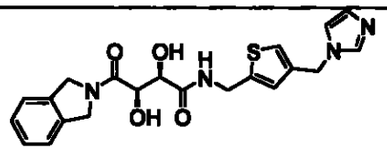
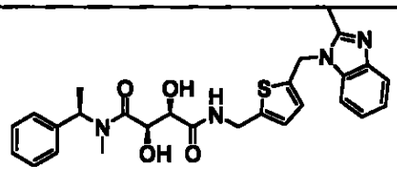
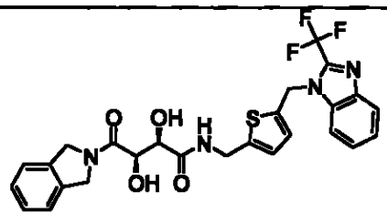
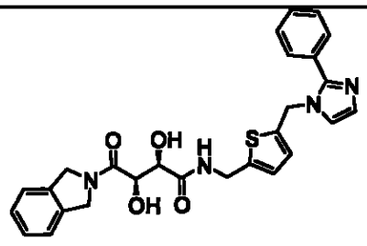
A **230** (12 mg, 0,036 mmol) en DMF (2 ml) se agregó **335** (12 mg, 0,045 mmol), DIEA (18 µl, 0,11 mmol) y HATU (17 mg, 0,045 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo (20 ml) y agua (20 ml). Las capas se separaron y la capa acuosa se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución de bicarbonato de sodio y salmuera, se secó sobre sulfato de sodio y se concentró. Compuesto **336** se usó sin purificación adicional. HPLC-MS t_R = 1,22 min (UV_{254} nm); masa calculada para la fórmula $C_{30}H_{30}N_4O_6S$ 574,2. LCMS observada m/z 575,0 (M+H).

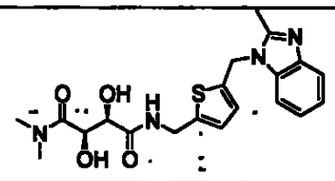
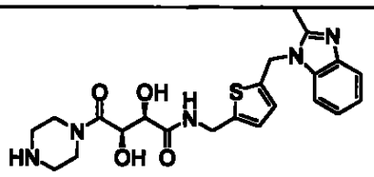
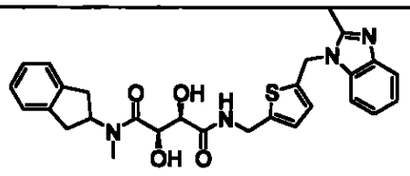
Parte G:

Se mezclaron compuesto **336** y carbonato de potasio (20 mg) en metanol (1,5 ml) y se agitó durante 30 minutos. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante LC preparativa de fase reversa dio **337** como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,23 (t, 1H, J = 6,4 Hz), 7,89 (m, 1H), 7,70 (m, 1H), 7,44 (m, 2H), 7,33 (m, 1H), 7,27 (m, 3H), 7,20 (s, 1H), 7,14 (s, 1H), 5,80 (s, 2H), 5,04 (d, 1H, J = 13,2 Hz), 4,88 (d, 1H, J = 15,2 Hz), 4,73 (m, 2H), 4,60 (m, 2H), 4,25 (m, 2H), 2,83 (s, 3H); HPLC-MS t_R = 2,04 min ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{28}H_{26}N_4O_4S$ 490,2. LCMS observada m/z 491,1 (M+H).

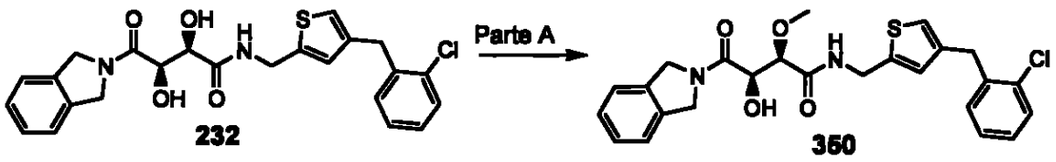
Los siguientes compuestos se prepararon usando los procedimientos descriptos en el Ejemplo 6A a 6C.

Compuesto #	Estructura	Masa Exacta	MS m/z (M+H)
338		426,1	427,1

339		454,2	455,2
340		490,2	491,2
341		552,2	553,2
342		488,1	489,0
343		426,1	427,1
344		506,2	507,2
345		544,1	545,1
346		502,2	503,2

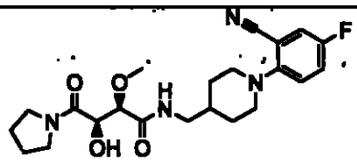
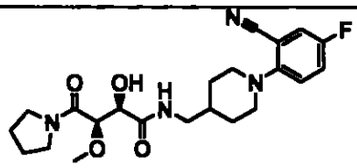
347		416,2	417,2
348		457,2	458,1
349		518,2	519,2

Ejemplo 7:

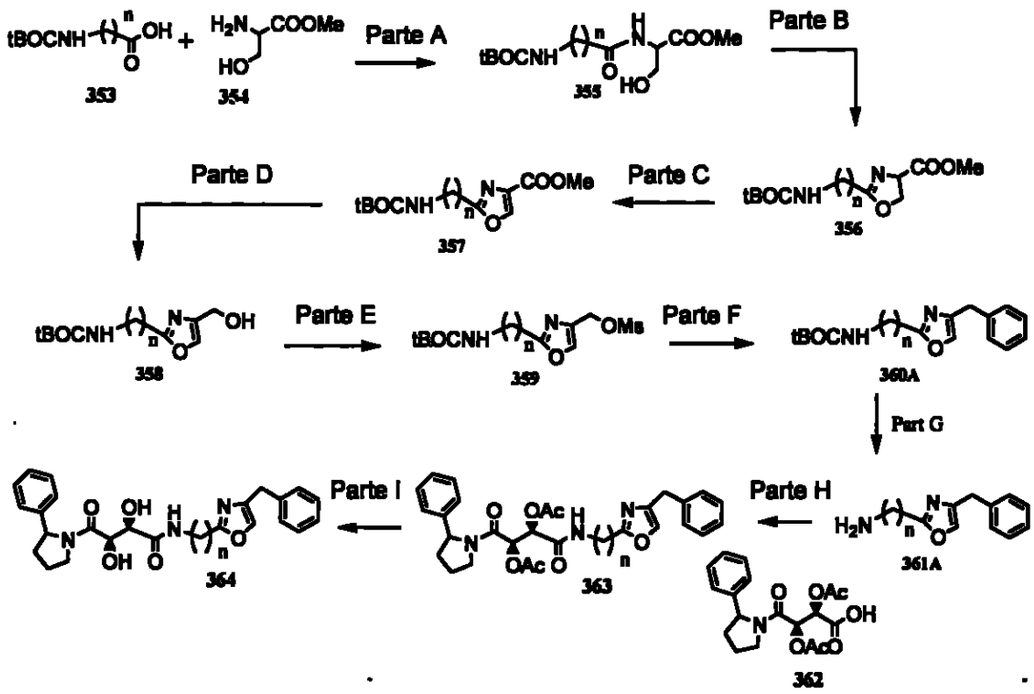


Parte A:

A **232** (26 mg, 0,056 mmol) en tolueno (5 ml) se agregó óxido de dibutiltino (20 mg, 0,08 mmol). La mezcla se calentó durante 3 horas a reflujo con una trampa Dean Stark. La mezcla se concentró. El residuo se disolvió en NMP (3 ml) y se trató con fluoruro de sodio (8,5 mg, 0,056 mmol) y yodometano (14 µl, 0,224 mmol). La mezcla de reacción se calentó a 50 °C hasta el día siguiente. La mezcla de reacción se vertió en agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante HPLC prep dio **350** (3,4 mg, 13%). HPLC-MS t_R = 5,26 min (UV_{254} nm, 10 min.); masa calculada para la fórmula $C_{25}H_{25}ClN_2O_4S$ 484,1. LCMS observada m/z 485,0 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
351		432,2	433,2
352		432,2	433,2

Ejemplo 8:



Parte A:

A BOC-glicina **(353)** (25,0 g, 0,143 mol) disuelta en THF seco (100 ml) y enfriada a -20 °C bajo una atmósfera de nitrógeno se agregó Base de Hunig (23,1 g, 31,1 ml, 0,357 mol) luego isobutilcloroformato (21,4 g, 20,4 ml, 0,157 mol). Se agitó a -20 °C durante 60 minutos. Se agregó metil éster de serina **(354)** (24,4 g, 0,157 mol) luego Base de Hunig (23,1 g, 31,1 ml, 0,357 mol). La mezcla de

reacción se calentó hasta temperatura ambiente, se calentó durante 18 h y se concentró. El residuo se dividió entre NaOH 0,5 N.(300 ml) CH_2Cl_2. Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2. La capa orgánica combinada se secó sobre sulfato de magnesio y se concentró. Se purificó mediante cromatografía de gel de sílice (eluyente: MeOH 1%-CH_2Cl_2 a 3% de MeOH-CH_2Cl_2) para dar 20,5 g (52%) del producto **355** como un sólido amarillo. MS m/e: 277 (M+H).

Para n=2: MS m/e: 291 (M+H)

Parte B:

Al compuesto **355** (4,55g, 16,5 mmol) disuelto en CH_2Cl_2 (200 ml) y enfriado a -50 °C bajo una atmósfera de nitrógeno se agregó trifluoruro de dietoaminoazufre (3,19 g, 2,4 ml, 19,8 mmol) gota a gota mediante jeringa. Se agitó a -50 °C durante 2 h, se agregó carbonato de potasio (3,88 g, 28,1 mmol), y se calentó lentamente hasta temperatura ambiente durante 2 h. Se agregó NaOH 0,2 N (100 ml) y capas separadas. Se extrajo la capa acuosa con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtró, y se concentró. Se purificó mediante cromatografía de gel de sílice (eluyente: MeOH 2 % -CH_2Cl_2 a 4% MeOH-CH_2Cl_2) para dar 3,06 g (72%) del producto **356** como un sólido amarillo. MS m/e: 259 (M+H).

Para n=2: MS m/e: 273 (M+H)

Parte C:

Al compuesto **356** (6,10 g, 23,6 mmol) disuelto en CH_2Cl_2 (250 ml) y se enfrió a 0 °C se agregó DBU (12,59 g, 12,4 ml, 82,7 mmol) y bromotriclorometano (16,40 g, 8,1 ml, 82,7 mmol). Se calentó lentamente hasta temperatura ambiente durante 2 h y se agitó durante 16 h. Se agregó NaOH 0,1 N (200 ml) y capas separadas. Se extrajo la capa acuosa con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtró y se concentró. Se purificó mediante cromatografía

de gel de sílice (eluyente: 2% de MeOH-CH_2Cl_2 a 3% de MeOH-CH_2Cl_2) para dar 4,27 g (71%) del producto **357** como un aceite anaranjado. MS m/e: 257 (M+H).

Para n=2: MS m/e: 271 (M+H).

Parte D:

Al compuesto **357** (4,25 g, 16,6 mmol) disuelto en Et_2O (100 ml) se agregó borohidruro de litio (1,44 g, 66,3 mmol) y MeOH (2,13 g, 2,7 ml, 66,3 mmol). Se reflujó durante 3 h, se enfrió hasta temperatura ambiente, y se concentró. Se agregó agua (100 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtró y se concentró. Se purificó mediante cromatografía de gel de sílice (eluyente: 5% MeOH-CH_2Cl_2 a 10% MeOH-CH_2Cl_2) para dar 2,43 g (64%) del producto **358** como un sólido amarillo. MS m/e: 229 (M+H).

Para n=2: MS m/e: 243 (M+H)

Parte E:

Al compuesto **358** (1,41 g, 6,18 mmol) disuelto en CH_2Cl_2 (35 ml) y se enfrió a -25 °C se agregó gota a gota trietilamina (1,25 g, 1,7 ml, 12,4 mmol) luego cloruro de mesilo (0,85 g, 0,57 ml, 7,41 mmol). Se calentó a 0 °C lentamente durante 60 minutos. Se agregó agua (50 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron, y se concentraron para dar 1,89 g (100%) del producto **359** como un sólido amarillo. MS m/e: 251 (M+2-tBu).

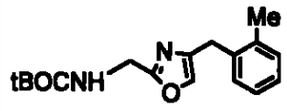
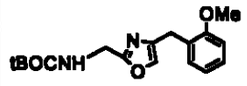
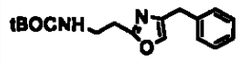
Para n=2: MS m/e: 265 (M+2-tBu)

Parte F:

Se suspendió cianuro de cobre (1,66 g, 18,5 mmol) en THF seco (70 ml) bajo una atmósfera de nitrógeno y se enfrió a -25 °C. Se agregó bromuro de fenil magnesio (3,0 M en Et_2O, 12,3 ml, 37,0 mmol) gota a gota mediante jeringa de manera que la temperatura interna < -20 °C. Se agitó a -20 °C durante 30 minutos luego a 0 °C durante 30 minutos. Se calentó a 15 °C , luego la temperatura interna se reenfrió a -25 °C. Se agregó compuesto **359** (1,89 g, 6,18 mmol)

disuelto en THF seco (20 ml) gota a gota mediante jeringa. Se agitó a -25 °C de temperatura interna durante 2 h luego a 0 °C durante 16 h. Se concentró, se agregó NH_4OH 2 N (100 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtró y se concentró. Se purificó mediante cromatografía de gel de sílice (eluyente: 5% EtOAc-hexano a EtOAc-hexano 20%) para dar 0,82 g (46%) del producto **360A** como un sólido amarillo. MS m/e: 289 (M+H).

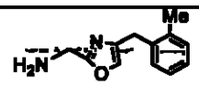
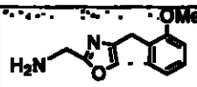
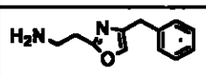
Los siguientes intermediarios se prepararon de acuerdo con el procedimiento anterior:

Compuesto #	*Estructura del Intermediario*	MS
360B		303 (M+H)
360C		319 (M+H)
360D		303 (M+H)

Parte G:

Al compuesto **360A** (1,00 g, 3,47 mmol) disuelto en 1:1 CH_2Cl_2:MeOH (30 ml) se agregó HCl 4 N en dioxano (7,8 ml, 31,2 mmol). Se agitó a temperatura ambiente durante 4 h, luego se concentró para dar 0,78 g (100%) del producto **361A** (sal clorhidrato) como un sólido amarillo. MS m/e: 189 (M+H).

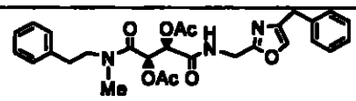
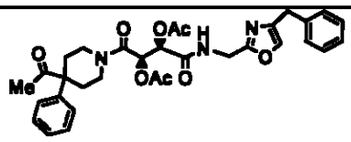
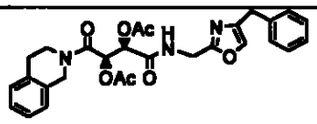
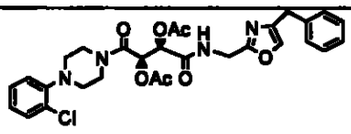
Los siguientes intermediarios se prepararon de acuerdo con el procedimiento anterior:

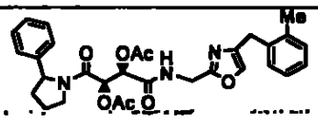
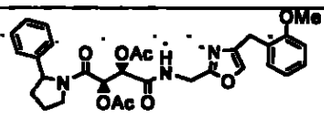
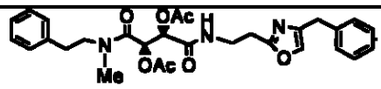
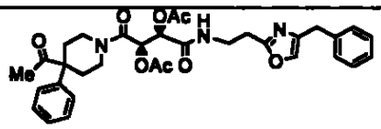
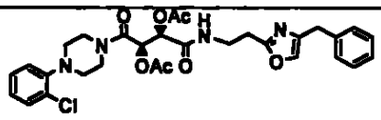
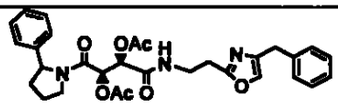
Compuesto #	Estructura del Intermediario	MS
361B		303 (M+H)
361C		219 (M+H)
361D		203 (M+H)

Parte H: (JFL 80324-023)

Se combinó el compuesto **361A** (0,20 g, 0,677 mmol), compuesto **362** (0,30 g, 0,812 mmol), HATU (0,51 g, 1,35 mmol), y trietilamina (0,21 g, 0,28 ml, 2,03 mmol) en DMF seco (8 ml). Se agitó a temperatura ambiente durante 16 h. Se concentró, se agregó NaOH 0,5 N (15 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron y se concentraron. Se purificó mediante cromatografía de gel de sílice (eluyente: 3% de MeOH-CH_2Cl_2) para dar 0,25 g (70%) del producto **363** como un aceite beige. MS m/e: 534 (M+H).

Los siguientes intermediarios se prepararon de acuerdo con el procedimiento anterior:

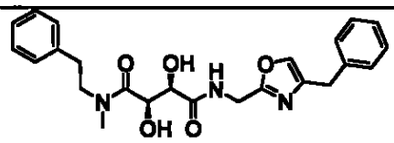
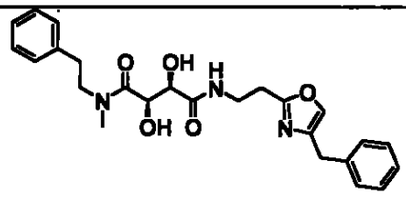
Compuesto #	Estructura del Intermediario	MS
365		522 (M+H)
366		590 (M+H)
367		520 (M+H)
368		583 (M+H)

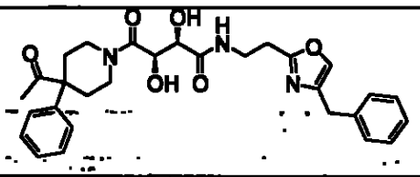
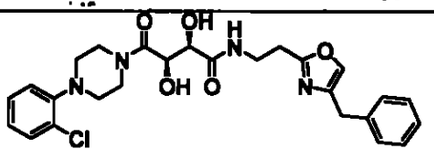
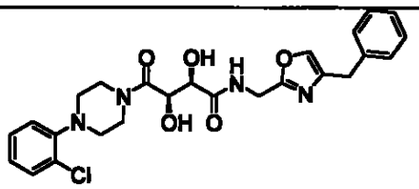
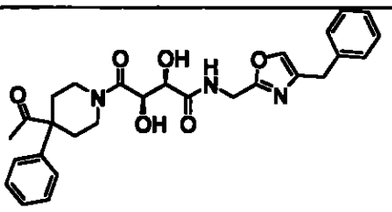
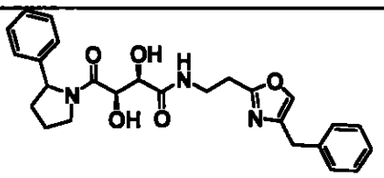
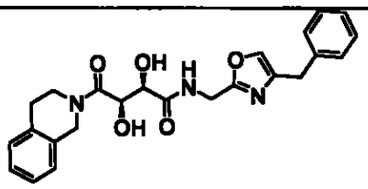
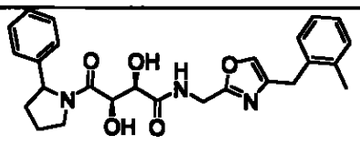
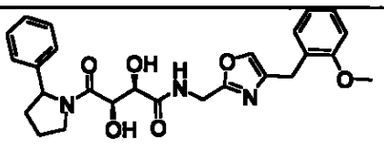
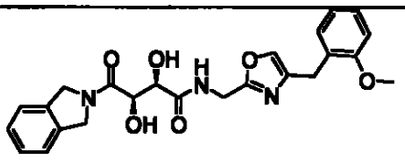
369		548 (M+H)
370		564 (M+H)
371		536 (M+H)
372		604 (M+H)
373		597 (M+H)
374		548 (M+H)

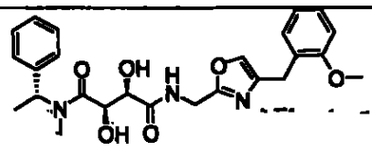
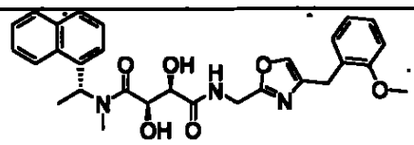
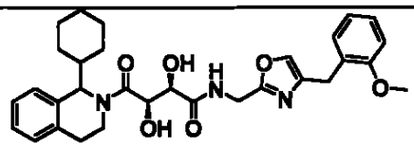
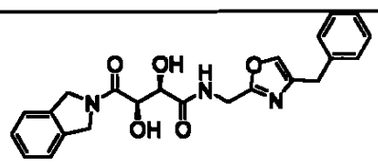
Parte I:

Al compuesto **363** (0,24 g, 0,450 mmol) disuelto en MeOH (10 ml) se agregó NaOMe 0,5 M en MeOH (0,09 ml, 0,045 mmol). Se agitó a temperatura ambiente durante 60 minutos. Se agregó HCl 4 N en dioxano (0,11 ml, 0,450 mmol) y se concentró para dar 0,20 g (100%) del producto **364** como una espuma marrón. MS m/e: 450 (M+H).

Los siguientes compuestos se prepararon de acuerdo con el Ejemplo 8:

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
375		437,2	438,0
376		451,2	452,0

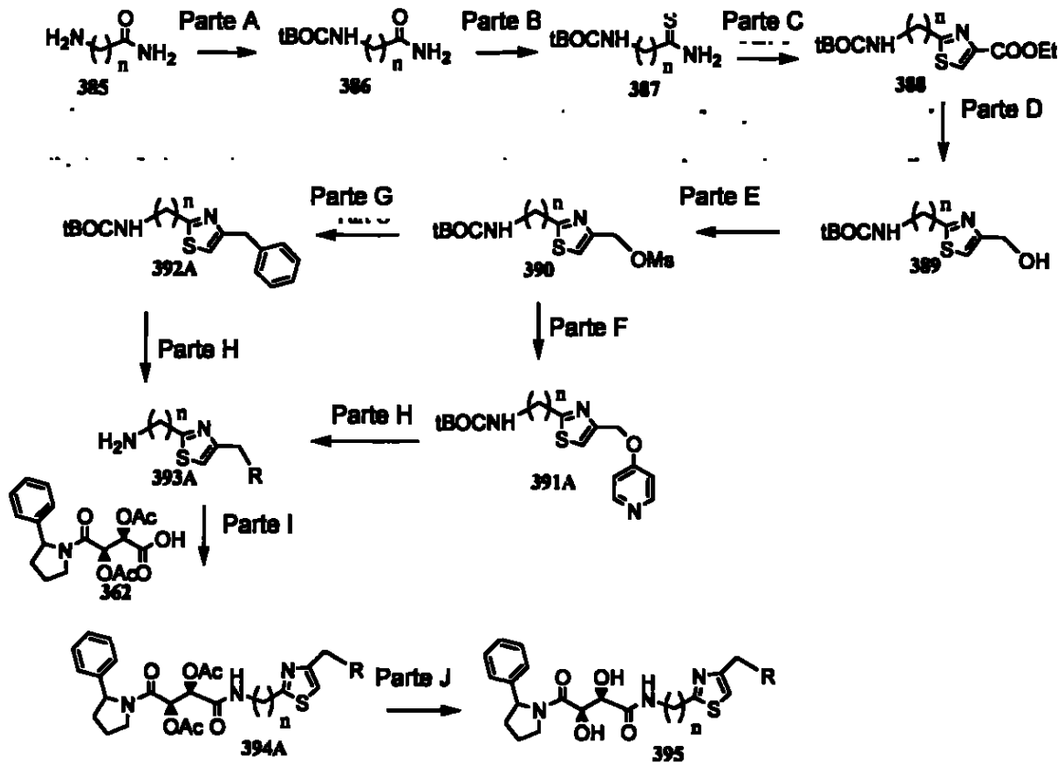
377		519,2	520,0
378		512,2	513,0
379		498,2	499,2
380		505,2	506,3
381		463,2	464,2
382		435,2	436,2
383		463,2	464,2
384		479,2	480,2
174		451,2	452,2

175		**467,2**	**468,3**
179		**517,2**	**518,3**
181		**547,3**	**548,3**
182		**421,2**	**422,2**

Ejemplo 9: Inhibidores con grupo tiazol-bencilo

Ejemplo 9A:

Esquema 1



Parte A:

A HCl de glicinamida **385** (60,0 g, 0,543 mol) suspendido en MeOH (1000 ml) y enfriado a 0°C se agregó trietilamina (109,9 g, 151,4 ml, 1,09 mol) y anhídrido tBOC (148,0 g, 0,678 mol) en porciones. Se calentó hasta temperatura ambiente y se agitó durante 24 h. Se concentró, se agregó NaOH 1 N (600 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtró y se concentró para dar 53,0 g (56%) del producto **396** como un sólido blanco. MS m/e: 175 (M+H).

Para n=2: MS m/e: 189 (M+H)

Parte B:

Al compuesto **386** (21,63 g, 0,124 mol) disuelto en THF (400 ml) se agregó Reactivo de Lawesson (30,13 g, 0,074 mol). Se agitó a temperatura ambiente durante 16 h luego se concentró. Se purificó mediante cromatografía de gel de

sílice (eluyente: 3% de MeOH-CH_2Cl_2) luego se re purificó mediante cromatografía de gel de sílice (eluyente: 2% MeOH-CH_2Cl_2) para dar 23,59 g (100%) del producto **387** como un sólido verde claro. MS m/e: 135 (M+2-tBu).

Para n=2: MS m/e: 149 (M+2-tBu)

Parte C:

Al compuesto **387** (6,00 g, 31,5 mmol) disuelto en CH_2Cl_2 (150 ml) se agregó etil bromopiruvato (6,76 g, 4,4 ml, 34,7 mmol). Se agitó a temperatura ambiente durante 5 h, luego se concentró. Se agregó 3 tamices A (6 g) y EtOH (150 ml) y se reflujó durante 16 h. Se filtró y se concentró para dar una espuma oscura. Se disolvió la espuma en CH_2Cl_2:EtOH 1:1 (100 ml) y se agregó trietilamina (6,40 g, 8,8 ml, 63,1 mmol) y anhídrido tBOC (7,60 g, 34,7 mmol). Se agitó a temperatura ambiente durante 5 h luego se concentró. Se agregó NaOH 0,25 N (100 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron y se concentraron. Se purificó mediante cromatografía de gel de sílice (eluyente: 10% de EtOAc-CH_2Cl_2 a 30% de EtOAc-CH_2Cl_2) para dar 6,00 g (67%) del producto **388** como un aceite marrón. MS m/e: 287 (M+H).

Para n=2: MS m/e: 301 (M+H)

Parte D:

Al compuesto **388** (4,70 g, 16,4 mmol) disuelto en Et_2O (140 ml) se agregó borohidruro de litio (1,43 g, 65,7 mmol) y MeOH (2,10 g, 2,7 ml, 65,7 mmol). Se reflujó durante 16 h, se enfrió hasta temperatura ambiente, y se concentró. Se agregó agua (100 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron y se concentraron. Se purificó mediante cromatografía de gel de sílice (eluyente: 2% de MeOH-CH_2Cl_2 a 5% de MeOH-CH_2Cl_2) para dar 3,70 g (92%) del producto **389** como un sólido amarillo. MS m/e: 245 (M+H).

Para n=2: MS m/e: 259 (M+H)

Parte E:

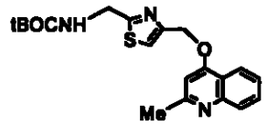
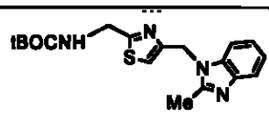
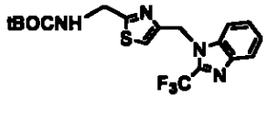
Al compuesto **389** (5,30 g, 21,7 mmol) disuelto en CH_2Cl_2 (130 ml) y se enfrió a -25 °C se agregó trietilamina (4,40 g, 6,0 ml, 43,4 mmol) luego cloruro de mesilo (3,00 g, 2,0 ml, 26,0 mmol) gota a gota. Se calentó hasta 0 °C lentamente durante 60 minutos. Se agregó agua (100 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron y se concentraron para dar 7,00 g (100%) del producto **390** como un sólido amarillo. MS m/e: 223 (M+2-tBOC).

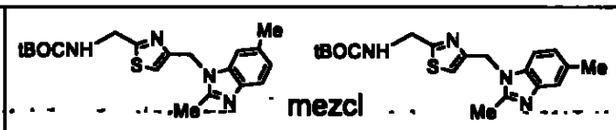
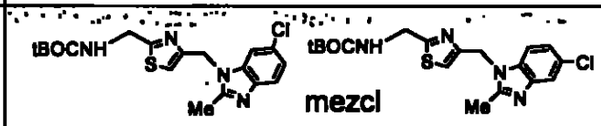
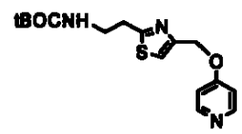
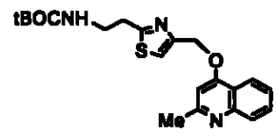
Para n=2: MS m/e: 237 (M+2-tBOC)

Parte F:

Al compuesto **390** (0,60 g, 1,86 mmol) disuelto en DMF seco (25 ml) se agregó 4-hidroxipiridina (0,22 g, 2,30 mmol) y carbonato de cesio (1,20 g, 3,72 mmol). Se agitó a temperatura ambiente durante 16 h luego se concentró. Se agregó agua (25 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron y se concentraron. Se purificó mediante cromatografía de gel de sílice (eluyente: 10% de MeOH con NH_3-CH_2Cl_2) para dar 0,40 g (68%) del producto **391A** como un aceite incoloro. MS m/e: 322 (M+H).

Los siguientes intermediarios se prepararon de acuerdo con el procedimiento anterior:

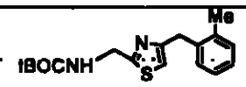
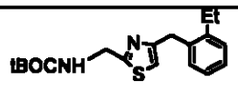
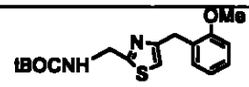
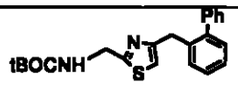
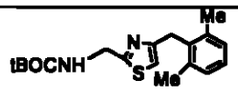
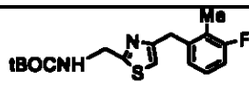
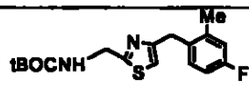
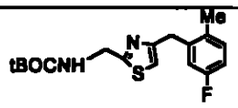
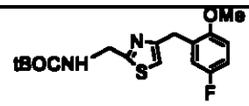
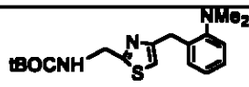
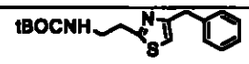
Compuesto #	Estructura del Intermediario	MS
391B		386 (M+H)
391C		359 (M+H)
391D		413 (M+H)

391E	 mezcl	373 (M+H)
391F	 mezcl	393 (M+H)
391G		336 (M+H)
391H		400 (M+H)

Parte G:

Se suspendió cianuro de cobre (1,65 g, 18,4 mmol) en THF seco (70 ml) bajo una atmósfera de nitrógeno y se enfrió a -25°C. Se agregó bromuro de fenil magnesio (3,0 M in Et_2O, 12,3 ml, 37,0 mmol) gota a gota mediante jeringa de manera que la temperatura interna < -20°C. Se agitó a -20°C durante 30 minutos luego a 0°C durante 30 minutos. Se calentó hasta 15°C de temperatura interna, luego se reenfrió a -25°C. Se agregó compuesto **390** (1,98 g, 6,14 mmol) disuelto en THF seco (20 ml) gota a gota mediante jeringa. Se agitó a -25°C de temperatura interna durante 2 h luego a 0°C durante 16 h. Se concentró, se agregó NH_4OH 2 N (100 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron y se concentraron. Se purificó mediante cromatografía de gel de sílice (eluyente: 5% de EtOAc-hexano a 20% de EtOAc-hexano) para dar 1,14 g (66%) del producto **392A** como un sólido amarillo. MS m/e: 305 (M+H).

Los siguientes intermediarios se prepararon de acuerdo con el procedimiento anterior:

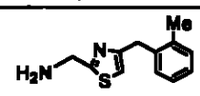
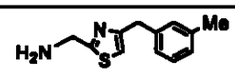
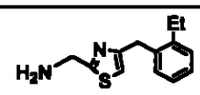
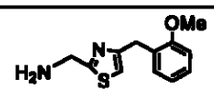
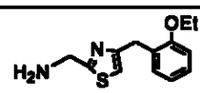
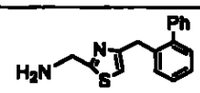
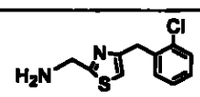
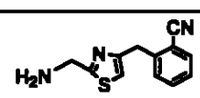
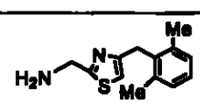
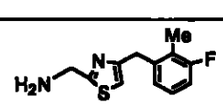
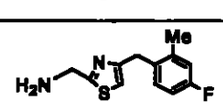
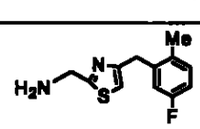
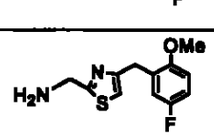
Compuesto #	Estructura del Intermediario	MS
392B		319 (M+H)
392C		319 (M+H)
392D		333 (M+H)
392E		335 (M+H)
392F		381 (M+H)
392G		333 (M+H)
392H		337 (M+H)
392I		337 (M+H)
392J		337 (M+H)
392K		353 (M+H)
392L		306 (M+H)
392M		306 (M+H)
392N		348 (M+H)
392O		319 (M+H)

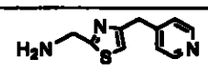
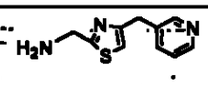
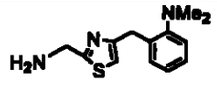
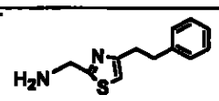
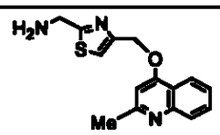
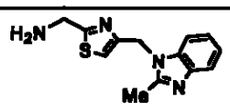
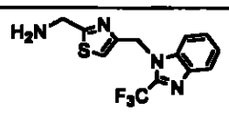
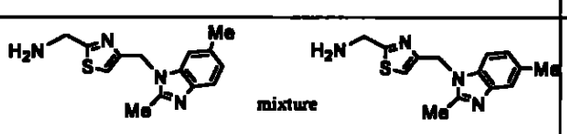
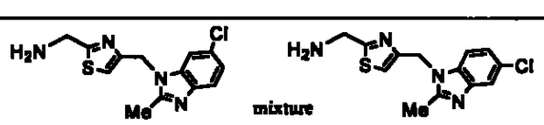
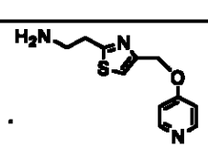
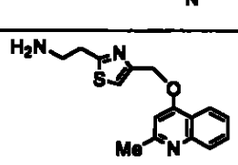
Parte H:

Al compuesto **392A** (0,30 g, 0,986 mmol) disuelto en CH_2Cl_2:MeOH·1:1 (10 ml) se agregó HCl 4 N en dioxano (2,4 ml, 9,86 mmol). Se agitó a temperatura ambiente durante 16 h luego se concentró para dar 0,23 g (100%) del producto **393A** (sal del clorhidrato) como una espuma beige. MS m/e: 205 (M+H).

~~65~~

Los siguientes intermediarios se prepararon de acuerdo con el procedimiento anterior: 1355

Compuesto #	Estructura del Intermediario	MS
393B		219 (M+H)
393C		219 (M+H)
393D		233 (M+H)
393E		235 (M+H)
393F		249 (M+H)
393G		281 (M+H)
393H		239 (M+H)
393I		230 (M+H)
393J		233 (M+H)
393K		237 (M+H)
393L		237 (M+H)
393M		237 (M+H)
393N		253 (M+H)

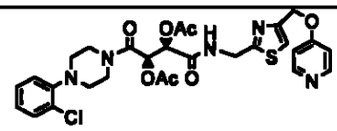
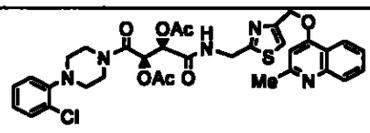
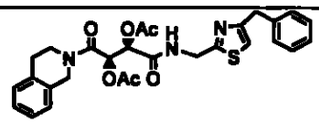
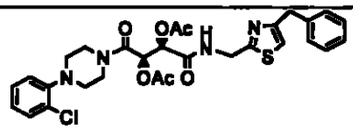
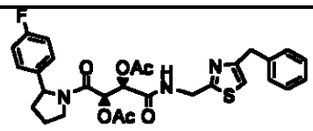
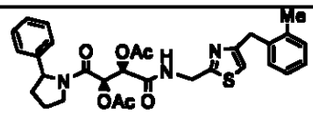
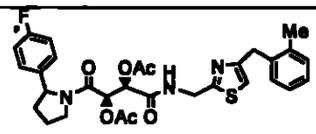
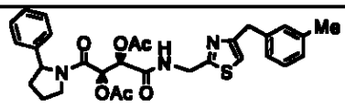
393		206 (M+H)
393P		206 (M+H)
393Q		248 (M+H)
393R		219 (M+H)
393S		219 (M+H)
393T		286 (M+H)
393U		259 (M+H)
393V		313 (M+H)
393W		273 (M+H)
393X		293 (M+H)
393Y		236 (M+H)
393Z		300 (M+H)

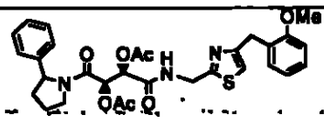
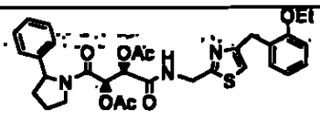
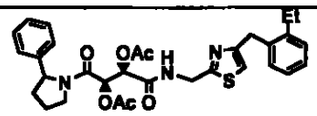
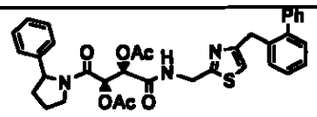
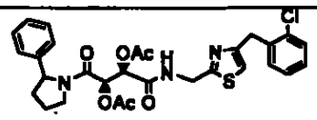
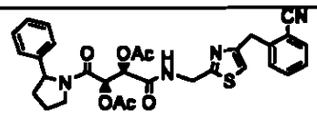
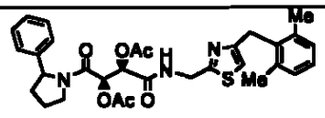
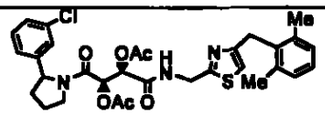
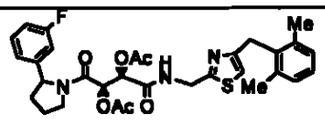
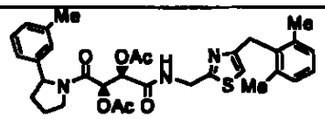
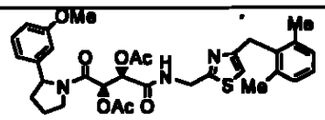
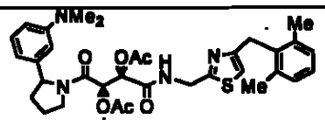
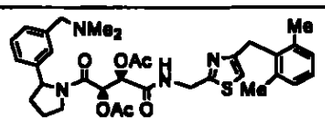
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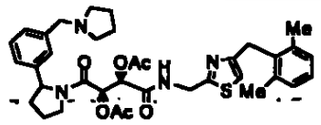
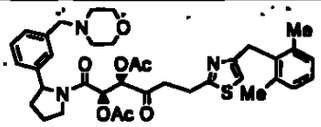
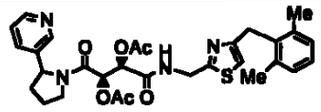
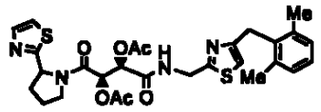
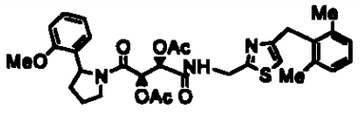
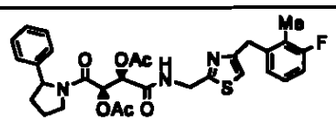
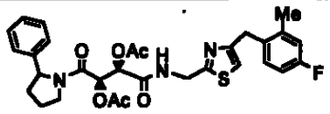
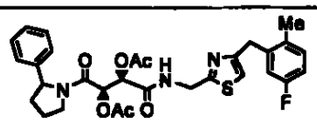
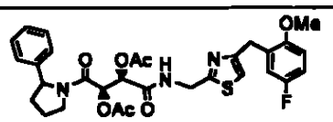
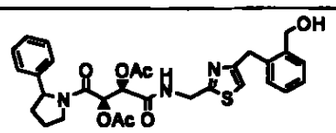
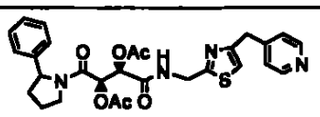
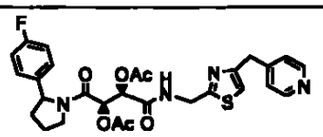
Se combinó el compuesto **393A** (100 mg, 0,416 mmol), compuesto **362** (181 mg, 0,499 mmol), HATU (316 mg, 0,832 mmol), y trietilamina (126 mg, 0,17

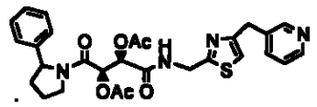
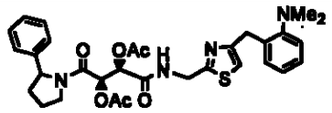
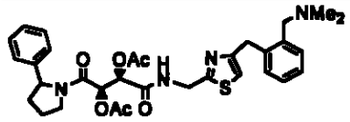
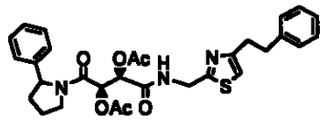
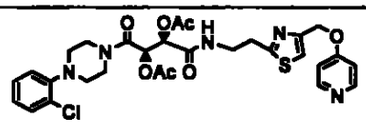
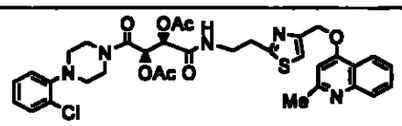
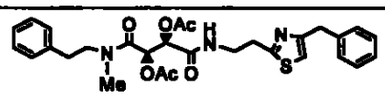
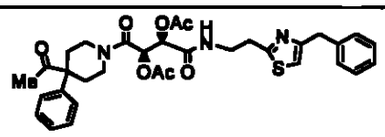
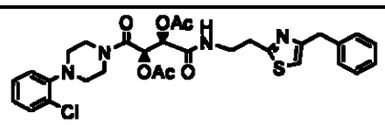
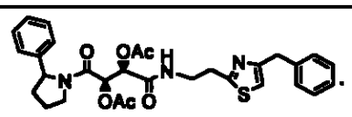
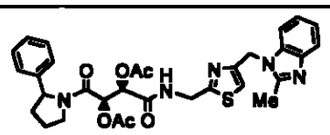
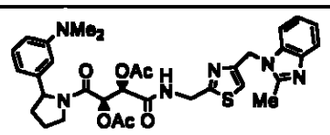
ml, 1,25 mmol) en DMF seco (6 ml). Se agitó a temperatura ambiente durante 16 h. Se concentró, se agregó NaOH 0,5 N (15 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron y se concentraron. Se purificó mediante cromatografía de gel de sílice (eluyente: 3% MeOH-CH_2Cl_2) para dar 120 mg (52%) del producto **394A** como un aceite incoloro. MS m/e: 550 (M+H).

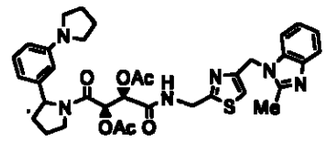
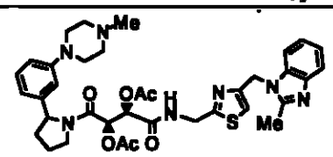
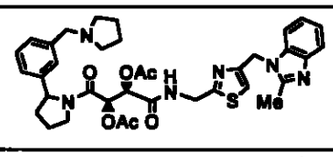
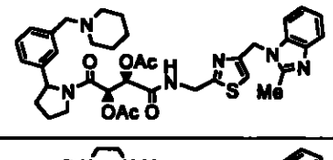
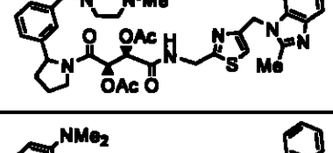
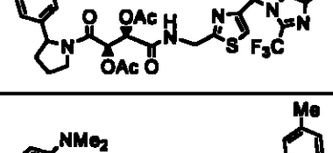
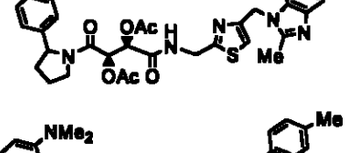
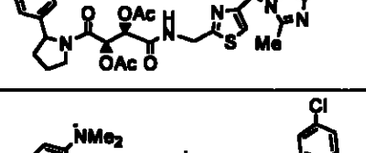
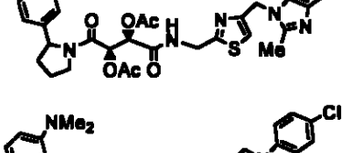
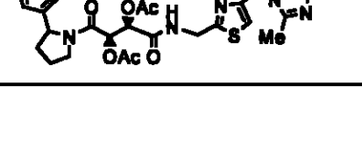
Los siguientes intermediarios se prepararon de acuerdo con el procedimiento anterior:

Compuesto #	Estructura del Intermediario	MS
394B		616 (M+H)
394C		680 (M+H)
394D		536 (M+H)
394E		600 (M+H)
394F		568 (M+H)
394G		564 (M+H)
394H		582 (M+H)
394I		564 (M+H)

394J		580 (M+H)
394K		594 (M+H)
394L		578 (M+H)
394M		626 (M+H)
394N		584 (M+H)
394O		575 (M+H)
394P		578 (M+H)
394Q		612 (M+H)
394R		596 (M+H)
394S		592 (M+H)
394T		608 (M+H)
394U		621 (M+H)
394V		635 (M+H)

394W		661 (M+H)
394X		677 (M+H)
394Y		579 (M+H)
394Z		585 (M+H)
394AA		608 (M+H)
394BB		582 (M+H)
394CC		582 (M+H)
394DD		582 (M+H)
394EE		598 (M+H)
394FF		580 (M+H)
394GG		551 (M+H)
394HH		569 (M+H)

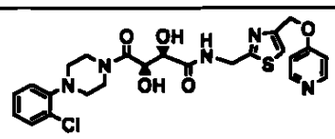
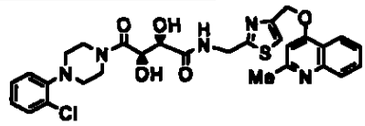
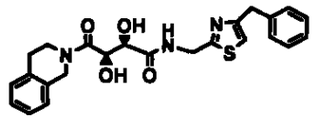
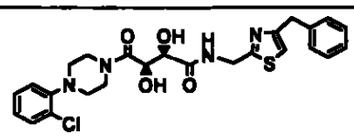
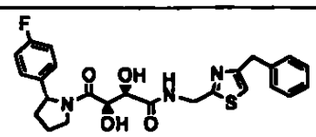
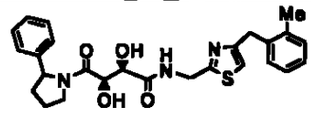
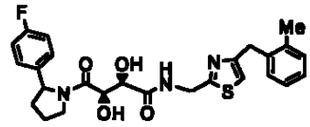
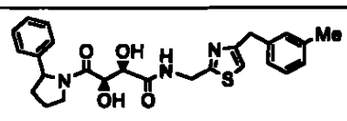
394II		551 (M+H)
394JJ		593 (M+H)
394KK		607 (M+H)
394LL		564 (M+H)
394MM		630 (M+H)
394NN		694 (M+H)
394OO		552 (M+H)
394PP		620 (M+H)
394QQ		613 (M+H)
394RR		564 (M+H)
394SS		604 (M+H)
394TT		647 (M+H)

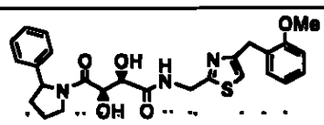
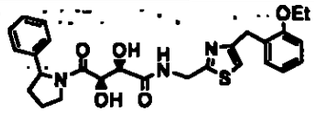
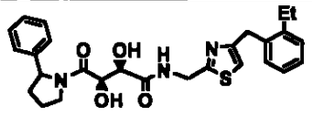
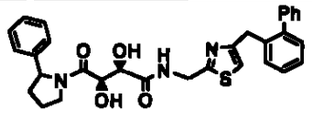
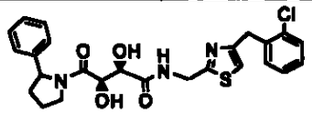
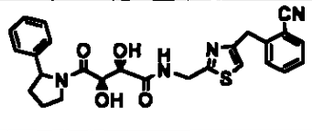
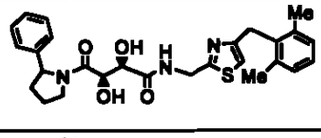
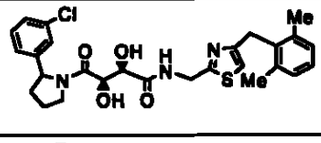
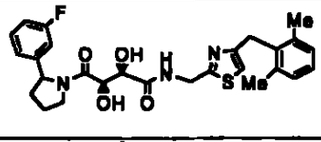
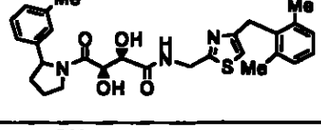
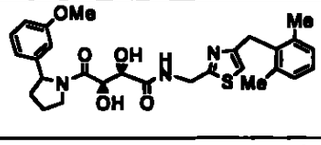
394UU		673 (M+H)
394VV		702 (M+H)
394WW		687 (M+H)
394XX		701 (M+H)
394YY		716 (M+H)
394ZZ		701 (M+H)
394AAA	 	661 (M+H)
394BBB	 	682 (M+H)

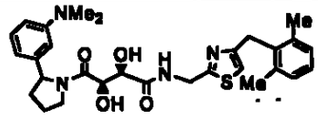
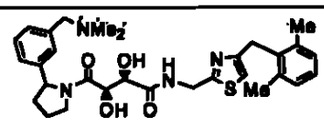
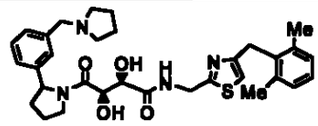
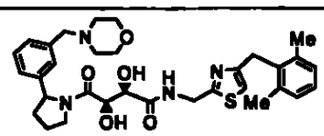
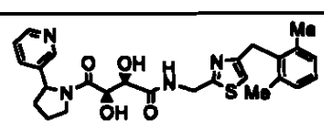
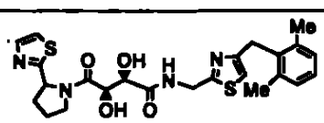
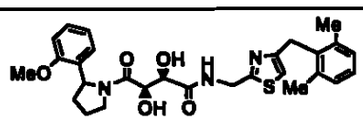
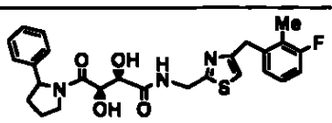
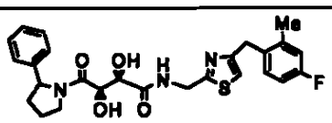
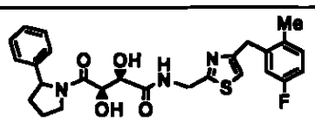
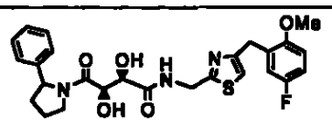
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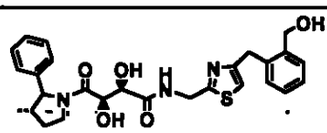
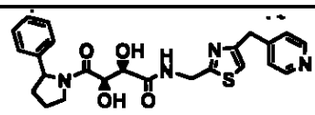
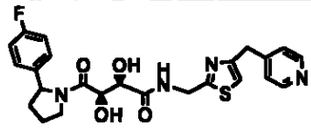
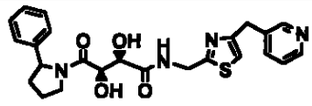
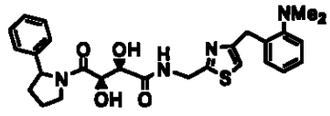
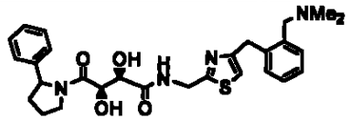
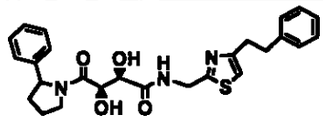
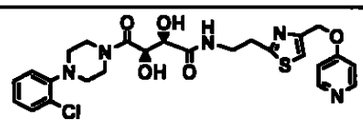
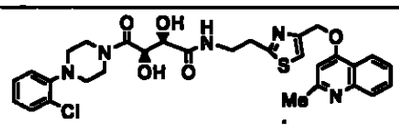
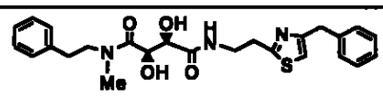
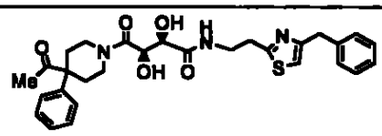
Al compuesto **394A** (0,12 g, 0,218 mmol) disuelto en MeOH (6 ml) se agregó NaOMe 0,5 M en MeOH (0,044 ml, 0,0218 mmol). Se agitó a temperatura ambiente durante 60 minutos. Se agregó 4 N HCl en dioxano (0,055 ml, 0,218 mmol) y se concentró para dar 0,10 g (100%) del producto **395** como una espuma amarillo claro. MS m/e: 466 (M+H).

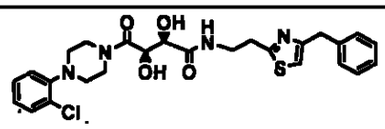
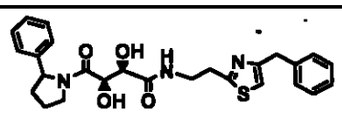
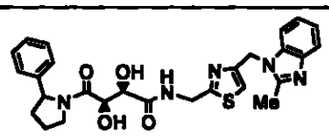
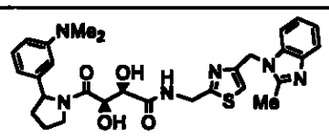
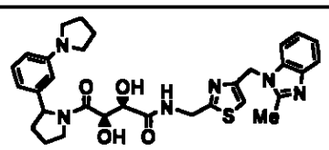
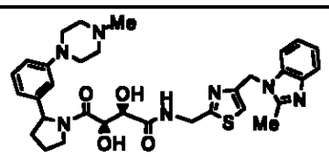
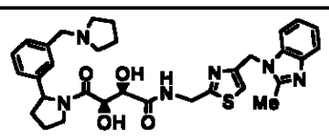
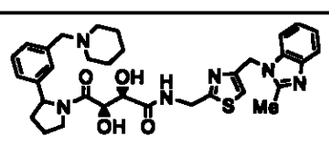
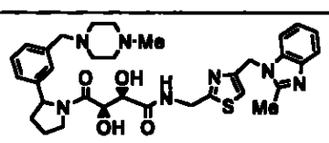
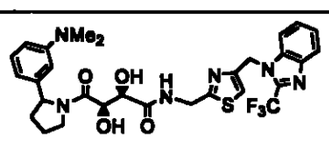
Los siguientes compuestos se prepararon de acuerdo con el procedimiento anterior:

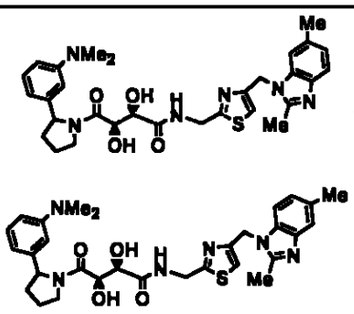
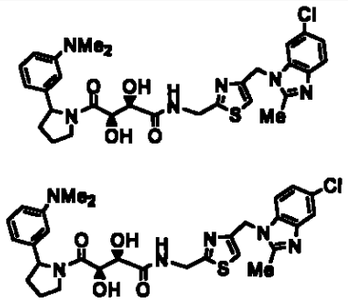
Compuesto #	Compuesto	MS
396		532 (M+H)
397		596 (M+H)
398		452 (M+H)
399		515 (M+H)
400		484 (M+H)
401		480 (M+H)
402		498 (M+H)
403		480 (M+H)

404		496 (M+H)
405		510 (M+H)
406		494 (M+H)
407		542 (M+H)
408		500 (M+H)
409		491 (M+H)
410		494 (M+H)
411		528 (M+H)
412		512 (M+H)
413		508 (M+H)
414		524 (M+H)

415		537 (M+H)
416		551 (M+H)
417		577 (M+H)
418		593 (M+H)
419		495 (M+H)
420		501 (M+H)
421		524 (M+H)
422		498 (M+H)
423		498 (M+H)
424		498 (M+H)
425		514 (M+H)

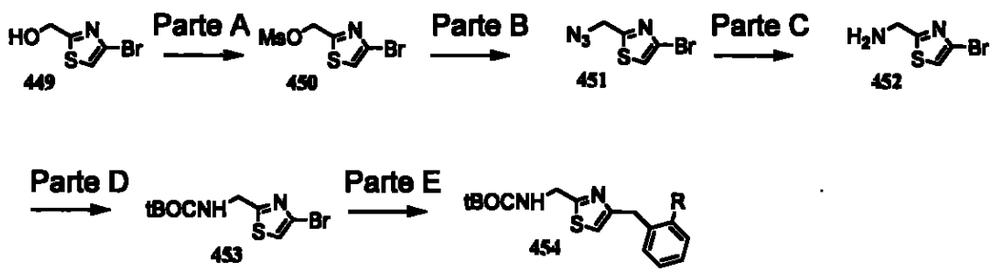
426		496 (M+H)
427		467 (M+H)
428		485 (M+H)
429		467 (M+H)
430		509 (M+H)
431		523 (M+H)
432		480 (M+H)
433		546 (M+H)
434		610 (M+H)
435		468 (M+H)
436		536 (M+H)

437		529 (M+H)
438		480 (M+H)
439		520 (M+H)
440		563 (M+H)
441		589 (M+H)
442		618 (M+H)
443		603 (M+H)
444		617 (M+H)
445		632 (M+H)
446		617 (M+H)

447		577 (M+H)
448		597 (M+H)

Ejemplo 9B

Esquema 1



Referencia para el compuesto **449**:

K. C. Nicolaou, N. P. King, M. R. V. Finlay, Y. He, F. Roschangar, D. Vourloumis, H. Vallberg, F. Sarabia, S. Ninkovic, D. Hepworth; *Bioorg. Med. Chem.* **1999**, *7*, 665-697.

Parte A:

Al compuesto **449** (4,86 g, 25,0 mmol) disuelto en CH_2Cl_2 (200 ml) y se enfrió a -30 °C se agregó trietilamina (5,07 g, 7,0 ml, 50,1 mmol) y luego, cloruro de mesilo (3,44 g, 2,3 ml, 30,1 mmol) gota a gota mediante jeringa. Se calentó lentamente hasta 0 °C durante 60 minutos. Se agregó agua (200 ml), se extrajo

con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron y se concentraron para dar 6,80 g (100%) del producto **450** como un aceite anaranjado. MS m/e: 272 (M+H).

Parte B:

Al compuesto **450** (6,80 g, 25,0 mmol) disuelto en DMF (100 ml) se agregó azida de sodio (3,25 g, 50,0 mmol) y se calentó a 80 °C durante 2 h. Se enfrió hasta temperatura ambiente y se concentró. Se agregó agua (200 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron y se concentraron. Se purificó mediante cromatografía de gel de sílice (eluyente: 5% de EtOAc-hexano a 10% de EtOAc-hexano) para dar 4,18 g (76%) del producto **451** como un aceite anaranjado. MS m/e: 219 (M+H).

Parte C:

Al compuesto **451** (4,18 g, 19,1 mmol) disuelto en 10:1 de THF:agua en volumen (150 ml) se agregó trifenilfosfina (20,0 g, 76,3 mmol) y se reflujó durante 2 h. Se enfrió hasta temperatura ambiente y se concentró. Se purificó mediante cromatografía de gel de sílice (eluyente: 3% MeOH con NH_3-CH_2Cl_2) para dar 6,18 g del producto **452** (con óxido de trifenilfosfina) como un sólido amarillo. 100% de rendimiento del producto **452** sería de 3,68 g. MS m/e: 194 (M+H).

Parte D:

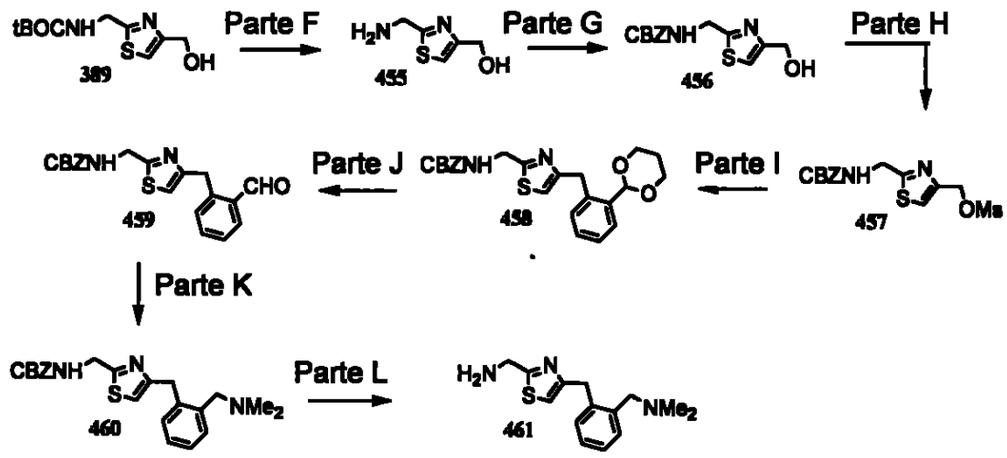
Al compuesto **452** (3,68 g, 19,1 mmol) disuelto en CH_2Cl_2 (100 ml) se agregó anhídrido tBOC (5,21 g, 23,9 mmol). Se agitó a temperatura ambiente durante 2 h luego se concentró. Se purificó mediante cromatografía de gel de sílice (eluyente: 3% MeOH-CH_2Cl_2) para dar 3,97 g (71%) del producto **453** como un sólido amarillo. MS m/e: 293 (M+H).

Parte E:

Al compuesto **453** (1,07 g, 3,65 mmol) disuelto en THF seco (10 ml) bajo una atmósfera de nitrógeno se agregó cloruro de 2-clorobencilzinc (0,5 M en THF,

14,6 ml, 7,30 mmol) y bis(tri-t-butilfosfina)paladio (0,14 g, 0,274 mmol). Se calentó a 60 °C durante 2 h. Se enfrió hasta temperatura ambiente y se concentró. Se agregó 0,2 N HCl (30 ml); se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron y se concentraron. Se purificó mediante cromatografía de gel de sílice (eluyente: 5% de EtOAc-hexano a 15% de EtOAc-hexano) para dar 0,61 g (49%) del producto **454** como un sólido amarillo. MS m/e: 339 (M+H).

Esquema 2



Parte F:

Al compuesto **389** (2,00 g, 8,18 mmol) disuelto en MeOH (40 ml) se agregó HCl 4 N en dioxano (20,5 ml, 81,8 mmol). Se agitó a temperatura ambiente durante 3 h. Se concentró para dar 1,48 g (100%) del producto **455** como un sólido blanco. MS m/e: 145 (M+H).

Parte G:

Al compuesto **455** (1,48 g, 8,18 mmol) suspendido en CH_2Cl_2 (50 ml) se agregó trietilamina (2,48 g, 3,4 ml, 24,5 mmol) y se enfrió a 0 °C. Se agregó CBZCl (1,54 g, 1,3 ml, 9,00 mmol) disuelto en CH_2Cl_2 (10 ml) gota a gota

mediante un embudo de adición. Se agitó a 0 °C durante 30 minutos luego a temperatura ambiente durante 2 h. Se agregó NaOH 0,2 N (100 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron y se concentraron. Se purificó mediante cromatografía de gel de sílice (eluyente: 5% MeOH-CH_2Cl_2 a 10% MeOH-CH_2Cl_2) para dar 1,41 g (62%) del producto **456** como un sólido blanco. MS m/e: 279 (M+H).

Parte H:

Al compuesto **456** (1,40 g, 5,03 mmol) disuelto en CH_2Cl_2 (40 ml) y se enfrió a -30 °C se agregó trietilamina (1,02 g, 1,4 ml, 10,1 mmol) y luego, cloruro de mesilo (0,69 g, 0,47 ml, 6,04 mmol) gota a gota mediante jeringa. Se calentó lentamente hasta 0 °C durante 60 minutos. Se agregó agua (50 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron y se concentraron para dar 1,79 g (100%) del producto **457** como un sólido amarillo. MS m/e: 357 (M+H).

Parte I:

A bromuro de 2-(1,3-dioxan-2-il)fenilmagnesio (0,25 M en THF, 100 ml, 25,0 mmol) bajo una atmósfera de nitrógeno y se enfrió a -25°C de temperatura interna se agregó cianuro de cobre (1,12 g, 12,5 mmol). Se agitó a -25°C durante 1 h luego a 0°C durante 1 h. Se calentó hasta 15 °C de temperatura interna luego se reenfrió a -25°C. Se agregó compuesto **457** (1,78 g, 4,99 mmol) disuelto en THF seco (15 ml) gota a gota mediante jeringa. Se agitó a -25°C temperatura interna durante 1 h luego a 0°C durante 16 h. Se concentró, se agregó NH_4OH 2 N (100 ml) y CH_2Cl_2 (100 ml), y se filtró a través de Celite. Se separaron las capas del filtrado, se extrajeron con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron y se concentraron. Se purificó mediante cromatografía de gel de sílice (eluyente: 10% de EtOAc-hexano a 40% de EtOAc-hexano) para dar 1,35 g (64%) del producto **458** como un sólido blanco. MS m/e: 425 (M+H).

Parte J:

Al compuesto **458** (1,34 g, 3,16 mmol) disuelto en CH_2Cl_2 (10 ml) se agregó agua (2 ml) y TFA (8 ml). Se agitó a temperatura ambiente durante 5 h, luego se concentró. Se agregó NaOH 1 N (50 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron y se concentraron. Se purificó mediante cromatografía de gel de sílice (eluyente: 20% de EtOAc-CH_2Cl_2 a 30% de EtOAc-CH_2Cl_2) para dar 1,05 g (91%) del producto **459** como un sólido amarillo. MS m/e: 367 (M+H).

Parte K:

Al compuesto **459** (0,74 g, 2,02 mmol) disuelto en CH_2Cl_2 (20 ml) se agregó dimetilamina (2 M en THF, 2,0 ml, 4,04 mmol), tamices 3A (0,60 g), ácido acético glacial (0,12 g, 0,12 ml, 2,02 mmol), luego triacetoxiborohidruro de sodio (0,64 g, 3,03 mmol). Se agitó a temperatura ambiente durante 16 h. Se agregó NaOH 0,5 N (25 ml), se extrajo con CH_2Cl_2, se secaron los extractos combinados ($MgSO_4$), se filtraron y se concentraron. Se purificó mediante cromatografía de gel de sílice (eluyente: MeOH 5% con NH_3-CH_2Cl_2 a MeOH 15% con NH_3-CH_2Cl_2) para dar 0,65 g (81%) del producto **460** como un sólido amarillo. MS m/e: 396 (M+H).

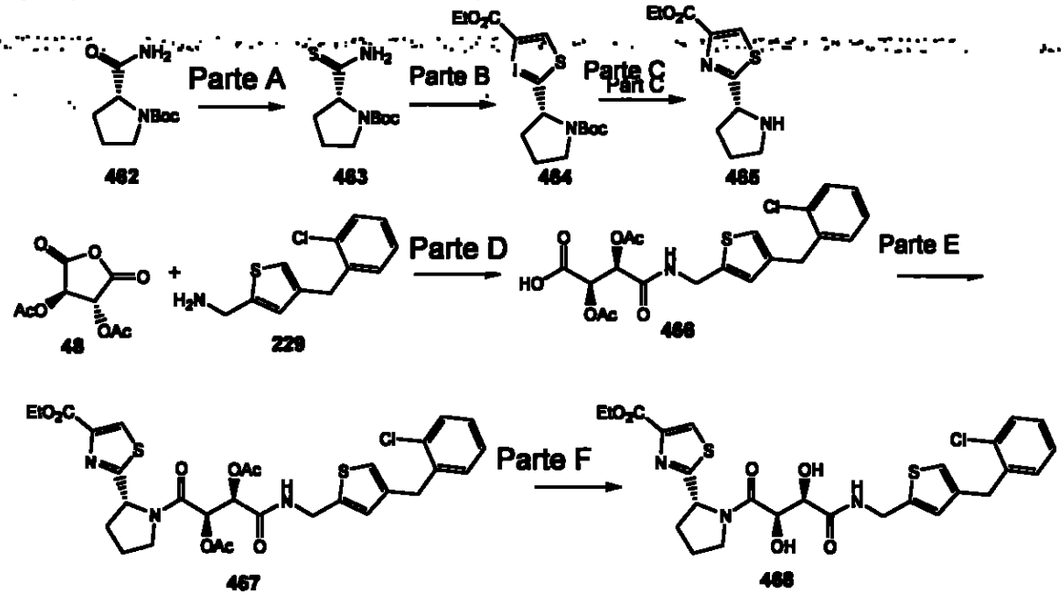
Parte L:

Al compuesto **460** (0,64 g, 1,62 mmol) disuelto en MeOH (5 ml) se agregó THF (2 ml) y NaOH 6,25 N (5 ml). Se reflujó durante 3 h. Se enfrió hasta temperatura ambiente y se concentró. Se purificó mediante cromatografía de gel de sílice (eluyente: 10% de MeOH con NH_3-CH_2Cl_2 a 15% de MeOH con NH_3-CH_2Cl_2) para dar 0,31 g (74%) del producto **461** como un aceite anaranjado. MS m/e: 262 (M+H).

Compuestos seleccionados preparados usando los procedimientos del Ejemplo 9B se ejemplificaron en la tabla precedente.

Ejemplo 10: 2-Heteroaril pirrolidinas & derivados

Ejemplo 10A:



Parte A:

A D-1-N-Boc-prolinamida **(462)** (2,5 g, 11,7 mmol) en THF (15 ml) se agregó Reactivo de Lawesson (2,36 g, 5,8 mmol) en porciones a temperatura ambiente. La mezcla de reacción se agitó durante 3,5 horas bajo atmósfera de argón. Los solventes se eliminaron in vacuo. La purificación mediante cromatografía en columna (SiO_2, 5% de MeOH/DCM) dio **463** como un sólido amarillo claro (2,5 g, 93%).

Parte B:

Una mezcla de **463** (500 mg, 2,15. mmol) y carbonato hidrogenado de potasio (1,74 g, 17,35 mmol) en DME (12 ml) se agitó durante 10 minutos. Se agregó gota a gota bromopiruvato de etilo (0,81 ml, 6,45 mmol) mediante una jeringa a la mezcla de reacción. La mezcla de reacción se agitó durante 30 minutos. La mezcla de reacción se enfrió a 0 °C y una mezcla de anhídrido trifluoroacético (1,21 ml, 8,6 mmol) y 2,6-lutidina (2,12 ml, 18,3 mmol) se agregó gota a gota mediante jeringa durante 10 minutos. La mezcla de reacción se agitó

durante 30 minutos a 0 °C. Los solventes se eliminaron in vacuo. El residuo se disolvió en cloroformo, se lavó con HCl 1,0 N, solución de bicarbonato y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 30% EtOAc/hexano) dio **464** como un sólido amarillo claro (520 mg, 74%). HPLC-MS t_R = 1,88 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{15}H_{22}N_2O_4S$ 326,1. LCMS observada m/z 327,1 (M+H).

Parte C:

A **464** (486 mg, 1,49 mmol) en dioxano (1 ml) se agregó 4 N HCl en dioxano (1 ml). La mezcla de reacción se agitó durante 1 hora a temperatura ambiente y se concentró. HPLC-MS t_R = 0,60 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{10}H_{14}N_2O_2S$ 226,1. LCMS observada m/z 227,1 (M+H).

Parte D:

A **48** (216 mg, 1,0 mmol) en THF (2 ml) se agregó material de **229** (238 mg, 1 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se concentró y se secó en freezer para dar un polvo blanco (410 mg, 90%). HPLC-MS t_R = 1,74 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{20}H_{20}ClNO_7S$ 453,0. LCMS observada m/z 454,0 (M+H).

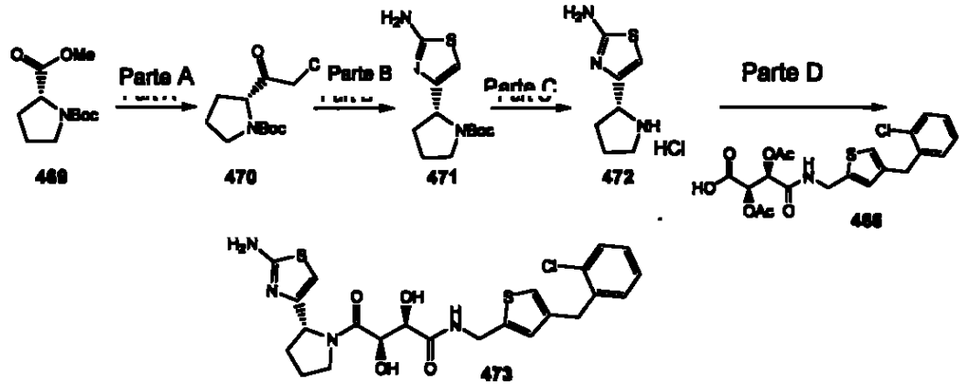
Parte E:

A **465** (26 mg, 0,1 mmol) en DMF (0,5 ml) se agregó DIEA (35 µl, 0,2 mmol), **466** (54 mg, 0,12 mmol) en DMF (1 ml) y luego HATU (57 mg, 0,15 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo (20 ml) y agua (20 ml) y las capas se separaron. La capa orgánica se lavó con NaOH 0,1 N, HCl 0,1 N y salmuera, se secó sobre sulfato de sodio y se concentró. Compuesto **467** se usó sin purificación adicional. HPLC-MS t_R = 2,06 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{30}H_{32}ClN_3O_8S_2$ 661,1. LCMS observada m/z 662,0 (M+H).

Parte F:

A **467** en metanol (1 ml) se agregó 7,0 M de amoníaco en metanol (1 ml). La mezcla de reacción se agitó durante 1 hora a temperatura ambiente y se concentró. La purificación mediante LC prep de fase reversa dio **468** como un polvo blanco (2 mg). HPLC-MS t_R = 5,04 min ($UV_{254\ nm}$, 10 min); Masa calculada para la fórmula $C_{26}H_{28}ClN_3O_6S_2$ 577,1. LCMS observada m/z 578,0 (M+H).

Ejemplo 10B:



Parte A:

Una solución de LDA se formó mediante la adición de *n*-butil litio 1,6 M (34 ml, 54,5 mmol) a diisopropilamina (8,47 ml, 60 mmol) en THF (20 ml) a –78°C. La mezcla de reacción se agitó a –78°C durante 20 minutos y se calentó hasta 0°C gradualmente. La solución de LDA se agregó gota a gota a una mezcla de metil éster de N-Boc-D-prolina (**469**) (2,5 g, 10,9 mmol) y cloroyodometano (3,17 ml, 43,6 mmol) en THF (20 ml) a – 78°C mediante una cánula durante 30 minutos. La mezcla de reacción se agitó a –78°C durante 30 minutos. Una solución de ácido acético (15 ml) en THF (15 ml) se agregó lentamente durante 20 minutos a –78°C. La mezcla de reacción se agitó durante 20 minutos y luego se calentó hasta temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo y se lavó con agua, solución de bicarbonato de sodio y salmuera. La capa orgánica se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 20% de EtOAc/hexano) dio **470** como un sólido

marrón claro (2,0 g, 74%). HPLC-MS t_R = 1,80 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{14}H_{18}ClNO_3$ 247,1; LCMS observada m/z 248,1 (M+H).

Parte B:

Una mezcla de **470** (250 mg, 1,0 mmol) y tiourea (152 mg, 2 mmol) se agitaron durante 72 horas. La mezcla de reacción se diluyó con acetato de etilo y se lavó con solución de bicarbonato de sodio y salmuera. La capa orgánica se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 80% de EtOAc/hexano) dio **471** como un sólido blanco (201 mg, 75%). HPLC-MS t_R = 0,67 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{12}H_{19}N_3O_2S$ 269,1. LCMS observada m/z 270,1 (M+H).

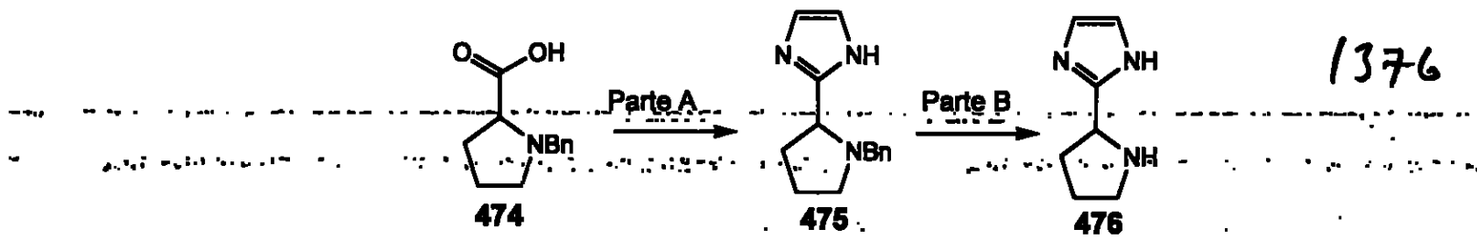
Parte C:

A **471** (201 mg, 0,75 mmol) en dioxano (1 ml) se agregó 4 N HCl en dioxano (1 ml). La mezcla de reacción se agitó durante 1 hora a temperatura ambiente y se concentró.

Parte D:

Una mezcla de **466** (45 mg, 0,1 mmol), **472** (29 mg, 0,12 mmol), DIEA (50 µl, 0,28 mmol) y HATU (57 mg, 0,15 mmol) en DMF (2 ml) se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo (20 ml) y agua (20 ml) y las capas se separaron. La capa orgánica se lavó con NaOH 0,1 N, HCl 0,1 N y salmuera, se secó sobre sulfato de sodio y se concentró. El residuo se disolvió en metanol (1 ml) y se agregó amoníaco 7,0 M en metanol (1 ml). La mezcla de reacción se agitó durante 1 hora a temperatura ambiente y se concentró. La purificación mediante LC preparativa de fase reversa dio **473** como un polvo blanco. HPLC-MS t_R = 1,42 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{23}H_{25}ClN_4O_4S_2$ 520,1. LCMS observada m/z 521,1 (M+H).

Ejemplo 10C:



474 475 476

Parte A:

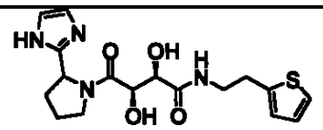
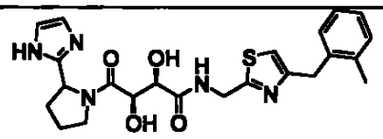
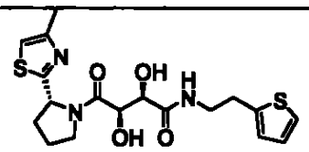
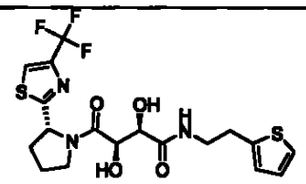
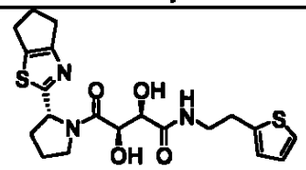
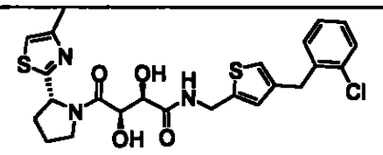
A ácido 1-bencil-pirrolidina-2-carboxílico (**474**) (Belokon, Y. N. at al; Tetrahedron Asymmetry **1998**, *9*, 4249-4252) en CH_2Cl_2 (20 ml) se agregó 2,2-dimetoxi-etilamina (614 mg, 5,84 mmol), EDCI (1,12 g, 5,84 mmol), HOBT (658 mg, 4,87 mmol), y NMM (1,08 ml, 9,8 mmol). La mezcla de reacción se agitó hasta el día siguiente a 25°C. Se agregó solución acuosa saturada de $NaHCO_3$ (50 ml). La capa acuosa se extrajo con CH_2Cl_2 (50 ml x3). Las capas orgánicas combinadas se lavaron con salmuera (50 ml), se secaron sobre Na_2SO_4, y se concentraron mediante evaporador de rotación para dar ácido 1-bencil-pirrolidin-2-carboxílico (2,2-dimetoxi-etil)-amida como un aceite amarillo. A ácido 1-bencil-pirrolidin-2-carboxílico (2,2-dimetoxi-etil)-amida se agregó ácido acético (10 ml) y acetato de amonio (11 g). La mezcla de reacción se calentó hasta 140°C hasta el día siguiente. Una vez que se enfrió, se vertió en 100 ml de agua congelada con agitación. Se agregó $NaHCO_3$ sólido en porciones pequeñas con agitación para regular el pH de la solución a 8~9, La solución acuosa se extrajo con EtOAc (100 ml x2). Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre Na_2SO_4, y se concentró con evaporador por rotación. El compuesto **475** (110 mg) se aisló mediante cromatografía de SiO_2 (CH_2Cl_2/MeOH/NH_3: 40:1:0,1 a 20:1:0,1). MS: m/z 228,3 $[M+H]^+$.

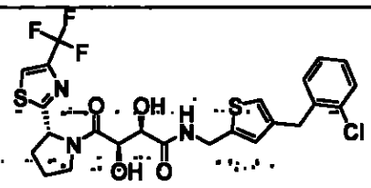
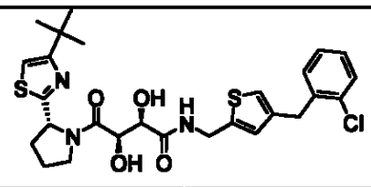
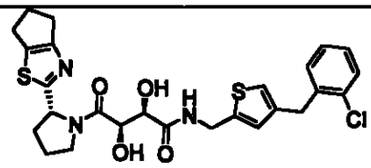
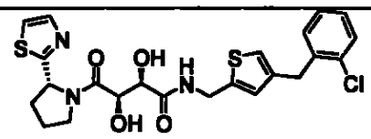
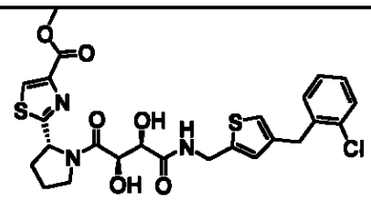
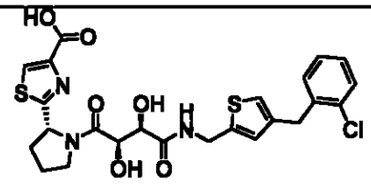
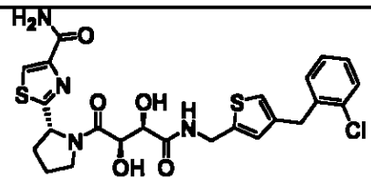
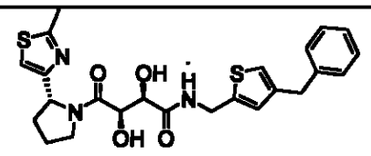
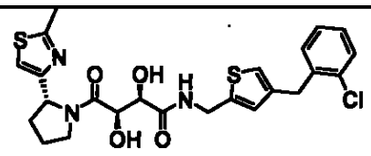
Parte B: 5-Pirrolidina-2-il-1*H*-imidazol:

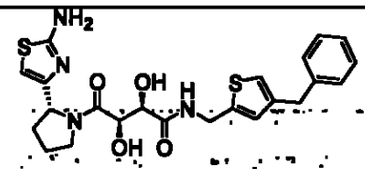
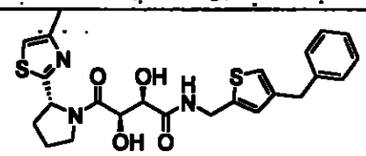
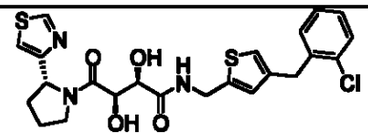
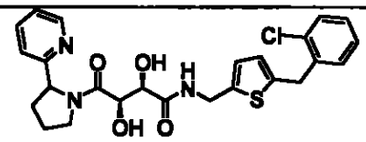
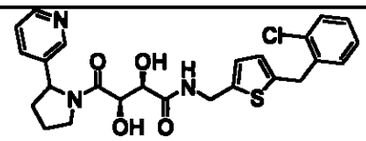
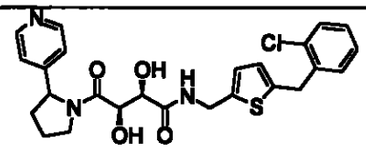
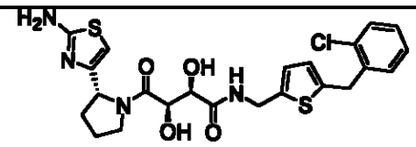
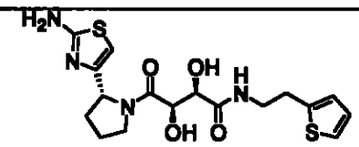
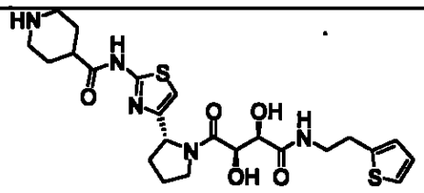
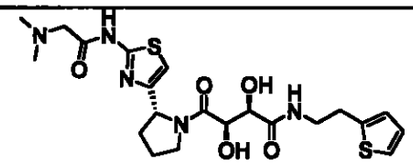
A **475** (110 mg) en 10 ml de EtOH se agregó Pd/C (10%, 50 mg). La mezcla de reacción se hidrogenó bajo hidrógeno [3,45 x 10^5 Pa (50 psi)] durante

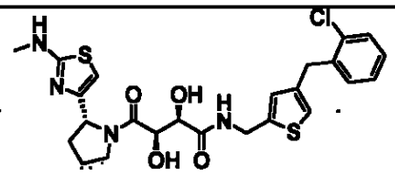
24 horas. El sólido se filtró y la solución se evaporó mediante evaporador rotativo para dar 5-pirrolidin-2-il-1*H*-imidazol (476) (67 mg). MS m/z 138,2 $[M+H]^+$. ^{1}H-RMN (300 MHz, $CDCl_3$): δ ppm: 6,95 (s, 2H), 4,35 (t, 1H, J = 7,4 Hz), 3,00 (m, 2H), 2,22-2,03 (m, 2H), 1,85 (m, 3H).

Los siguientes compuestos se prepararon mediante procedimientos descriptos en el Ejemplo 11. Las 2-(piridil)-pirrolidinas son aminas comerciales (entradas **495-497**). El amino-tiazol de **471** se funcionalizó adicionalmente mediante química de acilación para dar **500–501**.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
477		378,1	379,1
478		469,2	470,1
479		409,1	410,1
480		463,1	464,0
481		435,1	436,1
482		519,1	520,0

483		573,1	574,0
484		561,2	562,2
485		545,1	546,1
486		505,1	506,0
487		563,1	564,1
488		549,1	550,0
489		548,1	549,1
490		485,1	486,1
491		519,1	520,0

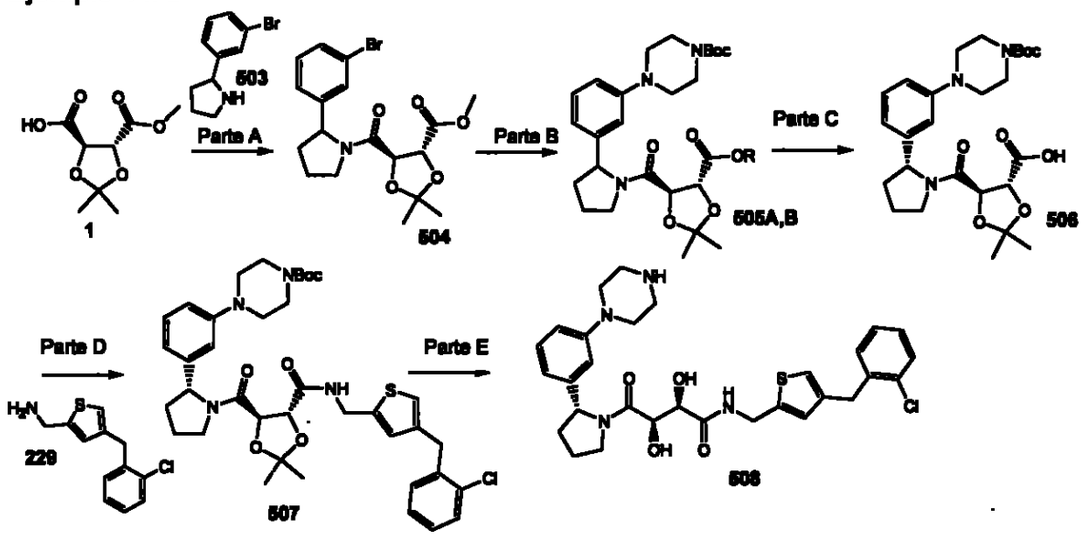
492		486,1	487,1
493		485,1	486,1
494		505,1	505,9
495		499,1	499,9
496		499,1	499,9
497		499,1	499,9
498		520,1	520,9
499		521,2	522,1
500		522,2	522,1
501		495,2	496,1

502		534,1	535,0

1380

Ejemplo 11: 2-Fenil pirrolidinas & derivados

Ejemplo 11A:



Parte A:

A **1** (925 mg, 4,53 mmol) en DMF (5 ml) se agregó 2-(3-bromofenil)-pirrolidina **(503)** (preparado mediante el método de Sorgi, K.L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E.; *J. Am. Chem. Soc.* **1990**, *112*, 3567) (1,12 g, 4,95 mmol), DIEA (1,75 ml, 10,0 mmol) y HATU (1,88 g, 4,95 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. El DMF se eliminó in vacuo y el residuo se dividió entre acetato de etilo (20 ml) y agua (20 ml). Las capas se separaron y la capa acuosa se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución de bicarbonato de sodio, HCl 1,0 N y salmuera, se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 10 - 20% EtOAc/DCM) dio **504** (1,22 g, 65%). HPLC-MS t_R = 2,00 min ($UV_{254\ nm}$);

masa calculada para la fórmula $C_{18}H_{22}BrNO_5$ 411,1. LCMS observada m/z 412,2 (M+H).

Parte B:

Al ter-butil éster del ácido piperazin-1-carboxílico (279 mg, 1,5 mmol), fosfato de potasio (530 mg, 2,5 mmol), $Pd_2(dba)_3$ (23 mg, 0,025 mmol) y 2-(diciclohexilfosfino)bifenil (35 mg, 0,1 mmol) bajo atmósfera de argón se agregó el material de la Parte A (414 mg, 1,0 mmol). La mezcla de reacción se evacuó y se saturó con argón. La mezcla se calentó hasta el día siguiente a 90 °C. La mezcla de reacción se diluyó con acetato de etilo, se filtró a través de Celite y se concentró para dar una mezcla de metil éster **505A** y ácido **505B** como una lámina anaranjada (679 mg). El material se usó sin purificación adicional. **505A**: HPLC-MS t_R = 2,08 & 2,14 min (éster, UV_{254} nm); masa calculada para la fórmula $C_{27}H_{39}N_3O_7$ 517,3. LCMS observada m/z 518,0 (M+H). **505B**: HPLC-MS t_R = 1,83 & 1,91 min (ácido, UV_{254} nm); masa calculada para la fórmula $C_{26}H_{37}N_3O_7$ 503,3. LCMS observada m/z 504,1 (M+H).

Parte C:

A la mezcla de **505A** y **505B** (~1 mmol) en THF (4 ml) y agua (1 ml) se agregó hidróxido de litio 1,0 M (1,2 ml, 1,2 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se diluyó con agua (10 ml) y el THF se eliminó in vacuo. La capa acuosa se lavó con dietil éter (3 x 10 ml), se acidó con HCl 1,0 N y se extrajo con acetato de etilo (3 x 10 ml). Las capas de acetato de etilo combinadas se secaron sobre sulfato de sodio y se concentró. La purificación mediante LC prep de fase reversa dio el isómero deseado **506** (107 mg, 96% de pureza). HPLC-MS t_R = 1,83 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{26}H_{37}N_3O_7$ 503,3. LCMS observada m/z 504,1 (M+H).

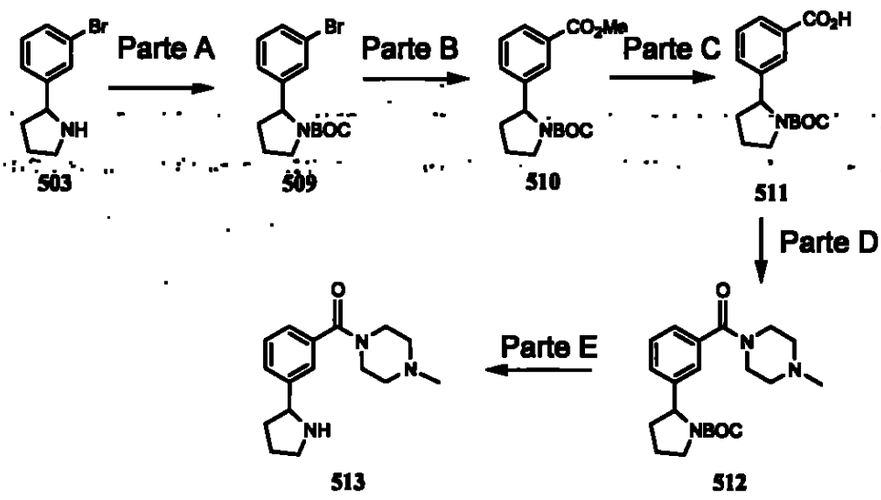
Parte D:

A **506** (107 mg, 0,21 mmol) en DMF (5 ml) se agregó **229** (55 mg, 0,23 mmol), DIEA (80 µl, 0,46 mmol) y HATU (87 mg, 0,23 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. El DMF se eliminó in vacuo y el residuo se dividió entre acetato de etilo y agua. Las capas se separaron. La capa orgánica se lavó con NaOH 0,1 N, HCl 0,1 N, y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 50% EtOAc/hexano) dio **507** (98 mg, 64%). HPLC-MS t_R = 2,49 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{38}H_{47}ClN_4O_6S$ 722,2. LCMS observada m/z 723,1 (M+H).

Parte E:

A **507** (98 mg, 0,14 mmol) se agregó TFA:agua 80:20 (4 ml) y la mezcla se agitó durante 4 horas a temperatura ambiente. La reacción se desactivó con 1:1 acetonitrilo:agua (10 ml) y se concentró. El residuo se disolvió en acetato de etilo y se lavó con solución de bicarbonato de sodio. A la capa acuosa se agregó cloruro de sodio y se extrajo con acetato de etilo. La capa orgánica combinada se secó sobre sulfato de sodio y se concentró. El residuo se disolvió en acetonitrilo (2 ml) y HCl 1,0 N (0,3 ml) y se concentró. El material se liofilizó para dar **508** como la sal del HCl como un polvo blanco (75 mg, 86%). HPLC-MS t_R = 1,27 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{30}H_{35}ClN_4O_4S$ 582,2. LCMS observada m/z 583,2 (M+H).

Ejemplo 11B



Parte A

A una solución del compuesto **503** (5,0 g, 22,1 mmol) en CH_2Cl_2 seco (80 ml) se agregó di-ter-butil carbonato (5,55 g, 25,4 mmol). La solución se agitó a temperatura ambiente durante 2 horas. El solvente se eliminó mediante evaporador rotatorio. El producto se aisló mediante cromatografía del gel de sílice (Hexano/EtOAc 5:1 a 3:1) para dar el compuesto **509** (5,7 g, 79%).

Parte B

En un matraz de doble boca se cargó el compuesto **509** (1,0 g, 3,06 mmol), MeOH (8 ml), trietilamina (6 ml), DMF (6 ml), y $Pd(PPh_3)_2Cl_2$. Se unió al matraz un condensador con una válvula de 3 vías sobre la parte superior. Un balón y un tanque de monóxido de carbono se unieron a la válvula de tres vías. El balón se llenó con CO y se saturó el sistema dos veces. Luego, el balón se llenó con CO y se conectó al sistema del matraz. El matraz se calentó in un baño de aceite de 80°C durante 36 horas. Después de enfriarse hasta temperatura ambiente, se agregaron agua (50 ml) y EtOAc (100 ml). La fase orgánica se separó, se lavó con agua (50 ml) dos veces y salmuera, se secó sobre Na_2SO_4, se concentró con evaporador por rotación, el producto se aisló con cromatografía del gel de sílice (Hexano/EtOAc 10:1 a 5:1) para dar el compuesto **510** (610 mg, 65%).

Parte C

El compuesto **510** (384 mg, 1,26 mmol) se disolvió en dioxano/agua (3:1, 4 ml) y se agregó LiOH (100 mg, 2,38 mmol). La solución se agitó a temperatura ambiente durante cuatro horas. Se agregó solución saturada de NH_4Cl (20 ml). La fase acuosa se extrajo con EtOAc (25 ml) dos veces. Las fases orgánicas se combinaron, se lavaron con salmuera, se secaron sobre Na_2SO_4, se concentraron mediante evaporador rotatorio, y se secaron en vacío para dar el compuesto **511** (368 mg, 100%).

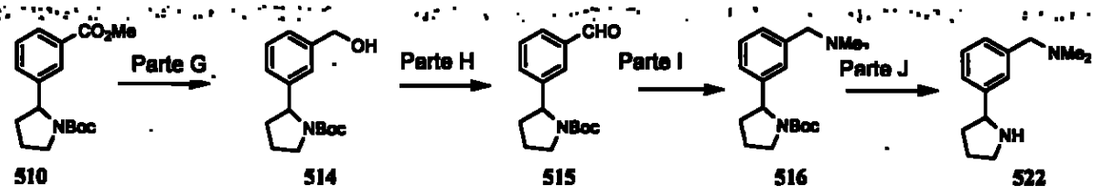
Parte E

El compuesto **511** (76 mg, 0,26 mmol) se disolvió en CH_2Cl_2 seco (1,5 ml). Se agregaron N-metil piperazina (0,035 ml, 0,31 mmol), EDCI (75 mg, 0,39 mmol), HOBT (43 mg, 0,31 mmol), y NMM (0,086 ml, 0,78 mmol). La solución se agitó a temperatura ambiente durante 16 horas. Se agregó solución saturada de $NaHCO_3$ (5 ml) y CH_2Cl_2 (5 ml) y las capas se separaron. La fase acuosa se extrajo con CH_2Cl_2 (5 ml) dos veces. Las fases orgánicas se combinaron, se secaron sobre Na_2SO_4, se concentraron mediante evaporador rotatorio. El producto se aisló mediante cromatografía del gel de sílice para dar el compuesto **512** (90 mg, 92%).

Parte F

El compuesto **512** (90 mg, 0,24 mmol) se disolvió en MeOH (1 ml) y se agregó HCl (4M en dioxano, 0,25 ml, 1 mmol). La solución se agitó a temperatura ambiente durante hasta el día siguiente. El solvente se eliminó mediante evaporador rotatorio para dar el compuesto **513** (83 mg, 100%).

Ejemplo 11C:



510 514 515 516 522

Parte G:

El compuesto **510** (3,68 g, 12,0 mmol) se disolvió en THF seco (60 ml), y se agregó borohidruro de litio (0,78 g, 36,2 mmol). La solución se calentó a reflujo durante 16 h luego se enfrió hasta temperatura ambiente. Se agregó MeOH (4 ml), y el solvente se eliminó mediante evaporador rotatorio. Se agregó agua (75 ml), y la solución acuosa se extrajo con CH_2Cl_2 (75 ml) tres veces. Los extractos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se concentraron. El producto se purificó mediante cromatografía de gel de sílice (eluyente: 5% de MeOH-CH_2Cl_2 a 10% de MeOH-CH_2Cl_2) para dar 3,28 g (98%) de compuesto **514**, MS (m/e para M+1): 278.

Parte H:

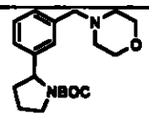
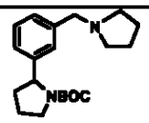
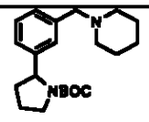
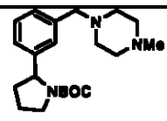
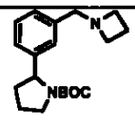
Se disolvió cloruro de oxalilo (1,87 g, 1,3 ml, 14,7 mmol) en CH_2Cl_2 seco (35 ml) y se enfrió a -78° C bajo una atmósfera de nitrógeno. Se agregó gota a gota DMSO (2,30 g, 2,1 ml, 29,5 mmol) disuelto en CH_2Cl_2 seco (5 ml) mediante un embudo de adición. La solución se agitó a -78° C durante 15 minutos luego se agregó el compuesto **514** (3,27 g, 11,8 mmol) disuelto en CH_2Cl_2 (15 ml). La mezcla de reacción se agitó a -78° C durante 60 minutos, luego se agregó trietilamina (3,58 g, 4,9 ml, 35,4 mmol). La mezcla de reacción se agitó a -78° C durante 15 minutos luego se calentó a 0° C. Se agregó agua (75 ml), y las capas se separaron. La fase acuosa se extrajo con CH_2Cl_2 (75 ml) dos veces. Los extractos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se

concentraron. El producto se purificó mediante cromatografía de gel de sílice (eluyente: 5% de EtOAc-CH_2Cl_2 a 10% de EtOAc-CH_2Cl_2) para dar 2,94 g (90%) del producto **515**, MS (m/e para M+1): 276.

Parte I:

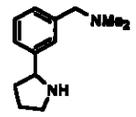
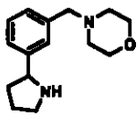
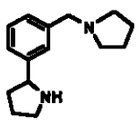
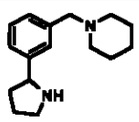
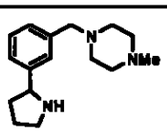
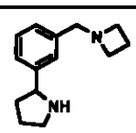
EL compuesto **515** (0,50 g, 1,82 mmol) se disolvió en CH_2Cl_2 (10 ml), y tamices 3A (0,50 g), dimetilamina en THF (2 M, 1,8 ml, 3,64 mmol), glacial ácido acético (0,109 g, 1,82 mmol), y triacetoxiborohidruro de sodio (0,579 g, 2,73 mmol) se agregaron. La mezcla de reacción se agitó a temperatura ambiente durante 24 h. Se agregó NaOH 1 N (25 ml), y la solución acuosa se extrajo con CH_2Cl_2 (25 ml) cuatro veces. Los extractos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se concentraron. El producto se purificó mediante cromatografía de gel de sílice (eluyente: 5% de MeOH-CH_2Cl_2 a 15% de MeOH-CH_2Cl_2) para dar 0,396 g (72%) del producto **516**, MS (m/e para M+1): 305.

También se prepararon los siguientes intermediarios.

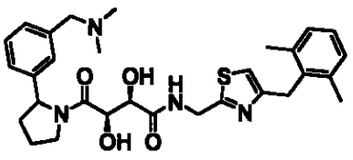
Compuesto #	Intermediario	MS (m/e para M+1)
517		347
518		331
519		345
520		360
521		317

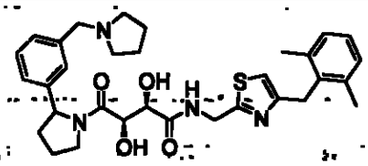
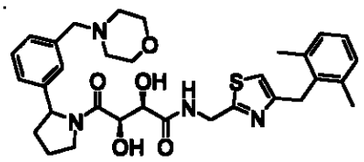
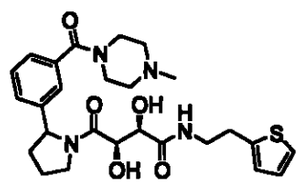
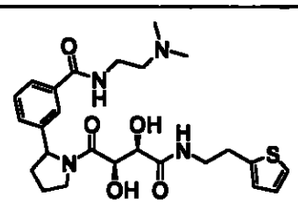
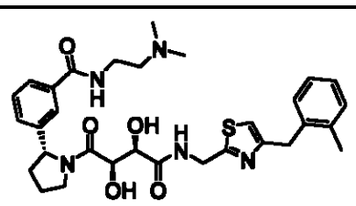
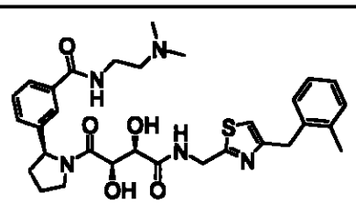
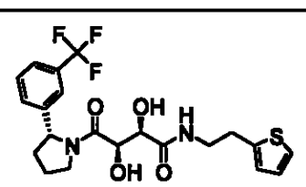
Parte J:

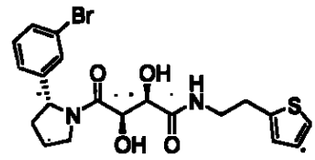
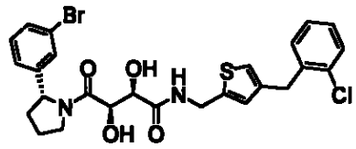
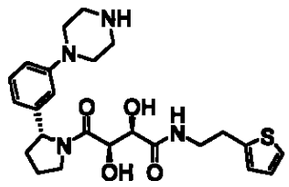
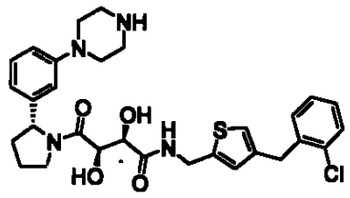
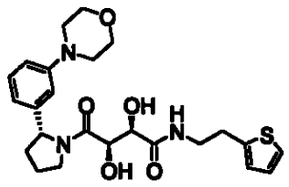
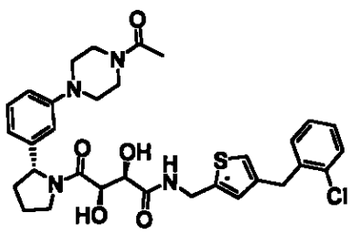
Los siguientes compuestos se prepararon usando el procedimiento descripto en el Ejemplo 11B Parte F.

Compuesto #	Intermediario	MS (m/e para M+1)
522		205
523		247
524		231
525		245
526		260
527		217

Los siguientes compuestos se prepararon usando los procedimientos descriptos en el Ejemplo 11.

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
416		550,3	551,3

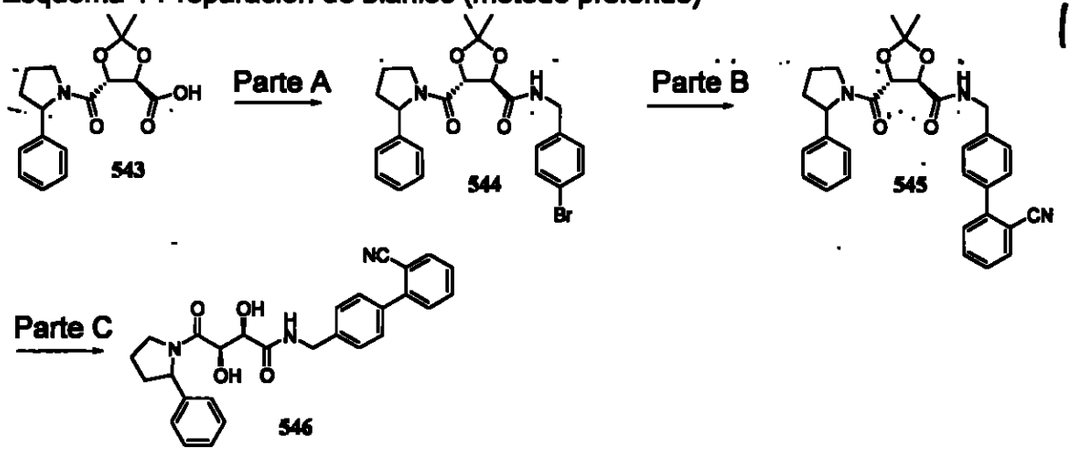
417		576,3	577,3
418		592,3	593,3
529		514,2	515,0
530		502,2	503,1
531		593,3	594,1
532		593,3	594,1
536		456,1	457,1

537		**466,1**	**467,0**
538		**576,1**	**577,0**
539		**472,2**	**473,2**
540		**582,2**	**583,2**
541		**473,2**	**474,2**
542		**624,2**	**625,1**

Ejemplo 12: Acoplamientos Aril-Arilo de Suzuki

Ejemplo 12A:

Esquema 1 Preparación de biarilos (método preferido)



El Compuesto **543** se preparó mediante los procedimientos descriptos en el Ejemplo 1.

Parte A:

A una solución de **543** (1,01 g, 3,17 mmol) y 4-bromobencialamina (0,71 g, 3,83 mmol) en CH_2Cl_2 (10 ml) enfriada a 0 °C se agregó DIEA (1,10 ml, 6,31 mmol) seguido por PyBrOP (1,10 g, 3,43 mmol). La reacción se calentó hasta temperatura ambiente y se agitó durante 16 horas. El líquido se concentró, y el aceite espeso se capturó en EtOAc. La capa orgánica se lavó con $KHSO_4$ 0,5 N (1x), sat. $NaHCO_3$ (1x), se secó (Na_2SO_4), se filtró y se concentró. El residuo se purificó mediante cromatografía de gel de sílice (eluyendo del 0% al 100% EtOAc/hexanos) para dar **544** (1,27 g, 2,61 mmol, 82% de rendimiento) como un aceite color tostado. MS m/e: 487,1 (M+H).

Parte B:

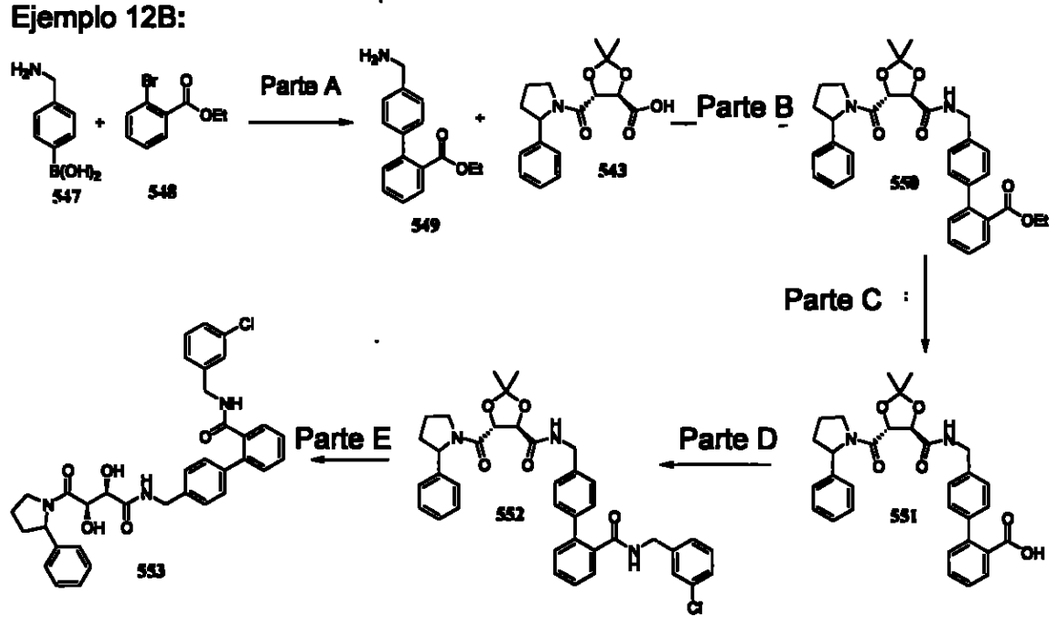
Una solución de **544** (0,105 g, 0,215 mmol), ácido 2-cianofenil borónico (0,032 g, 0,215 mmol), y $Pd(dppf)Cl_2$ (0,016 g, 0,021 mmol) en CH_3CN (1 ml) y K_2CO_3 1 N (1 ml) se calentó en un microondas SmithCreator (recipiente de 2-5 ml, 150 °C durante 10 minutos). La mezcla se concentró y el residuo se purificó mediante cromatografía de gel de sílice (eluyendo de 0% a 100 %

EtOAc/hexanos) para dar **545** (0,062 g, 0,12 mmol, 56% de rendimiento) como un aceite color tostado. MS m/e: 510,1 (M+H).

Parte C:

Una solución de **545** (0,049 g, 0,096 mmol) en una mezcla 70% de TFA/20% de CH_2Cl_2/10% de H_2O se agitó a temperatura ambiente durante 2 horas. La mezcla se concentró, y el residuo se purificó mediante HPLC de fase reversa (eluyendo 5:95 a 95:5 CH_3CN/H_2O (0,1% de HCO_2H)) para proporcionar **546** (0,023 g, 0,049 mmol, 51% de rendimiento) como un sólido blanco. MS m/e: 470,1 (M+H).

Ejemplo 12B:



Parte A:

Una solución de 2-bromobenzoato de etilo (**548**) (0,25 g, 1,1 mmol), ácido (4-aminometilfenil)borónico (**547**) (0,20 g, 1,1 mmol), y $Pd(dppf)Cl_2$ (0,040 g, 0,055 mmol) en CH_3CN (1 ml) y 1 N K_2CO_3 (1 ml) se calentó en un microondas SmithCreator (recipiente de 2-5 ml, 100°C durante 5 minutos). La reacción se diluyó con H_2O y EtOAc. La capa orgánica se eliminó, y la fase acuosa se extrajo con EtOAc (3x). Los orgánicos combinados se secaron (Na_2SO_4), se filtraron y se

concentraron. El residuo se purificó mediante cromatografía de gel de sílice (eluyendo de 0% a 20% CH_2Cl_2/MeOH) para dar **549** (0,14 g, 0,55 mmol, 50 % de rendimiento) como un aceite marrón. MS m/e: 256,1 (M+H).

Parte B:

A una solución de **549** (0,21 g, 0,82 mmol) y **543** (0,19 g, 0,59 mmol) en CH_2Cl_2 (5 ml) enfriada a 0°C se agregó DIEA seguida de PyBrOP. La reacción se agitó durante 20 horas calentando gradualmente hasta temperatura ambiente. La mezcla se concentró, y el aceite marrón se capturó en EtOAc. La fase orgánica se lavó con $KHSO_4$ 0,5 N (1x), sat. $NaHCO_3$ (1x), se secó (Na_2SO_4), se filtró y se concentró. El residuo se purificó mediante cromatografía de gel de sílice (eluyendo de 0% a 100% de EtOAc/hexanos) para dar **550** (0,29 g, 0,51 mmol, 87% de rendimiento) como un aceite marrón. MS m/e: 557,1 (M+H).

Parte C:

A una solución de **550** (0,26 g, 0,47 mmol) en una mezcla de THF (2 ml)/MeOH (2 ml)/H_2O (1 ml) se agregó $LiOH \cdot H_2O$ (0,052 g, 1,24 mmol) en una porción sólida. La reacción se agitó hasta el día siguiente y luego se acidó para pH ~ 3 con HCl 1N. Después de la dilución con EtOAc, la capa orgánica se eliminó, y la fase acuosa se extrajo con EtOAc (3x). Los orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se purificó mediante HPLC de fase reversa (eluyendo de 10:90 a 100:0 CH_3CN/H_2O (0,1% de HCO_2H) para dar **551** (0,22 g, 0,38 mmol, 88 % de rendimiento). MS m/e: 529,1 (M+H).

Parte D:

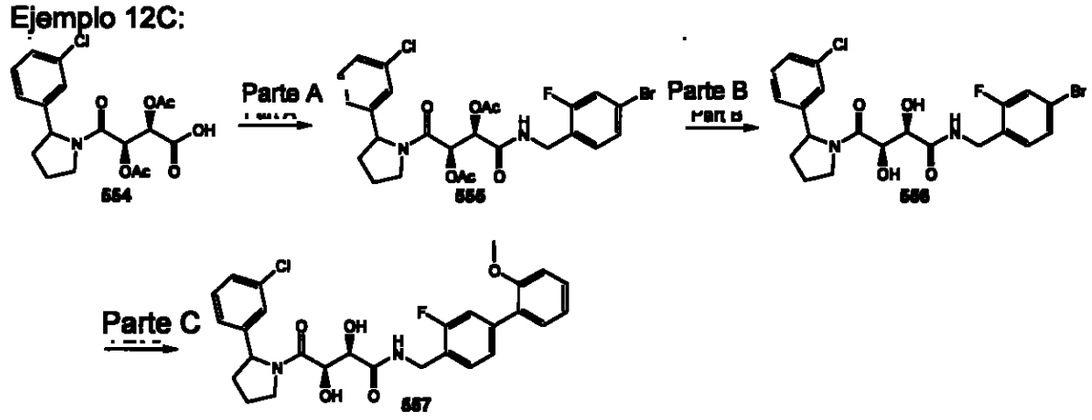
A una solución de **551** (55 mg, 0,104 mmol) in CH_2Cl_2 (1 ml) se agregó HOBt unido a poliestireno (109 mg, 0,095 mmol), DIC (0,067 ml, 0,427 mmol), y DMAP (7 mg, 0,057 mmol) y se agitó hasta el día siguiente. La mezcla se filtró, luego se lavó con DMF (3 x 3 ml), CH_2Cl_2 (3 x 3 ml), DMF (3 x 3 ml), y THF (3 x 3

ml). La resina se secó en vacío hasta el día siguiente. Al ácido unido a la resina (82 mg, 0,034 mmol) se agregó 3-clorobencilamina (8,33 µl, 0,068 mmol) en CH_2Cl_2 (1 ml) y la mezcla se agitó hasta el día siguiente. A la mezcla se agregó resina de isocianato unida a poliestireno (70 mg, 0,102 mmol) y se agitó durante 5 horas. Se filtró el producto deseado y se lavó el filtrado con CH_2Cl_2 (3 x 3 ml) y THF (3 x 3 ml). Se concentraron las porciones orgánicas *in vacuo* para dar **552** (14,6 mg, 0,022 mmol, 66 % de rendimiento). MS m/e: 652,2 (M+H).

Parte E:

A **552** (14,6mg, 0,022 mmol) se agregaron 2 ml de una mezcla de TFA/CH_2Cl_2/H_2O (7/2/1) y se agitó a temperatura ambiente durante 2 h. La mezcla se concentró *in vacuo*. La mezcla se purificó mediante HPLC de fase reversa para dar **553** (3,7 mg, 0,006 mmol, 27 % de rendimiento). MS m/e: 612,1 (M+H).

Ejemplo 12C:



El compuesto **554** se preparó mediante el procedimiento del Ejemplo 4 Parte C. HPLC-MS t_R = 1,39 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{14}H_{16}ClNO_5$ 397,1. LCMS observada m/z 398,1 (M+H).

Parte A:

A **554** (355 mg, 0,89 mmol) en DMF (5 ml) se agregó clorhidrato de 2-fluoro-4-bromobencilamina (257 mg, 1,07 mmol), DIEA (530 ul, 3,03 mmol) y HATU (407 mg, 1,07 mmol). La reacción se agitó hasta el día siguiente a

temperatura ambiente. La mezcla de reacción se vertió en agua y se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con NaOH 0,1 N, HCl 0,1 N, y salmuera; se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 80% acetato de etilo/hexanos) dio **555** como una espuma (320 mg, 62%). HPLC-MS t_R = 2,03 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{25}H_{25}BrClFN_2O_6$ 582,1. LCMS observada m/z 583,0 (M+H).

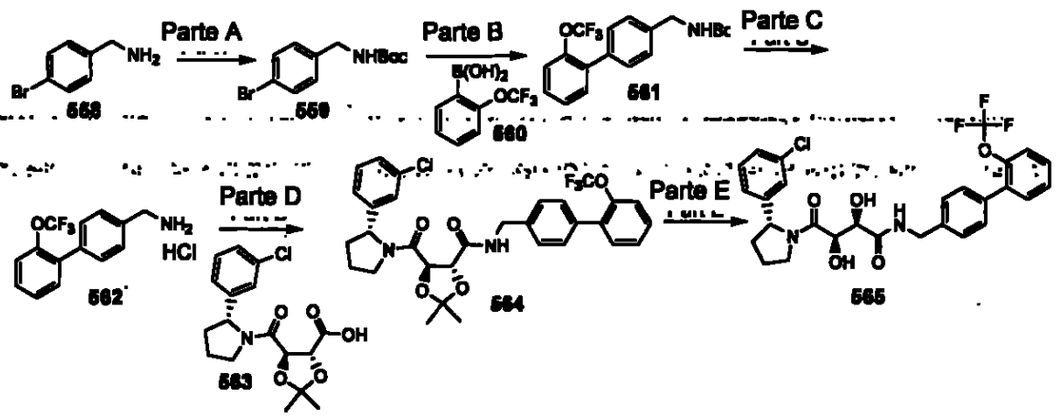
Parte B:

A **555** (320 mg, 0,55 mmol) en MeOH (5 ml) se agregó hidrazina anhídrida (28 µl, 0,88 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se concentró in vacuo y se liofilizó para dar **556** como un polvo blanco (275 mg, 100%). HPLC-MS t_R = 1,81 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{21}H_{21}BrClFN_2O_4$ 498,0. LCMS observada m/z 499,0 (M+H).

Parte C:

Se agregó el compuesto **556** (46 mg, 0,092 mmol) en dioxano (1 ml) a una solución de ácido 2-metoxifenil borónico (22 mg, 0,14 mmol), fosfato de potasio (42 mg, 0,2 mmol), y $PdCl_2$(dppf) (4 mg, 0,005 mmol) bajo atmósfera de argón. La mezcla de reacción se calentó hasta 80 °C hasta el día siguiente. Después de enfriar la mezcla se filtró a través de Celite y el lecho se enjuagó con acetato de etilo. El filtrado se concentró. La purificación mediante LC prep de fase reversa dio **557** como un sólido blanco (26 mg) después de la liofilización. HPLC-MS t_R = 1,97 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{28}H_{28}ClFN_2O_5$ 526,2. LCMS observada m/z 527,0 (M+H).

Ejemplo 12D:



Parte A:

Se agitó una mezcla de clorhidrato de 4-bromo-bencilamina (**558**) (1,0 g, 4,5 mmol), di-ter-butil carbonato (1,48 g, 6,8 mmol) y DIEA (2,4 ml, 13,8 mmol) en cloroformo (40 ml) hasta el día siguiente a temperatura ambiente. La mezcla de reacción se lavó con HCl 1,0 N, agua y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 20% acetato de etilo/hexano) dio una mezcla de **559** (1,17 g, 91%). ^1H RMN (400 MHz, $CDCl_3$) δ 7,44 (d, 2H, J = 8,8 Hz), 7,15 (d, 2H, J = 8,8 Hz), 4,85 (bs, 1H), 4,27 (d, 2H, J = 5,7 Hz), 1,48 (s, 9H).

Parte B:

Se calentó una mezcla de **559** (100 mg, 0,35 mmol), **560** (107 mg, 0,52 mmol) fosfato de potasio (223 mg, 1,05 mmol) y $PdCl_2$(dppf) (14 mg, 0,018 mmol) en dioxano (5 ml) bajo atmósfera de argón hasta 80 °C hasta el día siguiente. La mezcla de reacción se enfrió y se filtró a través de Celite. El lecho de Celite se lavó con acetato de etilo. El filtrado se lavó con bicarbonato de sodio saturado, agua y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 20% de acetato de etilo/hexano) dio **561** levemente impuro (146 mg). HPLC-MS t_R = 2,35 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{19}H_{20}F_3NO_3$ 367,1. LCMS observada m/z 390,1 (M+Na).

Parte C:

Se agitó el compuesto **561** (129 mg, 0,35 mmol) en DCM:TFA 3:1 (4 ml) durante 1 hora. El residuo se disolvió en DCM (5 ml) y se concentró. El residuo se disolvió en dietil éter (20 ml) y se trató con HCl 1,0 M en dietil éter (2 ml). El sólido blanco resultante se recolectó mediante filtración y se lavó con dietil éter para dar **562** (90 mg, 85% 2 pasos). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,3 (bs, 3H), 7,50 (m, 8H), 4,09 (s, 2H).

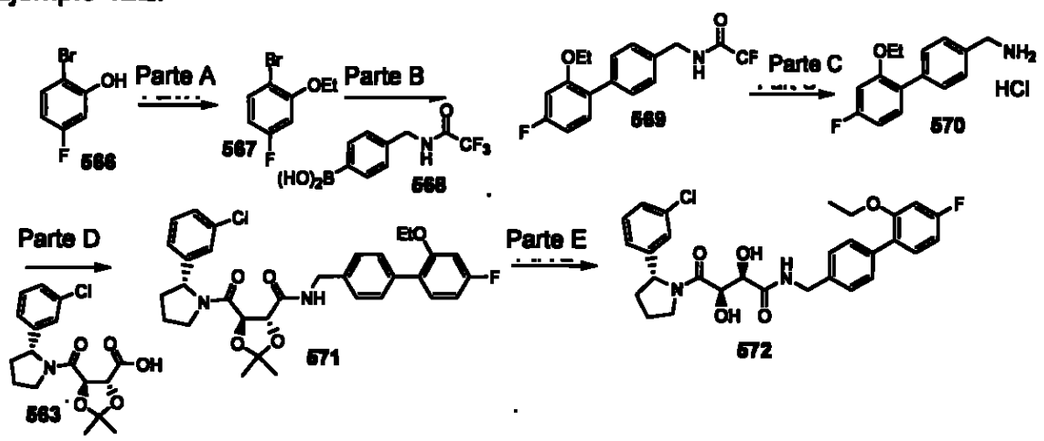
Parte D:

Se preparó el compuesto **563** usando procedimientos similares a aquellos descriptos en el Ejemplo 11A. Compuesto **564** se preparó a partir de **562** y **563** usando procedimientos similares a aquellos descriptos en el Ejemplo 1 Parte A. HPLC-MS t_R = 2,49 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{31}H_{30}ClF_3N_2O_5$ 602,2. LCMS observada m/z 603,2 (M+H).

Parte E:

Se preparó el compuesto **565** usando los procedimientos descriptos en el Ejemplo 1 Parte B. HPLC-MS t_R = 2,16 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{28}H_{28}ClF_3N_2O_5$ 562,2. LCMS observada m/z 563,0 (M+H).

Ejemplo 12E:



Parte A:

A 2-bromo-5-fluoro-fenol (**566**) (2,28 g, 11,94 mmol) en DMF (15 ml) se agregó yodoetano (1,16 ml, 14,32 mmol) y carbonato de cesio (4,28 g, 13,13 mmol). La mezcla de reacción se agitó durante 72 horas. La mezcla se filtró y el DMF se eliminó in vacuo. El residuo se dividió en acetato de etilo y agua. Las capas se separaron y la capa orgánica se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró para dar **567** (1,76 g, 67%) como un aceite incoloro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,46 (dd, 1H, J = 6,3, 8,8 Hz), 6,62 (dd, 1H, J = 2,7, 10,5 Hz), 6,57 (m, 1H, J = 2,7), 4,08 (q, 2H, J = 6,9 Hz), 1,50 (t, 3H, J = 7,0 Hz).

Parte B:

Se preparó compuesto **569** (607 mg, 58%) a partir de **567** y **568** (preparado mediante los procedimientos de Maku, S. et. al. (*J. Comb. Chem.* **2003**, *5*, 379)) usando los procedimientos descriptos en el Ejemplo 12D Parte B. HPLC-MS t_R = 2,13 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{17}H_{15}F_4NO_2$ 341,1. LCMS observada m/z 342,1 (M+H).

Parte C:

A **569** (607 mg, 1,78 mmol) en metanol (6 ml) se agregó 10% carbonato de potasio en metanol:agua 2:1 (20 ml). Para obtener una solución clara se agregó agua adicional (5 ml). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. El metanol se eliminó in vacuo. El residuo se dividió entre agua y acetato de etilo. Las capas se separaron y la capa acuosa se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre sulfato de sodio y se concentró. El residuo se disolvió en dietil éter (20 ml) y se trató con HCl 1,0 M en dietil éter (5 ml). El sólido blanco resultante se recolectó mediante filtración y se lavó con dietil éter para dar **570** (377 mg, 75%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,27 (bs, 3H), 7,49 (m, 4H), 7,29 (dd, 1H, J = 6,9,

8,3 Hz), 7,00 (dd, 1h J = 2,5, 11,4 Hz), 6,83 (dt, 1H, J = 2,8, 8,6, 10,8Hz) 4,05 (m, 4H), 1,27 (t, 3H, J = 6,5 Hz).

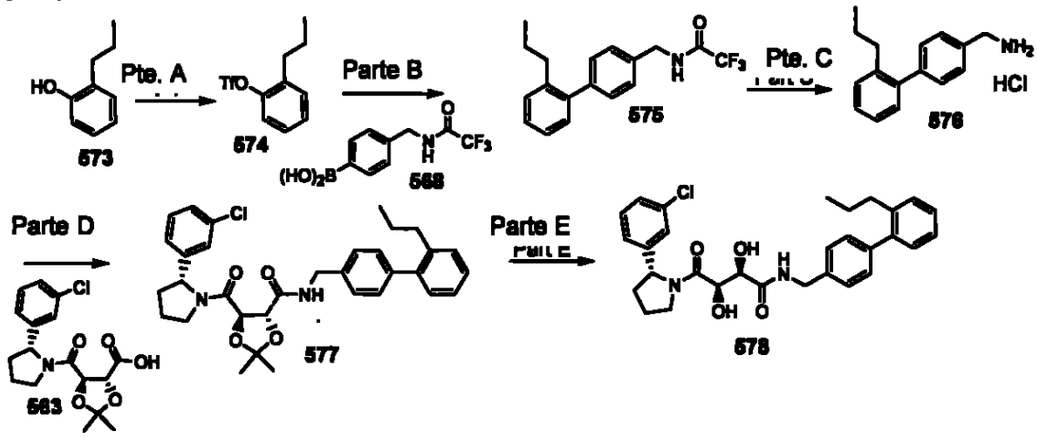
Parte D:

Se preparó compuesto **571** usando procedimientos descriptos en el Ejemplo 12E Parte D. La purificación mediante cromatografía en columna (SiO_2, 20% de acetato de etilo/hexano) dio **571** (104 mg, 95%). HPLC-MS t_R = 2,40 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{32}H_{34}ClFN_2O_5$ 580,2. LCMS observada m/z 581,2 (M+H).

Parte E:

Se preparó compuesto **572** usando los procedimientos descriptos en el Ejemplo 12D Parte E. HPLC-MS t_R = 2,06 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{28}H_{30}ClFN_2O_5$ 540,2. LCMS observada m/z 541,2 (M+H).

Ejemplo 12F:



Parte A:

A una mezcla de 2-propil fenol **(573)** (0,5 ml, 3,63 mmol) y DIEA (0,950 ml, 5,45 mmol) en DCM (20 ml) a 0°C se agregó anhídrido tríflico (0,734 ml, 4,36 mmol) en DCM (10 ml) mediante un embudo de adición. La mezcla de reacción se agitó durante 45 minutos. La mezcla se vertió en agua. Las capas se separaron y la capa orgánica se lavó con solución de bicarbonato de sodio saturada y salmuera, se secó sobre sulfato de sodio y se concentró. La

purificación mediante cromatografía en columna (SiO_2, 5% acetato de etilo/hexano) dio **574** (916 mg, 100%). ^1H RMN (400 MHz, $CDCl_3$) δ 7,30 (m, 2H), 7,26 (m, 2H), 2,70 (m, 2H), 1,68 (m, 2H), 1,00 (t, 3H, J = 7,3 Hz).

Parte B:

Se preparó el compuesto **575** (288 mg, 89%) usando los procedimientos descriptos en el Ejemplo 12D Parte B y una temperatura de reacción de 100 °C. HPLC-MS t_R = 2,30 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{18}H_{18}F_3NO$ 321,1. LCMS observada m/z 322,2 (M+H).

Parte C:

Se preparó el compuesto **576** (203 mg, 86%) usando el procedimiento descripto en el Ejemplo 12E Parte C. ^1H RMN (400 MHz, DMSO-d_6) δ 8,27 (bs, 3H), 7,52 (d, 2H, J = 8,0 Hz), 7,32 (d, 2H, J = 8,1 Hz), 7,31 (m, 2H), 7,22 (m, 1H), 7,10 (d, 1H, J = 7,1 Hz), 4,08 (s, 2H,) 2,54 (m, 2H), 1,44 (m, 2H), 0,75 (t, 3H, J = 7,7 Hz).

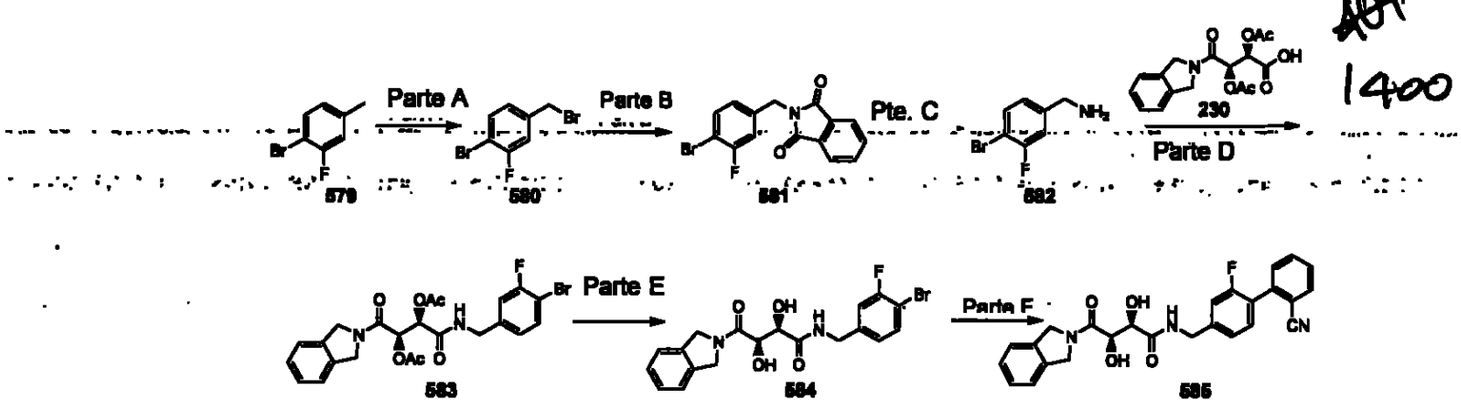
Parte D:

Se preparó el compuesto **577** (62 mg, 92%) de acuerdo con el procedimiento descripto en el Ejemplo 12D Parte D. HPLC-MS t_R = 2,55 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{33}H_{37}ClN_2O_4$ 560,2. LCMS observada m/z 561,2 (M+H).

Parte E:

Se preparó el compuesto **578** (53 mg, 93%) de acuerdo con el procedimiento descripto en el Ejemplo 12D Parte E. HPLC-MS t_R = 2,21 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{30}H_{33}ClN_2O_4$ 520,2. LCMS observada m/z 521,2 (M+H).

Ejemplo 12G:



Parte A:

Se calentó una mezcla de 4-bromo-3-fluoro-tolueno (**579**) (2,0 ml, 15,8 mmol), N-bromosuccinimida (3,38 g, 19,0 mmol) y benzoilperóxido (48 mg, 0,2 mmol) en tetracloruro de carbono (50 ml) hasta reflujo bajo una atmósfera de nitrógeno durante 16 horas. La mezcla de reacción se enfrió y se filtró. El filtrado se lavó con agua (2x), solución saturada de bicarbonato de sodio y salmuera, se secó sobre sulfato de sodio y se concentró para dar una mezcla de **580** y producto dibromado (4,02 g). El material se usó sin purificación adicional. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,52 (dd, 1H, J = 6,6, 7,6 Hz), 7,17 (dd, 1H, J = 2,0, 8,9 Hz), 7,11 (dd, 1H, J = 2,0, 8,2 Hz), 4,42 (s, 2H).

Parte B:

Una mezcla de **580** (4,02 g, 15,0 mmol), ftalamida (2,65 g, 18 mmol) y carbonato de cesio (5,38 g, 16,5 mmol) en DMF (30 ml) se agitó durante 72 horas. La mezcla de reacción se vertió en agua (100 ml) y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua (3X) y salmuera, se secó sobre sulfato de sodio y se concentró. La recristalización a partir de 30% acetato de etilo/hexanos dio **581** levemente impuro (3,28 g) como un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,86 (m, 2H), 7,74 (m, 2H), 7,49 (dd, 1H, J = 7,3, 8,4 Hz), 7,20 (dd, 1H, J = 1,9, 9,3 Hz), 7,06 (dd, 1H, J = 2,0, 7,9 Hz), 4,80 (s, 2H).

Parte C:

Se calentó una mezcla de **581** (1,00 g, 3,0 mmol) y monohidrato de hidrazina (580 ul, 12,0 mmol) in etanol (25 ml) hasta reflujo durante 1 hora. La mezcla de reacción se diluyó con acetato de etilo y se filtró. El precipitado se lavó con acetato de etilo. El filtrado se concentró y el residuo se disolvió en agua y acetato de etilo. Las capas se separaron. La capa orgánica se lavó con solución saturada de bicarbonato de sodio, agua y salmuera, se secó sobre sulfato de sodio y se concentró para dar **582** (375 mg) como un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,48 (t, 1H, J = 8,5 Hz), 7,12 (dd, 1H, J = 2,2, 9,5 Hz), 6,99 (dd, 1H, J = 1,6, 8,2 Hz), 3,86 (s, 2H).

Parte D:

Se preparó el compuesto **583** usando procedimientos similares a aquellos descriptos en el Ejemplo 12C Parte A. HPLC-MS t_R = 1,82 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{23}H_{22}BrFN_2O_6$ 520,0. LCMS observada m/z 521,0 (M+H).

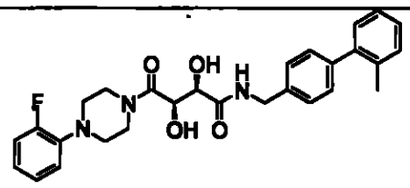
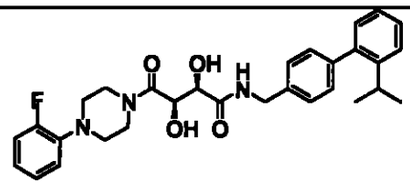
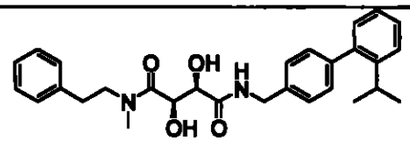
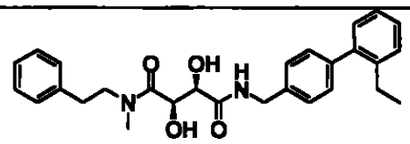
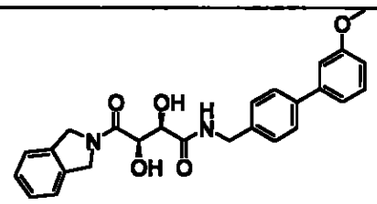
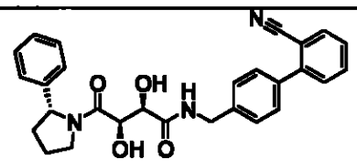
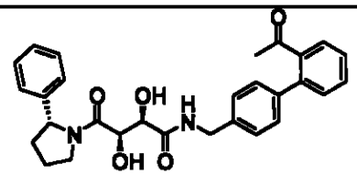
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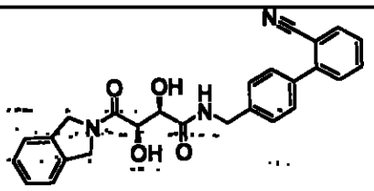
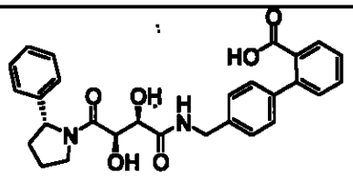
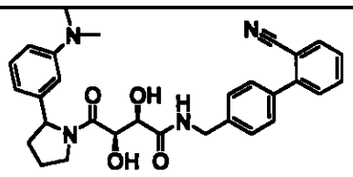
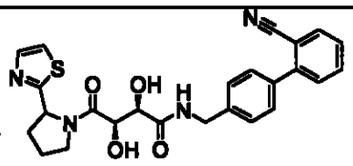
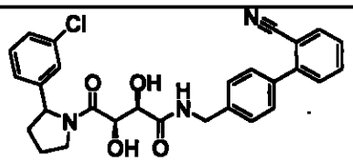
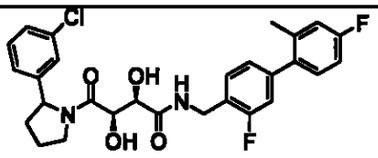
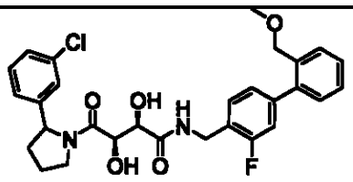
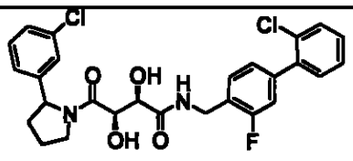
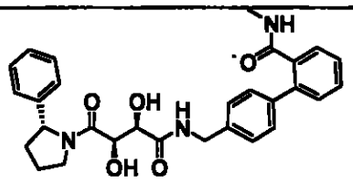
Se preparó el compuesto **584** usando los procedimientos descriptos en el Ejemplo 12C Parte B. HPLC-MS t_R = 1,81 min ($UV_{254\ nm}$); masa calculada para la fórmula $C_{19}H_{18}BrFN_2O_4$ 436,0. LCMS observada m/z 437,0 (M+H).

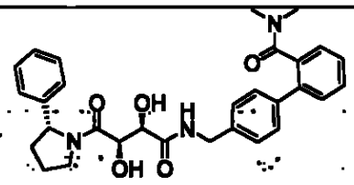
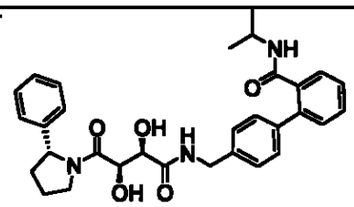
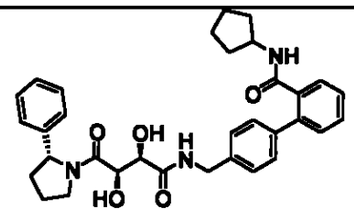
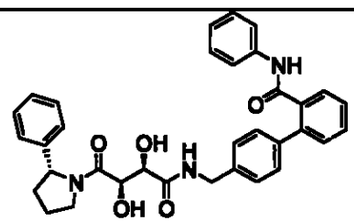
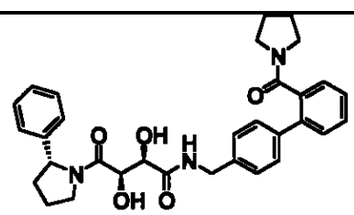
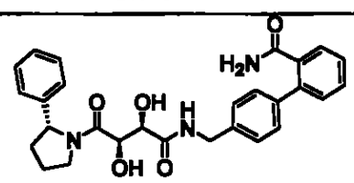
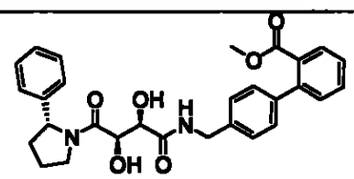
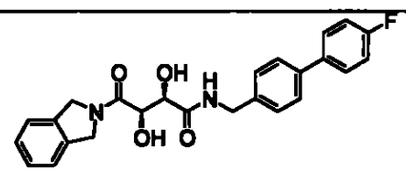
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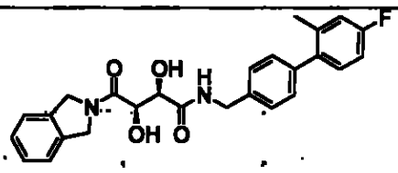
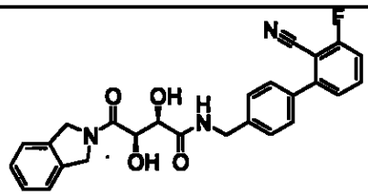
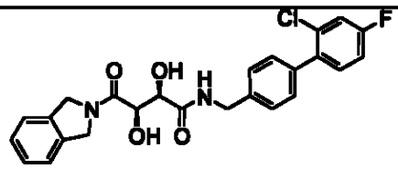
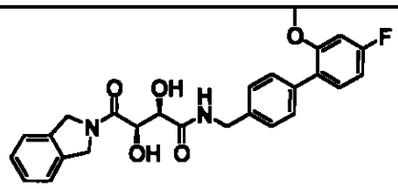
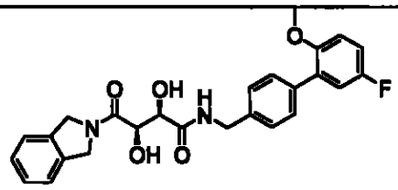
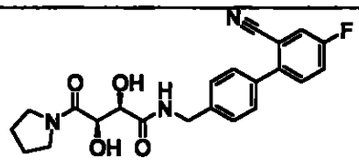
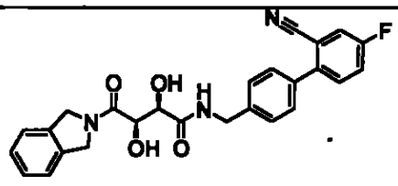
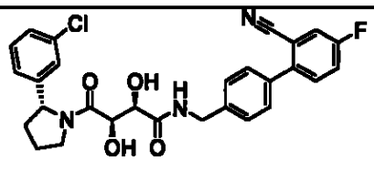
Se preparó el compuesto **585** usando procedimientos similares a aquellos descriptos en el Ejemplo 12C Parte C. HPLC-MS t_R = 4,12 min ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{28}H_{22}FN_3O_4$ 459,2. LCMS observada m/z 460,1 (M+H).

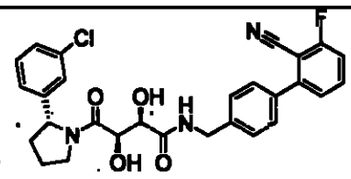
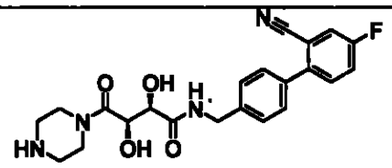
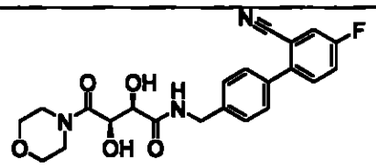
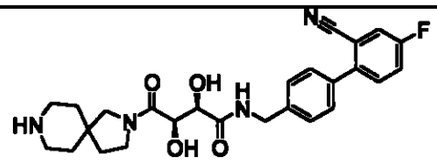
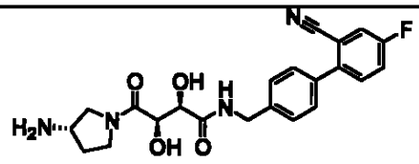
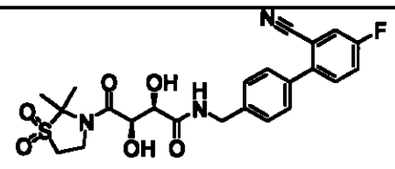
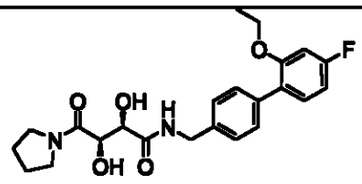
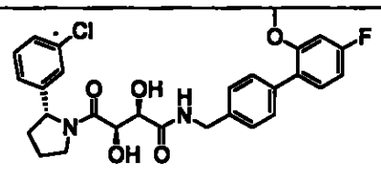
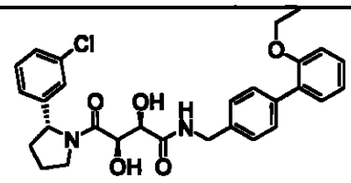
La siguiente tabla contiene compuestos preparados usando los procedimientos descriptos en el Ejemplo 12 A–G.

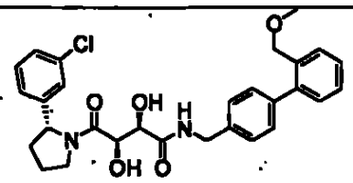
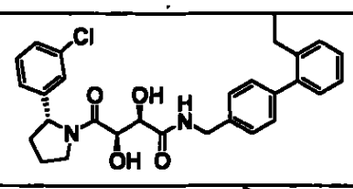
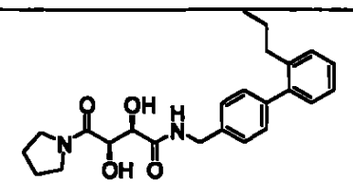
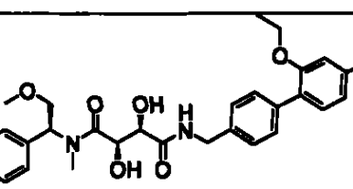
Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
586		491,2	492,2
587		519,3	520,3
588		474,3	475,3
589		460,2	461,2
590		446,2	447,2
591		469,2	470,1
592		486,2	487,1

593		441,2	442,1
594		488,2	489,1
595		512,2	513,3
596		476,2	477,2
597		503,2	504,2
598		528,2	529,2
599		540,2	541,2
600		530,1	531,0
601		501,2	502,3

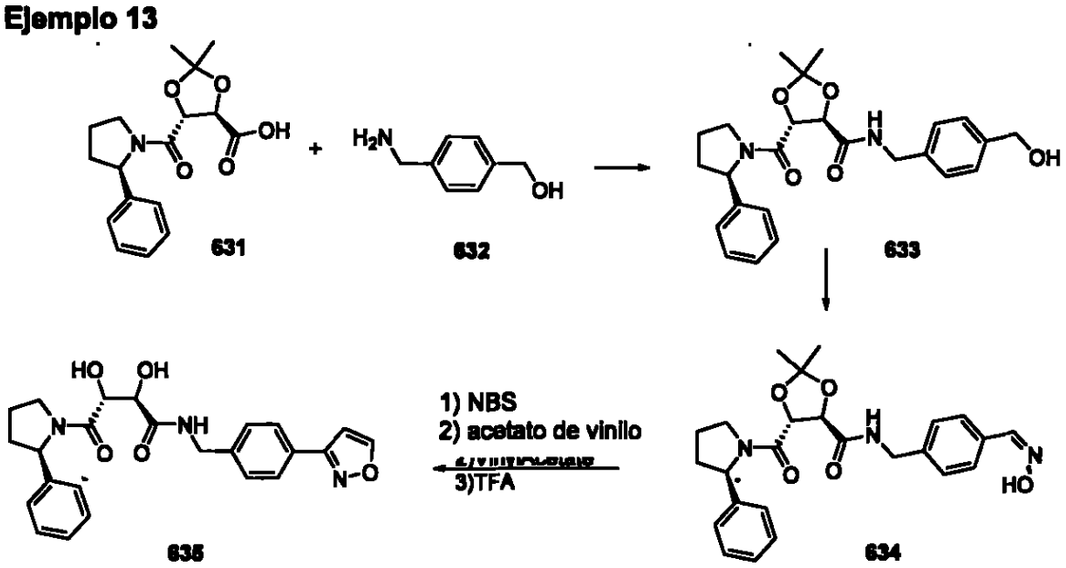
602		515,2	516,3
603		529,3	530,3
604		555,3	556,3
605		563,2	564,3
606		541,3	542,3
607		487,2	488,1
608		502,2	503,1
609		434,2	435,2

610		448,2	449,2
611		459,2	460,1
612		468,1	469,1
613		464,2	465,1
614		464,2	465,1
615		411,2	412,1
616		459,2	460,1
617		521,2	522,1

618		521,2	522,1
619		426,2	427,1
620		427,2	428,1
621		480,2	481,2
622		426,2	427,1
623		489,1	490,1
624		430,2	431,2
625		526,2	527,2
626		522,2	523,2

627		522,2	523,2
628		506,2	507,2
629		410,2	411,2
630		524,2	525,2

Ejemplo 13



Se preparó el compuesto **631** mediante los procedimientos descriptos en el Ejemplo 11A.

Parte A.

A una solución de **631** (0,46 g) y **632** (1,2 eq) en 10 ml DMF a 0°C se agregó HATU (1,5 eq) y HOBt (1,5 eq). La reacción se agitó a t.a. hasta el día

siguiente antes de la eliminación del solvente in vacuo y el residuo se cromatografió usando acetato de etilo in Hexano (0 - 100 %) para dar 0,46 gramos del producto deseado **633**.

Parte B.

A una solución de 0,46 g de **633** en 10 ml de DCM se agregó reactivo Dess-Martin (1,1 eq) y la reacción se agitó a t.a. durante 30 min antes de tratarla con solución acuosa saturada de bicarbonato de sodio y tiosulfato de sodio 7:1 (p/p). La capa acuosa se extrajo con DCM (2X) y las capas orgánicas combinadas se secaron sobre sulfato de sodio anhídrido. Después de la remoción del solvente, el producto bruto de reacción se disolvió en 2 ml de piridina. A la solución se agregó 1,5 eq de clorhidrato de hidroxilamina y la solución se calentó hasta reflujo durante 30 min antes de la eliminación del solvente in vacuo y el residuo se cromatografió usando acetato de etilo in Hexano (0 - 100 %) para dar 0,4 gramos del producto **634**.

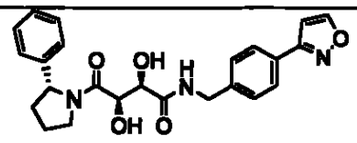
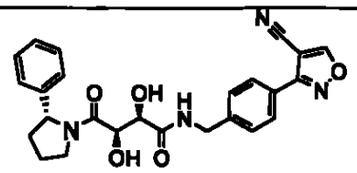
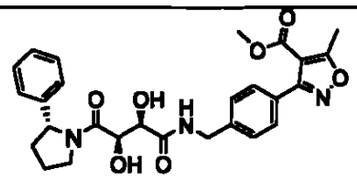
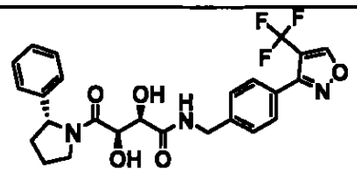
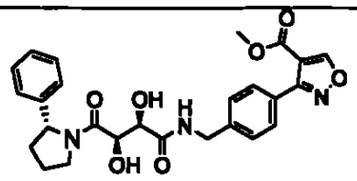
Parte C

A un matraz que contenía **634** (0,42 g) en DMF anhidro a 0 °C se agregó NBS (1 eq) y se permitió que la solución se caliente hasta t.a. hasta el día siguiente antes del agregado de otro equivalente de NBS y la solución se calentó hasta el día siguiente. La mezcla de reacción final se vertió sobre hielo y se extrajo con DCM. La fase orgánica se lavó con agua y salmuera, se secó sobre sulfato de sodio. Después de la remoción del solvente, el residuo se sometió a cromatografía usando acetato de etilo en hexano (0 - 100 %) para dar 0,38 gramos del producto deseado.

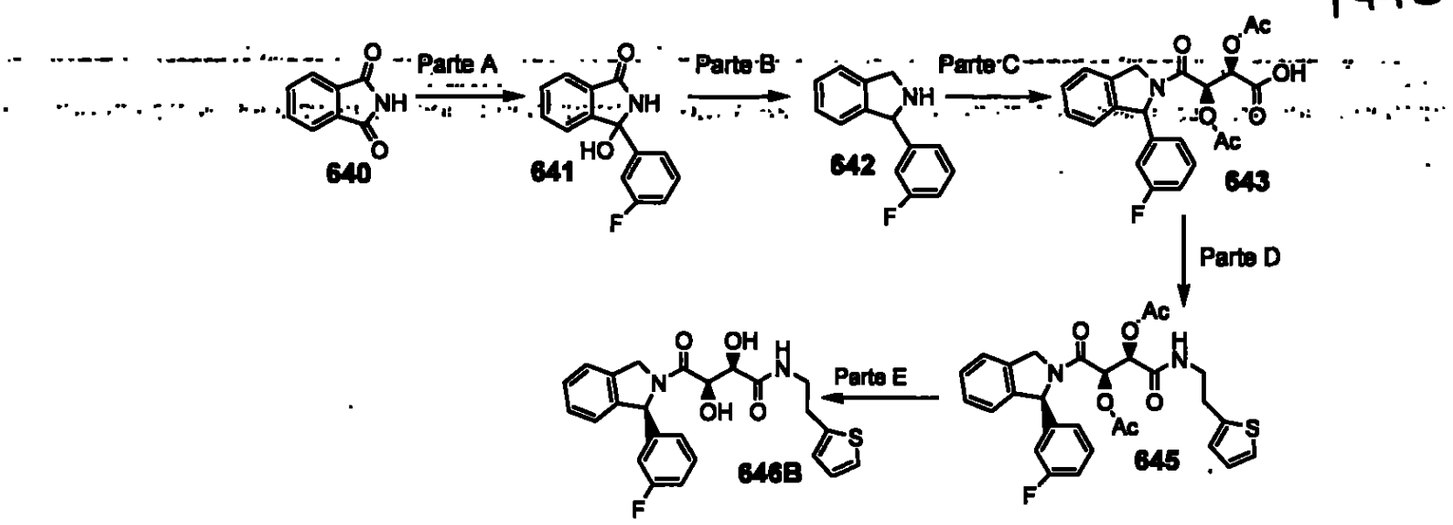
A una solución de 0,035 gramos del compuesto anterior en 2 ml de DCM se agregó vinilacetato (2 eq) y DIEA (3,5 eq) y la solución se agitó a t.a. hasta el día siguiente. Después de la remoción del solvente, el residuo se sometió a cromatografía usando acetato de etilo en hexano (0 - 100 %) para dar 20 mg del

producto que se trató con 50% de TFA en DCM durante 2h. Antes de purificarlo usando un sistema de HPLC RP para dar 10 mg del producto deseado **635**,

Los siguientes compuestos se generaron usando procedimientos similares:

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
635		435,2	436,0
636		460,2	461,0
637		507,2	508,0
638		503,2	504,0
639		493,2	494,0

Ejemplo 14:



Parte A:

Un matraz Schlenck se secó con llama bajo flujo de N_2, se tapó con un septum, y se permitió que se enfríe a ta. Se agregó ftalamida (**640**) (4,13 g, 28,1 mmol) seguida por THF anhídrido (100 ml). Una vez disuelta la ftalamida, la matraz se colocó en un baño de agua helada y se permitió que se enfríe durante 20 min. Una solución de 1 M de 3-fluorobromuro de fenil magnesio en THF (25 ml) se agregó haciendo que se forme un precipitado. Se agregó DMPU (5 ml), haciendo que la mezcla de reacción se torne clara nuevamente. Se agregó 3-fluorobromuro adicional de fenil magnesio (35 ml) durante 10 min. La mezcla de reacción se agitó a 0 °C durante 3,5 h, luego se desactivó con buffer de fosfato de sodio 1,0 M pH 6,5. La mezcla resultante se diluyó con EtOAc y las capas se separaron. La capa orgánica se lavó con agua y salmuera, luego se secó con $MgSO_4$. La evaporación del solvente dio un sólido blanco (7,4 g). Este material se trituró en CH_2Cl_2/hexanos para dar 4,0 g de **641** puro, MS (EI) m/z Obs. M+H 244,0

Parte B:

Un matraz Schlenck se secó con flama bajo flujo de N_2, se tapó con un septum, y se dejó que se enfríe a ta. Se agregó $LiAlH_4$ (1,26 g, 33,2 mmol) y $AlCl_3$

(1,47 g, 11,0 mmol) al matraz, seguidos por THF anhídrido. El matraz se colocó inmediatamente en un baño de agua helada y se permitió que se enfríe con agitación. Se agregó compuesto **641** al matraz en porciones. La mezcla de reacción se agitó durante 3 h, durante este tiempo se calentó hasta 15°C. La reacción se re-enfrió a 0°C y agua (3 ml) se agregó. Se agregó hidróxido de sodio acuoso 3,0 N (6 ml) seguido por agua (9 ml). La mezcla de reacción se filtró a través de un lecho de Celite que se enjuagó con EtOAc. El filtrado resultante se concentró hasta secarse dando un sólido verde. El producto bruto se purificó parcialmente mediante sgc usando una gradiente 40%-50% de EtOAc/hexanos, seguido por 98% de EtOAc/2% de Et_3N. Las fracciones que contienen el producto impuro deseado ase combinaron para dar un aceite azul. Este material se disolvió en CH_2Cl_2 (6 ml). Se agregó TFA (4 ml) y trietil silano (2 ml) y la mezcla de reacción se dejó en agitación hasta el día siguiente. La mezcla de reacción se concentró para dar un aceite verde. Este material se purificó mediante sgc flash usando hexanos:EtOAc2:1, seguido por 98% de EtOAc/2% de Et_3N como la fase móvil. El compuesto **642** se aisló como un sólido amarillo (0,56 g). MS (EI) m/z Obs M+H 214,2.

Parte C:

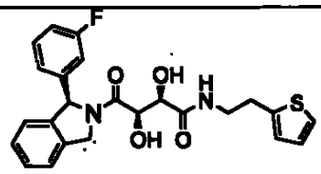
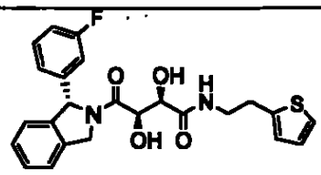
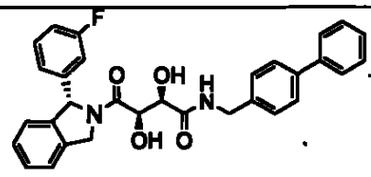
Se disolvió el compuesto **642** (0,56 g, 2,6 mmol) en CH_2Cl_2 (8 ml). se agregó trietil amina (1 ml) seguida por anhídrido (+)-diacetil-(L)-tartárico (0,65 g, 3,00 mmol). La mezcla de reacción se dejó en agitación a ta hasta el día siguiente. La mezcla de reacción se concentró hasta que se secó y se purificó mediante sgc usando 2%-5% de MeoH/ CH_2Cl_2 de fase móvil con 1% de ácido acético se agregó al mismo. Después de la evaporación del solvente y de la remoción azeotópica del ácido acético con heptano, se obtuvo compuesto **643** como un sólido blanco (0,33 g). MS (EI) m/z Obs M+H 430,1.

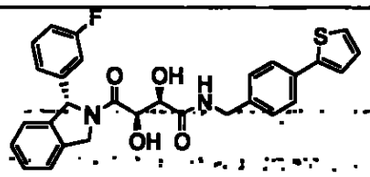
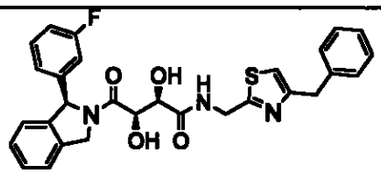
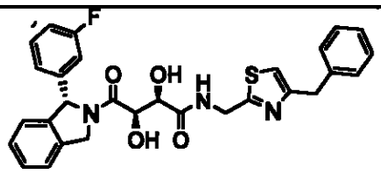
Parte D:

Se agregó el compuesto **643** (92 mg, 0,214 mmol), HOBT (36 mg, 0,26 mmol), DMF (1,5 ml), 2-tiofeno etilamina (44 mg, 0,34 mmol), y N-metilmorfolina (50 µL) a un matraz. Se agregó EDC y la mezcla de reacción se dejó en agitación hasta el día siguiente a ta. La mezcla de reacción se diluyó con EtOAc y se lavó con $NaHCO_3$ acuoso, ácido cítrico, agua, y salmuera. La capa orgánica se secó con $MgSO_4$ y se concentró para dar un aceite marrón. El producto bruto se purificó mediante sgc flash usando una gradiente 10%-80% de EtOAc/Hexanos. Se aislaron dos compuestos diaestereoméricos -**644** Diastereómero A (0,02 g) MS (EI) m/z Obs M+H 539,06 y **645** Diastereómero B (0,03 g) MS (EI) m/z Obs M+H 539,03.

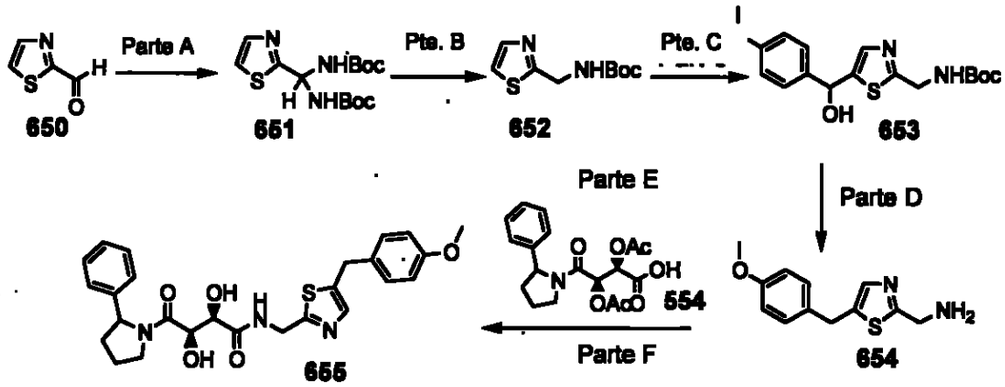
Parte E:

Se disolvió el compuesto **645** en amoníaco metanólico 2 M y se agitó a ta durante 30 m. La reacción se purificó hasta que se secó. El producto bruto se purificó mediante TLC prep sobre placas de sílice usando 1:1 EtOAc: Hexanos como la fase móvil. **646B**: MS (EI) m/z Obs M+H 455,1.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
646A		454,1	455,1
646B		454,1	455,1
647		510,2	511,1

648		516,2	517,1
649A		531,2	532,1
649B		531,2	532,1

Ejemplo 15:



Parte A:

Se disolvió el compuesto **650** (8,36 g, 73,9 mmol) y carbamato de ter-butilo (25,96 g, 222 mmol) en acetonitrilo (300 ml) y se agregó ácido trifluoroacético. La reacción se agitó hasta el día siguiente a ta bajo N_2, luego se concentró. La mezcla resultante se disolvió en EtOAc y se lavó con agua. La capa orgánica se secó con Na_2SO_4 y se concentró hasta que se secó. El producto bruto se purificó mediante sgc flash usando 1:3 EtOAc: Hexanos como la fase móvil para dar 30,27 g del producto **651**, ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,78 (s, 1H), 7,40 (s, 1H), 6,38-6,30 (m, 1H), 1,51 (s, 18H) MS (EI) m/z Obs M+H 330,1.

Parte B:

Se disolvió el compuesto **651** (30,27 g, 91,89 mmol) en 2-propanol (1500 ml) y se agregó borohidruro de sodio (17,0 g, 46 mmol). La mezcla de reacción se reflujó durante 3 h, luego se concentró sobre el rotovap. El material resultante se diluyó con EtOAc, se lavó con agua, y se secó con Na_2SO_4. Se evaporaron los solventes y el producto bruto se purificó mediante sgc flash usando 1:2 EtOAc: Hexanos como la fase móvil para dar 11,58 g de **652**, Producción = 73% en los pasos uno y dos. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,78 (s, 1H), 7,33 (s, 1H), 5,35 (s, 1H), 4,69 (s, 2H), 1,53 (s, 9H); MS (EI) MS (EI) m/z Obs M+H 215,0.

Parte C:

Se disolvió el compuesto **652** (0,30 g, 1,40 mmol) en 5 ml de THF anhídrido (5 ml). El matraz se tapó con un septum, colocado bajo una cobertura de N_2, y se enfrió en un baño de hielo seco/2-propanol. Se agregó una solución de LDA (1,71 ml, 1,8 M) mediante jeringa y la mezcla de reacción se agitó durante 0,5 h. Se agregó una solución de benzaldehído de 4-metoxi (0,21 g, 1,54 mmol) en 5 ml de THF anhídrido mediante jeringa. La mezcla de reacción se agitó durante 1 h. El baño de hielo se eliminó y la reacción se dejó en agitación hasta el día siguiente a ta. Se agregó agua y la mezcla de reacción se diluyó con EtOAc. Las capas se separaron. La capa orgánica se lavó con agua y se secó con Na_2SO_4. El solvente se evaporó y el producto bruto se purificó mediante sgc flash usando 1:1 EtOAc: Hexanos para dar 0,28 g of **653**, ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,42 (s, 1H), 7,37-7,32 (m, 2H), 6,89-6,94 (m, 2H), 6,02 (s, 1H), 5,38 (amplio s, 1H), 4,55 (s, 2H), 3,86 (s, 3H) 3,28 (s, 1H), 1,49 (s, 9H).

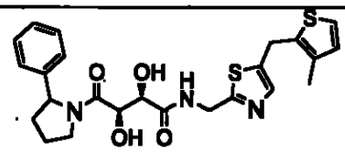
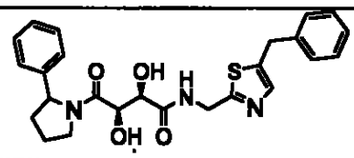
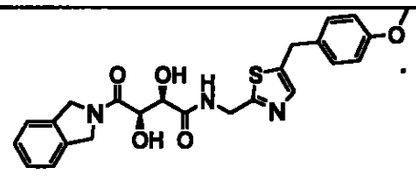
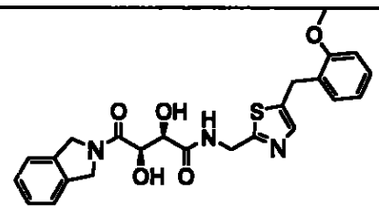
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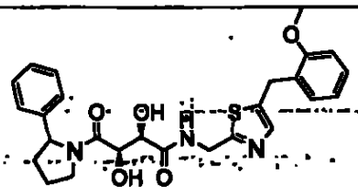
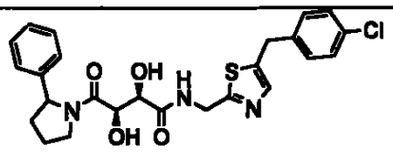
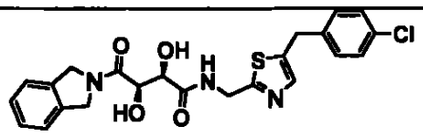
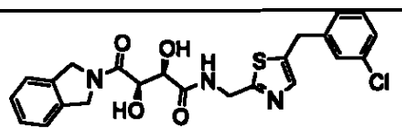
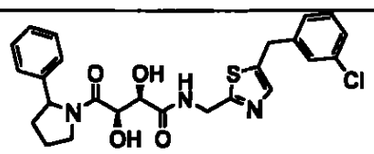
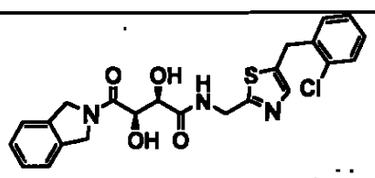
Se disolvió el compuesto **653** (0,28 g, 0,80 mmol) en trietilsilano (2 ml) y TFA (0,6 ml). La mezcla de reacción se reflujó durante 3 h luego se permitió que se enfríe a ta y se agitó hasta el día siguiente. La mezcla de reacción se

concentró. Metanol se agregó y la mezcla de reacción se concentró. Se agregaron hidróxido de litio (10 ml, 1,0 M ac) y dioxano (10 ml). La mezcla de reacción se agitó durante 3 h luego se concentró parcialmente. Se agregó EtOAc y las capas se separaron. La capa orgánica se lavó con agua y se secó con Na_2SO_4. La mezcla de reacción se concentró para dar 0,23 g del compuesto **654**, ^{1}HRMN (400 MHz, $CDCl_3$) δ 7,44 (s, 1H), 7,19 (d, J=9 Hz, 2 H), 6,89 (d, J=9 Hz, 2H), 4,16 (s, 2H), 4,11 (s, 2H), 3,84 (s, 3H), 1,77 (s amplio, 2H).

Partes E y F:

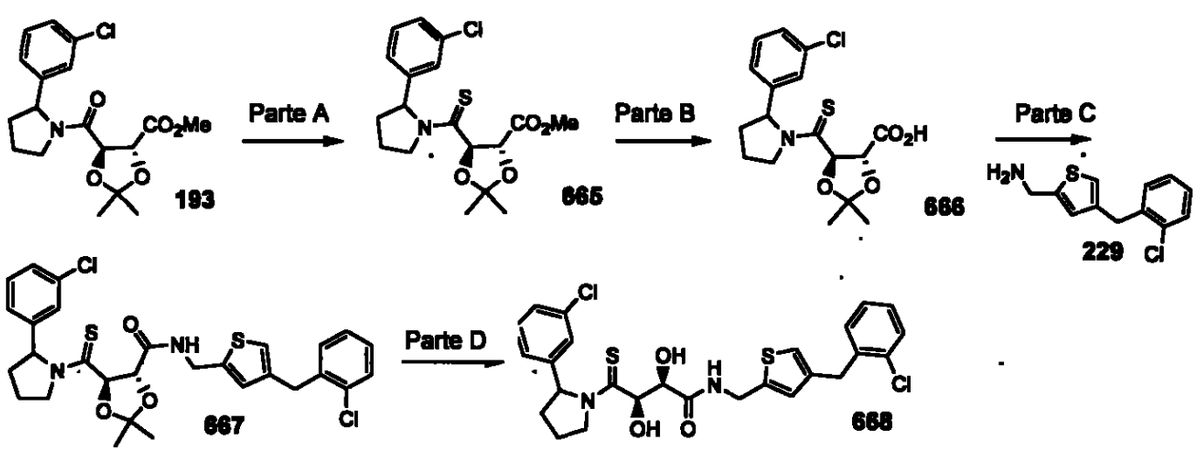
Se transformó el compuesto **654** en el compuesto **655** usando procedimientos descriptos en el Ejemplo 2. Datos sobre **655**: ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,41-7,26 (m, 5H), 7,22-7,14 (M, 4H), 6,89-6,81 (m, 2H), 5,50-5,17 (m, 1H), 4,98-4,54 (m, 4H), 4,53-4,31 (m, 2H), 4,06-3,98 (m, 2H), 3,84 (s, 3H), 2,47-2,27 (m, 1H), 2,12-1,75 (m, 1H). MS (EI) m/z Obs M+H 496,1.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
656A		485,1	486,3
656B		465,2	466,1
657		467,2	468,1
658		467,2	468,1

659		495,2	496,1
660		499,1	500,1
661		471,1	472,1
662		471,1	472,1
663		499,1	500,1
664		471,1	472,1

Ejemplo 16: Tioamidas

Ejemplo 16A:



Parte A:

A una solución del compuesto **193** (200 mg, 0,54 mmol) en THF (5 ml) se agregó reactivo de Lawesson de (203 mg, 0,5 mmol) en porciones. La mezcla de reacción se agitó hasta el día siguiente bajo argón a temperatura ambiente, y se diluyó con EtOAc. La capa orgánica se lavó con $NaHCO_3$ saturado, salmuera, se secó sobre Na_2SO_4, y se concentró. La cromatografía en columna sobre gel de sílice (EtOAc/hexano, 20:80) dio compuesto **665**, masa calculada para la fórmula $C_{18}H_{22}ClNO_4S$ 383,1. LCMS observada m/z 384,1 (M+H).

Parte B:

Al compuesto **665** en MeOH (5 ml) se agregó K_2CO_3 (50 mg) en polvo. La mezcla se agitó a temperatura ambiente durante 1 h y el solvente se eliminó in vacuo. El residuo se disolvió en agua y se acidó con HCl 1 N. Se extrajo con EtOAc, las capas orgánicas combinadas se lavaron con HCl 1N, salmuera, se secaron sobre Na_2SO_4, y se concentraron para dar el compuesto **666** como un aceite (45 mg). Masa calculada para la fórmula $C_{17}H_{20}ClNO_4S$ 369,1. LCMS observada m/z 370,1 (M+H).

Parte D:

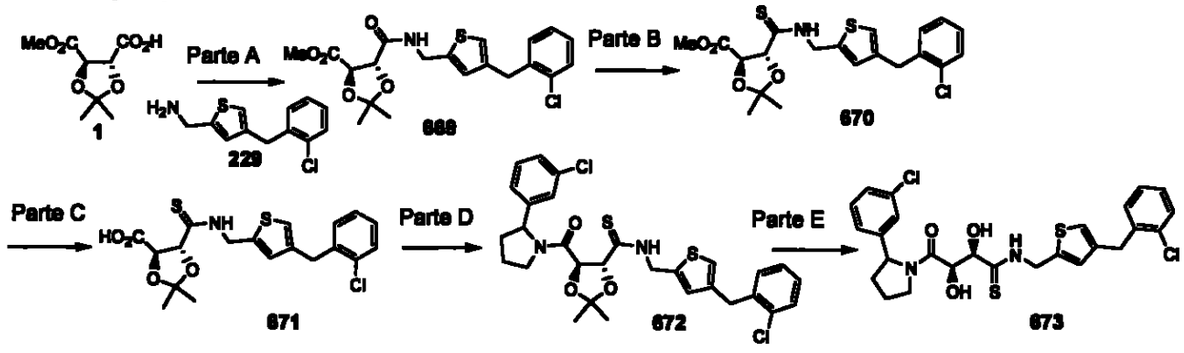
Al compuesto **666** (10 mg, 0,027 mmol) en DMF (0,5 ml) se agregó **229** (11 mg, 0,041 mmol) y HATU (20,5 mg, 0,054 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 h, y se diluyó con acetato de etilo y agua. La capa orgánica se lavó con HCl 1 N, $NaHCO_3$ saturado y salmuera. Se secó sobre Na_2SO_4, y se concentró, dando el compuesto **667** como un aceite. Masa calculada para la fórmula $C_{29}H_{30}Cl_2N_2O_3S_2$ 588,1. LCMS observada m/z 589;1 (M+H).

Parte E:

Se disolvió el compuesto **667** en 0,5 ml de TFA/H_2O (80:20) y se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se desactivó con

ACN/H_2O (50:50) y se concentró in vacuo. La purificación mediante LC prep de fase reversa dio el compuesto **668** como un sólido blanco. HPLC-MS t_R = 6,97 min ($UV_{254\ nm}$; 10 min); Masa calculada para la fórmula $C_{28}H_{28}Cl_2N_2O_3S_2$ 548,1, LCMS observada m/z 549,1 (M+H).

Ejemplo 16B:



Parte A:

A **1** (204 mg, 1mmol) en DMF (2 ml) se agregó **229** (320 mmol, 1,2 mmol) y HATU (570 mg, 1,5 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente, y se diluyó con acetato de etilo y agua. La capa orgánica se lavó con HCl 1 N, $NaHCO_3$ saturado, y salmuera. Se secó sobre Na_2SO_4, y se concentró, dando **669** como un aceite levemente amarillo (280 mg, 66%).

Parte B:

A una solución de **669** (280 mg, 0,54 mmol) en THF (5 ml) se agregó reactivo de Lawesson (202 mg, 0,5 mmol) en porciones de. La mezcla de reacción se agitó hasta el día siguiente bajo argón a temperatura ambiente, y se diluyó con EtOAc. La capa orgánica se lavó con $NaHCO_3$ saturado, salmuera, se secó sobre Na_2SO_4, y se concentró. La cromatografía en columna sobre gel de sílice (EtOAc/hexano, 20:80) dio compuesto **670**. Masa calculada para la fórmula $C_{20}H_{22}ClNO_4S$ 439,1. LCMS observada m/z 440,1 (M+H).

Parte C:

A 670 en MeOH (5 ml) se agregó K_2CO_3 en polvo (50 mg). La mezcla se agitó a temperatura ambiente durante 1 h y el solvente se eliminó in vacuo. El residuo se disolvió en agua y se acidó con HCl 1 N. It se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con HCl 1N, salmuera, se secó sobre Na_2SO_4, y se concentró para dar el compuesto **671** como un aceite (80 mg). Masa calculada para la fórmula $C_{17}H_{20}ClNO_4S$ 425,1. LCMS observada m/z 426,1 (M+H).

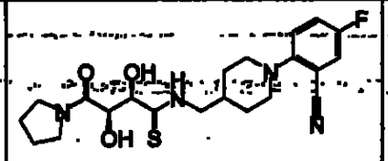
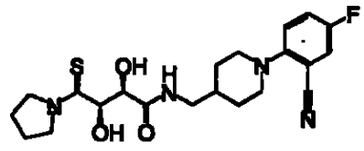
Parte D:

Al compuesto **671** (10 mg, 0,027 mmol) en DMF (0,5 ml) se agregó 2-(3-clorofenil)pirrolidina racémica (6,5 mg, 0,035 mmol) y HATU (17,5 mg, 0,046 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 h, y se diluyó con acetato de etilo y agua. La capa orgánica se lavó con HCl 1 N, saturado $NaHCO_3$, y salmuera. Se secó sobre Na_2SO_4, y se concentró, dando compuesto **672** como un aceite. Masa calculada para la fórmula $C_{29}H_{30}Cl_2N_2O_3S_2$ 588,1. LCMS observada m/z 589,1 (M+H).

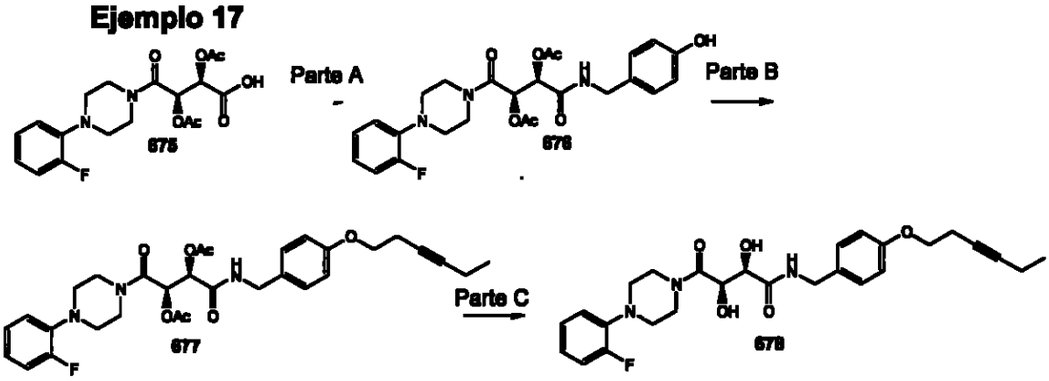
Parte E:

Se disolvió el compuesto **672** en 0,5 ml de TFA/H_2O (80:20) y se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se desactivó con ACN/H_2O (50:50) y se concentró in vacuo. La purificación mediante LC prep de fase reversa dio compuesto **673** como un sólido blanco. HPLC-MS t_R = 7,04 min ($UV_{254\ nm}$, 10 min), Masa calculada para la fórmula $C_{28}H_{28}Cl_2N_2O_3S_2$ 548,1. LCMS observada m/z 549,1 (M+H).

Los siguientes compuestos se prepararon mediante los métodos descriptos anteriormente. Se sustituyó el reactivo de Lawesson por el reactivo de Belleau.

Compuesto #	Estructura	Masa Exacta	MS m/e (M+H)
673		434,2	435,2
674		434,2	435,1

Ejemplo 17



Se preparó el compuesto **675** según se describió en el Ejemplo 4A Parte C.

Parte A:

A **675** (1,34 g, 3,38 mmol) en DMF (20 ml) se agregó 4-hidroxibencilamina (0,5 g, 4,06 mmol), DIEA (0,71 ml, 4,06 mmol) y HATU (1,54 g, 4,06 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se diluyó con agua y la capa acuosa se extrajo con acetato de etilo. Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 80% EtOAc/hexano) dio **676** (1,41 g, 83%). HPLC-MS t_R = 1,56 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{25}H_{28}FN_3O_7$ 501,2. LCMS observada m/z 502,1 (M+H).

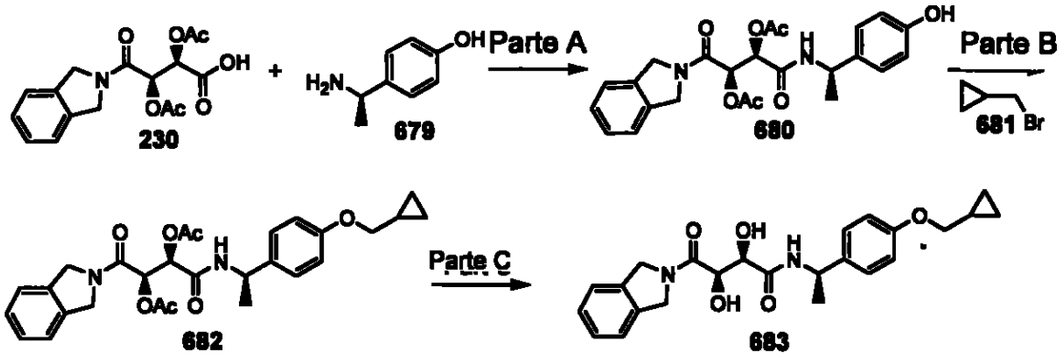
Parte B:

A una mezcla de **676** (50 mg, 0,1 mmol), trifenilfosfina (79 mg, 0,3 mmol), 3-hexin-1-ol (33 µl; 0,3 mmol) en THF (0,5 ml) a 0ºC se agregó DEAD (47 µl, 0,3 mmol). La mezcla de reacción se calentó hasta temperatura ambiente y se agitó durante 5 horas. La mezcla de reacción se diluyó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 20% de EtOAc/hexano a 100% de EtOAc) dio **677** (9 mg, 15%). HPLC-MS t_R = 2,09 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{31}H_{36}FN_3O_7$ 581,3. LCMS observada m/z 582,2 (M+H).

Parte C:

A **677** (9 mg, 0,02 mmol) en metanol (0,5 ml) se agregó hidrazina anhidra (2 µl, 0,04 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. Los solventes se eliminaron in vacuo y el material se secó en freezer para dar **678** como un polvo blanco (2 mg). HPLC-MS t_R = 1,89 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{27}H_{32}FN_3O_5$ 497,2. LCMS observada m/z 498,2 (M+H).

Ejemplo 17B:



Parte A:

Se preparó compuesto el **680** a partir de los compuestos **230** & **679** usando procedimientos descriptos en el Ejemplo 17A Parte A. HPLC-MS t_R = 1,37 min

($UV_{254\ nm}$); Masa calculada para la fórmula $C_{24}H_{26}N_2O_7$ 454,2. LCMS observada m/z 455,2 (M+H).

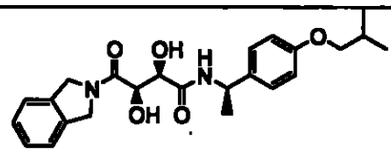
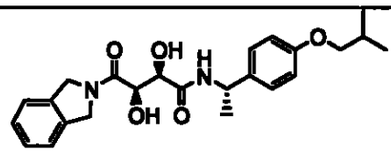
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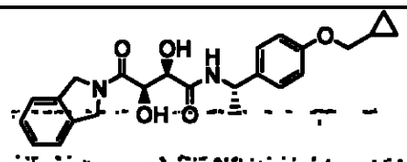
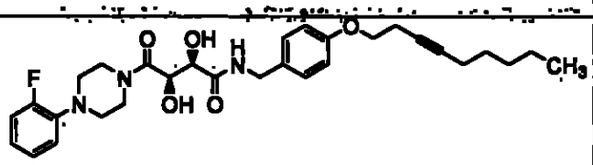
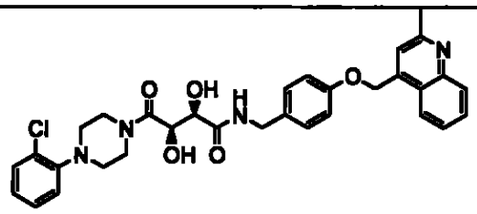
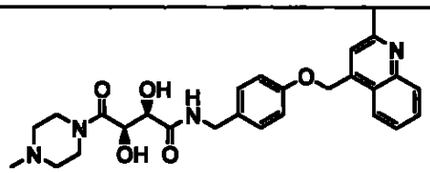
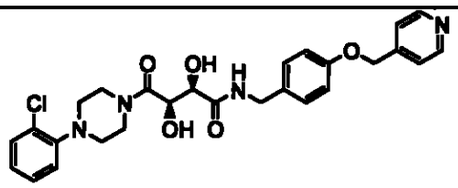
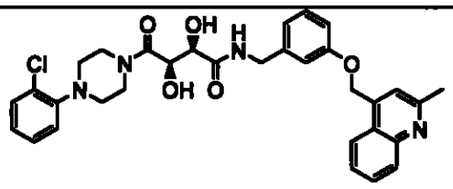
Una mezcla de **680** (49 mg, 0,11 mmol), **681** (14 ul, 0,14 mmol) y carbonato de cesio (46 mg, 0,14 mmol) en DMF (2 ml) se agitó 24 horas. La mezcla de reacción se vertió en agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre sulfato de sodio y se concentró para dar **682** (33 mg). El material se usó sin purificación adicional. HPLC-MS t_R = 1,91 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{28}H_{32}N_2O_7$ 508,2. LCMS observada m/z 509,2 (M+H).

Parte C:

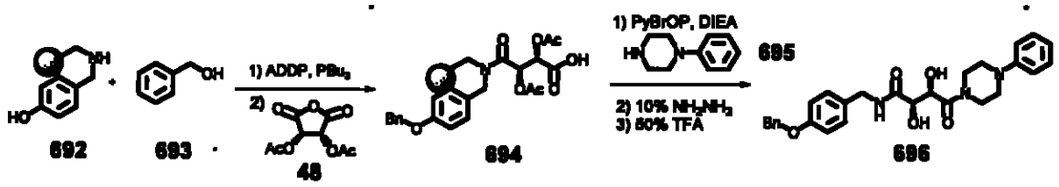
Al compuesto **682** (33 mg, 0,06 mmol) en metanol (2 ml) se agregó amoníaco 7,0 M en metanol (2 ml). La mezcla de reacción se agitó durante 1 hora y se concentró. La purificación mediante HPLC prep. de fase reversa dio **683** (8 mg). HPLC-MS t_R = 4,28 min ($UV_{254\ nm}$, 10 min); Masa calculada para la fórmula $C_{24}H_{28}N_2O_5$ 424,2. LCMS observada m/z 425,2 (M+H).

Los siguientes compuestos se prepararon usando procedimientos descriptos en el Ejemplo 17A & 17B.

Compuesto #	Estructura	Masa exacta	Masa Observ
684		426,2	427,1
685		426,2	427,1

686		424,2	425,2
687		539,3	540,3
688		588,2	589
689		492,2	493
690		524,1	525
691		588,2	589

Ejemplo 17C:



Paso A1:

A resina de MB-CHO pre-hinchada (5,0 g, 1,0 mmol/g) en 40 ml de DCE se agregó 4-hidroxibencilamina (1,5 eq) y triacetoxiborohidruro (2 eq) y la mezcla se

agitó hasta el día siguiente antes de drenar la solución y la resina se lavó con ciclos de MeOH, DCM y THF 5 para dar la resina **692** después del secado in vacuo hasta el día siguiente.

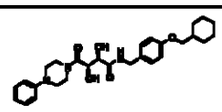
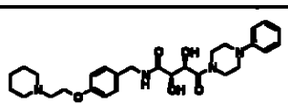
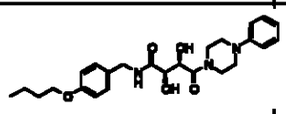
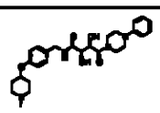
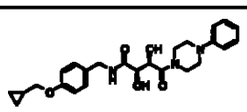
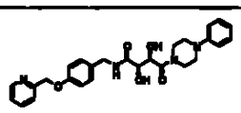
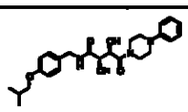
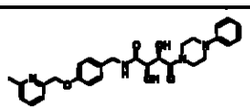
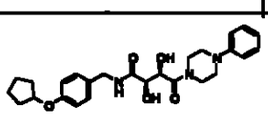
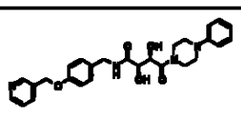
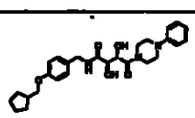
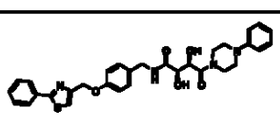
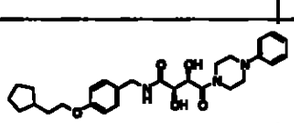
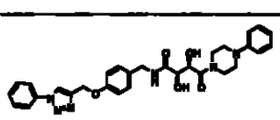
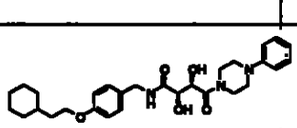
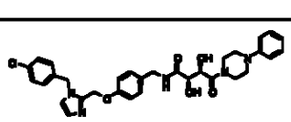
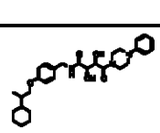
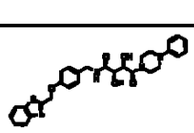
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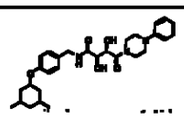
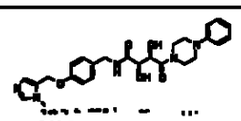
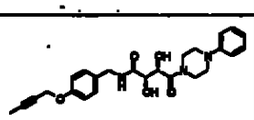
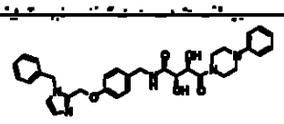
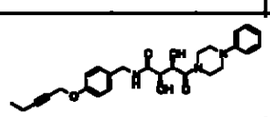
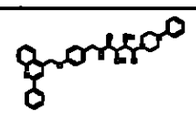
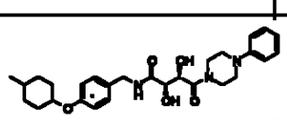
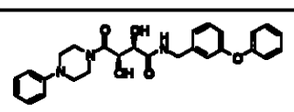
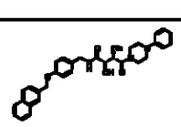
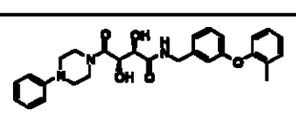
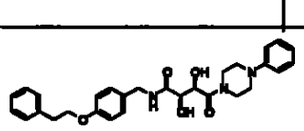
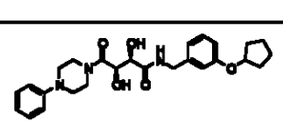
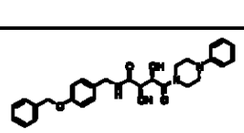
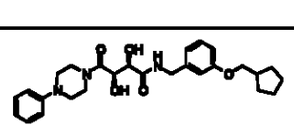
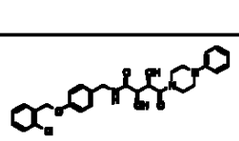
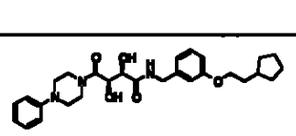
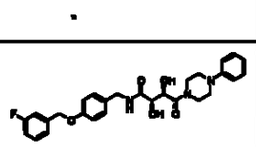
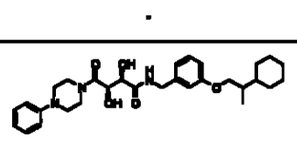
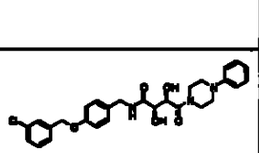
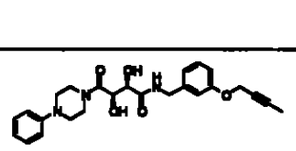
A una resina pre- inflamada **692** (150 mg, 1 mmol/g) en THF anhídrido se agregó bencilalcohol (5 eq) y PPh_3 (7 eq) en 1,5 ml de THF y ADDP (5 eq) en 0,5 ml de DCM. La reacción se agitó a temperatura ambiente durante el fin de semana. La solución de la reacción se drenó y la resina se lavó con 5 ciclos de MeOH, DCM y THF y se secó in vaccuo antes de embeberla en NMP seguida por la adición de 1,5 mlde solución NMP 1M de compuesto **48**. La mezcla de reacción se agitó hasta el día siguiente antes de drenar la solución y la resina se lavó con 5 ciclos de MeOH, DCM y THF y se secó in vacuo para dar la resina **694**,

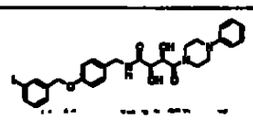
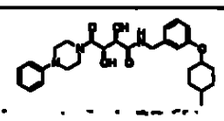
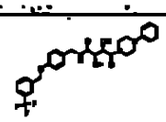
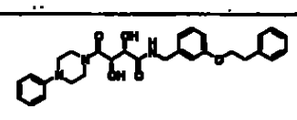
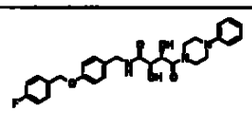
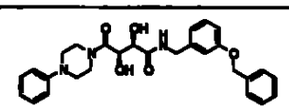
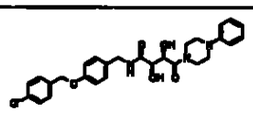
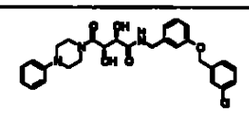
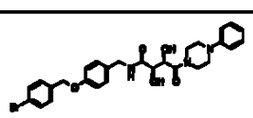
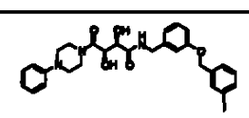
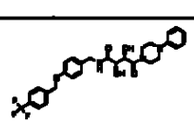
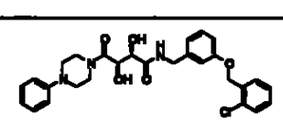
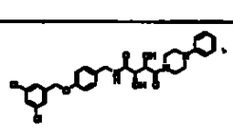
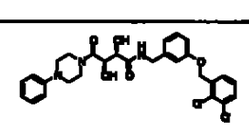
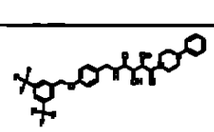
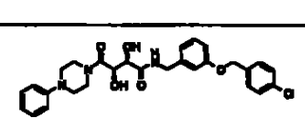
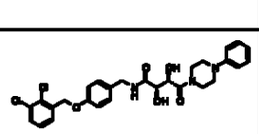
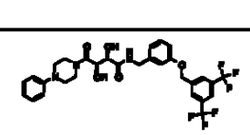
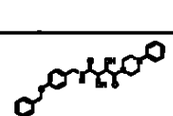
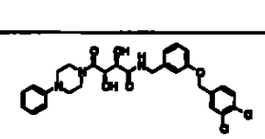
Paso B:

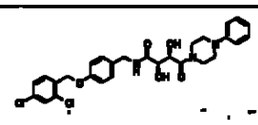
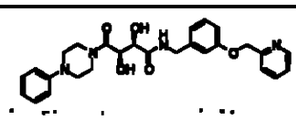
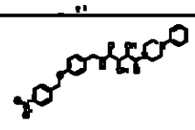
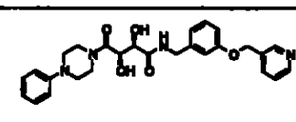
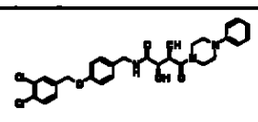
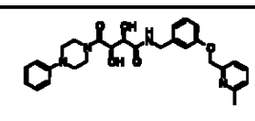
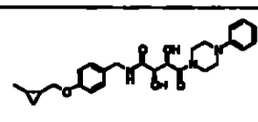
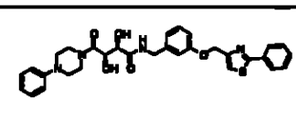
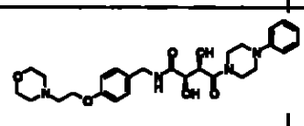
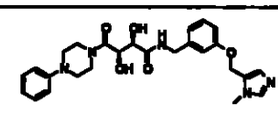
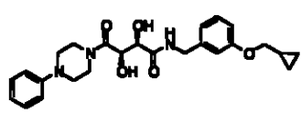
La resina **694** se hinchó previamente en DCM, antes de agregar sal clorhídrica de 1-fenilpiperazina (695)(6 eq) seguida por la adición de PyBrop (3 eq) y DIEA (9 eq) en 3 ml de DCM. La solución de la reacción se agitó hasta el día siguiente antes de que se drenara y la resina se lavó con 5 ciclos de MeOH, DCM y THF antes de que se trate con 10% de hidrazina en metanol durante 2h. Luego, la resina se lavó adicionalmente con 5 ciclos de MeOH, DCM y THF seguido por la separación usando 50% de TFA en DCM. La solución de separación se evaporó y el residuo se purificó con un sistema RP-HPLC para dar 5 mg del producto deseado **696**.

Los siguientes compuestos se generaron mediante el uso de métodos similares.

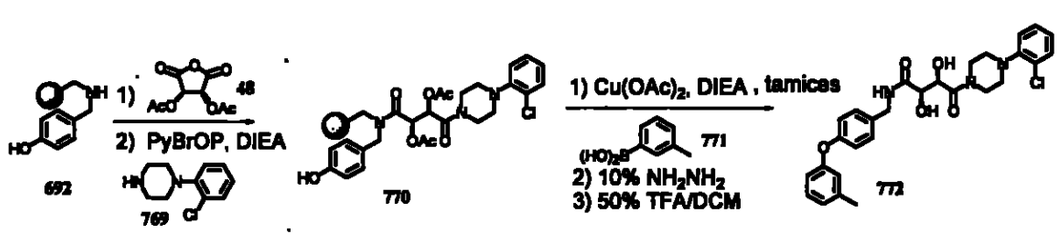
Compuesto #	Estructura	MS Obs.		Compuesto #	Estructura	MS Obs.
697		496		698		511
699		456		700		497
701		454		702		491
703		456		704		505
705		468		706		491
707		482		708		573
709		496		710		557
711		510		712		604
713		524		714		547

715		510		716		494
717		452		718		570
719		466		720		617
721		496		722		476
723		540		724		490
725		504		726		468
696		490		728		482
729		524		730		496
731		508		732		524
733		524		734		452

735		616		736		496
737		558		738		504
739		508		740		490
741		524		742		524
743		569		744		616
745		558		746		524
747		558		748		558
749		626		750		524
751		558		752		626
753		535		754		558

755		558		**756**		491
757		535		**758**		491
759		558		**760**		505
761		468		**762**		573
763		513		**764**		494
765		454				

Ejemplo 17D:



Paso A.

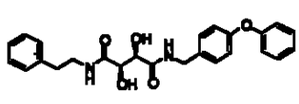
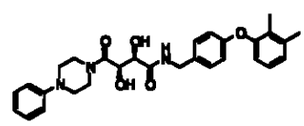
A la resina **692** (2,6 g, 1mmol/g), hinchada previamente en NMP se agregó **48** (5 eq) y la mezcla se agitó durante 48 h. Antes de drenar la solución y

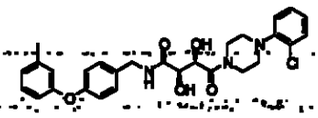
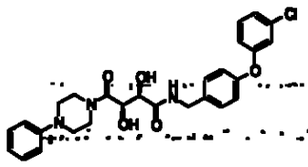
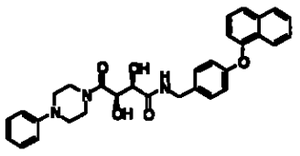
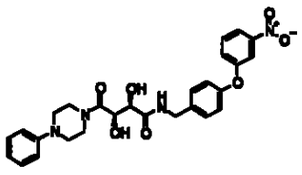
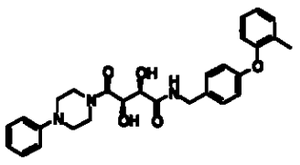
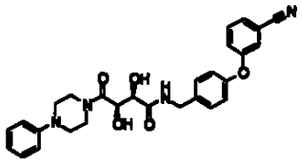
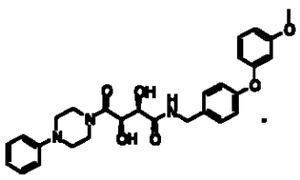
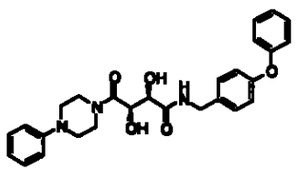
la resina se lavó con 5 ciclos de MeOH, DCM y THF y se secó in vacuo. Luego, la resina se embebió en DCM anhídrido (25 ml) antes de agregar **769** (6 eq., sal de HCl) y DIEA (9 eq) seguido por la adición de PyBrop. La reacción se agitó a t.a. hasta el día siguiente antes de drenar la solución y la resina se lavó con 5 ciclos de MeOH, DCM y THF y se secó in vacuo para dar resina **770** (0,9 mmol/g de carga).

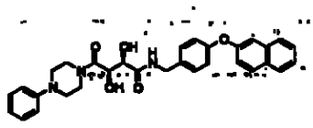
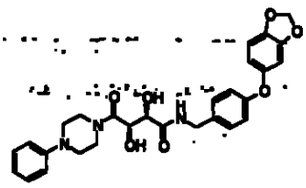
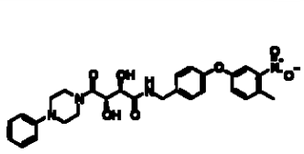
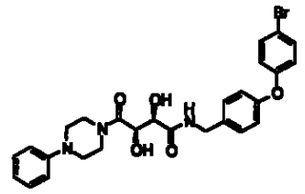
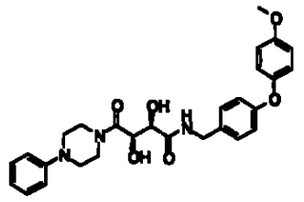
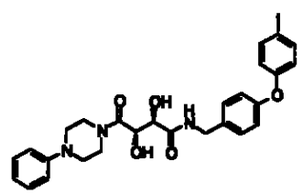
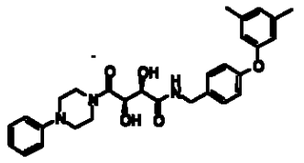
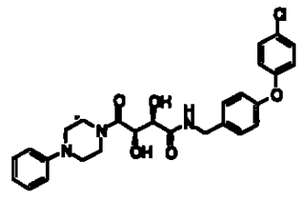
Paso B.

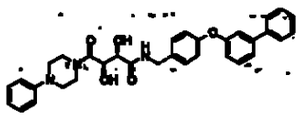
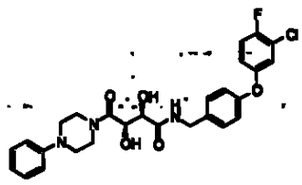
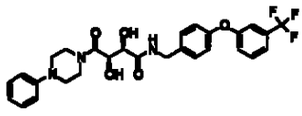
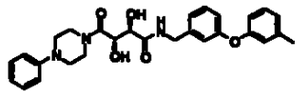
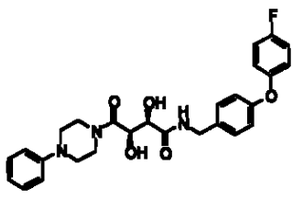
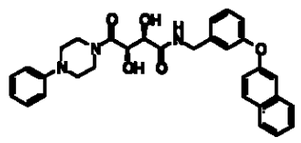
A una resina **770** hinchada previamente (0,095 g, 0,9 mmol/g) en DCM anhídrido se agregó $Cu(OAc)_2$ anhídrido (3 eq), **771** (5 eq), tamices moleculares 4 A (tamaño de partícula de 5 micron, 100 mg) y DIEA (7eq) en 2 ml de DCM anhídrido. La reacción se agitó durante 48 h. antes de drenar la mezcla y la resina se lavó con 5 ciclos de H_2O, MeOH, DCM y THF antes de que se trate con 10% de hidrazina en metanol durante 2h. La resina se lavó luego adicionalmente con 5 ciclos de MeOH, DCM y THF seguido por la ruptura usando 50% de TFA en DCM. La solución de separación se evaporó y el residuo se purificó con un sistema RP-HPLC para dar 5 mg del producto deseado **772.**

Los siguientes compuestos se sintetizaron de manera similar.

Compuesto #	Estructura	Masa Obs.		Com-puesto #	Estructura	Masa Obs
773		435		**774**		504

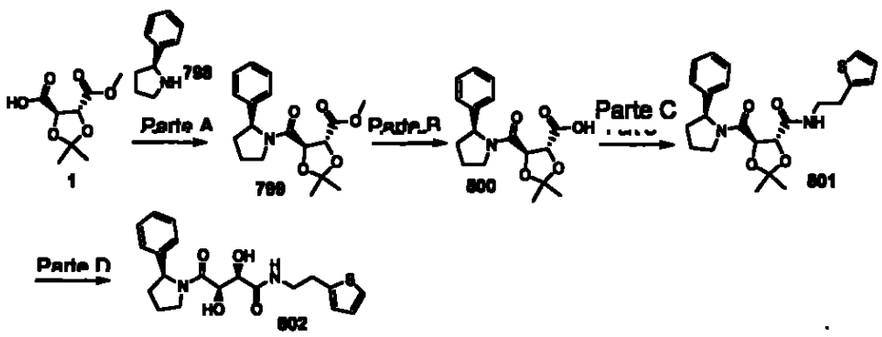
772		524	776		510
777		526	778		521
779		490	780		501
781		506	782		476

783		526	784		520
785		535	786		555
787		506	788		490
789		504	790		510

791		**552**	**792**		**528**
793		**544**	**794**		**490**
795		**494**	**796**		**526**

Ejemplo 18

Ejemplo 18A:



Parte A:

Siguiendo el procedimiento descripto en el Ejemplo 1 Parte A, **1** (163 mg, 0,8 mmol), 2S-fenil-pirrolidina (**798**) (Burgess, L.E.; Meyers, A.I.; *J. Org. Chem.* **1991**, *56*, 2294) (147 mg, 0,8 mmol), DIEA (560 µl, 3,2 mmol) y HATU (304 mg, 0,8 mmol) se mezclaron juntos en DMF (2 ml). La purificación mediante cromatografía en columna (SiO_2, 5%-20% EtOAc/DCM) dio **799** como un aceite (115 mg, 43%). HPLC-MS t_R = 1,82 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{18}H_{23}NO_5$ 333,2. LCMS observada m/z 334,1 (M+H).

Parte B:

Siguiendo el procedimiento en el Ejemplo 1 Parte B se saponificó el material de la Parte A. **800**: HPLC-MS t_R = 1,54 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{17}H_{21}NO_5$ 319,1. LCMS observada m/z 320,2 (M+H).

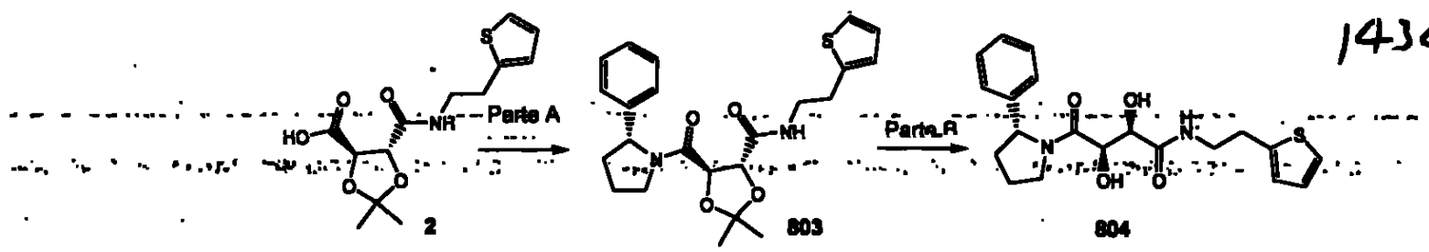
Parte C:

Se mezclaron juntos el compuesto **800**, 2-tiofenetilamina (6 µl, 0,05 mmol), DIEA (18 µl, 0,103 mmol) y HATU (19 mg, 0,05 mmol) siguiendo el procedimiento descripto en el Ejemplo 1 Parte A. **801**: HPLC-MS t_R = 2,01 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{23}H_{28}N_2O_4S$ 428,2. LCMS observada m/z 429,2 (M+H).

Parte D:

Se disolvió el Compuesto **801** en 90:10 TFA:agua (2 ml) y se agitó durante 4 horas. La mezcla de reacción se desactivó con 1:1 acetonitrilo:agua (4 ml) y se concentró. La purificación mediante LC prep de fase reversa dio **802** como un polvo blanco (9 mg, 50%, 2 steps). HPLC-MS t_R = 1,54 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{20}H_{24}N_2O_4S$ 388,2. LCMS observada m/z 389,2 (M+H).

Ejemplo 18B:

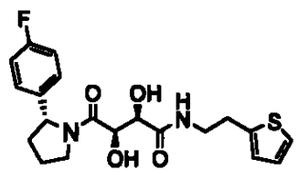
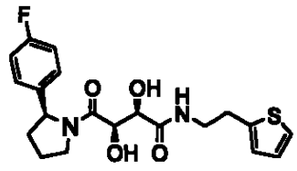
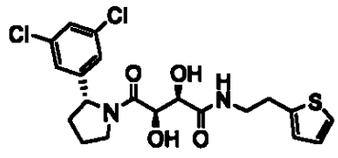


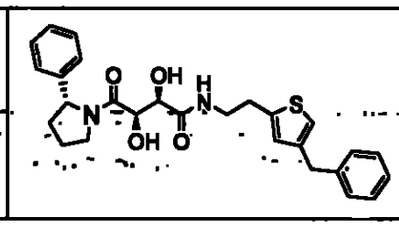
Parte A:

Se mezclaron juntos el compuesto **2** (42 mg, 0,14 mmol), 2-fenil pirrolidina (22 mg, 0,15 mmol), DIEA (63 µl, 0,36 mmol) y HATU (61 mg, 0,16 mmol) siguiendo el procedimiento descripto en el Ejemplo 1 Parte A. El isómero deseado se separó mediante LC prep de fase reversa para dar **803** como un sólido blanco. HPLC-MS t_R = 1,96 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{23}H_{28}N_2O_4S$ 428,2. LCMS observada m/z 429,1 (M+H).

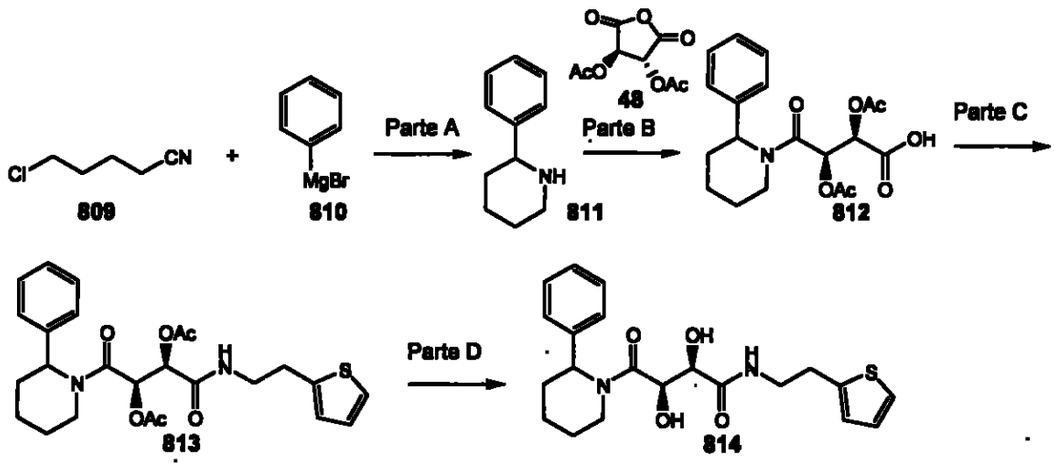
Parte B:

Se desprotegió el compuesto **803** usando el procedimiento descripto en el Ejemplo 1 Parte D para dar **804** como un polvo blanco (5 mg, 19% 2 pasos). HPLC-MS t_R = 1,50 min ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{20}H_{24}N_2O_4S$ 388,2. LCMS observada m/z 389,2 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
805		406,1	407,2
806		406,1	407,2
807		456,1	457,1

808		478,2	479,2

Ejemplo 19:



Parte A: 2-Fenil piperidina

A 5-clorovaleronitrilo (**809**) (1,23 ml, 11 mmol) y cloruro de trimetilsililo (4,32 ml, 34 mmol) en tolueno (50 ml) bajo argón a 0°C se agregó bromuro de fenilmagnesio (**810**) (3M en dietil éter, 3,67 ml, 11 mmol) gota a gota. La mezcla de reacción se agitó a 0°C durante 1 hora. A la mezcla de reacción se agregó metanol (50 ml). Se agregó borohidruro de sodio (1,04 g, 27,5 mmol) en porciones. Una vez que cesó el burbujeo intenso, la mezcla de reacción se agitó durante 1 hora a temperatura ambiente. Se agregó una solución de 50% de hidróxido de sodio (5 ml) a la mezcla y se agitó hasta el día siguiente. La mezcla de reacción se filtró para eliminar el precipitado y los sólidos se lavaron con acetato de etilo. El filtrado se concentró in vacuo. La mezcla de reacción bruta se disolvió en acetato de etilo y agua. La capa acuosa poseía un pH de 9. Las capas se separaron y la capa orgánica se lavó con solución de salmuera, se secó sobre sulfato de sodio y se concentró in vacuo para dar un aceite naranja. El producto

se purificó mediante cromatografía en columna (SiO_2, 20% de acetato de etilo/hexano a 20% de acetato de etilo hexano + 2% de trietilamina) para dar **811** como un aceite amarillo polar (927 mg, 52%). ^1H RMN (400 MHz, $CDCl_3$) δ 7,4 - 7,3 (m, 4H), 7,24 (m, 1H), 3,60 (dd, 1H, J = 2,4, 10,4 Hz), 3,21 (m, 1H), 2,81 (dt, 1H, J = 3,2, 10,8 Hz), 1,90 (m, 1H), 1,81 (m, 1H), 1,68 (m, 1H), 1,56 (m, 3H); HPLC-MS t_R = 0,73 min (MS); masa calculada para la fórmula $C_{11}H_{15}N$ 161,1. LCMS observada m/z 162,1 (M+H).

Parte B:

A **48** (108 mg, 0,5 mmol) en DCM (3 ml) se agregó **811** (80 mg, 0,5 mmol). La mezcla de reacción se agitó hasta el día siguiente antes de verterla en HCl 1,0 N y se extrajo con DCM. Las capas orgánicas combinadas se secaron sobre sulfato de sodio, se concentraron y se secaron en freezer para dar **812** como un sólido blanco (119 mg, 63%). Masa calculada para la fórmula $C_{19}H_{23}NO_7$ 377,2. LCMS observada m/z 378,1 (M+H).

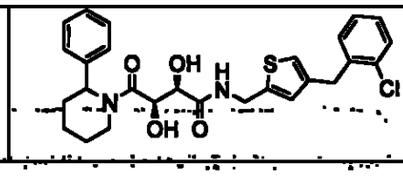
Parte C:

Se preparó según se describió en el Ejemplo 1 Parte A usando **812** (19 mg, 0,05 mmol) para dar una espuma **813** (24 mg, 100%). Masa calculada para la fórmula $C_{19}H_{23}NO_7$ 486,2. LCMS observada m/z 487,1 (M+H).

Parte D:

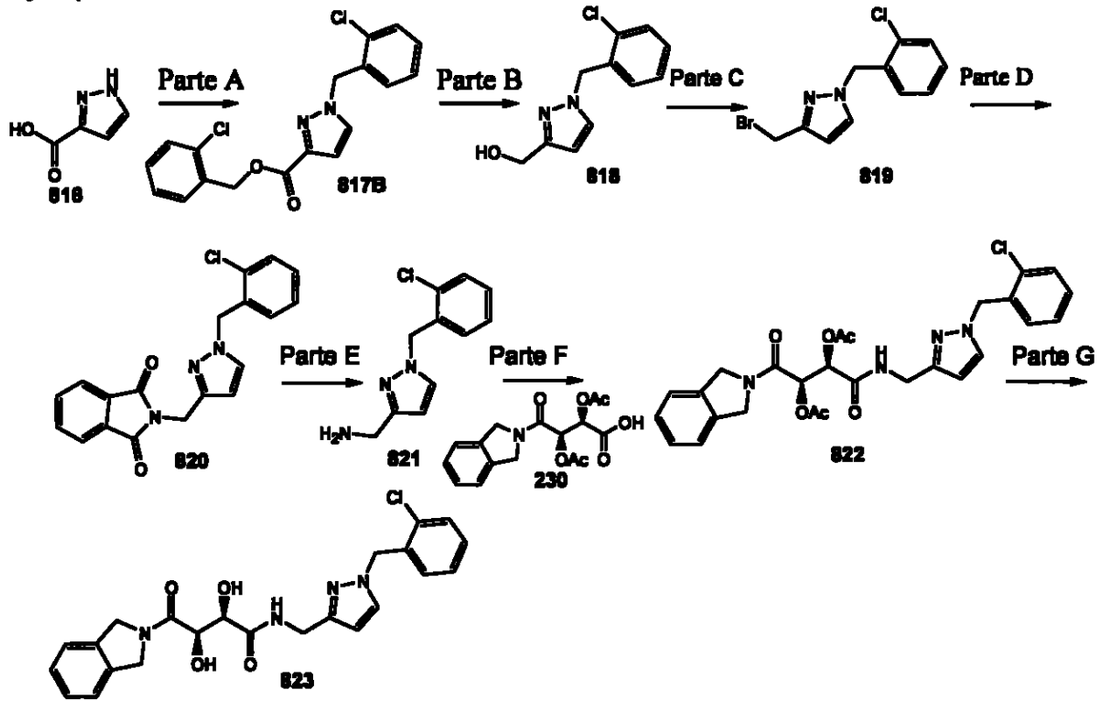
Se desprotegió el compuesto **813** (24 mg, 0,05 mmol) usando el procedimiento descripto en el Ejemplo 2A Parte B. La purificación mediante LC prep. De fase reversa dio **814** como un polvo blanco (9 mg, 45%). HPLC-MS t_R = 4,38 y 4,42 min ($UV_{254\ nm}$, 10 min); Masa calculada para la fórmula $C_{21}H_{26}N_2O_4S$ 402,2. LCMS observada m/z 403,1 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)

815		512,2	513,1

Ejemplo 20:

Ejemplo 20A:



Parte A:

A ácido 1H-pirazol-3-carboxílico (**816**) (274 mg, 2,44 mmol) en DMF (10 ml) se agregó bromuro de 2-clorobencilo (698 µl, 5,38 mmol) y carbonato de cesio (1,67 g, 5,12 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. Los sólidos se eliminaron mediante filtración y el filtrado se concentró. La purificación mediante cromatografía en columna (SiO_2, 20% a 30% de EtOAc/Hex) separó los regioisómeros para dar el **817A** como un aceite (136 mg, 15%) y **817B** como un sólido blanco (685 mg, 78%).

2-cloro-bencil éster del ácido 1-(2-cloro-bencil)-1H-pirazol-5-carboxílico (**817A**): ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,61 (d, 1H, J = 2,0 Hz), 7,37 (m, 3H), 7,31 - 7,11 (m, 4H), 7,02 (d, 1H, J = 2,0 Hz), 6,53 (dd, 1H, J = 2,0, 7,6 Hz), 5,91 (s, 2H), 5,39 (s, 2H). HPLC-MS t_R = 2,40 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{18}H_{14}Cl_2N_2O_2$ 360,0, LCMS observada m/z 361,0 (M+H).

2-cloro-bencil éster del ácido 1-(2-Cloro-bencil)-1H-pirazol-3-carboxílico (**817B**): ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,51 (m, 1H), 7,44 (d, 1H, J = 2,4 Hz), 7,40 (m, 2H), 7,27 (m, 4H), 7,08 (dd, 1H, J = 1,6, 7,6 Hz), 6,87 (d, 1H, J = 2,4 Hz), 5,54 (s, 2H), 5,51 (s, 2H); HPLC-MS t_R = 2,22 min. (UV_{254} nM); masa calculada para la fórmula $C_{18}H_{14}Cl_2N_2O_2$ 360,0, LCMS observada m/z 361,0 (M+H).

Parte B:

A **817B** (685 mg, 1,90 mmol) en THF (10 ml) se agregó $LiAlH_4$ 1,0 M (1,14 ml, 1,14 mmol) con enfriamiento con hielo. La mezcla de reacción se agitó durante 1 hora. La reacción se desactivó con agua (1 ml), NaOH 3 M (1 ml) y agua (3 ml). La capa orgánica se decantó y el precipitado se lavó con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 1:1 DCM:EtOAc) dio **818** como un aceite (350 mg, 83%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,42 (d, 1H, J = 2,4 Hz), 7,39 (dd, 1H, J = 2,4, 8,0 Hz), 7,25 (m, 2H), 7,02 (dd, 1H, J = 1,6, 7,2 Hz), 6,30 (d, 1H, J = 2,4 Hz), 5,43 (s, 2H), 4,73 (s, 2H), 2,5 (bs, 1H, OH); HPLC-MS t_R = 1,29 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{11}H_{11}ClN_2O$ 222,1, LCMS observada m/z 223,1 (M+H).

Parte C:

A **818** (350 mg, 1,57 mmol) en tolueno (5 ml) se agregó tribromuro de fósforo (163 µl, 1,73 mmol). La mezcla de reacción se calentó hasta reflujo en un baño de aceite calentado previamente durante 15 minutos. La mezcla se enfrió, se vertió sobre hielo y se extrajo con EtOAc. La capa orgánica combinada se lavó

con solución de bicarbonato y salmuera, se secó sobre sulfato de sodio y se concentró para dar **819** como un sólido blanco (414 mg, 93%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,39 (m, 2H), 7,25 (m, 2H), 7,00 (dd, 1H, J = 2,0, 7,2 Hz), 6,36 (d, 1H, J = 2,4 Hz), 5,41 (s, 2H), 4,53 (s, 2H); HPLC-MS t_R = 1,96 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{11}H_{10}BrClN_2$ 284,0, LCMS observada m/z 285,1 (M+H).

Parte D:

A **819** (412 mg, 1,44 mmol) en DMF (5 ml) se agregó ftalamida (255 mg, 1,73 mmol) y carbonato de cesio (515 mg, 1,58 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. Los sólidos se eliminaron mediante filtración y el filtrado se concentró. El residuo se disolvió en EtOAc y agua. Las capas se separaron. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 5% de EtOAc/DCM) dio **820** como un sólido (418 mg, 82%). HPLC-MS t_R = 1,96 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{19}H_{14}ClN_3O_2$ 351,1, LCMS observada m/z 352,2 (M+H).

Parte E:

A **820** (418 mg, 1,19 mmol) en etanol (20 ml) se agregó monohidrato de hidracina (231 µl, 4,75 mmol) y la reacción se calentó hasta reflujo durante 3 horas. La mezcla se enfrió y se diluyó con 50% de EtOAc/hexanos (40 ml). Los sólidos se eliminaron mediante filtración y se lavaron cuidadosamente con 50% de EtOAc/hexanos (30 ml). El filtrado se concentró. El residuo se disolvió en EtOAc y se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró para dar **821** como un semi-sólido (205 mg, 78%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,39 (m, 1H), 7,38 (d, 1H, J = 2,0 Hz), 7,23 (m, 2H), 6,92 (dd, 1H, J = 2,0, 7,2 Hz), 6,22 (d, 1H, J = 2,0 Hz), 5,39 (s, 2H), 3,91 (s, 2H); HPLC-MS t_R = 0,91 min. (UV_{254}

$_{nm}$); masa calculada para la fórmula $C_{11}H_{12}ClN_3$ 221,07, LCMS observada m/z 222,1 (M+H).

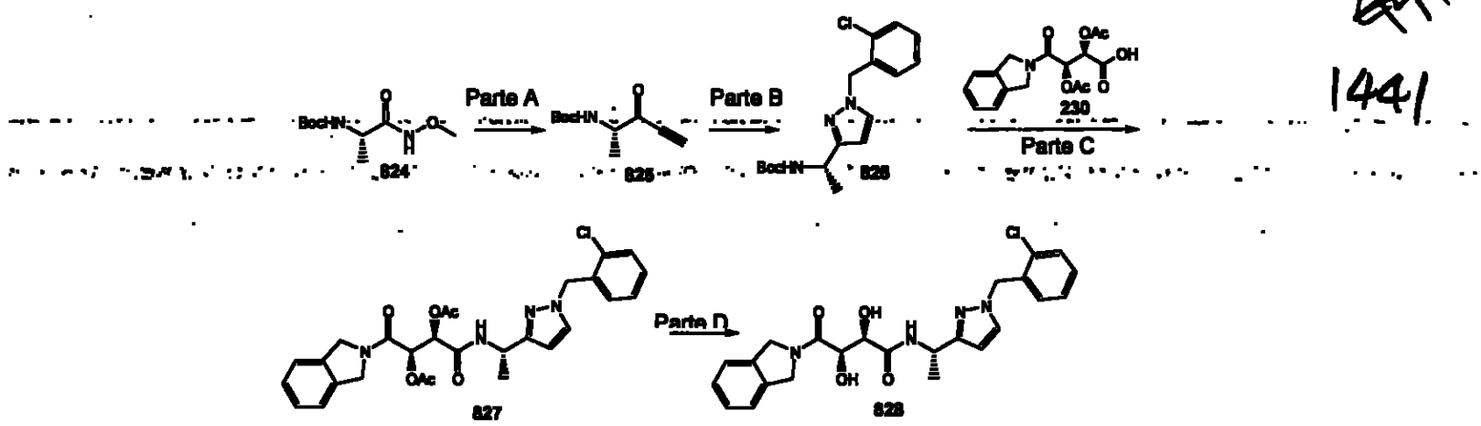
Parte F:

A **821** (49 mg, 0,22 mmol) en DMF (2 ml) se agregó **230** (67 mg, 0,2 mmol), DIEA (77 µl, 0,44 mmol) y HATU (84 mg, 0,22 mmol). La mezcla de reacción se agitó hasta el día siguiente. El DMF se eliminó en *vacuo* y el residuo se disolvió en EtOAc. La capa orgánica se lavó con solución de bicarbonato, HCl 0,1 N, y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 80% de EtOAc/Hex) dio **822** como un sólido (70 mg, 65%). HPLC-MS t_R = 1,80 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{27}H_{27}ClN_4O_6$ 538,2, LCMS observada m/z 539,2 (M+H).

Parte G:

Se agitó una mezcla de **822** (70 mg, 0,13 mmol) y carbonato de potasio (90 mg, 0,65 mmol) en MeOH (2 ml) 1 hora. La reacción se diluyó con EtOAc y se vertió en solución de salmuera. Se agregó sal adicional y las capas se separaron. La capa acuosa se extrajo con EtOAc. La capa orgánica combinada se secó sobre sulfato de sodio y se concentró para dar **823** como un sólido blanco (45 mg, 76%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,05 (t, 1H, J = 6,0 Hz), 7,70 (d, 1H, J = 2,0 Hz), 7,46 (dd, 1H, J = 2,0, 8,0 Hz), 7,36 – 7,27 (m, 6H), 6,94 (dd, 1H, J = 2,0, 7,6 Hz), 6,20 (d, 1H, J = 2,0 Hz), 5,68 (d, 1H, J = 6,8 Hz), 5,35 (s, 2H), 5,06 (d, 1H, J = 14,4 Hz), 5,03 (d, 1H, J = 7,6 Hz), 4,91 (d, 1H, J = 14,4 Hz), 4,76 (d, 1H, J = 15,6 Hz), 4,62 (dd, 1H, J = 2,8, 7,6 Hz), 4,61 (d, 1H, J = 14,8 Hz), 4,26 (m, 3H); HPLC-MS t_R = 1,55 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{23}H_{23}ClN_4O_4$ 454,1, LCMS observada m/z 455,2 (M+H).

Ejemplo 20B: Espaciador Pirazólico



Parte A:

A la amida de Weinreb **824** (preparada usando el método de De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534) (200 mg, 0,85 mmol) en THF (15 ml) se agregó (trimetilsilil)acetilida de litio (4,3 ml, 2,14 mmol) gota a gota a 0 °C. La mezcla de reacción se agitó durante 1 hora luego se diluyó con EtOAc (50 ml). La mezcla se lavó con HCl 0,1 N (50 ml), se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 20% de EtOAc/Hex) dio **825** (91 mg, 54%).

Parte B:

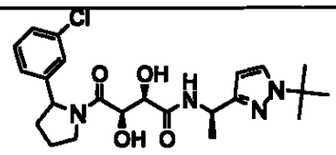
Se agitaron una mezcla de **825** (71 mg, 0,33 mmol), diclorhidrato de (2-cloro-fenil)-hidracina (89 mg, 0,39 mmol) y carbonato de potasio (200 mg, 1,64 mmol) en metanol (5 ml) a reflujo durante 12 horas. La mezcla de reacción se enfrió y se diluyó con EtOAc (50 ml) y agua (50 ml). La capa orgánica se separó, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 20% de EtOAc/Hex) dio **826** (50 mg, 15%). HPLC-MS t_R = 2,10 min. (ELSD); masa calculada para la fórmula $C_{17}H_{22}ClN_3O_2$ 335,1, LCMS observada m/z 336,2 (M+H).

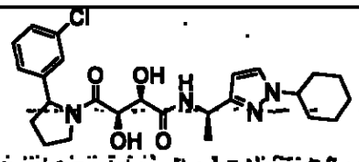
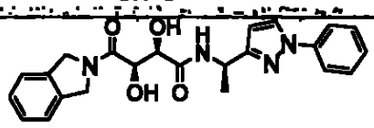
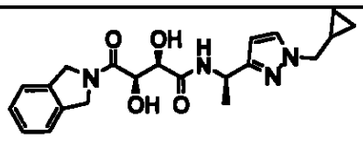
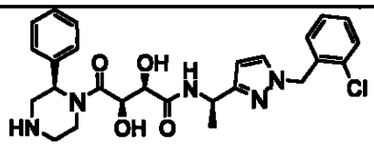
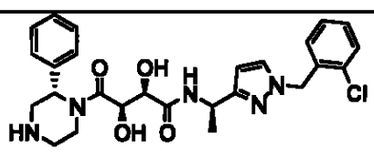
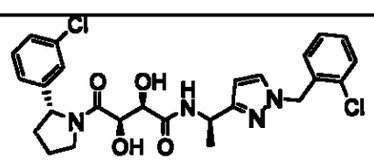
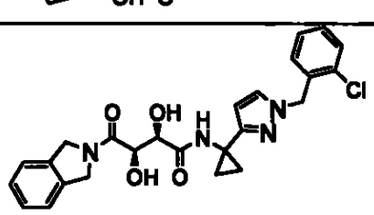
Parte C:

Se disolvió el compuesto **826** (45 mg, 0,13 mmol) en 25% de TFA/DCM (4 ml) y se agitó durante 30 minutos. Los solventes se eliminaron en *vacuo* y el material se usó sin purificación adicional. El residuo se disolvió en DMF (5 ml) y se agregaron **230** (25 mg, 0,07 mmol), DIEA (300 µl, 1,68 mmol) y HATU (32 mg, 0,09 mmol). La mezcla de reacción se agitó hasta el día siguiente. El DMF se eliminó en *vacuo* y el residuo se disolvió en EtOAc y agua. La capa orgánica se separó y se lavó con NaOH 0,1 N, HCl 0,1 N y salmuera, se secó sobre sulfato de sodio y se concentró. El Compuesto **827** se usó sin purificación adicional.

Parte D:

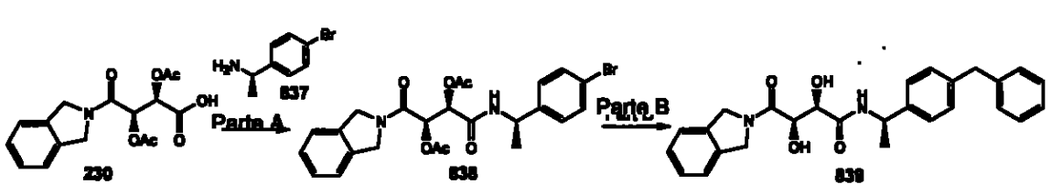
Se disolvió el compuesto **827** (~25 mg, 0,05 mmol) en metanol (5 ml) y se agregó una solución sobre carbonato de potasio (50 mg) en agua (1 ml). La reacción se agitó durante 30 minutos. La mezcla de reacción se diluyó con acetato de etilo y salmuera. La capa orgánica se separó, se secó sobre sulfato de sodio y se concentró. La purificación mediante LC prep. de fase reversa dio **828** como un polvo blanco (15 mg, 65%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,81 (d, 1H, J = 8,0 Hz), 7,70 (d, 1H, J = 1,6 Hz), 7,47 (dd, 1H, J = 1,6, 7,6 Hz), 7,35 – 7,26 (m, 6H), 6,89 (dd, 1H, J = 1,6, 7,2 Hz), 6,29 (d, 1H, J = 2,0 Hz), 5,38 (s, 2H), 5,04 (d, 1H, J = 15,2 Hz), 4,97 (m, 2H), 4,90 (d, 1H, J = 14,0 Hz), 4,76 (d, 1H, J = 16,4 Hz), 4,61 (m, 2H), 4,27 (d, 1H, J = 2,4 Hz), 1,39 (d, 3H, J = 6,8 Hz); HPLC-MS t_R = 4,25 min. ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{24}H_{25}ClN_4O_4$ 468,2, LCMS observada m/z 469,1 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
829		462,2	463,1

830		488,2	489,2
831		420,2	421,1
832		398,2	399,1
833		511,2	512,2
834		511,2	512,2
835		530,2	531,1
836		480,2	481,1

Ejemplo 21: α-Metil bencil aminas

Ejemplo 21A:



Parte A:

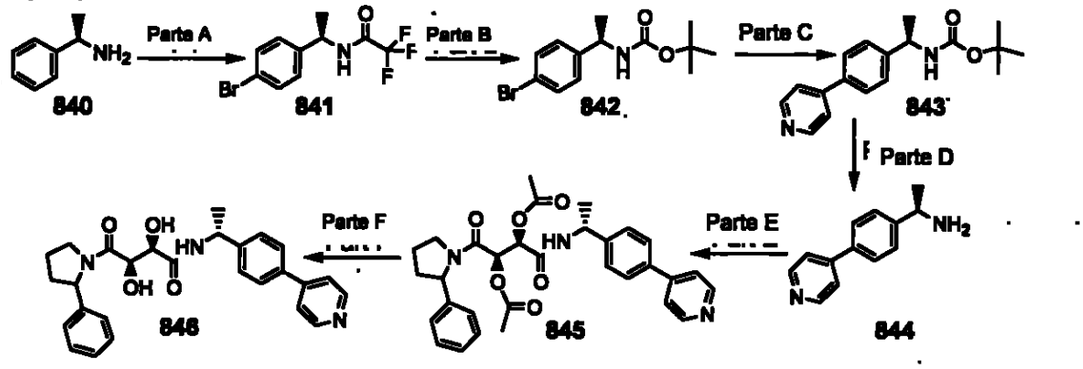
Se agitó una mezcla de 1R-(4-bromo-fenil)-etilamina (837) (0,18 ml, 1,25 mmol), **230** (349 mg, 1,0 mmol), DIEA (357 µl, 2,0 mmol) y HATU (456 mg, 1,2

mmol) en NMP (10 ml) hasta el día siguiente a temperatura ambiente. La mezcla de reacción se vertió en agua y se extrajo con EtOAc. La capa orgánica se lavó con solución de bicarbonato, HCl 0,1 N, y salmuera; se secó sobre sulfato de sodio y se concentró. **838**: ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,72 (d, 1H, J = 7,6 Hz), 7,49 (dd, 2H, J = 2,0, 6,8 Hz), 7,37 – 7,25 (m, 6H), 5,56 (ABq, 2H, J = 6,8 Hz), 4,99 (d, 1H. J = 13,2 Hz), 4,89 (m, 2H), 4,70 (d, 1H, J = 16,0 Hz), 4,51 (d, 1H, J = 16,4 Hz), 2,09 (s, 3H), 2,03 (s, 3H), 1,32 (d, 3H, J = 7,2 Hz).

Parte B:

A **838** (135 mg, 0,26 mmol), $PdCl_2$(dppf) (22 mg, 0,03 mmol), fosfato de potasio (166 mg, 0,78 mmol) en dioxano (5 ml) bajo atmósfera de argón se agregó bencil-9-BBN (0,5 M en THF, 1,3 ml, 0,65 mmol). La mezcla de reacción se calentó hasta 60 °C hasta el día siguiente. La mezcla de reacción se filtró a través de un lecho de Celite y el lecho se enjuagó con acetato de etilo. El filtrado se concentró. El producto bruto se disolvió en metanol (5 ml) y se agregó carbonato de potasio (4 mg). La mezcla de reacción se agitó durante 1 hora, se filtró y se concentró para dar **839** como un sólido (50 mg, 42%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,97 (d, 1H, J = 7,6 Hz), 7,34 – 7,10 (m, 13H), 5,03 (d, 1H. J = 14,4 Hz), 4,90 (m, 2H), 4,72 (d, 1H, J = 16,8 Hz), 4,58 (m, 2H), 4,20 (d, 1H, J = 3,2 Hz), 3,87 (s, 2H), 1,37 (d, 3H, J = 7,2 Hz); HPLC-MS t_R = 1,89 min. (UV_{254nm}); masa calculada para la fórmula $C_{27}H_{28}N_2O_4$ 444,2, LCMS observada m/z 445,1 (M+H).

Ejemplo 21B:



Parte A:

Se agregaron CH_2Cl_2 (300 ml) y anhídrido trifluoroacético (100 g, 0,476 mol) a un matraz de 3 bocas de 2 litros. El matraz estaba equipado con un tubo de secado y se enfrió en un baño de agua helada. Se agregó una solución de (R)-α-metilbencilamina (**840**) (53,72 g, 0,443 mol) disuelta en 100 ml de CH_2Cl_2 durante 40 min. El baño de hielo se eliminó y la mezcla de reacción se agitó a ta durante 3 h. La mezcla de reacción se enfrió con un baño de agua helada y se agregó ácido metansulfónico (110 ml, 1,69 mol). Se agregó dibromodimetilhidantoina (65 g, 0,227 mol) en porciones durante 1 hr 15 min. La mezcla de reacción se dejó en agitación hasta el día siguiente luego se vertió en una solución preparada a partir de 60 ml de $NaHSO_3$ 1 M y 500 ml de hielo y agua. Las capas se separaron y la capa acuosa se extrajo con 100 ml de CH_2Cl_2. La capa orgánica combinada se lavó con agua y salmuera, luego se secó con $MgSO_4$. El solvente se evaporó para dar un sólido blanco. Este material se recristalizó a partir de Et_2O/hexanos para dar el compuesto **841**, MS (EI) m/z M+H Obs 297,16.

Parte B:

Se disolvió el compuesto **841** (8,09 g, 27,3 mmol) en 40 ml de dioxano, 10 ml de metanol, y 40 ml de LiOH acuoso 1 M. La mezcla de reacción se agitó a ta durante 2,5 h bajo N_2. Se agregaron anhídrido Boc (7,45 g, 34,1 mmol) y EtOAc (25 ml) y la mezcla de reacción se agitó a ta bajo N_2 durante 1,5 h. La mezcla de reacción se diluyó con EtOAc y salmuera. Las capas se separaron y la capa acuosa se extrajo con EtOAc. La capa orgánica combinada se lavó con ácido cítrico, agua, y salmuera, luego se secó con $MgSO_4$. Los solventes se evaporaron y el producto bruto se purificó mediante sgc flash usando un gradiente de 5%-10% de EtOAc/hexanos como la fase móvil. Se obtuvo sólido blanco **842** (7,95 g) como producto. MS (EI) m/z M+Na Obs 324,01.

Parte C:

Se suspendieron el compuesto **842** (1,11 g, 3,69) y ácido 4-piridin borónico (0,55 g, 4,48 mmol) en 1-propanol (8 ml) y se agitó durante 25 min a 40 °C. Se agregaron acetato de paladio (II) (55 mg, 0,24 mmol) y agua (4 ml), seguidos por carbonato de sodio (0,47 g, 4,43 mmol) y trifenil fosfina (197 mg 0,75 mmol). La mezcla de reacción se agitó bajo N_2 a 80 °C durante 21 h. La mezcla de reacción se dejó enfriar hasta ta y se diluyó con EtOAc y $NaHCO_3$ 0,5 M. Las capas se separaron y la capa acuosa se extrajo con EtOAc. La capa orgánica combinada se lavó con salmuera, se secó con $MgSO_4$, se filtró y se concentró para dar un sólido anaranjado. El producto bruto se purificó mediante sgc usando 30% de EtOAc/hexanos, seguido por 30% de EtOAc/hexanos con 2% de agregado de diisopropiletilamina, seguido por 40% de EtOAc/hexanos como la fase móvil. Sólido blanco **843** se obtuvo como producto (0,71 g). MS (EI) m/z M+H Obs 299,10.

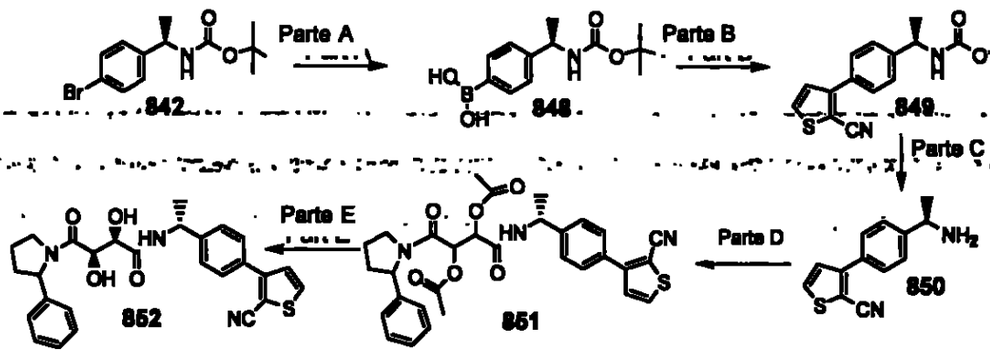
Parte D:

Se suspendió el compuesto **843** (0,70, 2,3 mmol) en 22 ml de HCl 4 M en dioxano y 8 ml de CH_2Cl_2. La mezcla de reacción se agitó bajo N_2 a ta durante 6 h, luego se concentró para dar sólido blanco **844** (0,70 g). MS (EI) m/z M+H Obs 199,09.

Partes E & F:

Se preparó el Compuesto **846** usando procedimientos similares a aquellos descriptos en el Ejemplo 14, Pasos E&F. MS (EI) m/z M+H Obs 460,1.

Ejemplo 21C:



Parte A:

Un matraz Schlenck de 500 ml equipado con una barra agitadora se secó con flama bajo flujo de N_2, cubierta con un septum, y se permitió que se enfríe hasta ta. Se agregó una solución de n-butil litio en hexanos (55 ml, 2,5 Molar, 137,4 mmol) mediante jeringa. El matraz se enfrió en un baño de hielo seco /2-propanol. Se agregó tetrametiletilen diamina (TMEDA-19,0 g, 167 mmol). Se disolvió el compuesto **842** (20 g, 66,8 mmol) en THF anhídrido (200 ml) y se agregó a la mezcla de reacción durante 30 min. mediante un embudo de adición. La mezcla de reacción se agitó a -78 C durante 15 min. Se agregó trietil borato (21,4 ml, 176 mmol) como una solución en 40 ml de THF anhídrido. La mezcla de reacción se agitó durante 30 min. La mezcla de reacción se desactivó a -78 °C con HCl 1,0 M ac. Para un pH de 2, luego se dejó calentar hasta ta. La mezcla de reacción se extrajo con EtOAc. La capa orgánica se secó con $MgSO_4$ y se concentró hasta que se secó. El producto bruto se purificó mediante sgc usando 5:95 MeOH:CH_2Cl_2 como la fase móvil. Se obtuvo sólido blanco **848** como producto (3,8 gramos). Datos para **848**: ^{1}H RMN (400 MHz, CD_3OD) δ 7,56 (d, J = 8Hz, 2H), 7,29 (d, J = 8Hz, 2H), 4,58-4,64 (m, 1H), 1,41-1,36 (m, 12H).

Parte B:

Se agregaron compuesto **848** (300 mg, 1,13 mmol), 3-bromo-2-cianotiofeno (192 mg, 1,02 mmol), acetonitrilo (4 ml), dicloruro de dicloro[1, 1'-bis(difenilfosfino) ferroceno] paladio(II) (Strem, 171 mg, 0,23 mmol), y 1,25 ml de K_2CO_3 1 M ac. a

un tubo de microondas equipado con una barra de agitación. N_2 se burbujeó a través de la solución y se recubrió el tubo. La mezcla de reacción se irradió a 150 °C durante 5 min. en un horno microondas Personal-Chemistry "Companion". El material resultante se filtró a través de Celite que se lavó con EtOAc. El filtrado se dividió entre EtOAc y agua. La capa orgánica se lavó con agua y se trató con Na_2SO_4 y carbono activado Darco. La mezcla se filtró y se concentró hasta que se secó. El producto bruto se purificó mediante sgc usando 60:40 hexanos: EtOAc como la fase móvil. Se obtuvo Compuesto **849** como un aceite amarillo (224 mg) que se cristalizó en reposo. m/z Obs. M+Na 350,93.

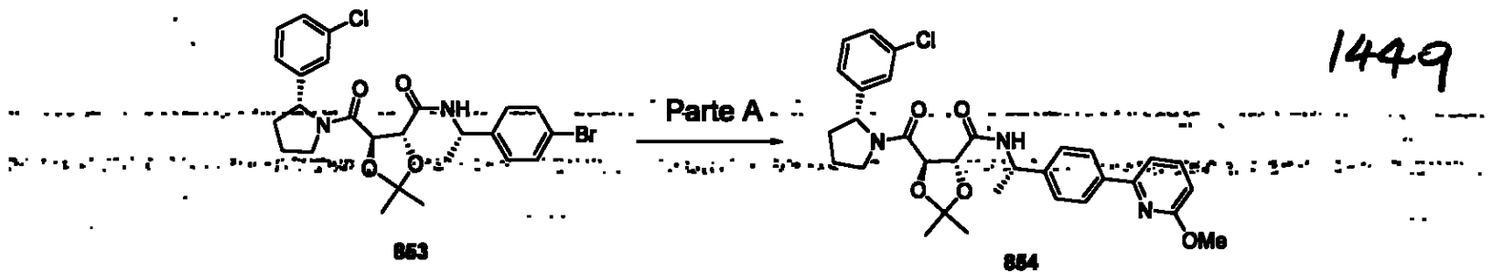
Parte C:

Se disolvió compuesto **849** (224 mg, 0,682 mmol) en 2,8 ml de CH_2Cl_2 y 1,2 ml de ácido trifluoroacético. La mezcla de reacción se agitó a ta durante 2 horas, luego se concentró hasta que se secó. El producto bruto se purificó mediante sgc usando CH_2Cl_2 :MeOH (NH_3) 9:1 como fase móvil para dar 110 mg de **850** como un aceite. m/z Obs. M+H 229,10

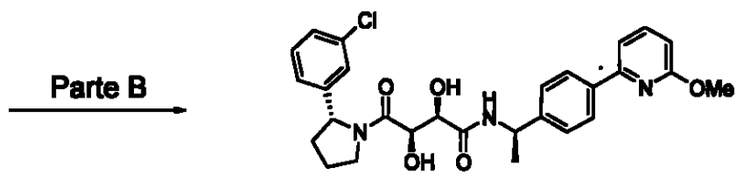
Partes D y E:

Se prepararon los compuestos **851** y **852** mediante procedimientos similares a aquellos descriptos en el Ejemplo 14, Partes D y E. Datos para **851**: m/z Obs. M+H 574,05, Datos para **852**: m/z Obs. M+Na 511,91.

Ejemplo 21D:



853 854



855

El compuesto **853** se sintetizó usando los procedimientos descriptos en el Ejemplo 1.

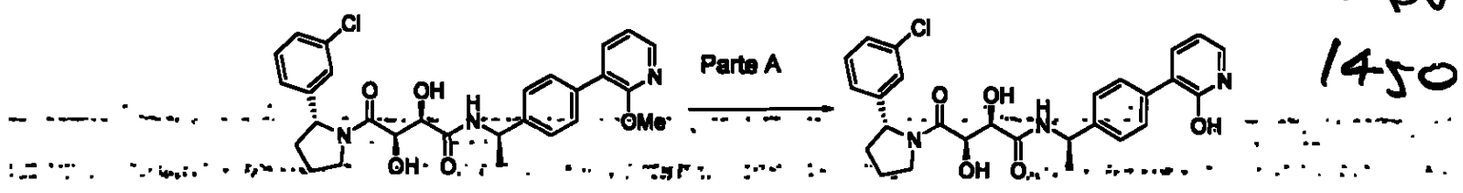
Parte A:

Se disolvió Compuesto **853** (25 mg, 0,050 mmol) en THF (1 ml) y $PdP(t\text{-}Bu_3)_2$ (5 mg, 0,0097 mmol) se agregó bajo una atmósfera de argón. Se agregó bromuro de 6-Metoxi-2-piridilcinc (0,5 M en THF, 0,2 ml) y la reacción se agitó a 50 °C hasta el día siguiente. La mezcla de reacción se filtró sobre un lecho de Celite y luego se evaporó bajo presión reducida. La purificación mediante LC prep. de fase reversa dio un sólido blancuzco **854** (10 mg, 38%) después de la liofilización. HPLC-MS t_R = 6,138 min. ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{31}H_{34}ClN_3O_5$ 563,2, LCMS observada m/z 564,1 (M+H).

Parte B:

Se disolvió el compuesto **854** (10 mg, 0,0188 mmol) en MeOH (0,3 ml) y TFA (4 ml) y se agitó durante 2 horas a temperatura ambiente. El solvente se eliminó para dar el producto bruto **855** (9,36 mg, 95%). HPLC-MS t_R = 5,098 min. ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{28}H_{30}ClN_3O_5$ 523,1, LCMS observada m/z 524,1 (M+H).

Ejemplo 21E:



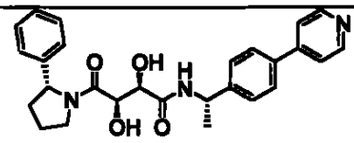
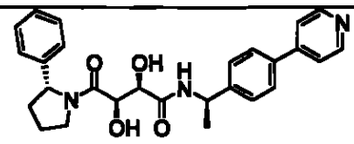
856 857

Se sintetizó el compuesto **856** usando los procedimientos Suzuki descriptos en el Ejemplo 12.

Parte A:

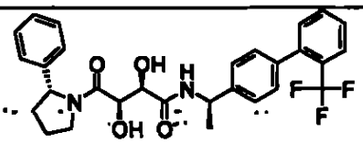
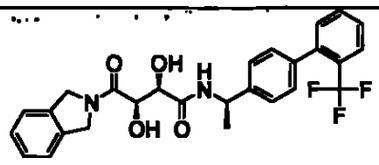
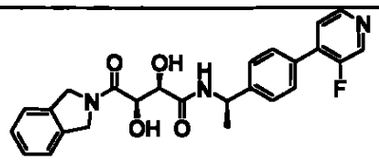
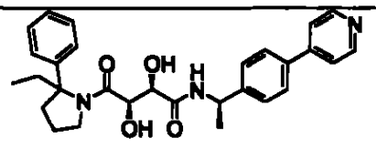
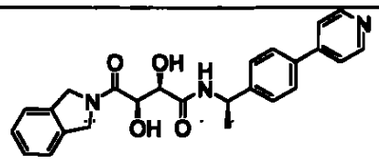
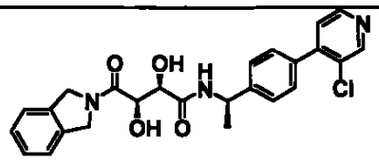
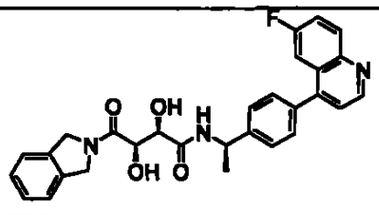
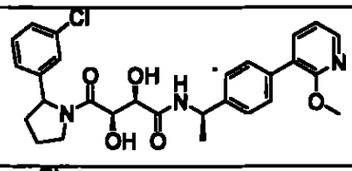
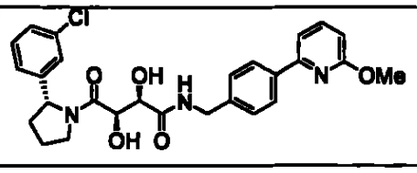
Se disolvió el compuesto **856** (160 mg, 0,30 mmol) en acetonitrilo (5 ml) y se agregó yoduro de sodio (140 mg, 1,0 mmol) seguido por trimetilsililcloruro (105 mg, 1,0 mmol). Se agregó agua (0,1 ml) y la mezcla de reacción se agitó a reflujo durante 4 horas. La reacción se desactivó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron. La purificación mediante LC prep. de fase reversa dio un sólido blancuzco **857** (86 mg, 56%) después de la liofilización. HPLC-MS t_R = 3,72 min. ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{27}H_{28}ClN_3O_5$ 509,1, LCMS observada m/z 510,1 (M+H).

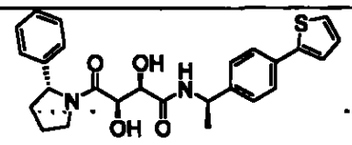
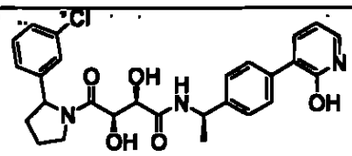
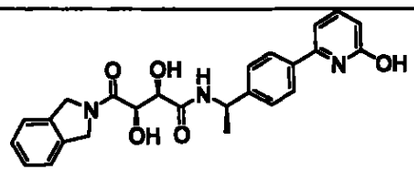
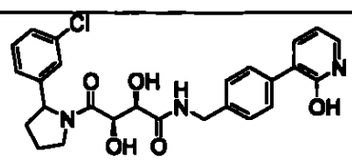
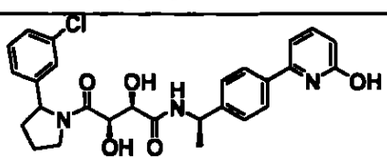
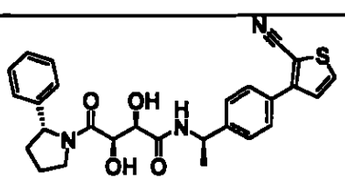
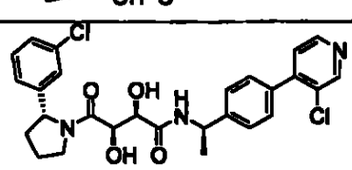
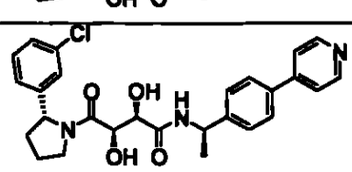
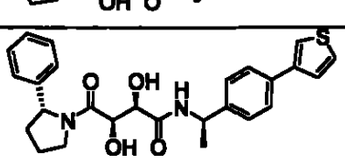
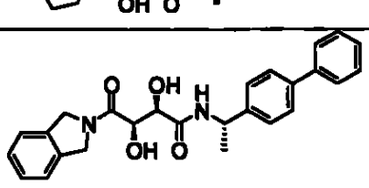
La siguiente tabla contiene compuestos preparados usando los procedimientos descriptos en el Ejemplo 21 A–E.

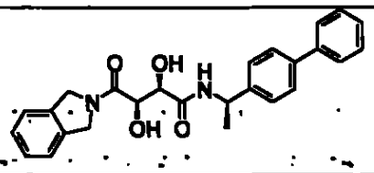
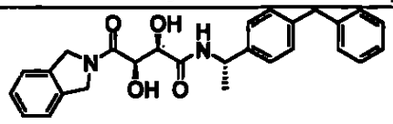
Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
858		459,2	460,1
859		459,2	460,1

459

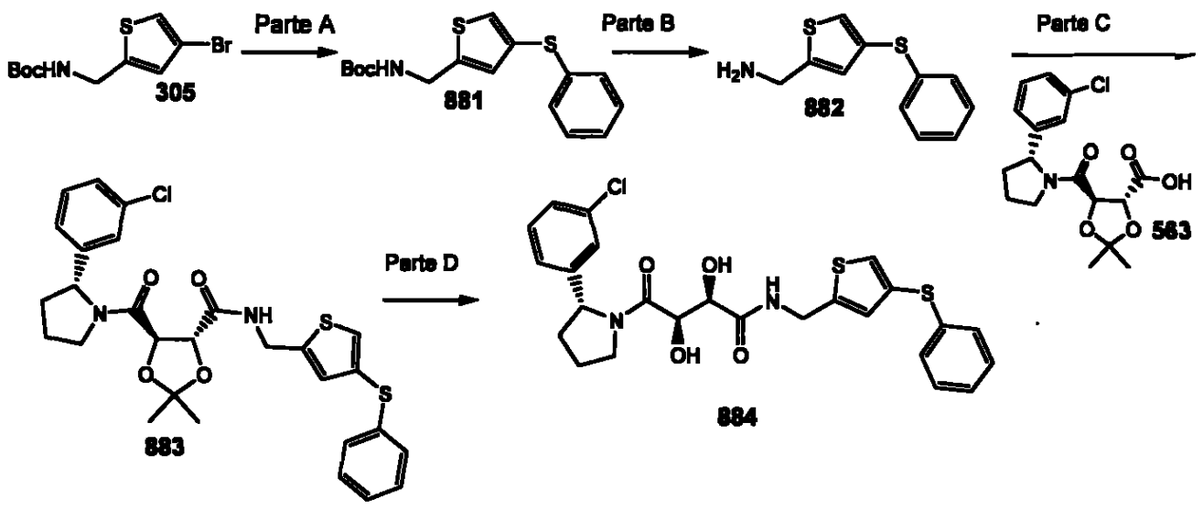
14 JI

860		526,2	527,7
861		498,2	499,0
862		449,2	450,0
863		487,3	488,1
864		431,2	432,1
865		465,2	466,1
866		499,2	500,0
867		523,2	524,2
868		509,2	510,1

869		464,2	464,9
870		509,2	510,2
871		447,2	448,2
872		495,2	496,2
873		509,2	510,2
874		489,2	511,9 (M+Na)
875		527,1	528,1
876		493,1	494,1
877		464,2	464,9
878		430,2	431,2

879		430,2	431,2
880		444,2	445,2

Ejemplo 22



Parte A:

A **305** (100 mg, 0,34 mmol) en THF (2 ml) a –90 °C bajo argón se agregó n-butil litio (1,6 M, 0,140 ml, 0,22 mmol) gota a gota. La mezcla de reacción se agitó durante 30 minutos a –90 °C. Luego se agregó lentamente disulfuro difenilo (90 mg, 0,4 mmol) en THF (1 ml). La mezcla de reacción se agitó durante 30 minutos a –90 °C. La mezcla de reacción se desactivó con solución de cloruro de amonio saturado y se calentó hasta temperatura ambiente. La mezcla se diluyó con acetato de etilo (10 ml) y las capas se separaron. La capa orgánica se lavó con agua y salmuera. Se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 5% de EtOAc/hexano) dio **881** (19 mg,

59%). HPLC-MS t_R = 2,28 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{18}H_{19}NO_2S_2$ 321,09, LCMS observada m/z 322,2 (M+H).

Parte B:

A **881** (66 mg, 0,2 mmol) se agregó HCl 4N en dioxano (1 ml). La mezcla de reacción se agitó durante 1 hora. Los solventes se eliminaron en *vacuo* y el producto bruto se usó sin purificación adicional. HPLC-MS t_R = 1,12 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{11}H_{11}NS_2$ 221,0, LCMS observada m/z 222,1 (M+H).

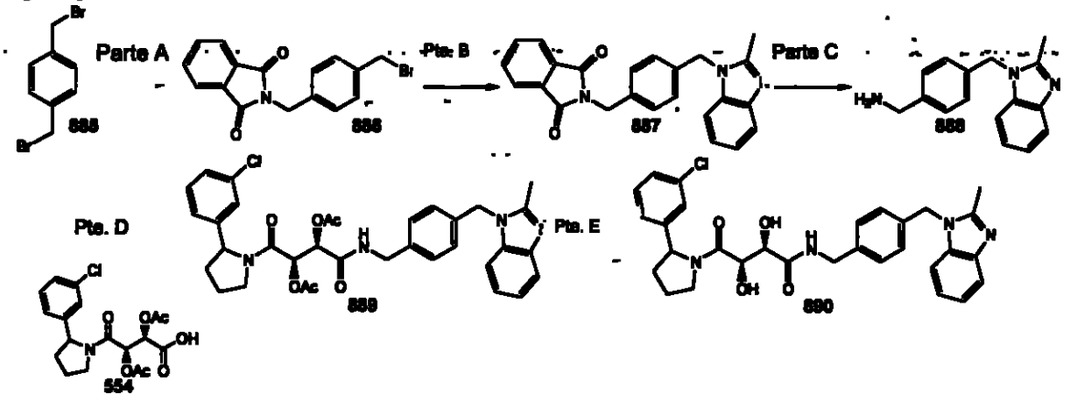
Parte C:

A **563** (56 mg, 0,16 mmol) en DMF (2 ml) se agregó **882** (66 mg, 0,26 mmol), DIEA (82 µl, 0,46 mmol) y HATU (78 mg, 0,24 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo (20 ml) y agua (20 ml). Las capas se separaron y la capa acuosa se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución de bicarbonato de sodio y salmuera, se secaron sobre sulfato de sodio y se concentraron. Se usó el compuesto **883** (43 mg, 48%) sin purificación adicional. HPLC-MS t_R = 2,40 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{28}H_{29}ClN_2O_4S_2$ 556,1, LCMS observada m/z 557,0 (M+H).

Parte D:

Se disolvió el Compuesto **883** (25 mg, 0,04 mmol) en TFA:agua 80:20 (1 ml) y se agitó durante 1,5 horas. La reacción se desactivó con 1:1 agua:acetonitrilo (1 ml) y los solventes se eliminaron en *vacuo*. La purificación mediante LC prep. de fase reversa dio **884** como un sólido blanco (5 mg, 22%). HPLC-MS t_R = 2,04 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{25}H_{25}ClN_2O_4S_2$ 516,1, LCMS observada m/z 517,1 (M+H).

Ejemplo 23:



Parte A:

Se agitó una mezcla de 1,1'-dibromo-p-xileno (**885**) (528 mg, 2,0 mmol), ftalamida (294 mg, 2,0 mmol) y carbonato de cesio (717 mg, 2,2 mmol) en DMF (5 ml) durante 4 horas. La mezcla de reacción se filtró y el filtrado se concentró. El residuo se disolvió en DCM y se lavó con solución de bicarbonato y salmuera. La capa orgánica se secó sobre sulfato de sodio y se concentró. La recristalización a partir de 75% de EtOAc/hexanos eliminó el producto dialquilado. La mezcla madre se concentró y el producto monoalquilado **886** se aisló mediante cromatografía en columna (SiO_2, 50% DCM/Hex) como un sólido blanco (110 mg, 16%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,84 (d, 2H, J = 2,4 Hz), 7,72 (d, 2H, J = 2,4 Hz), 7,41 (d, 2H, J = 7,2 Hz), 7,34 (d, 2H, J = 7,2 Hz), 4,84 (s, 2H), 4,46 (s, 2H).

Parte B:

Se agitó una mezcla de **886** (110 mg, 0,33 mmol), 2-metil benzoimidazol (44 mg, 0,33 mmol) y carbonato de cesio (114 mg, 0,35 mmol) en DMF (5 ml) hasta el día siguiente a temperatura ambiente. La mezcla de reacción se filtró y se concentró. El residuo se dividió entre solución de bicarbonato y acetato de etilo. Las capas se separaron y la capa acuosa se extrajo con acetato de etilo. La capa orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio y se

concentró para dar **887** como un sólido blancuzco (120 mg, 95%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,82 (m, 2H), 7,70 (m, 2H), 7,37 (d, 2H, J = 8,0 Hz), 7,25 – 7,18 (m, 4H), 7,00 (d, 2H, J = 8,7 Hz), 5,30 (s, 2H), 4,82 (s, 2H), 2,57 (s, 3H).

Parte C:

Se calentó una mezcla de **887** (120 mg, 0,31 mmol) e hidrato de hidracina (61 µl, 1,26 mmol) en etanol (10 ml) hasta reflujo durante 3 horas. La mezcla de reacción se concentró. El residuo se disolvió en acetato de etilo y se lavó con solución de bicarbonato. La capa acuosa se extrajo con acetato de etilo. La capa orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio y se concentró para dar **888** como un aceite amarillo (31 mg, 40%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,72 (dd, 1H, J = 1,2, 8,4 Hz), 7,51 (dd, 1H, J = 3,2, 6,4 Hz), 7,26 – 7,17 (m, 4H), 7,01 (d, 2H, J = 8 Hz), 5,30 (s, 2H), 3,85 (s, 2H), 2,60 (s, 2H), 2,57 (s, 3H).

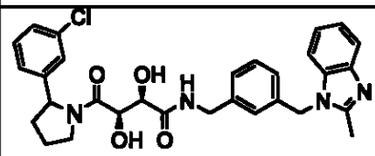
Parte D:

Una mezcla de **888** (31 mg, 0,12 mmol), **554** (40 mg, 0,1 mmol), DIEA (38 µl, 0,22 mmol) y HATU (46 mg, 0,12 mmol) en DMF (2 ml) se agitó hasta el día siguiente. El DMF se eliminó en *vacuo*. El residuo se disolvió en acetato de etilo, se lavó con solución de bicarbonato y salmuera, se secó sobre sulfato de sodio y se concentró para dar **889** as a film (61 mg, 96%). HPLC-MS t_R = 1,38 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{34}H_{35}ClN_4O_6$ 630,2, LCMS observada m/z 631,2 (M+H).

Parte E:

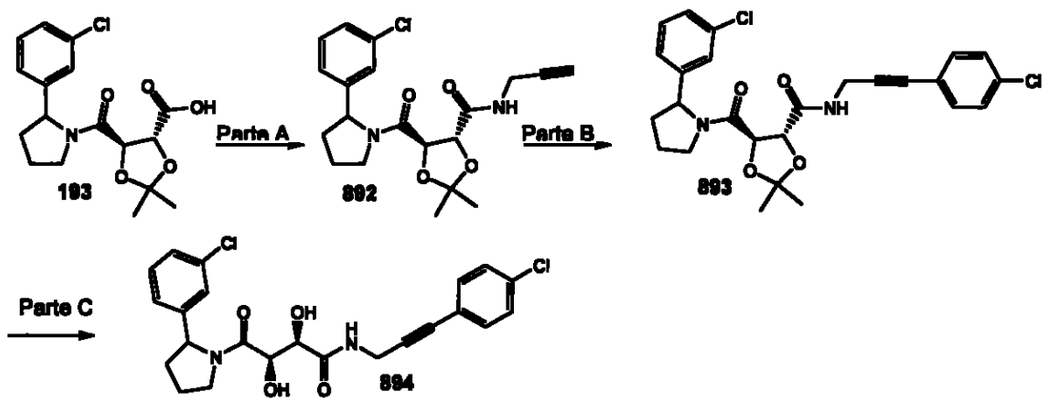
A **889** (61 mg, 0,097 mmol) en metanol (2 ml) se agregó hidracina anhídrida (5 µl, 0,16 mmol). La mezcla de reacción se agitó hasta el día siguiente, se concentró, se purificó mediante LC prep. de fase reversa y se trató con HCl para dar **890** como una sal de HCl (19 mg, 33%). HPLC-MS t_R = 3,42 min. (UV_{254}

$_{nm}$, 10 min); masa calculada para la fórmula $C_{30}H_{31}ClN_4O_4$ 546,2, LCMS observada m/z 547,2 (M+H). 1457

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
891		546,2	547,2

Ejemplo 24: Enlaces de alquino

Ejemplo 24A:



Parte A:

A **193** (200 mg, 0,57 mmol) en DCM (5 ml) se agregó propargil amina (62 mg, 1,13 mmol), DIEA (396 µl, 1,71 mmol), DMAP (7 mg, 0,06 mmol) y EDC (140 mg, 0,74 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 60% de acetato de etilo/hexanos) dio **892** como un aceite (136 mg, 62%). HPLC-MS t_R = 1,76 y 1,83 min. ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{20}H_{23}ClN_2O_4$ 390,1, LCMS observada m/z 391,1 (M+H).

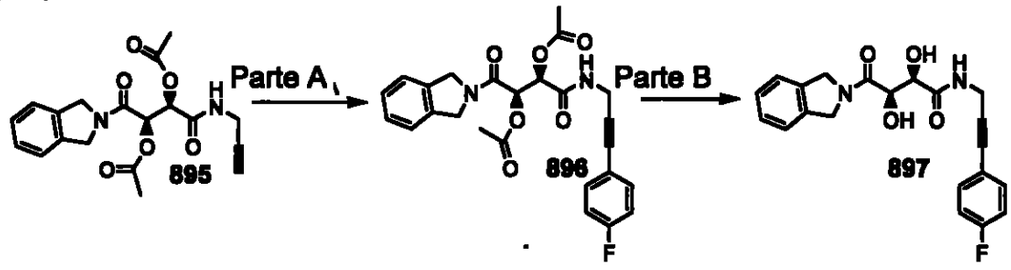
Parte B:

A **892** (20 mg, 0,05 mmol) en DMF (1 ml) se agregó 4-cloro-yodobenceno (24 mg, 0,10 mmol), yoduro de cobre (I) (1 mg, 0,005 mmol), $PdCl_2(Ph_3P)_2$ (1,8 mg, 0,003 mmol) y trietilamina (1 ml). La mezcla de reacción se agitó hasta el día siguiente a 50 °C bajo atmósfera de argón. La mezcla de reacción se diluyó con acetato de etilo, se lavó con HCl 0,1 N, se secó sobre sulfato de sodio y se concentró. El material se usó sin purificación adicional. **893**: HPLC-MS t_R = 2,28 y 2,32 min. ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{26}H_{26}Cl_2N_2O_4$ 500,1, LCMS observada m/z 501,1 (M+H).

Parte C:

Se disolvió Compuesto **893** en 4:1 TFA:agua (2 ml) y se agitó a temperatura ambiente durante 1,5 horas. La reacción se desactivó con 1:1 agua:acetonitrilo (2 ml) y se concentró. La purificación mediante LC prep. de fase reversa dio **894** como un sólido (2 mg). HPLC-MS t_R = 5,02 min. ($UV_{254\ nm}$, 10 min); Masa calculada para la fórmula $C_{23}H_{22}Cl_2N_2O_4$ 460,1, LCMS observada m/z 461,2 (M+H).

Ejemplo 24 B:



Se obtuvo el compuesto **895** mediante procedimientos descriptos en el Ejemplo 2A Parte A usando isoindolina para abrir el anhídrido (+)-diacetil-L-tartárico y propargil amina en el procedimiento de acoplamiento.

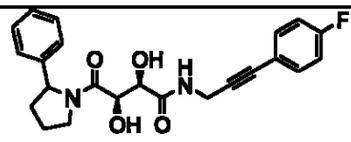
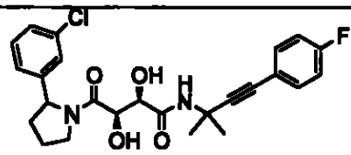
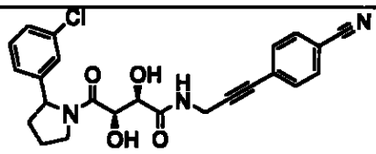
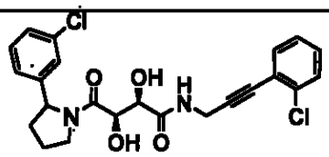
Parte A:

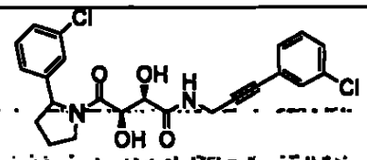
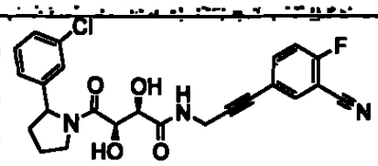
Se disolvieron Compuesto **895** (138 mg, 0,371 mmol), p-bromofluorobenceno (244 mg, 1,39 mmol), y diclorobis(trifenilfosfina) paladio (II)

(26 mg, 0,037 mmol) en 1,5 ml de CH_3CN y 1,5 ml de Et_3N. La mezcla de reacción se calentó en un tubo sellado bajo N_2 a 80 °C durante 2 h. La mezcla de reacción se dejó enfriar hasta ta. Se agregaron EtOAc y buffer de fosfato de sodio 1,0 M de pH 7,0. Las capas se separaron. La capa orgánica se lavó con agua y se secó con $MgSO_4$. El solvente se evaporó y el producto bruto se purificó mediante sgc usando 3:1 EtOAc:hexanos como la fase móvil para dar 20 mg del compuesto **896**, MS (El) m/z Obs M+H 467,19.

Parte B:

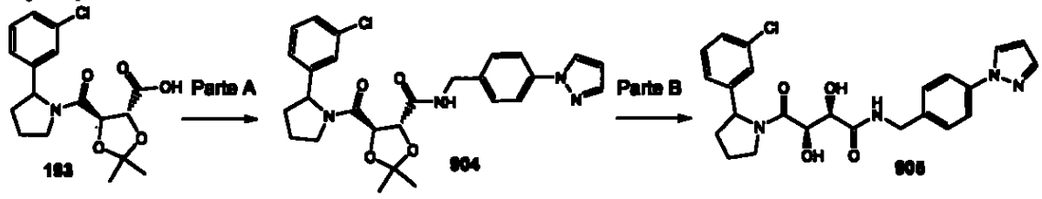
Se disolvió Compuesto **896** (20 mg, 0,043 mmol) en 3 ml de amoníaco metanólico 2 M. La mezcla de reacción se agitó a ta durante 1 h. La mezcla de reacción se concentró hasta que se secó. El producto bruto se purificó mediante TLC prep. sobre placas de sílice usando CH_2Cl_2 :MeOH 97:3 como la fase móvil para dar 12 mg de **897**, MS (El) m/z Obs M+H 383,2.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
898		410,2	411,1
899		472,2	473,2
900		451,1	452,1
901		460,1	461,2

902		460,1	461,2
903		469,1	470,2

Ejemplo 25: Biarilos unidos por N

Ejemplo 25A:



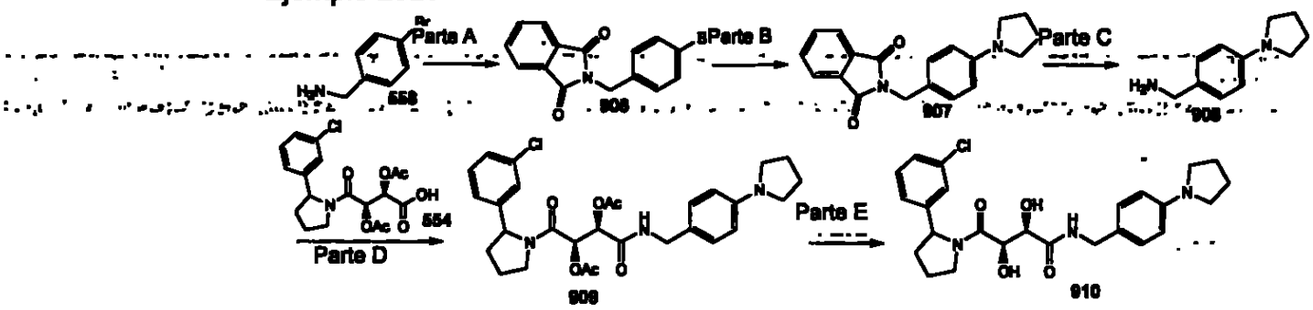
Parte A:

A **193** (42 mg, 0,12 mmol) en DMF (2 ml) se agregó 4-pirazol-1-il-bencilamina (25 mg, 0,14 mmol), DIEA (50 µl, 0,29 mmol) y HATU (53 mg, 0,13 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se vertió en agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con NaOH 0,1 N y salmuera, se secaron sobre sulfato de sodio y se concentraron. El material bruto se usó sin purificación adicional. **904**: HPLC-MS t_R = 1,97 y 2,03 min. ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{27}H_{29}ClN_4O_4$ 508,2, LCMS observada m/z 509,2 (M+H).

Parte B:

Se disolvió Compuesto **904** en TFA:agua 4:1 (2 ml) y se agitó a temperatura ambiente durante 2 horas. La reacción se desactivó mediante el agregado de 1:1 acetonitrilo:agua (4 ml) y los solventes se eliminaron en *vacuo*. La purificación mediante LC prep. de fase reversa dio **905** como un sólido blanco (33 mg). HPLC-MS t_R = 4,16 min. ($UV_{254\ nm}$, 10 min); Masa calculada para la fórmula $C_{24}H_{25}ClN_4O_4$ 468,2, LCMS observada m/z 469,2 (M+H).

Ejemplo 25B:



Parte A:

Se agitó una mezcla de clorhidrato de 4-bromobencil amina (**558**) (2,0 g, 9,0 mmol), monometil ftalato (1,94 g, 10,8 mmol), EDC (2,07 g, 10,8 mmol), HOBt (1,82 g, 13,5 mmol) y trietilamina (3,8 ml, 27,0 mmol) en DCM (50 ml) hasta el día siguiente. La mezcla de reacción se diluyó con DCM y se lavó con HCl 1,0 N, agua, solución de bicarbonato y salmuera, se secó sobre sulfato de sodio y se concentró. La recristalización de la mezcla del acetato de etilo dio **906** como un sólido (1,72 g, 61%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,83 (m, 2H), 7,70 (m, 2H), 7,42 (d, 2H, J = 8,2 Hz), 7,29 (d, 2H, J = 8,2 Hz), 4,79 (s, 2H). HPLC-MS t_R = 2,05 min. ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{15}H_{10}BrNO_2$ 315,0, LCMS observada m/z 316,0 (M+H).

Parte B:

Se agitaron una mezcla de **906** (100 mg, 0,32 mmol), pirrolidina (34 mg, 0,48 mmol), fosfato de potasio (171 mg, 0,80 mmol), $Pd_2(dba)_3$ (8 mg, 0,008 mmol) y 2-(diciclohexilfosfino)bifenil (11 mg, 0,032 mmol) en dioxano (3 ml) bajo atmósfera de argón a 90 °C hasta el día siguiente. La mezcla de reacción se filtró a través de Celite y se concentró. El residuo amarillo se purificó mediante cromatografía en columna (SiO_2, 5% de EtOAc/DCM) para dar **907** (82 mg, 84%). HPLC-MS t_R = 2,13 min. (UV_{254nm}); Masa calculada para la fórmula $C_{19}H_{18}N_2O_2$ 306,1, LCMS observada m/z 307,2 (M+H).

Parte C:

A **907** (82 mg, 0,268 mmol) en etanol:DCM 1:1 (4 ml) se agregó monohidrato de hidracina (52 µl, 1,07 mmol). La mezcla de reacción se calentó hasta reflujo hasta el día siguiente. El precipitado se eliminó mediante filtración y el filtrado se concentró. El residuo se disolvió en acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró para dar **908** como un sólido blanco (23 mg, 49%). HPLC-MS t_R = 0,86 min. (UV_{254nm}); Masa calculada para la fórmula $C_{11}H_{16}N_2$ 176,1, LCMS observada m/z 177,1 (M+H).

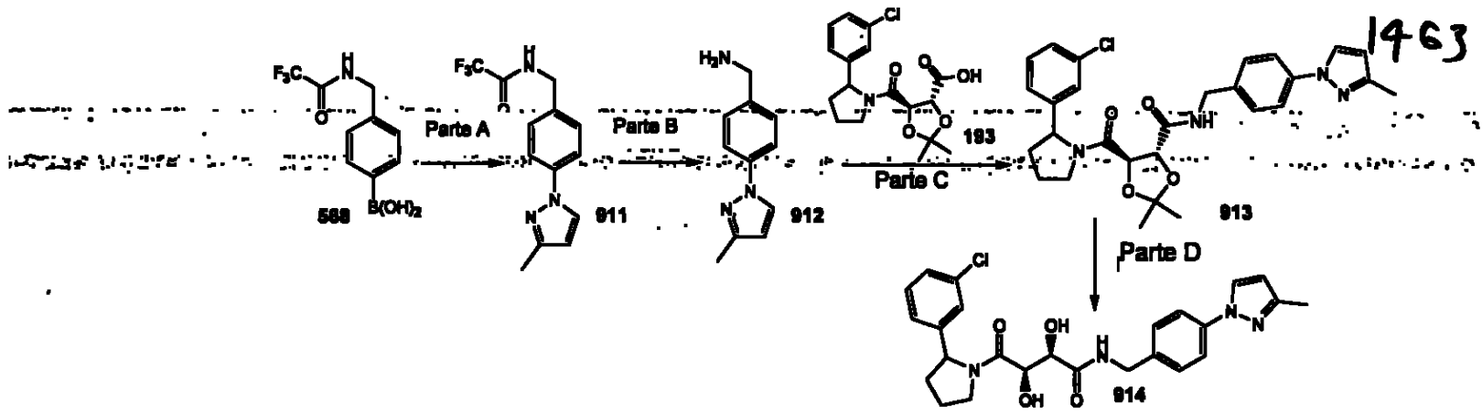
Parte D:

Se agitó una mezcla de **554** (30 mg, 0,076 mmol), **908** (17,3 mg, 0,098 mmol), DIEA (40 µl, 0,226 mmol), DMAP (1 mg) y HATU (37 mg, 0,098 mmol) en DMF (1 ml) hasta el día siguiente. La mezcla de reacción se vertió en agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con NaOH 0,1 N, agua y salmuera, se secaron sobre sulfato de sodio y se concentraron. El compuesto **909** se usó sin purificación adicional.

Parte E:

A **909** en metanol:agua 3:1 (2 ml) se agregó carbonato de potasio (20 mg). La mezcla de reacción se agitó durante 30 minutos. La mezcla de reacción se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante LC prep. de fase reversa dio **910** como un sólido (2 mg). HPLC-MS t_R = 3,57 min. ($UV_{254\ nm}$ 10 min); Masa calculada para la fórmula $C_{25}H_{30}ClN_3O_4$ 471,2, LCMS observada m/z 472,2 (M+H).

Ejemplo 25C:



Se preparó Compuesto **568** de acuerdo con el procedimiento de Maku, S. et. al. (*J. Comb. Chem.* **2003**, *5*, 379)

Parte A:

Se agitó una mezcla del compuesto **568** (740 mg, 3 mmol), 3-metilpirazol (123 mg, 1,5 mmol), acetato de cobre (II) (409 mg, 2,25 mmol), piridina (0,25 ml), 3 mmol) en tetrahidrofurano (10 ml) a temperatura ambiente expuesto a aire durante 60 horas. La mezcla de reacción se diluyó con acetato de etilo, se filtró a través de Celite y se concentró. La purificación mediante cromatografía en columna (SiO_2, 30% de acetato de etilo/hexanos a 50% de acetato de etilo/ hexano) dio el producto como un sólido blanco impuro (450 mg). La purificación adicional mediante cromatografía en columna (SiO_2, diclorometano a 5% de acetato de etilo/diclorometano) dio **911** como un sólido (295 mg, 70% de Pureza). ^{1}H RMN (400 MHz, acetona-d_6) δ 8,97 (bs, 1H, NH), 8,16 (d, 1H, J = 2,4 Hz), 7,76 (d, 2H, J = 8,4 Hz), 7,42 (d, 2H, J = 8,8 Hz), 6,27 (d, 1H, J = 2,4 Hz), 4,55 (d, 2H, J = 5,6 Hz), 2,28 (s, 3H); HPLC-MS t_R = 1,62 min. ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{13}H_{12}F_3N_3O$ 283,1, LCMS observada m/z 284,2 (M+H).

Parte B:

A **911** (165 mg, 0,43 mmol) en metanol: agua 1:1 (2 ml) se agregó 10% de carbonato de potasio en metanol:agua 2:1 (7 ml). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se

concentró y el residuo se disolvió en acetato de etilo. La capa de acetato de etilo se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró para dar **912** como un sólido blanco (69 mg, 86%). HPLC-MS t_R = 0,75 min. ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{11}H_{13}N_3$ 187,1, LCMS observada m/z 188,1 (M+H).

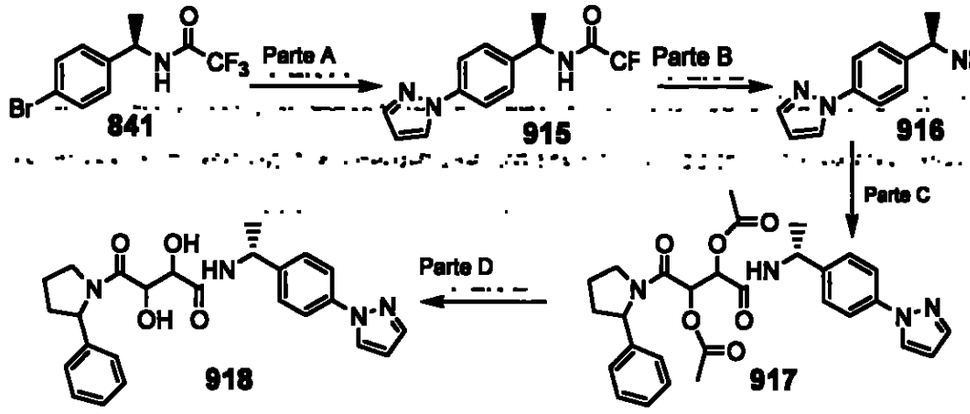
Parte C:

A **193** (65 mg, 0,18 mmol) en DMF (2 ml) se agregó **912** (38 mg, 0,2 mmol), DIEA (70 µl, 0,4 mmol) y HATU (76 mg, 0,21 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se vertió en agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con NaOH 0,1 N y salmuera, se secaron sobre sulfato de sodio y se concentraron. Se usó Compuesto **913** sin purificación adicional. HPLC-MS t_R = 2,05 y 2,09 min. ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{28}H_{31}ClN_4O_4$ 522,2, LCMS observada m/z 523,2 (M+H).

Parte D:

Se disolvió Compuesto **913** en TFA:agua 4:1 (2 ml) y se agitó a temperatura ambiente durante 2 horas. La reacción se desactivó mediante el agregado de 1:1 acetonitrilo:agua (4 ml) y los solventes se eliminaron en *vacuo*. La purificación mediante LC prep. de fase reversa dio **914** como un sólido blanco (35 mg). HPLC-MS t_R = 4,31 min. ($UV_{254\ nm}$, 10 min); Masa calculada para la fórmula $C_{25}H_{27}ClN_4O_4$ 482,1, LCMS observada m/z 483,1 (M+H).

Ejemplo 25D:



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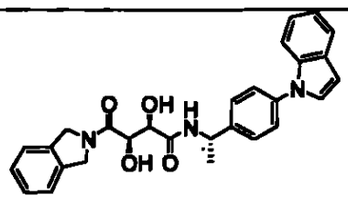
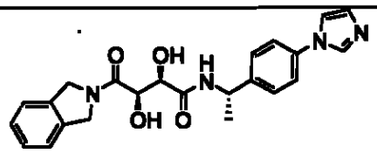
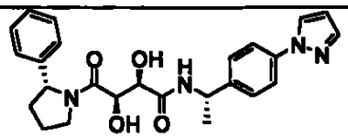
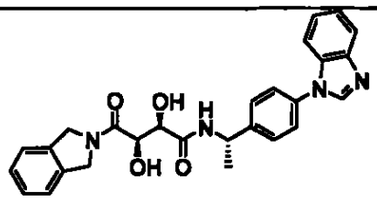
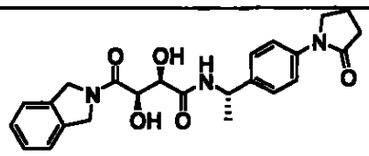
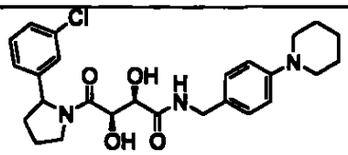
Se disolvieron Compuesto **841** (0,5 g, 1,69 mmol), pirazol (0,14 g, 2,05 mmol), CuI (0,064 g, 0,336 mmol), 1,10-fenantrolina (0,12 g, 0,66 mmol), y Cs_2CO_3 (1,1 g, 3,37 mmol) en dimetilacetamida y se agitó durante 20 h a 140 °C bajo N_2. La mezcla de reacción se dejó enfriar hasta ta y se diluyó con EtOAc. La mezcla resultante se lavó con agua y se concentró hasta que se secó. El material resultante se purificó mediante sgc flash usando CH_2Cl_2:MeOH: NH_4OH conc - (200:10:1) como la fase móvil para dar 0,30 g de **915**, Datos para **915**: ^1H RMN (400 MHz, $CDCl_3$) δ 7,98 (s, 1H), 7,80-7,74 (m, 3H), 7,48 (d, 2H), 6,55 (s, 1H), 5,23 (m, 1H), 1,68 (d, J=4 Hz, 2H). MS (EI) de m/z Obs. M+H 283,97

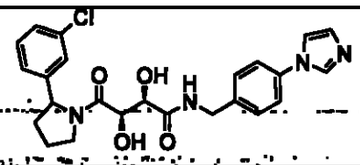
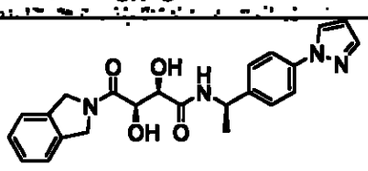
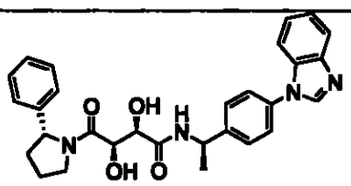
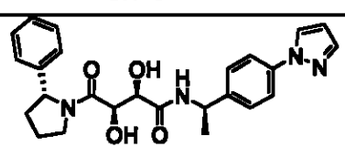
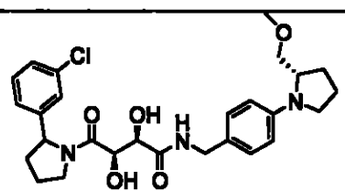
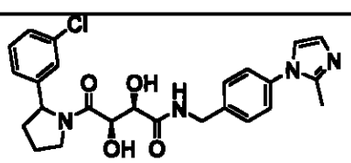
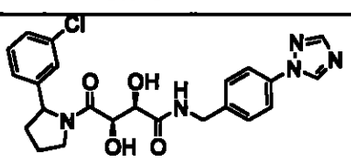
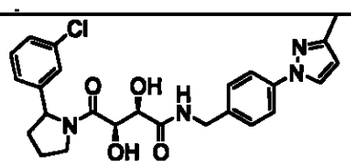
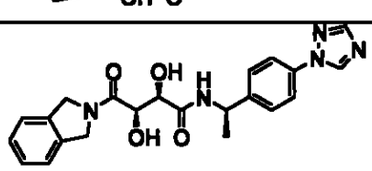
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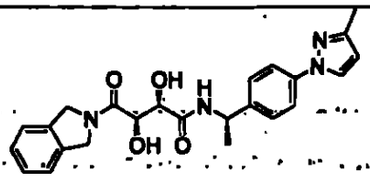
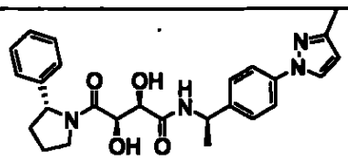
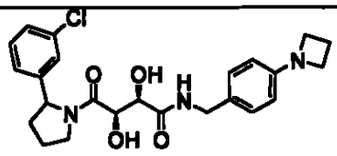
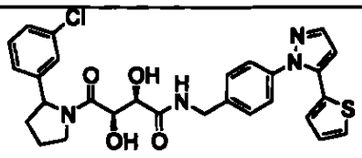
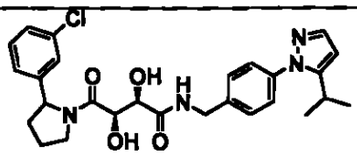
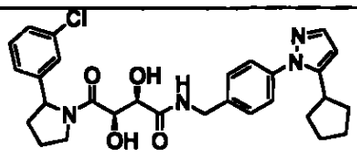
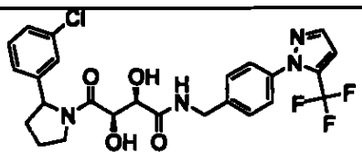
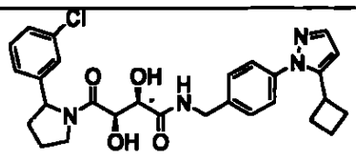
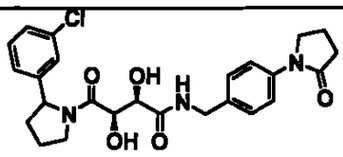
Se disolvió Compuesto **915** (0,20 g, 0,67 mmol) en 10 ml de MeOH. Se agregó LiOH acuoso (10 ml/ 1,0 M). La mezcla de reacción se agitó a ta durante 4 h. La solución se concentró parcialmente en *vacuo* para eliminar el MeOH. El material resultante se extrajo con EtOAc. La capa orgánica se lavó con agua, se secó con Na_2SO_4, se filtró y se concentró para dar 0,14 g de **916**, Datos para **916**: ^1H RMN (400 MHz, $CDCl_3$) δ 7,94 (s, 1H), 7,75 (s, 1H), 7,68 (d, J= 9 Hz, 2H), 7,47 (d, J= 9 Hz, 2H), 4,26-4,13 (m, 1H), 1,44 (d, J= 7 Hz, 3H).

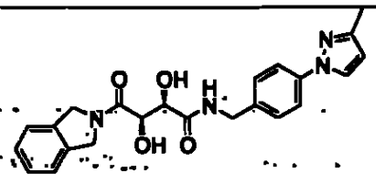
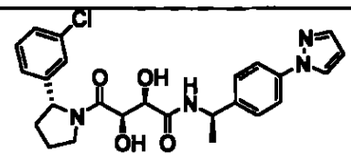
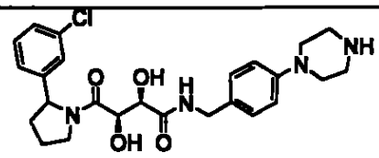
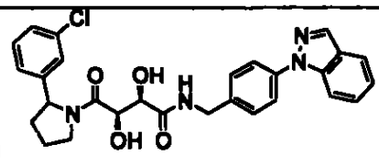
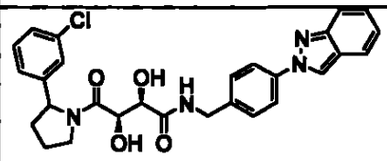
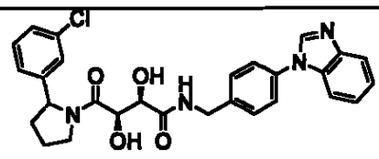
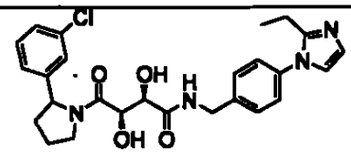
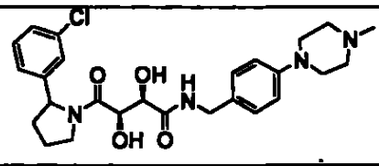
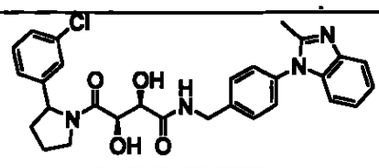
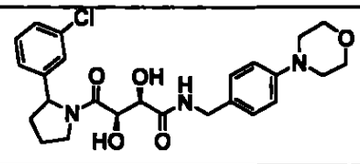
Partes C y D:

Se prepararon Compuestos **917** y **918** mediante procedimientos similares a aquellos descriptos en el Ejemplo 14 - Partes D y E. Datos para **917**: ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,98-7,62 (m, 4H), 7,46-7,13 (m, 8H), 6,68-6,47 (m, 2H), 5,86-5,41 (m, 2H), 5,24-5,10 (m, 2H), 4,05-3,48 (m, 2H), 2,22-1,79 (m, 10H), 1,58-1,55 (m, 2H). Datos para **918**: ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,96 (s, 1H), 7,80 (s, 1H), 7,75-7,59 (m, 2H), 7,48-6,95 (m, 8H), 6,52 (s, 1H), 5,32-5,13 (m, 2H), 4,97-4,05 (m, 2H), 3,99-3,68 (m, 3H), 2,46-1,80 (m, 4H), 1,62-1,51 (m, 3H); MS (EI) m/z Obs. M+H 449,1.

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
919		469,2	470,1
920		420,2	421,1
921		448,2	449,1
922		470,2	471,1
923		437,2	438,2
924		485,2	486,2

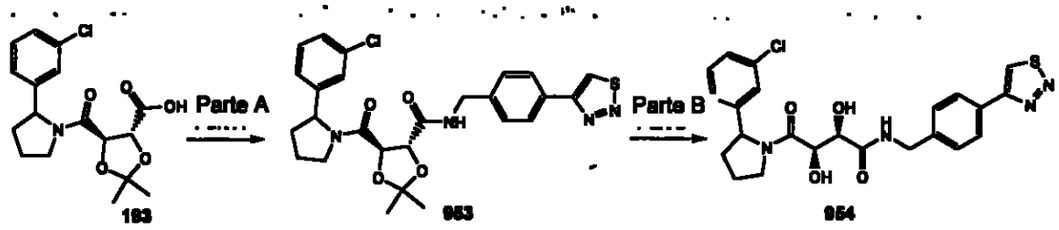
925		468,2	469,1
926		420,2	421,1
927		498,2	499,1
928		448,2	449,1
929		515,2	516,3
930		482,2	483,1
931		469,2	470,0
932		482,2	483,1
933		421,2	422,1

934		434,2	435,1
935		462,2	463,1
936		457,2	458,2
937		550,1	551,0
938		510,2	511,1
939		536,2	537,1
940		536,1	537,1
941		522,2	523,2
942		485,2	486,1

943		**420,2**	**421,1**
944		**482,1**	**483,1**
945		**486,2**	**487,3**
946		**518,2**	**519,2**
947		**518,2**	**519,2**
948		**518,2**	**519,2**
949		**496,2**	**497,2**
950		**500,2**	**501,2**
951		**532,2**	**533,2**
952		**487,2**	**488,2**

Ejempl 26: Compuestos con estructura de aril-heteroaril biarilo

Ejemplo 26A:



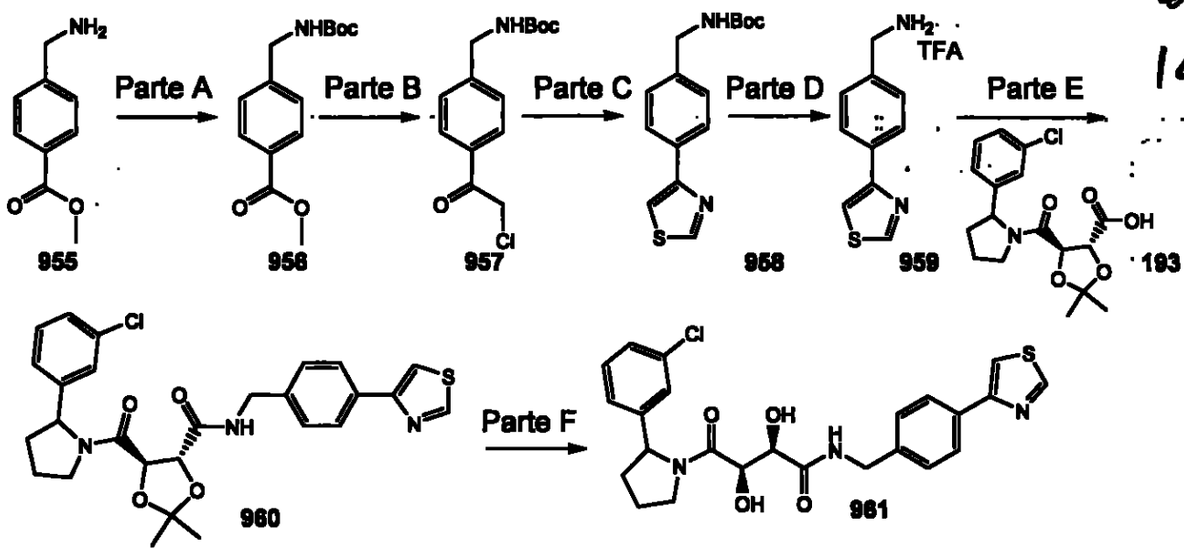
Parte A:

A **193** (42 mg, 0,12 mmol) en DMF (2 ml) se agregó 4-[1,2,3]tiadiazol-4-il-bencilamina (25 mg, 0,13 mmol), DIEA (45 µl, 0,26 mmol) y HATU (50 mg, 0,13 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se vertió en agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con NaOH 0,1 N y salmuera, se secaron sobre sulfato de sodio y se concentraron. El material bruto se usó sin purificación adicional. **953**: Masa calculada para la fórmula $C_{28}H_{27}ClN_4O_4S$ 526,1, LCMS observada m/z 527,1 (M+H).

Parte B:

Se disolvió Compuesto **953** en TFA:agua 4:1 (2 ml) y se agitó a temperatura ambiente durante 2 horas. La reacción se desactivó mediante el agregado de acetonitrilo:agua 1:1 (4 ml) y los solventes se eliminaron en *vacuo*. La purificación mediante LC prep. de fase reversa dio **954** como un sólido blanco (21 mg). HPLC-MS t_R = 4,21 min. ($UV_{254\ nm}$, 10 min); Masa calculada para la fórmula $C_{23}H_{23}ClN_4O_4S$ 486,1, LCMS observada m/z 487,1 (M+H).

Ejemplo 26B: Enlace biarilo de C-C



Parte A:

Al metil éster del ácido 4-aminometil-benzoico (**955**) (2 g, 9,92 mmol) en diclorometano (25 ml) se agregó Boc anhidro (2,27 g, 10,4 mmol) y trietilamina (2,76 ml, 19,84 mmol). La mezcla de reacción se agitó hasta el día siguiente. La mezcla de reacción se diluyó con diclorometano, se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró para dar **956** como un sólido blanco (2,40 g, 91%). HPLC-MS t_R = 1,76 min. (UV_{254nm}); Masa calculada para la fórmula $C_{14}H_{19}NO_4$ 265,1, LCMS observada m/z 288,2 (M+Na).

Parte B:

Se sintetizó Compuesto **957** (257 mg, 80%) siguiendo el procedimiento descripto en el Ejemplo 10B Parte A. HPLC-MS t_R = 1,77 min. (UV_{254nm}); Masa calculada para la fórmula $C_{14}H_{18}ClNO_3$ 283,1, LCMS observada m/z 306,1 (M+Na).

Parte C:

A **957** (49 mg, 0,17 mmol) en DMF (2 ml) se agregó tioformamida (21 mg, 0,35 mmol) y piridina (50 µl). La mezcla de reacción se agitó durante 72 horas. La mezcla se diluyó con acetato de etilo, se lavó con hidróxido de sodio 0,1 N,

agua y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 25% de acetato de etilo/hexanos) dio **958** (25 mg, 50%). HPLC-MS t_R = 1,80 min. (UV_{254nm}); Masa calculada para la fórmula $C_{15}H_{18}N_2O_2S$ 290,1, LCMS observada m/z 291,1 (M+H).

Parte D:

Se agitó Compuesto **958** (25 mg, 0,084 mmol) en diclorometano (2 ml) y TFA (1 ml) a temperatura ambiente durante 1 hora. Los solventes se eliminaron en *vacuo* para dar **959** como un aceite (26 mg). ^1H RMN (400 MHz, CD_3OD) δ 9,07 (d, 1H, J = 2,0 Hz), 8,03 (d, 2H, J = 8,4 Hz), 7,96 (d, 1H, J = 1,6 Hz), 7,52 (d, 2H, J = 8,0 Hz), 4,16 (s, 2H).

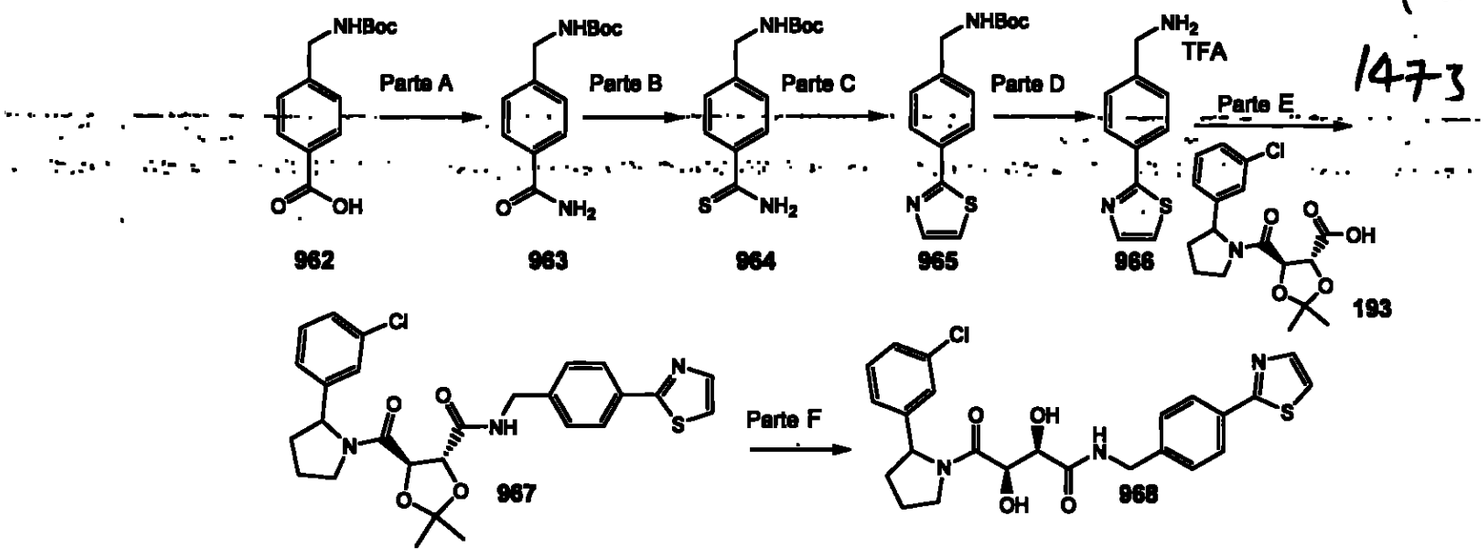
Parte E:

A **193** (23 mg, 0,065 mmol) en DMF (2 ml) se agregó **959** (26 mg, 0,084 mmol), DIEA (34 µl, 0,20 mmol) y HATU (32 mg, 0,084 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se vertió en agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con NaOH 0,1 N y salmuera, se secaron sobre sulfato de sodio y se concentraron. El material bruto se usó sin purificación adicional. **960**: HPLC-MS t_R = 2,00 y 2,05 min. ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{27}H_{28}ClN_3O_4S$ 525,2, LCMS observada m/z 526,1 (M+H).

Parte F:

Se disolvió Compuesto **960** en TFA:agua 4:1 (2 ml) y se agitó a temperatura ambiente durante 2 horas. La reacción se desactivó mediante el agregado de 1:1 acetonitrilo:agua (4 ml) y los solventes se eliminaron en *vacuo*. La purificación mediante LC prep. de fase reversa dio **961** como un sólido blanco (14 mg). HPLC-MS t_R = 4,17 min. ($UV_{254\ nm}$, 10 min); Masa calculada para la fórmula $C_{24}H_{24}ClN_3O_4S$ 485,1, LCMS observada m/z 486,1 (M+H).

Ejemplo 26C: Enlace biarilo de C-C



Parte A:

Al ácido 4-(ter-butoxicarbonilamino-metil)-benzoico (**962**) (500 mg, 1,99 mmol) en tetrahidrofurano (5 ml) en un baño de hielo se agregó DIEA (347 µl, 1,99 mmol). La mezcla de reacción se agitó durante 15 minutos y se agregó cloroformoato de etilo (190 µl, 1,99 mmol). La mezcla de reacción se agitó durante 15 minutos adicionales y se agregó amoníaco en dioxano (0,5 M, 4,18 ml, 2,09 mmol). La mezcla de reacción se calentó hasta temperatura ambiente y se agitó durante 2 horas. El solvente se eliminó en *vacuo* y el residuo se dividió entre acetato de etilo y agua. Las capas se separaron y la capa acuosa se saturó con cloruro de sodio cloruro y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron salmuera, se secaron sobre sulfato de sodio y se concentraron para dar **963** como un sólido blanco (540 mg), que contenía un poco de anhídrido mezclado como una impureza. ^{1}H RMN (400 MHz, CD_3OD) δ7,81 (d, 2H, J = 8,0 Hz), 7,35 (d, 2H, J = 8,4 Hz), 7,21 (bs, 1H, NH), 4,28 (s, 2H), 1,47 (s, 9H).

Parte B:

A **963** (500 mg, 2,0 mmol) en tetrahidrofurano (20 ml) se agregó Reactivo de Lawesson (485 mg, 1,2 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. El solvente se eliminó en *vacuo* y el residuo se disolvió en acetato de etilo. La mezcla se lavó con hidróxido de sodio 0,1 N, agua y salmuera, se secó sobre sulfato de sodio y se concentró par un residuo amarillo. La purificación mediante cromatografía en columna (SiO_2, 40% de acetato de etilo/hexanos) dio **964** como un sólido amarillo pálido (432 mg, 81%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,84 (d, 2H, J = 8,4 Hz), 7,32 (d, 2H, J = 8,4 Hz), 4,36 (d, 2H, J = 5,6 Hz), 1,48 (s, 9H).

Parte C:

A **964** (70 mg, 0,263 mmol) en DMF (2 ml) se agregó cloroacetaldehído (50% en agua, 41 mg, 0,526 mmol). La reacción se agitó hasta el día siguiente a temperatura ambiente. Se agregó un adicional de 2 equivalentes de cloroacetaldehído y la reacción se agitó durante 24 horas. La reacción aún no se había completado, entonces la mezcla se calentó hasta 50 °C durante 2 días. La mezcla se diluyó con acetato de etilo, se lavó con hidróxido de sodio 0,1 N, agua y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 25% de acetato de etilo/hexanos) dio **965** (31 mg). HPLC-MS t_R = 1,84 min. ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{15}H_{18}N_2O_2S$ 290,1, LCMS observada m/z 291,1 (M+H).

Parte D:

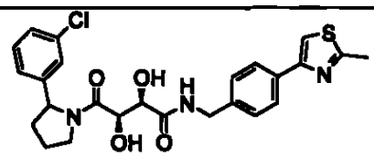
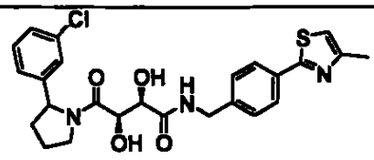
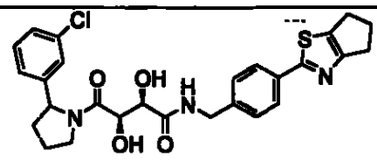
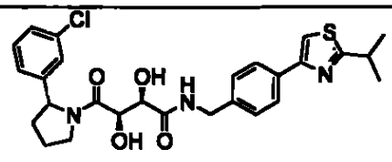
Se agitó Compuesto **965** (31 mg, 0,106 mmol) en diclorometano (2 ml) y TFA (1 ml) a temperatura ambiente durante 1 hora. Los solventes se eliminaron en *vacuo* para dar **966** como un aceite (60 mg). ^{1}H RMN (400 MHz, CD_3OD) δ 8,03 (d, 2H, J = 8,8 Hz), 7,90 (d, 1H, J = 3,2 Hz), 7,65 (d, 1H, J = 3,6 Hz), 7,56 (d, 2H, J = 8,8 Hz), 4,18 (s, 2H).

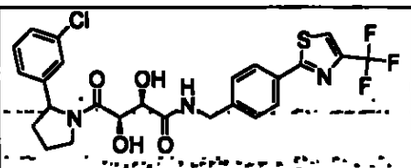
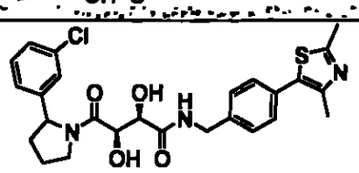
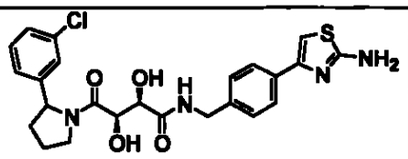
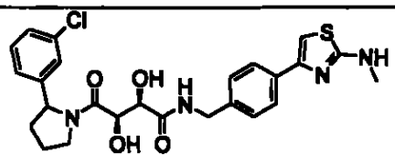
Parte E:

A **193** (29 mg, 0,082 mmol) en DMF (2 ml) se agregó **966** (32 mg, 0,106 mmol), DIEA (43 µl, 0,25 mmol) y HATU (40 mg, 0,106 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se vertió en agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con NaOH 0,1 N y salmuera, se secaron sobre sulfato de sodio y se concentraron. El material bruto se usó sin purificación adicional. **967**: HPLC-MS t_R = 2,03 y 2,08 min. ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{27}H_{28}ClN_3O_4S$ 525,2, LCMS observada m/z 526,1 (M+H).

Parte F:

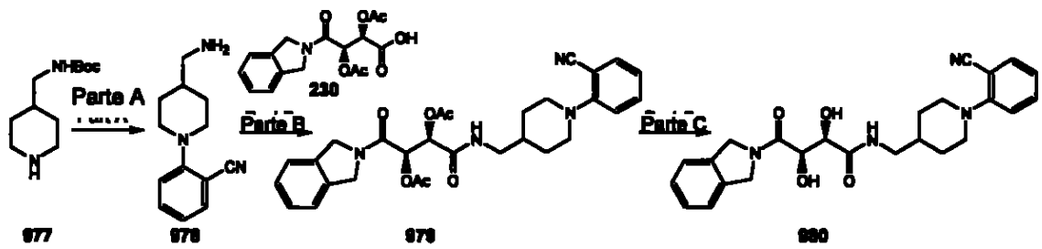
Se disolvió Compuesto **967** en TFA:agua 4:1 (2 ml) y se agitó a temperatura ambiente durante 2 horas. La reacción se desactivó mediante el agregado de acetonitrilo:agua 1:1 (4 ml) y los solventes se eliminaron en *vacuo*. La purificación mediante LC prep. de fase reversa dio **968** como un sólido blanco (15 mg). HPLC-MS t_R = 4,21 min. ($UV_{254\ nm}$, 10 min); Masa calculada para la fórmula $C_{24}H_{24}ClN_3O_4S$ 485,1, LCMS observada m/z 486,1 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
969		499,1	500,1
970		499,1	500,1
971		525,2	526,2
972		527,2	528,1

973		553,1	554,0
974		513,2	514,2
975		500,1	501,1
976		514,1	515,1

Ejemplo 27: Compuestos con grupo piperidin-arilo

Ejemplo 27A: Piperidin-arilo



Parte A:

Paso 1: Se agitó Una mezcla de ter-butil éster del ácido piperidin-4-ilmetil-carbámico (**977**) (2,5 g, 11,66 mmol), 2-fluoro-3-cianobenceno (1,55 g, 12,8 mmol) y DIEA (3 ml, 17,5 mmol) en NMP (5 ml) bajo atmósfera de argón hasta el día siguiente a 120 °C. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 25% de acetato de etilo/hexanos) dio un sólido blanco (3,1 g).

Paso 2: Al material del Paso 1 (2 g) en diclorometano (5 ml) a 0 °C se agregó TFA (5 ml). La mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla se desactivó con acetonitrilo y se concentró. El residuo se disolvió en acetato de etilo, se lavó con solución de carbonato de sodio y salmuera, se secó sobre sulfato de sodio y se concentró para dar **978** como un aceite que se solidificó para un sólido ceroso (920 mg). HPLC-MS t_R = 0,63 min. ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{13}H_{17}N_3$ 215,1, LCMS observada m/z 216,2 (M+H).

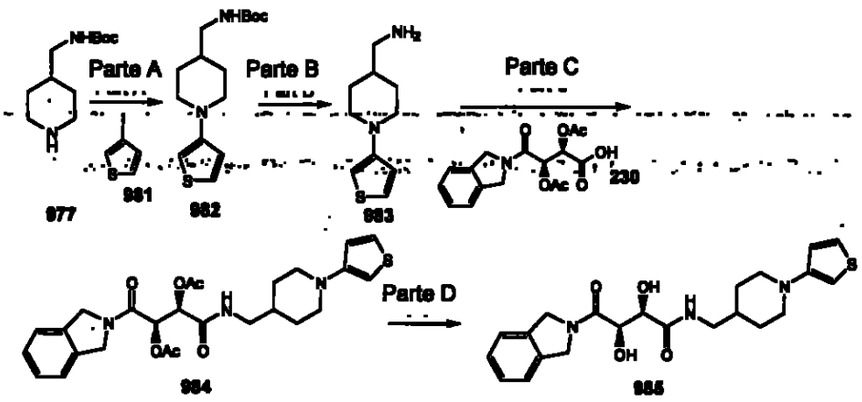
Parte B:

A **978** (120 mg, 0,55 mmol) en DMF (2 ml) se agregó **230** (167 mg, 0,5 mmol), DIEA (0,21 ml, 1,2 mmol) y HATU (211 mg, 0,55 mmol). La mezcla se agitó durante 3 horas a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo, se lavó con bicarbonato de sodio saturado y salmuera, se secó sobre sulfato de sodio y se concentró. El material se usó sin purificación adicional.

Parte C:

A **979** en metanol (4 ml) se agregó amoníaco 7,0 N en metanol (2 ml) agregado. La mezcla se agitó durante 2 horas a temperatura ambiente y se concentró. La purificación mediante LC prep. de fase reversa dio **980** como un polvo blanco (80 mg) en la liofilización. HPLC-MS t_R = 4,03 min. ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{25}H_{28}N_4O_4$ 448,2, LCMS observada m/z 449,2 (M+H).

Ejemplo 27B: Piperidin-arilo



Parte A:

Se agitó una mezcla de **977** (200 mg, 0,93 mmol), 3-yodotiofeno (981) (294 mg, 1,4 mmol), yoduro de cobre(I) (36 mg, 0,19 mmol), prolina (43 mg, 0,37 mmol) y carbonato de potasio (258 mg, 1,87 mmol) en DMSO (1,5 ml) hasta el día siguiente a 80 °C en a 4 ml vial. La mezcla de reacción se diluyó con acetato de etilo y se lavó con agua (3X) y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 25% de acetato de etilo/hexanos) dio **982** (94 mg, 34%).

Parte B:

Se disolvió Compuesto **982** (42 mg, 0,14 mmol) en DCM (2 ml) y TFA (1 ml). La mezcla se agitó durante 1 hora y se concentró para dar **983** en rendimiento cuantitativo. HPLC-MS t_R = 0,35 min. ($UV_{254\ nm}$); Masa calculada para la fórmula $C_{10}H_{16}N_2S$ 196,1, LCMS observada m/z 197,2 (M+H).

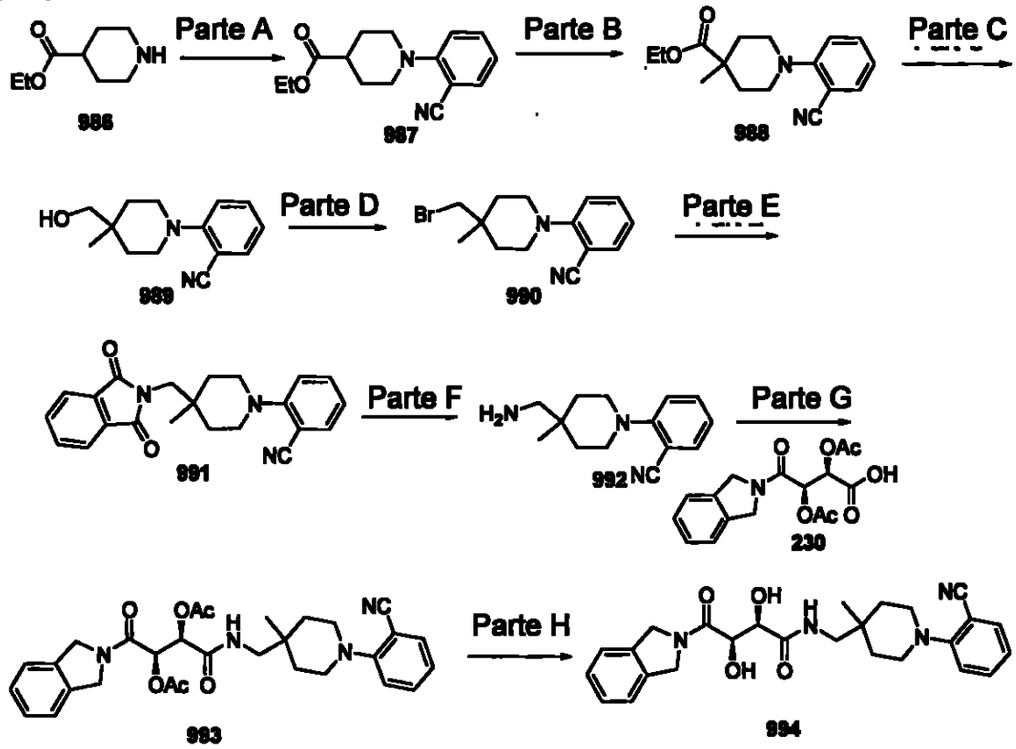
Parte C:

Se preparó Compuesto **984** de acuerdo con el procedimiento descripto en el Ejemplo 27A Parte B. HPLC-MS t_R = 1,36 min. (UV_{254nm}); Masa calculada para la fórmula $C_{26}H_{31}N_3O_6S$ 513,2, LCMS observada m/z 514,2 (M+H).

Parte D:

Se preparó Compuesto **985** de acuerdo con el método descripto en el Ejemplo 25, Parte E. HPLC-MS t_R = 2,85 min. (UV_{254nm}, 10 min); Masa calculada para la fórmula $C_{22}H_{27}N_3O_4S$ 429,2, LCMS observada m/z 430,1 (M+H). 1479

Ejemplo 27C:



Parte A:

Se disolvió Compuesto **986** (1,13 g, 7,23 mmol) en N-metilpirrolidinona (4 ml) y se agregó 2-fluorobenzonitrilo (0,90 g, 7,5 mmol) seguido por DIEA (2,5 ml, 14,4 mmol). La reacción se agitó a 120 °C hasta el día siguiente. La mezcla de reacción enfriada se desactivó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 25% de acetato de etilo/hexanos) dio un sólido blanco **987** (1,5 g, 81%). HPLC-MS t_R = 1,95 (UV_{254nm}); masa calculada para la fórmula $C_{15}H_{18}N_2O_2$ 258,14, LCMS observada m/z 259,1 (M+H).

Parte B:

Se disolvió diisopropilamina (0,330 ml, 2,32 mmol) en THF (20 ml) y se enfrió en un baño de hielo. Una solución de n-Buli (2,5M en hexanos, 1 ml) se agregó gota a gota y se agitó durante 15 minutos. La mezcla de reacción se enfrió entonces hasta –78 °C y se agregó gota a gota una solución de compuesto **987** (400 mg, 1,6 mmol) en THF (10 ml). Se continuó la agitación a esta temperatura durante 30 minutos antes de agregar gota a gota una solución de yodometano (450 mg, 3,2 mmol) en THF (10 ml). La reacción se agitó durante 30 minutos a esta temperatura y luego 1 hora a temperatura ambiente. La reacción se desactivó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron para dar el producto **988** que se usó sin purificación adicional. HPLC-MS t_R = 2,10 (UV_{254nm}); masa calculada para la fórmula $C_{16}H_{20}N_2O_2$ 272,15, LCMS observada m/z 273,2 (M+H).

Parte C:

Se disolvió Compuesto **988** en THF (20 ml) y se agregó borohidruro de litio (60 mg, 2,6 mmol). La mezcla de reacción se reflujó durante 5 horas. La mezcla de reacción enfriada se desactivó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 50% de acetato de etilo/hexanos) dio un sólido blanco **989** (300 mg). HPLC-MS t_R = 1,57 ($UV_{254\ nm}$); masa calculada para la fórmula $C_{14}H_{18}N_2O$ 230,1, LCMS observada m/z 231,3 (M+H).

Parte D:

Se disolvió Compuesto **989** (300 mg, 1,3 mmol) en tolueno (5 ml) y se agregó tribromuro de fósforo (0,06 ml, 0,52 mmol). La reacción se agitó a reflujo durante 3 horas. La reacción enfriada se desactivó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución de

bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron para dar el producto **990** que se usó sin purificación adicional.

Parte E:

Se disolvió Compuesto **990** en DMF (10 ml) y se agregaron carbonato de cesio (850 mg, 2,6 mmol) y ftalamida (190 mg, 1,3 mmol) y se agitó hasta el día siguiente. La reacción se desactivó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 25% de acetato de etilo/hexanos) dio un sólido blanco **991** (90 mg). HPLC-MS t_R = 2,14 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{22}H_{21}N_3O_2$ 359,1, LCMS observada m/z 360,1.

Parte F:

Se disolvió Compuesto **991** (90 mg, 0,25 mmol) en etanol (3 ml) y se agregó hidrato de hidracina (0,5 ml). La reacción se agitó durante 3 horas y se filtraron los sólidos. El solvente se evaporó para dar el producto deseado **992** que se usó sin purificación adicional.

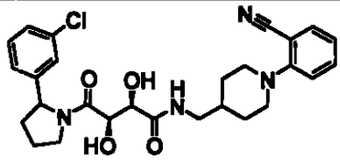
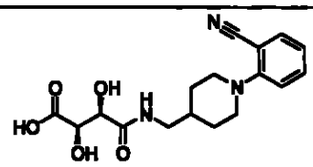
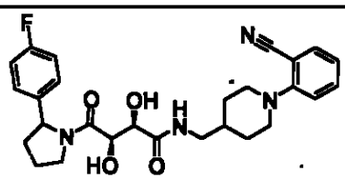
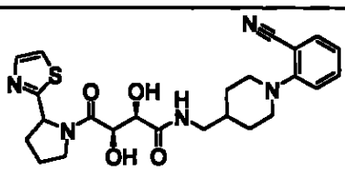
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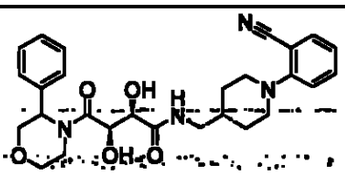
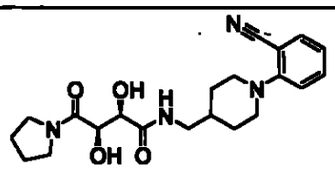
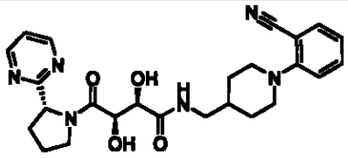
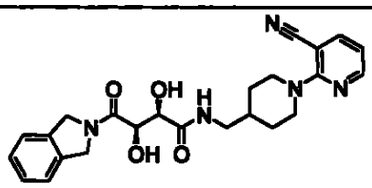
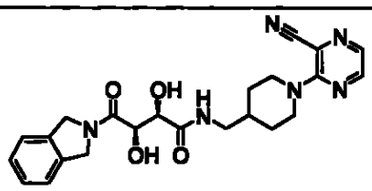
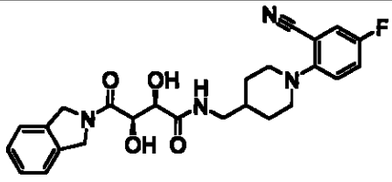
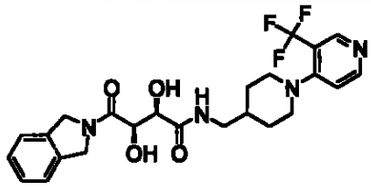
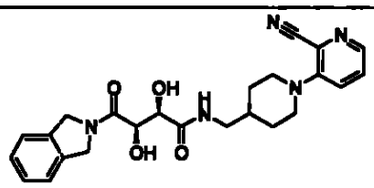
Se disolvió Compuesto **992** en DMF (5 ml) y se agregaron compuesto **230** (84 mg, 0,25 mmol) y HATU (114 mg, 0,30 mmol) y se agitó hasta el día siguiente. La reacción se desactivó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, acetato de etilo) dio una espuma blanca **993** (100 mg). HPLC-MS t_R = 1,99 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{30}H_{34}N_4O_8$ 546,2, LCMS observada m/z 547,2.

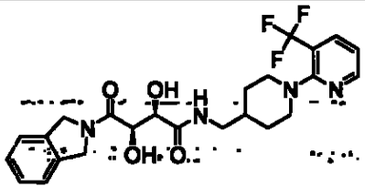
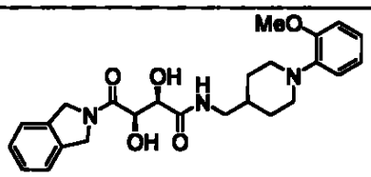
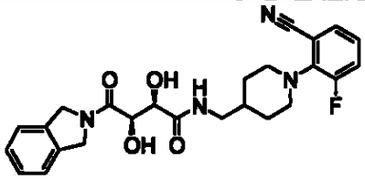
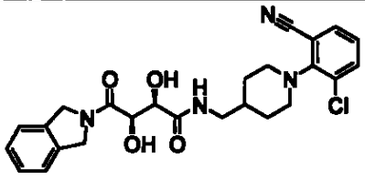
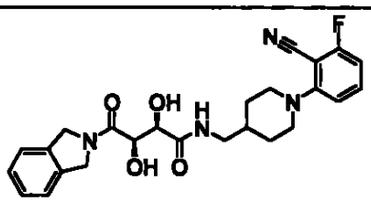
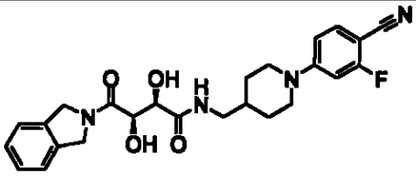
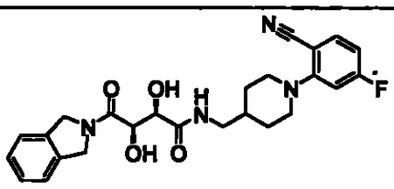
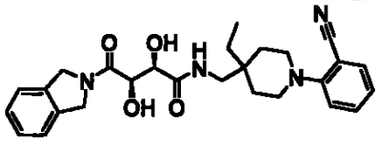
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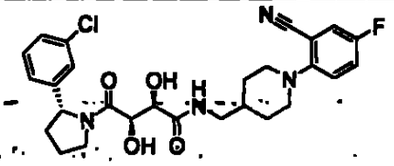
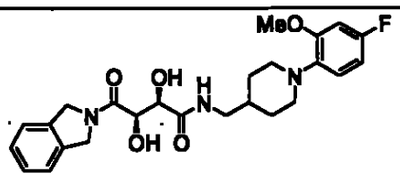
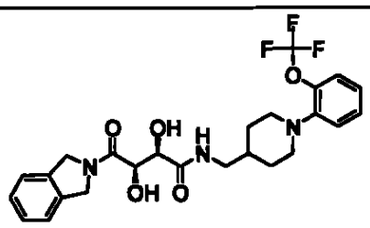
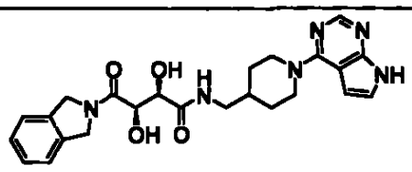
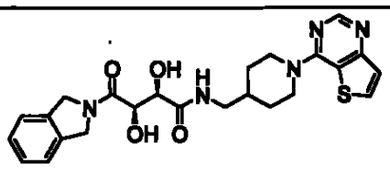
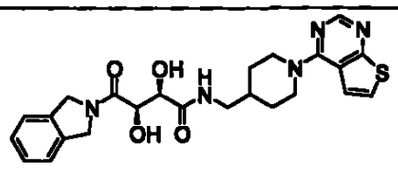
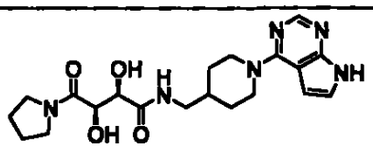
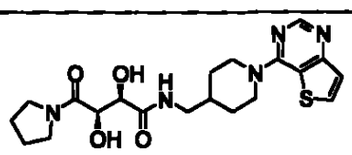
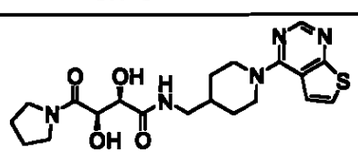
Se disolvió Compuesto **993** (100 mg, 0,182 mmol) en metanol (5 ml) y se agregó carbonato de potasio (100 mg) y se agitó durante 30 minutos. La reacción se desactivó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron. La purificación mediante LC prep. de fase reversa dio un sólido blanco **994** (7 mg, 8%) después de la liofilización. HPLC-MS t_R = 4,32 min. ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{28}H_{30}N_4O_4$ 462,23, LCMS observada m/z 463,1 (M+H).

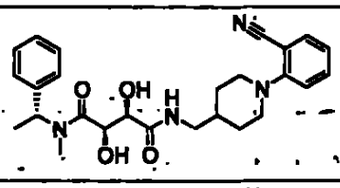
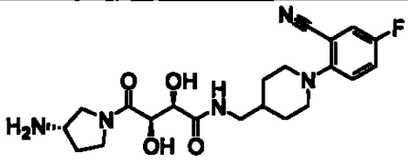
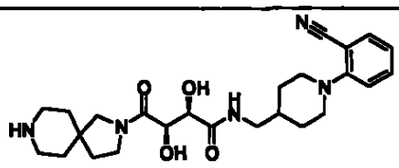
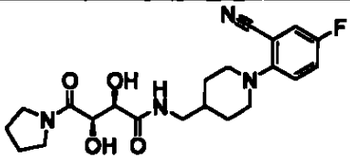
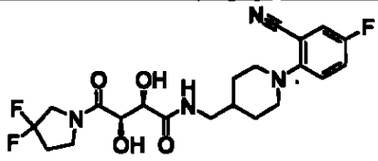
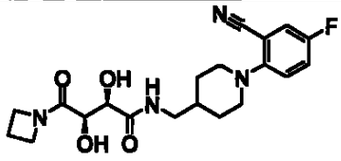
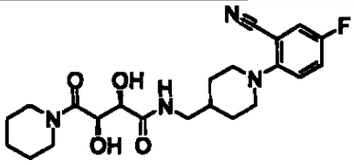
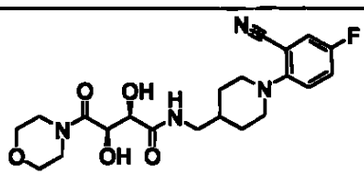
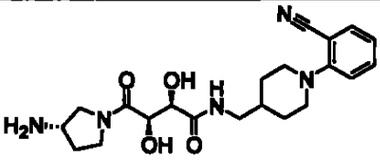
La siguiente tabla contiene compuestos que se prepararon usando los procedimientos descriptos en el Ejemplo 27 A–C. Los compuestos tales como **1002** se prepararon a partir del precursor de cloropiridilo usando los procedimientos descriptos en el Ejemplo 27A Parte A.

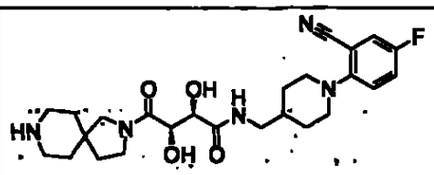
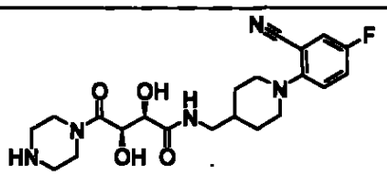
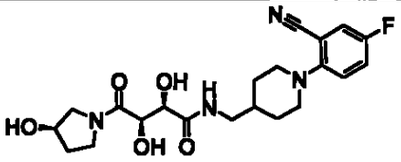
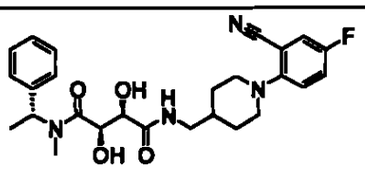
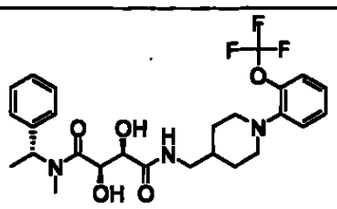
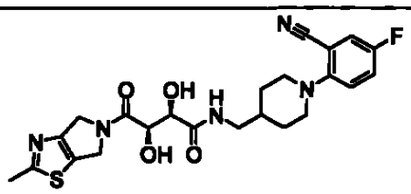
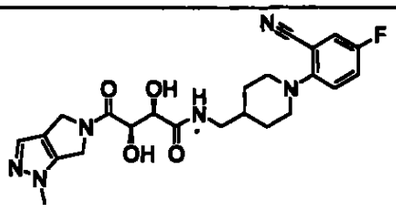
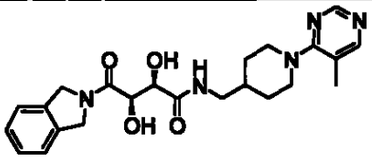
Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
995		510,2	511,1
996		347,1	348,3
997		494,2	495,2
998		483,2	484,1

999		492,2	493,1
1000		400,2	401,2
1001		478,2	479,2
1002		449,2	450,2
1003		450,2	451,1
1004		466,2	467,2
1005		492,2	493,1
1006		449,2	450,1

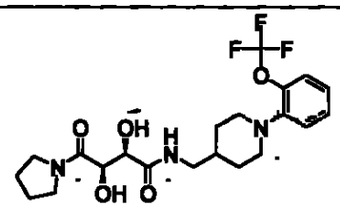
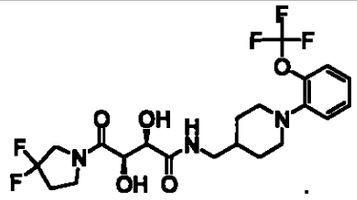
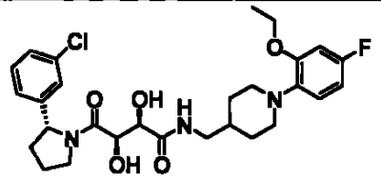
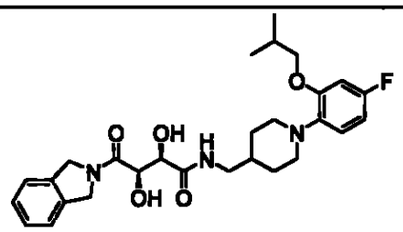
1007		492,2	493,1
1008		453,2	454,2
1009		466,2	467,2
1010		482,2	483,1
1011		466,2	467,2
1012		466,2	467,2
1013		466,2	467,2
1014		476,2	477,1

1015		528,2	529,2
1016		471,2	472,1
1017		507,2	508,2
1018		464,2	465,2
1019		481,2	482,2
1020		481,2	482,2
1021		416,2	417,3
1022		433,2	434,2
1023		433,2	434,2

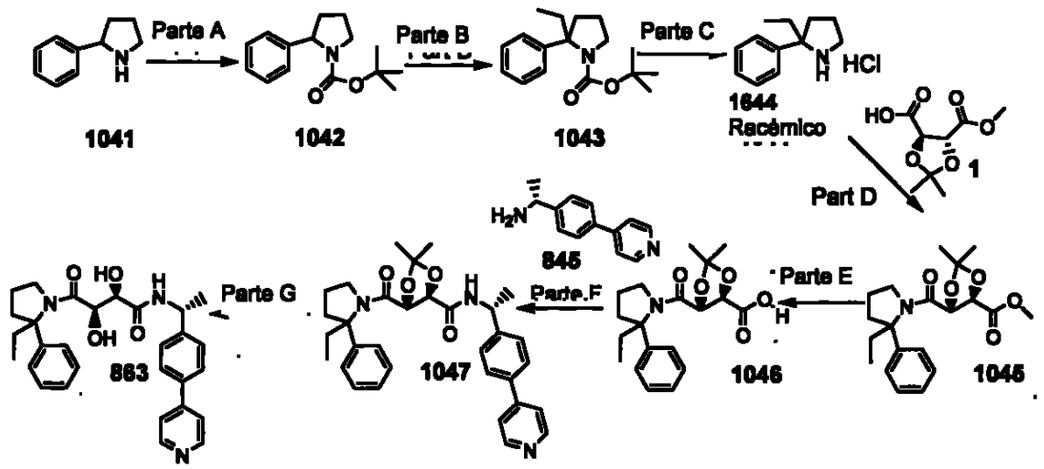
1024		464,2	465,2
1025		433,2	434,2
1026		469,3	470,2
1027A		418,2	419,2
1027B		454,2	455,2
1027C		404,2	405,2
1028		432,2	433,2
1029		434,2	435,2
1030		415,2	416,2

1031		**487,3**	**488,2**
1032		**433,2**	**434,2**
1033		**434,2**	**435,2**
1034A		**482,2**	**483,3**
1034B		**523,2**	**524,2**
1035		**487,2**	**488,2**
1036		**470,2**	**471,2**
1037		**439,2**	**440,2**

1488

1038A		459,2	460,1
1038B		495,2	496,2
1039		547,2	548,2
1040		513,3	514,3

Ejemplo 28: Fenil pirrolidinas alquiladas



Parte A:

Se disolvió 2-fenil pirrolidina (**1041**) (3,14 g, 21,4 mmol) en THF (40 ml). Se agregó NaOH acuoso (12 ml, 25%), seguido por Boc anhidro. La mezcla de

reacción se agitó a ta durante 70 h. Las capas se separaron. La capa acuosa se extrajo con EtOAc. La capa orgánica combinada se lavó con buffer de fosfato de sodio 1,0 M de pH=7,0 y salmuera, luego se secó con $MgSO_4$. La evaporación de los solventes dio un aceite amarillo que se purificó mediante cromatografía en columna (SiO_2, hexanos:EtOAc 9:1) para dar 5,1 g de un aceite claro como producto **1042**, MS (El) m/z M+Na Obs 270,08.

Parte B:

Un matraz Schlenck de 100 ml se equipó con una barra para revolver, se secó con flama bajo flujo de N_2, se cubrió con un septum, y se permitió que se enfriara hasta ta. Se agregó Compuesto **1042** (0,50 g, 2,02 mmol) y el matraz se recubrió. Se agregó THF anhidro (8,5 ml) mediante jeringa y el matraz se enfrió en un baño de hielo seco/2-propanol. Se agregó sec butil litio (1,6 ml, 2,34 mmol) mediante jeringa. La mezcla de reacción se dejó en agitación a -78 °C durante 30 m. Se agregó yodoetano (180 µl, 2,25 mmol) y la mezcla de reacción se agitó durante 2 hrs. Se agregó yodoetano adicional (80 µl, 1,0 mmol) y la mezcla de reacción se agitó durante 45 minutos. La mezcla de reacción se desactivó con buffer de fosfato de sodio 1,0 M de pH 7,0 y se diluyó con EtOAc. Las capas se separaron y la capa acuosa se extrajo con EtOAc. La capa orgánica combinada se lavó con agua y salmuera, luego se secó con $MgSO_4$ y se concentró para un aceite claro. El producto bruto se purificó mediante cromatografía en columna (SiO_2, 0%-20% de EtOAc/hexanos) para dar 0,12 g del compuesto **1043**, MS (El) m/z M+Na Obs 298,15.

Parte C:

Se disolvió Compuesto **1043** (0,12 g, 0,43 mmol) en 10 ml de HCl 4 M en dioxano. La mezcla de reacción se agitó a ta durante 2,25 h. La mezcla de reacción se concentró hasta que se secó dando sólido blanco **1044** (112 mg). MS (El) m/z Obs M+H 176,12.

~~498~~
1490

Parte D:

Se disolvieron Compuesto **1044** (104 mg, 0,49 mmol) y **1** (0,120 g, 0,588 mmol) en CH_2Cl_2 (2 ml). Se agregó diisopropil etilamina (200 µl, 1,12 mmol), seguido por PyBrop (249 mg, 0,78 mmol). La mezcla de reacción se dejó en agitación hasta el día siguiente a ta bajo N_2. La mezcla de reacción se diluyó con CH_2Cl_2 luego se lavó con buffer de fosfato de sodio 1,0 m de pH 7,0, $NaHCO_3$ ac. y salmuera. La capa orgánica se secó con $MgSO_4$ y se concentró para un aceite claro. El producto bruto purificado se purificó mediante cromatografía en columna (SiO_2, 0%-40% de EtOAc/hexanos) para dar 0,16 g del compuesto **1045**, MS (El) m/z Obs M+H 362,08.

Parte E:

Se disolvió Compuesto **1045** (0,15 g, 0,42 mmol) en dioxano (1,6 ml) y agua (0,4 ml). Se agregó hidróxido de litio (19 mg, 0,45 mmol). La mezcla de reacción se agitó a ta durante 2 h 15 m. La solución se concentró para dar **1046** como un aceite claro. MS (El) m/z Obs. M+H 348,09.

Parte F:

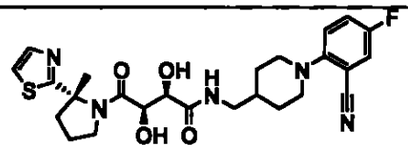
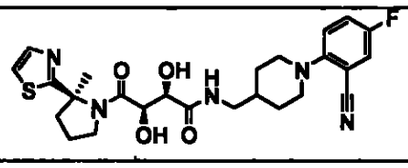
Se disolvieron Compuesto **1046** (69 mg, 0,19 mmol) y **845** (51 mg, 0,22 mmol) en DMF (1 ml) y diisopropilamina (100 µl, 0,58 mmol). Se agregó PyBrop (108 mg, 0,338 mmol) y la reacción se agitó hasta el día siguiente a ta. La mezcla de reacción se diluyó con EtOAc y se lavó con buffer de fosfato de sodio 1,0 M de pH 8,0 y salmuera. La capa orgánica se secó con $MgSO_4$ y se concentró para un aceite amarillo. El producto bruto se purificó mediante TLC prep. sobre placas de sílice usando 95:5 CH_2Cl_2:MeOH como la fase móvil. Se obtuvo Compuesto **1047** como un aceite claro (74 mg). MS (El) m/z Obs M+H 528,20.

Parte G:

Se disolvió Compuesto **1047** (74 mg, 0,14 mmol) en 5 ml de solución de ácido trifluoroacético:agua 9:1. La mezcla de reacción se agitó a ta durante 3 h 10

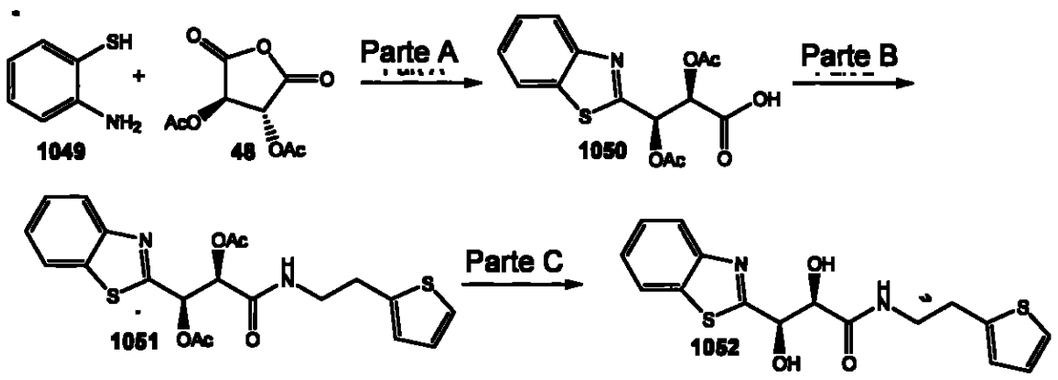
m, luego se concentró hasta que se secó. El producto bruto se purificó mediante cromatografía en columna (SiO_2, 0%-7% de MeOH/ CH_2Cl_2) para dar 26 mg del compuesto **863**, MS (El) m/z Obs M+H 488,1.

Se preparó el compuesto **1048A,B** a partir de Boc-prolina OMe usando los procedimientos de alquilación anteriores y el anillo tiazol se construyó según se describe en el Ejemplo 10A.

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
1048A		515,2	516,2
1048B		515,2	516,2

Ejemplo 29:

Ejemplo 29A:



Parte A:

Se calentó una mezcla de 2-amino-bencenotiol (**1049**) (247 ul, 2,31 mmol) y **48** (500 mg, 2,31 mmol) en benceno a reflujo hasta el día siguiente con un sifón simple. La mezcla de reacción se enfrió y se concentró. La mezcla se recristalizó a partir de 30% de acetato de etilo/hexanos para dar **1050** (267 mg) como un

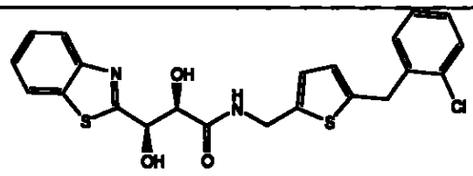
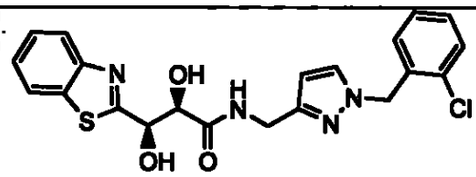
polvo marrón. HPLC-MS t_R = 1,35 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{14}H_{13}NO_6S$ 323,1, LCMS observada m/z 324,1 (M+H).

Parte B:

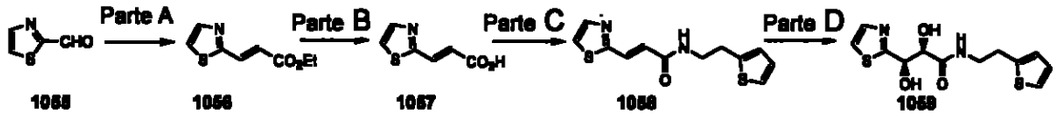
Se preparó Compuesto **1051** a partir del compuesto **1050** (32 mg, 0;1 mmol) usando la estrategia de acoplamiento HATU estándar descripta en el Ejemplo 2 Parte A. La purificación mediante cromatografía en columna (SiO_2, 10% de acetato de etilo/diclorometano) dio el producto as un sólido anaranjado (27 mg). HPLC-MS t_R = 1,78 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{20}H_{20}N_2O_5S_2$ 432,1, LCMS observada m/z 433,0 (M+H).

Parte C:

Se preparó Compuesto **1052** siguiendo el procedimiento descripto en el Ejemplo 2 Parte B. HPLC-MS t_R = 1,39 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{16}H_{16}N_2O_3S_2$ 348,1, LCMS observada m/z 349,0 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
1053		458,1	459,0
1054		442,1	443,0

Ejemplo 29B:



Parte A:

A hidruro de sodio (95%, 115 mg, 4,55 mmol) en DME (10 ml) bajo argón 1493 se agregó gota a gota trietilfosfonacetato. En unos pocos minutos la mezcla de reacción se aclaró. Después de 1 hora, se agregó el aldehído **1055** (400 ul, 4,55 mmol). Después de 15 minutos se agregaron agua y dietil éter a la mezcla de reacción. Las capas se separaron y la capa acuosa se extrajo con dietil éter. La capa orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio y se concentró para dar **1056** como un aceite anaranjado (666 mg, 80%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,92 (d, 1H, J = 3,2 Hz), 7,79 (d, 1H, J = 16,0 Hz), 7,43 (d, 1H, J = 3,2 Hz), 6,71 (d, 1H, J = 16,0 Hz), 4,29 (q, 2H, J = 7,5 Hz), 1,36 (t, 3H, J = 7,5 Hz).

Parte B:

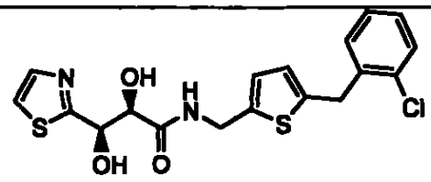
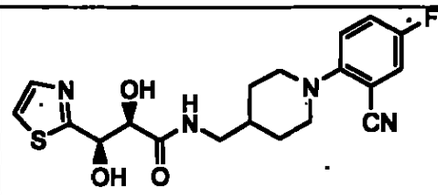
A éster **1056** (84 mg, 0,46 mmol) en THF (2 ml) se agregó solución de hidróxido de litio 1,0 M (0,5 ml, 0,5 mmol). La mezcla de reacción se agitó hasta el día siguiente. La mezcla de reacción se acidó con solución de HCl 1,0 N y se extrajo con acetato de etilo. Cloruro de sodio se agregó a la capa acuosa durante las extracciones. La capa orgánica combinada se secó sobre sulfato de sodio y se concentró para dar **1057** as a film (65 mg, 92%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,97 (d, 1H, J = 3,0 Hz), 7,89 (d, 1H, J = 15,7 Hz), 7,49 (d, 1H, J = 3,0 Hz), 6,75 (d, 1H, J = 15,7 Hz).

Parte C:

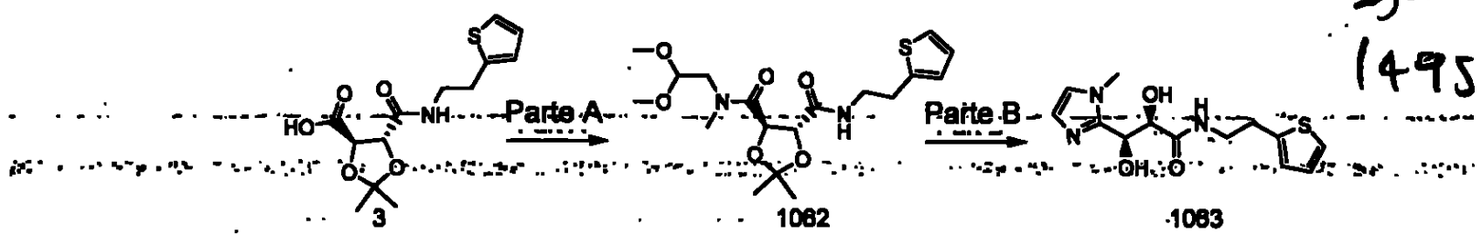
Se preparó Compuesto **1058** a partir de compuesto **1057** (32 mg, 0,21 mmol) usando la estrategia de acoplamiento HATU estándar descripta en el Ejemplo 2 Parte A. La purificación mediante cromatografía en columna (SiO_2, 50% de acetato de etilo/hexano) dio el producto as a film (35 mg, 63%). HPLC-MS t_R = 1,35 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{12}H_{12}N_2OS_2$ 264,0, LCMS observada m/z 265,1 (M+H).

Parte D:

Se preparó Compuesto **1059** usando un procedimiento de dihidroxilación modificado Sharpless (*Chem. Rev.* **1994**, *94*, 2483). Se cargó una matraz con $(DHQ)_2PHAL$ (10 mg; 10 mol %), $K_3Fe(CN)_6$ (128 mg; 0,39 mmol), carbonato de potasio (54 mg, 0,39 mmol), metano sulfonamida (24 mg, 0,26 mmol) y tetróxido de potasio y osmio dihidrato (1 mg, 2 mol%). A los sólidos se agregó alqueno 4 (35 mg, 0,13 mmol) en ter-butanol:agua (1:1, 2,5 ml). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se enfrió en un baño de hielo y se agregó metabisulfito de sodio (38 mg, 0,2 mmol). La mezcla se agitó durante 30 minutos. La mezcla de reacción se diluyó con acetato de etilo y agua. Las capas se separaron y la capa acuosa se extrajo con acetato de etilo. La capa orgánica combinada se lavó con solución de hidróxido de potasio 2,0 N y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 80% de acetato de etilo/hexano) dio el producto como un sólido blanco después de la liofilización (5 mg, 13%). HPLC-MS t_R = 1,00 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{12}H_{14}N_2O_3S_2$ 298,0, LCMS observada m/z 299,0 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
1060		408,0	409,0
1061		404,1	405,1

Ejemplo 29C:



Parte A:

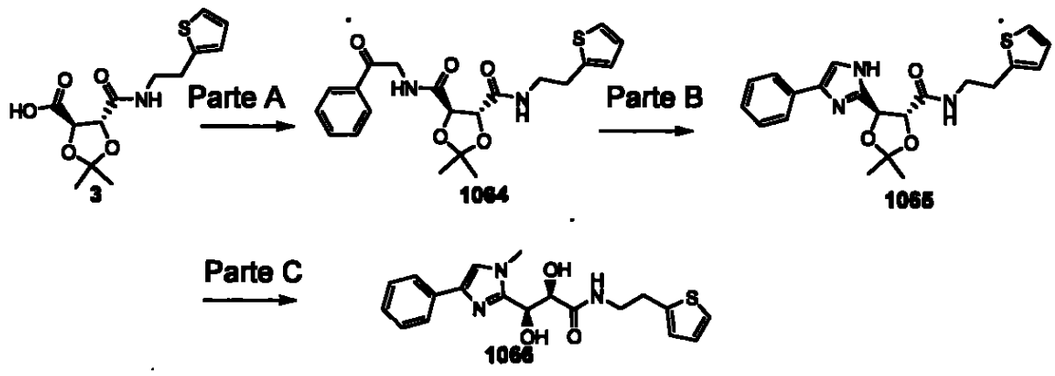
Se preparó Compuesto **1062** siguiendo los procedimientos descriptos en el Ejemplo 1.

HPLC-MS t_R = 1,69 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{18}H_{28}N_2O_6S$ 400,2, LCMS observada m/z 401,2 (M+H).

Parte B:

Se calentaron Compuesto **1062** (198 mg, 0,69 mmol) y acetato de amonio (1,9 g, 24,7 mmol) en ácido acético (6 ml) hasta el día siguiente a 110°C. La mezcla de reacción se concentró. El residuo se suspendió en DCM y los sólidos se eliminaron mediante filtración. El filtrado se concentró para dar una mezcla de producto protegido de acetonida y **1063**. El residuo se trató con 80% de TFA:agua (2 ml) y se agitó hasta el día siguiente. Los solventes se eliminaron. La purificación mediante HPLC prep. dio **1063** (11 mg, 4%) como una sal de TFA. HPLC-MS t_R = 0,79 min. ($UV_{254\ nm}$); masa calculada para la fórmula C13H17N3O3S 295,1, LCMS observada m/z 296,1 (M+H).

Ejemplo 29D:



Parte A:

Se preparó Compuesto **1064** siguiendo los procedimientos descriptos en el Ejemplo 1. HPLC-MS t_R = 1,77 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{21}H_{24}N_2O_5S$ 416,14, LCMS observada m/z 417,1 (M+H).

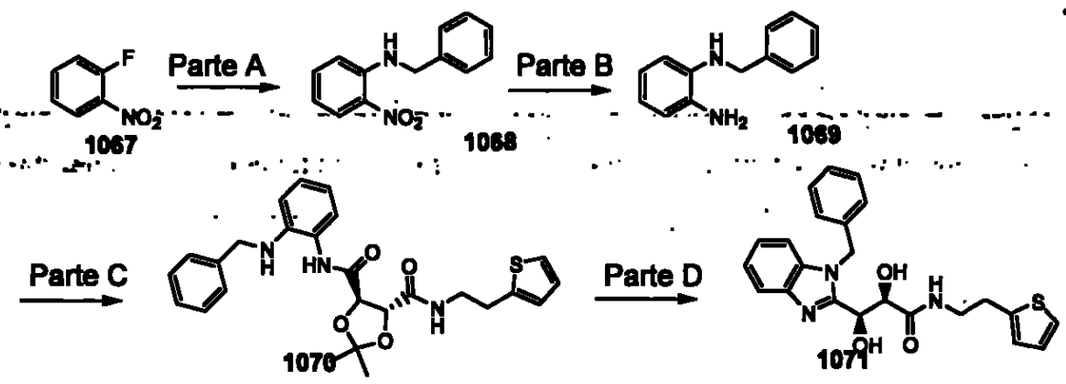
Parte B:

Se calentaron Compuesto **1064** (216 mg, 0,52 mmol) y acetato de amonio (2 g, 25,9 mmol) en ácido acético (6 ml) hasta el día siguiente a 110 °C. La mezcla de reacción se concentró. El residuo se suspendió en DCM y los sólidos se eliminaron mediante filtración. El filtrado se concentró y se purificó mediante cromatografía de fase reversa (Gilson) para dar **1065** (80 mg, 30%) como una sal de TFA (80% de Pureza). HPLC-MS t_R = 1,38 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{21}H_{23}N_3O_3S$ 397,1, LCMS observada m/z 398,2 (M+H).

Parte C:

Se agitó una mezcla del compuesto **1065** (63 mg, 0,127 mmol), yodometano (10 µl, 0,16 mmol) y carbonato de cesio (206 mg, 0,634 mmol) en DMF (6 ml) hasta el día siguiente a temperatura ambiente. La mezcla de reacción se concentró. El residuo se suspendió en acetato de etilo y los sólidos se eliminaron mediante filtración. El filtrado se concentró para dar el producto bruto protegido de acetonida. El residuo se trató con 90% de TFA:agua (3 ml) y se agitó durante 3 h a 50 °C. Los solventes se eliminaron. La purificación mediante HPLC prep. dio **1066** (12 mg, 19%) como una sal de TFA. HPLC-MS t_R = 2,87 min. (10 min; $UV_{254\ nm}$); masa calculada para la fórmula $C_{19}H_{21}N_3O_3S$ 371,1, LCMS observada m/z 372,1 (M+H).

Ejemplo 29E:



Parte A:

De acuerdo con una modificación de un procedimiento de Goker, H. et. al. *(Il Farmaco* **1998**, *53*, 415-420) se calentó una mezcla de 1-fluoro-2-nitro-benceno (**1067**) (1,1 ml, 10,4 mmol) y bencilamina (2,35 ml, 21,5 mmol) en DMF (5 ml) hasta el día siguiente a 80 °C. La mezcla de reacción se concentró para dar un sólido anaranjado que se filtró, se lavó con agua y se secó para dar bencil-(2-nitro-fenil)-amina (**1068**) (2,5 g, 100%). ^{1}H RMN δ (400 MHz, $CDCl_3$) 8,44 (b, 1H, NH), 8,22-8,19 (dd, 1H), 7,41-7,27 (m, 6H), 6,84-6,81 (dd, 1H), 6,70-6,66 (m, 1H), 4,58-4,57 (d, 2H).

Parte B:

A una solución de bencil-(2-nitro-fenil)-amina (**1068**) (2,5 g, 10,43 mmol) en etanol (150 ml) y agua (10 ml) se agregó acero (8,7 g, 155,7 mmol) seguido por 30 gotas de HCl concentrado, y la mezcla resultante se calentó hasta el día siguiente a reflujo. La mezcla de reacción se desactivó con agua, se diluyó con DCM y las capas se separaron. La capa orgánica se lavó con solución de bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio y se concentró para dar un residuo aceitoso marrón. La purificación adicional mediante cromatografía en columna (SiO_2, 20 % de acetato de etilo/hexanos) dio N-bencil-benceno-1,2-diamina (**1069**) como un aceite amarillo oscuro (1,18 g, 57%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,41-7,24 (m, 5H), 6,82-6,67 (m, 4H), 4,32 (s, 2H), 3,56 (b, 3H, NH).

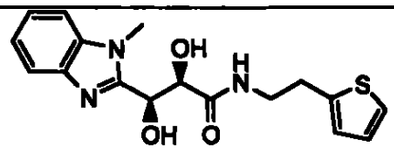
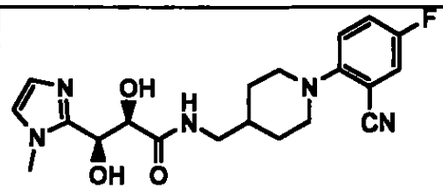
Parte C:

Se preparó Compuesto 1070 siguiendo los procedimientos descriptos en el Ejemplo 29C Parte A. HPLC-MS t_R = 2,13 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{26}H_{29}N_3O_4S$ 479,2, LCMS observada m/z 480,1 (M+H).

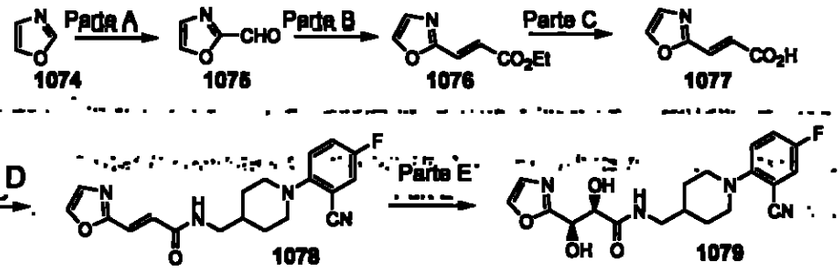
Parte D:

Se calentó una mezcla del compuesto **1070** (75 mg, 0,156 mmol) y monohidrato del ácido p-toluensulfónico (30 mg, 0,156 mmol) en tolueno (3 ml) hasta el día siguiente a reflujo. La mezcla de reacción se concentró para un residuo identificado como el producto desprotegido de acetonida mediante LC-MS. La purificación adicional mediante cromatografía de fase reversa dio **1071** (40 mg, 48%) como una sal de TFA (95% de Pureza). HPLC-MS t_R = 3,52 min. (10 min; $UV_{254\ nm}$); masa calculada para la fórmula $C_{23}H_{23}N_3O_3S$ 421,1, LCMS observada m/z 422,2 (M+H).

Los siguientes compuestos se sintetizaron mediante procedimientos descriptos en el Ejemplo 29C-E.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
1072		345,1	346,1
1073		401,2	402,2

Ejemplo 29F:



Parte A:

De acuerdo con un procedimiento de Hodges, J. C. et al (*J. Org. Chem.* **1991**, *56*, 449-452) a una solución fría (–78 °C) de oxazol **(1074)** (1g, 14,4 mmol) en 45 ml de THF se agregó gota a gota nBuli (9 ml, 14,4 mmol, solución 1,6 M en hexano), y la solución resultante se agitó a –78 °C durante 25 min. Luego se agregó gota a gota DMF (1,12 ml, 14,4 mmol), seguido por THF (5 ml) y la mezcla resultante se dejó calentar lentamente hasta temperatura ambiente, y se agitó hasta el día siguiente. La mezcla de reacción se desactivó mediante el agregado de gel de sílice (3 g), se concentró, y la suspensión resultante se diluyó con DCM y se cargó en una columna de gel de sílice. La cromatografía flash (3% de acetato de etilo/DCM) dio oxazol-2-carbaldehído **(1075)** (165 mg, 12%) como un aceite amarillo; ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,79 (s, 1H), 7,9 (s, 1H), 7,46 (s, 1H).

Parte B:

Se preparó Compuesto **1076** a partir de compuesto **1075** (165 mg, 1,7 mmol) usando el procedimiento descripto en el Ejemplo 29B Parte A. La purificación mediante cromatografía en columna (SiO_2, 20% de acetato de etilo/hexano) dio el producto como un sólido amarillo (107 mg, 34%); ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,69 (s, 1H), 7,45 (d, 1H, J = 16,0 Hz), 7,27 (s, 1H), 6,74 (d, 1H, J = 16,0 Hz), 4,29 (q, 2H, J = 7,3 Hz), 1,36 (t, 3H, J = 7,3 Hz).

Parte C:

Se preparó Compuesto **1077** a partir de compuesto **1076** (107 mg, 0,58 mmol) usando el procedimiento descripto en el Ejemplo 29B Parte B. El proceso dio el producto como un sólido amarillo pálido (77 mg, 85%). ^{1}H RMN (400 MHz,

DMSO-d_6) δ 12,9 (s, 1H), 8,25 (s, 1H), 7,44 (s, 1H), 7,27 (d, 1H, J = 16,0 Hz), 6,62 (d, 1H, J = 16,0 Hz).

Parte D:

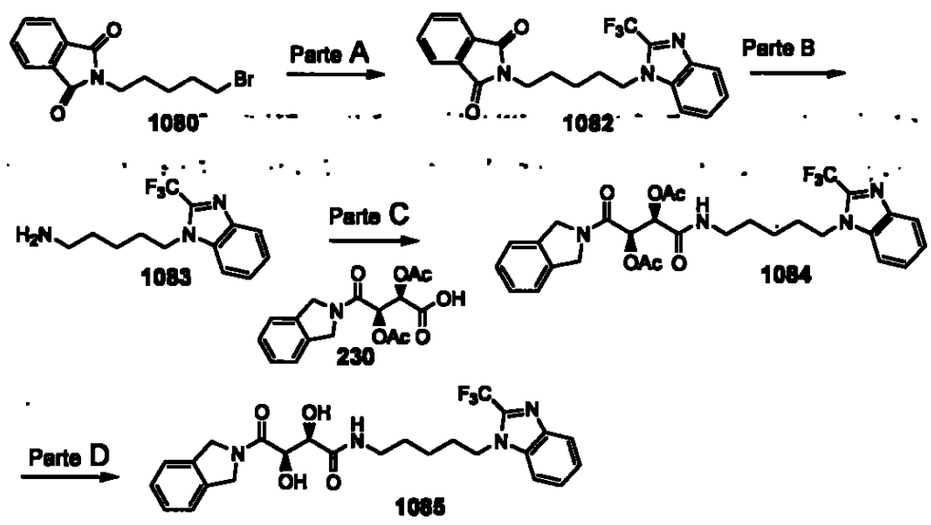
Se preparó Compuesto **1078** a partir de compuesto **1077** (165 mg, 1,7 mmol) usando el procedimiento descripto en el Ejemplo 29B Parte C. Después del proceso de acoplamiento estándar HATU, el residuo sólido se trituró con 1:1 DCM/hexano, se filtró y se lavó con DCM/hexano 1:1 para dar **1078** (123 mg, 70%) como un sólido amarillo pálido; ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,49 (t, 1H), 8,20 (s, 1H), 7,69-7,66 (dd, 1H), 7,49-7,44 (m, 1H), 7,38 (s, 1H), 7,20-7,16 (dd, 1H), 7,14 (d, 1H, J = 16,0 Hz), 6,94 (d, 1H, J = 16,0 Hz), 3,41-3,38 (d, 2H), 3,16 (t, 2H), 2,72 (t, 2H), 1,81-1,78 (d, 2H), 1,64-1,58 (m, 1H), 1,40-1,30 (m, 2H). HPLC-MS t_R = 1,63 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{19}H_{19}FN_4O_2$ 354,15, LCMS observada m/z 355,1 (M+H).

Parte E:

Se preparó Compuesto **1079** a partir de compuesto **1078** (118 mg, 0,33 mmol) usando el procedimiento descripto en el Ejemplo 29B Parte D. La purificación mediante cromatografía en columna (SiO_2, 5% de MeOH/DCM) dio el producto como un sólido blanco (28 mg, 22%); ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,02 (s, 1H), 7,88 (t, 1H); 7,69-7,66 (dd, 1H), 7,48-7,43 (m, 1H), 7,20-7,16 (dd, H), 7,14 (s, 1H), 5,83-5,81 (d, 1H), 5,72-5,70 (d, 1H), 4,93-4,90 (dd, 1H), 4,23-4,21 (d of d, 1H), 3,38-3,36 (d, 2H), 3,04 (t, 2H), 2,69 (t, 2H), 1,77-1,72 (d, 2H), 1,62-1,56 (m, 1H), 1,32-1,23 (m, 2H). ^{19}F RMN (400 MHz, DMSO-d_6) δ -120,6 ppm. HPLC-MS t_R = 3,32 min. (10 min; $UV_{254\ nm}$); masa calculada para la fórmula $C_{19}H_{21}FN_4O_4$ 388,15, LCMS observada m/z 389,2 (M+H).

Ejemplo 30:

Ejemplo 30A:



Parte A:

Se agitó una mezcla de 2-(5-bromo-pentil)-isoindol-1,3-diona (**1080**) (2,0 g, 6,77 mmol), 2-trifluorometil-1H-benzoimidazol (1,2 g, 6,45 mmol) y carbonato de potasio (1,78 g, 12,9 mmol) en NMP (5 ml) hasta el día siguiente a temperatura ambiente. La mezcla de reacción se dividió entre acetato de etilo y agua, y la capa orgánica resultante se lavó con agua, salmuera, se secó sobre sulfato de sodio y se concentró para dar un aceite. La purificación adicional mediante cromatografía en columna (SiO_2, 25% de acetato de etilo/hexanos) dio el compuesto **1082** como un aceite incoloro (1,88 g, 73%). ^1H RMN (400 MHz, $CDCl_3$) δ 7,88-7,86 (d, 1H), 7,85-7,83 (m, 2H), 7,73-7,71 (m, 2H), 7,49-7,34 (m, 3H), 4,31 (t, 2H), 3,72 (t, 2H), 1,99-1,92 (m, 2H), 1,80-1,73 (m, 2H), 1,53-1,45 (m, 2H).

Parte B:

A una solución de compuesto **1082** (1,88 g, 4,68 mmol) en EtOH (50 ml) se agregó monohidrato de hidracina (0,45 ml, 9,36 mmol) y la mezcla resultante se calentó durante 3 h a 60 °C, durante ese tiempo se formó un precipitado blanco. La mezcla de reacción se filtró, se lavó con EtOH y el filtrado se concentró. El residuo se suspendió en éter, se agitó durante 10 min. a temperatura ambiente,

se filtró y se lavó con éter, y el filtrado resultante se concentró para dar compuesto **1083** como un aceite (1,10 g, 87%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,90-7,88 (d, 1H), 7,46-7,37 (m, 3H), 4,33 (t, 2H), 2,76 (t, 2H), 2,02-1,40 (m, 6H).

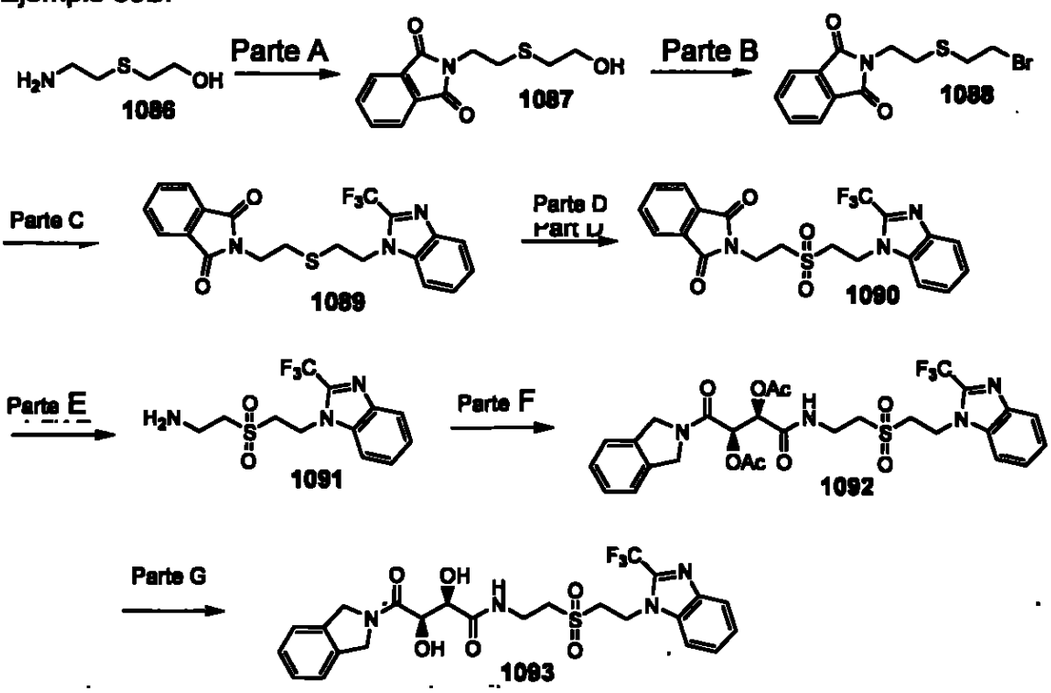
Parte C:

Se preparó Compuesto **1084** a partir de **1083** y **230** siguiendo los procedimientos descriptos en el Ejemplo 2.

Parte D:

Se preparó Compuesto **1085** siguiendo los procedimientos descriptos en el Ejemplo 2, HPLC-MS t_R = 4,14 min. (10 min; $UV_{254\ nm}$); masa calculada para la fórmula $C_{25}H_{27}F_3N_4O_4$ 504,2, LCMS observada m/z 505,1 (M+H).

Ejemplo 30B:



Parte A:

De acuerdo con una modificación de un procedimiento de Lown, J. W. et. al. (*J. Org. Chem.* **1982**, *47*, 2027-2033), se calentó una mezcla de 2-(2-amino-etilsulfanil)-etanol (**1086**) (1,82, 15 mmol) y ftalamida (2,22 g, 15 mmol) en tolueno

(35 ml) a reflujo hasta el día siguiente. La mezcla de reacción se concentró para un residuo, que se purificó mediante cromatografía en columna (SiO_2, 25% de acetato de etilo/DCM a 50% de acetato de etilo/DCM) para dar compuesto **1087** como un sólido blancuzco (2,98 g, 79%). ^{1}H RMN (400 MHz, $CDCl_3$) δ7,87-7,85 (m, 2H), 7,75-7,72 (m, 2H), 3,94 (t, 2H), 3,80 (t, 2H), 2,89-2,82 (m, 4H).

Parte B:

De acuerdo con una modificación de un procedimiento de Nair, S. A. et. al. (*Synthesis* **1995**, 810-814), a una solución helada del compuesto **1087** (628 mg, 2,5 mmol) y tetrabromuro de carbono (1,04 g, 3,12 mmol) en DCM (25 ml) se agregó trifenilfosfina (920 mg, 3,5 mmol) en dos porciones durante 10 min. La mezcla de reacción se dejó calentar hasta temperatura ambiente y se agitó hasta el día siguiente a temperatura ambiente. La mezcla se concentró y el residuo resultante se purificó mediante cromatografía en columna (SiO_2, 30 % de acetato de etilo/hexanos) para dar compuesto **1088** como un sólido blanco (733 mg, 93%). ^{1}H RMN (400 MHz, $CDCl_3$) δ7,88-7,86 (m, 2H), 7,75-7,73 (m, 2H), 3,92 (t, 2H), 3,53 (t, 2H), 3,04 (t, 2H), 2,90 (t, 2H).

Parte C:

Se preparó Compuesto **1089** siguiendo los procedimientos descriptos en el Ejemplo 30A, Parte A. ^{1}H RMN (400 MHz, $CDCl_3$) δ7,89-7,87 (d, 1H), 7,86-7,84 (m, 2H), 7,74-7,72 (m, 2H), 7,58-7,56 (d, 1H), 7,46 (t, 1H), 7,38 (t, 1H), 4,52 (t, 2H), 3,92 (t, 2H), 3,02 (t, 2H), 2,89 (t, 2H); ^{19}F RMN (400 MHz, $CDCl_3$) δ–64,7 ppm.

Parte D:

A una solución de compuesto **1089** (250 mg, 0,6 mmol) en DCM (5 ml) se agregó ácido m-cloroperoxibenzoico (336 mg, 1,5 mmol) y la mezcla resultante se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se diluyó con DCM, se lavó con solución de bicarbonato de sodio saturado,

salmuera, se secó sobre sulfato de sodio y se concentró para dar el compuesto **1090** (284 mg) como un sólido blanco que se usó sin purificación adicional. ^{1}H RMN (400 MHz, $CDCl_3$) δ7,92-7,90 (d, 1H), 7,90-7,88 (m, 2H), 7,78-7,76 (m, 2H), 7,66-7,62 (d de t, 1H), 7,54-7,51 (t de d, 1H), 7,46-7,44 (t de d, 1H), 4,89 (t, 2H), 4,20 (t, 2H), 3,65 (t, 2H), 3,46 (t, 2H); ^{19}F RMN (400 MHz, $CDCl_3$) δ –62,5 ppm.

Parte E:

Se preparó Compuesto **1091** siguiendo los procedimientos descriptos en el Ejemplo 30A, Parte B. ^{1}H RMN (400 MHz, $CDCl_3$) δ7,91-7,89 (d, 1H), 7,63-7,61 (d, 1H), 7,51-7,48 (t de d, 1H), 7,44-7,40 (t de d, 1H), 4,90 (t, 2H), 3,71 (t, 2H), 3,31 (t, 2H), 3,12 (t, 2H); ^{19}F RMN (400 MHz, $CDCl_3$) δ–62,5 ppm.

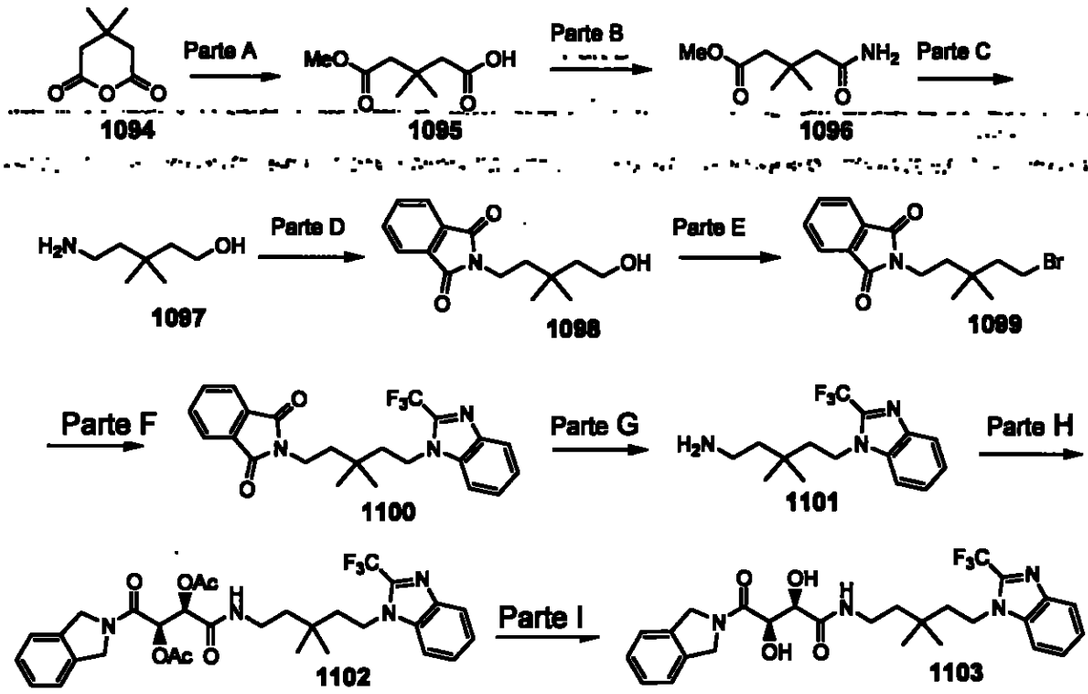
Parte F:

Se preparó Compuesto **1092** siguiendo los procedimientos descriptos en el Ejemplo 27A, Parte B, y se usó sin purificación adicional. HPLC-MS t_R = 1,65 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{28}H_{29}F_3N_4O_6S$ 638,17, LCMS observada m/z 639,1 (M+H).

Parte G:

Se preparó Compuesto **1093** siguiendo los procedimientos descriptos en el Ejemplo 27A, Parte C. HPLC-MS t_R = 3,57 min. (10 min; $UV_{254\ nm}$); masa calculada para la fórmula $C_{24}H_{25}F_3N_4O_6S$ 554,14, LCMS observada m/z 555,1 (M+H).

Ejemplo 30 C:



Parte A:

De acuerdo con una modificación de un procedimiento de Brown, R. F. et. al. (*J. Am. Chem.* Soc. **1955**, *77*, 1083-1089), se calentó una mezcla de anhídrido 3,3-dimetil glutárico (**1094**) (7,1 g, 50 mmol) y metanol (40 ml) hasta el día siguiente a reflujo. La mezcla de reacción se concentró para dar el compuesto **1095** como un aceite incoloro (8,46 g, 97%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,70 (s, 3H), 2,50 (s, 2H), 2,48 (s, 2H), 1,16 (s, 6H).

Parte B:

A una solución helada del compuesto **1095** (8,46 g, 48,5 mmol) en DCM (30 ml) se agregó gota a gota cloruro de oxalilo (7 ml, 80 mmol), seguido por DMF (2 gotas) y la mezcla resultante se calentó durante 3,5 h a reflujo. La mezcla de reacción se concentró para dar el cloruro correspondiente del ácido (metil éster del ácido 4-clorocarbonil-3,3-dimetil-butírico) como un aceite marrón (7,89 g, 84%) que se usó sin purificación adicional en el paso siguiente.

A una solución helada del amoníaco en 1,4-dioxano (30 ml de una solución que contiene 2,2 g de amoníaco disuelto en 100 ml de 1,4-dioxano, 38,8 mmol aprox) se agregó gota a gota una solución de metil éster del ácido 4-clorocarbonil-3,3-dimetil-butírico (3 g, 15,5 mmol) en 1,4-dioxano (3 ml) y una vez completada la adición, la suspensión blanca resultante se agitó 45 min. a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo, se filtró y se concentró para dar el compuesto **1096** como un aceite amarillo viscoso (2,62 g, 97%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,71 (s, 3H), 2,43 (s, 2H), 2,31 (s, 2H), 1,14 (s, 6H).

Parte C:

A una solución helada del LAH (42 ml, 1 M sol en THF, 42 mmol) se agregó gota a gota una solución de compuesto **1096** (2,02 g, 11,6 mmol) en THF y la mezcla resultante se calentó hasta el día siguiente a reflujo. La mezcla de reacción se enfrió hasta 0 °C y se desactivó mediante la adición gota a gota de salmuera, cuando se formó un sólido similar a la pasta. Este sólido se trituró y se sonicó varias veces con acetato de etilo, y los extractos orgánicos combinados se concentraron para dar el compuesto **1097** como un aceite (1,17 g, 76%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,71 (t, 2H), 2,71 (t, 2H), 1,53 (t, 2H), 1,41 (t, 2H), 0,92 (s, 6H).

Parte D:

Se preparó Compuesto **1098** siguiendo los procedimientos descriptos en el Ejemplo 30B, Parte A. HPLC-MS t_R = 1,88 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{15}H_{19}NO_3$ 261,14, LCMS observada m/z 262,0 (M+H).

Parte E:

Se preparó Compuesto **1099** siguiendo los procedimientos descriptos en el Ejemplo 30B, Parte B. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,84-7,82 (m, 2H), 7,71-7,69 (m, 2H), 3,70-3,66 (m, 2H), 3,47-3,42 (m, 2H), 1,97-1,92 (m, 2H), 1,61-1,57 (m, 2H), 1,03 (s, 6H).

Parte F:

Se preparó Compuesto **1100** siguiendo los procedimientos descriptos en el Ejemplo 30B, Parte C. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,89-7,87 (d, 1H), 7,86-7,84 (m, 2H), 7,73-7,71 (m, 2H), 7,5-7,57 (d, 1H), 7,47-7,43 (t de d, 1H), 7,39-7,35 (t de d, 1H), 4,46-4,41 (m, 2H), 3,79-3,75 (m, 2H), 1,89-1,85 (m, 2H), 1,74-1,69 (m, 2H), 1,18 (s, 6H); ^{19}F RMN (400 MHz, $CDCl_3$) δ –62,7 ppm.

Parte G:

Se preparó Compuesto **1101** siguiendo los procedimientos descriptos en el Ejemplo 30B, Parte E. HPLC-MS t_R = 1,13 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{15}H_{20}F_3N_3$ 299,16, LCMS observada m/z 300,1 (M+H).

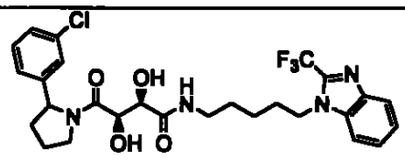
Parte H:

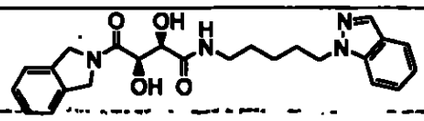
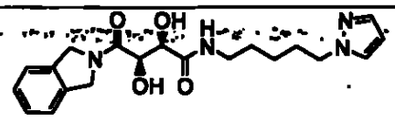
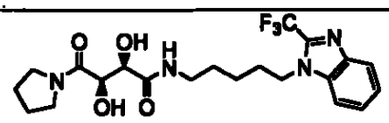
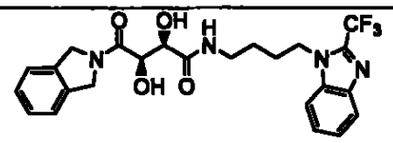
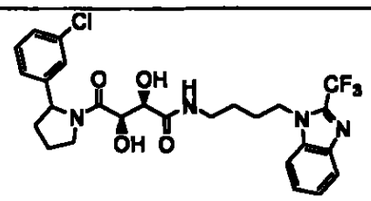
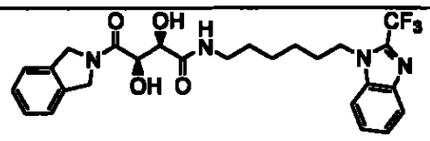
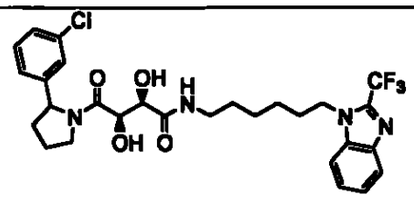
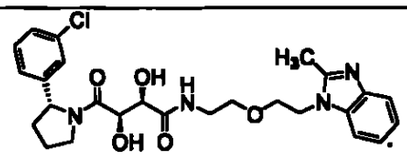
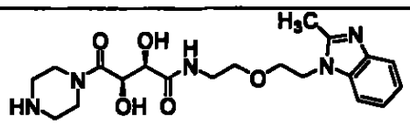
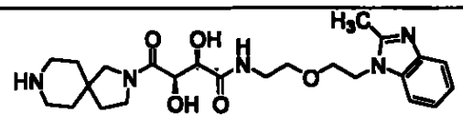
Se preparó Compuesto **1102** siguiendo los procedimientos descriptos en el Ejemplo 27A, Parte B, y se usó sin purificación adicional. HPLC-MS t_R = 2,0 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{31}H_{35}F_3N_4O_8$ 616,25, LCMS observada m/z 617,2 (M+H).

Parte I:

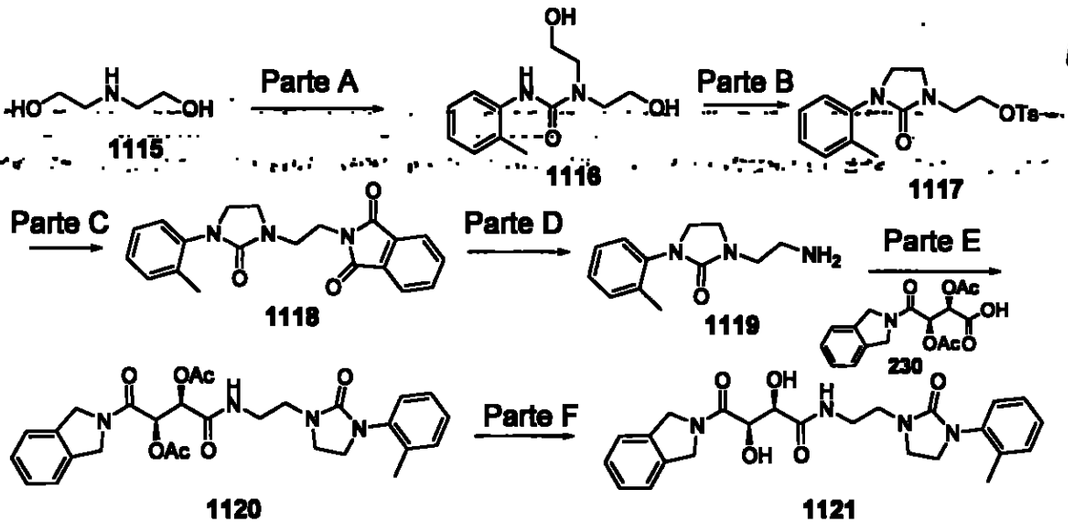
Se preparó Compuesto **1103** siguiendo los procedimientos descriptos en el Ejemplo 27A, Parte C. HPLC-MS t_R = 4,52 min. (10 min, $UV_{254\ nm}$); masa calculada para la fórmula $C_{27}H_{31}F_3N_4O_4$ 532,23, LCMS observada m/z 533,2 (M+H).

Los siguientes compuestos se sintetizaron usando procedimientos descriptos en el Ejemplo 30 A-C.

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
1104		566,2	567,2

1105		436,21	437,2
1106		386,2	387,2
1107		456,2	457,1
1108		490,18	491,1
1109		552,18	553,2
1110		518,2	519,1
1111		580,21	581,2
1112		514,2	515,2
1113		419,2	420,2
1114		473,3	474,3

Ejemplo 31:



Parte A:

Se disolvió Compuesto **1115** (790 mg, 7,5 mmol) en THF (10 ml) y se enfrió en un baño de hielo. Se agregó 2-metilfenilisocianato (500 mg, 3,75 mmol) en porciones y la solución resultante se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se desactivó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución HCl 1 N, solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 50% de acetato de etilo/hexanos) dio un sólido blanco **1116** (1,02 g, 56%). HPLC-MS t_R = 0,95 (UV_{254nm}); masa calculada para la fórmula $C_{12}H_{18}N_2O_3$ 238,1, LCMS observada m/z 239,2 (M+H).

Parte B:

Se disolvió Compuesto **1116** (1,02 g, 4,2 mmol) en THF (25 ml) y se enfrió en un baño de hielo. Se agregó T-butóxido de potasio (1,5 g, 13,2 mmol) en porciones y la mezcla de reacción se agitó durante 10 minutos. Se agregó gota a gota una solución de cloruro de *p*-toluensulfonilo (1,91 g, 10,8 mmol) en THF (5 ml) y la reacción se agitó 30 minutos a 0°C y 30 minutos a temperatura ambiente. La reacción se desactivó con agua y se extrajo con acetato de etilo. Las capas

orgánicas combinadas se lavaron con solución HCl 1 N, solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 50% de acetato de etilo/hexanos) dio un sólido blanco **1117** (0,750 g, 48%). HPLC-MS t_R = 1,87 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{19}H_{22}N_2O_4S$ 374,1, LCMS observada m/z 375,1 (M+H).

Parte C:

Se disolvió Compuesto **1117** (750 mg, 2,0 mmol) en DMF (10 ml) y se agregaron ftalamida (441 mg, 3,0 mmol) y carbonato de cesio (1,95 g, 6,0 mmol) y se agitó hasta el día siguiente. La mezcla de reacción se desactivó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución HCl 1 N, solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron. El residuo sólido se recristalizó a partir de acetato de etilo/hexanos para dar **1118** (500 mg, 72%) como un sólido blanco. HPLC-MS t_R = 1,63 ($UV_{254\ nm}$); masa calculada para la fórmula $C_{20}H_{19}N_3O_3$ 349,1, LCMS observada m/z 350,2 (M+H).

Parte D:

Se disolvió Compuesto **1118** (110 mg, 0,29 mmol) en etanol (3 ml) y se agregó hidrato de hidracina (0,10 ml). La reacción se agitó durante 3 horas a temperatura ambiente. Los sólidos se eliminaron mediante filtración y la solución se evaporó bajo presión reducida. El residuo se disolvió en solución de NaOH 1 N y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera; se secaron sobre sulfato de sodio y se concentraron para dar compuesto **1119** que se usó sin purificación adicional.

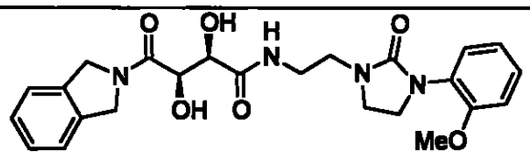
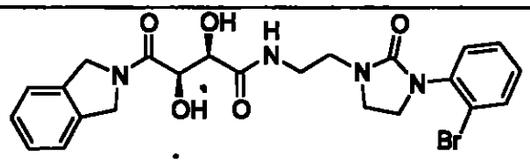
Parte E:

Se combinaron Compuesto **1119**, **230** (97 mg, 0,29 mmol), DIEA (0,125 ml, 0,7 mmol) y HATU (133 mg, 0,348 mmol) en DMF (3 ml) y se agitó hasta el día siguiente. La reacción se desactivó con agua y se extrajo con acetato de etilo.

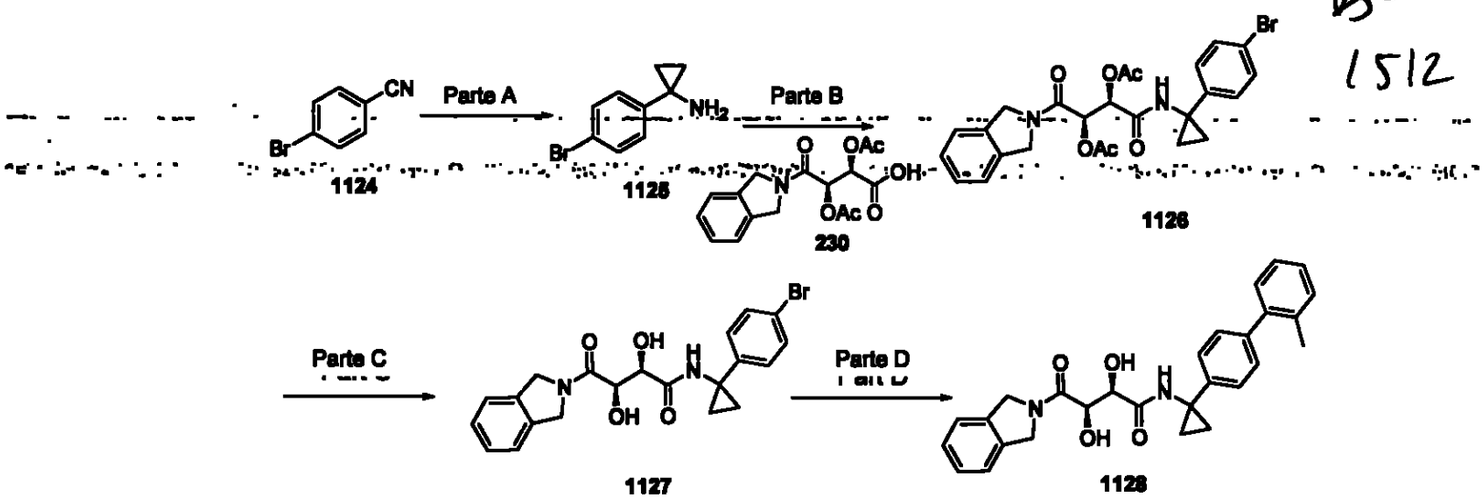
Las capas orgánicas combinadas se lavaron con solución HCl 1 N, solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron para dar compuesto **1120** que se usó en el paso siguiente sin purificación adicional. HPLC-MS t_R = 1,68 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{28}H_{32}N_4O_7$ 536,2, LCMS observada m/z 537,3(M+H).

Parte F:

Se disolvió Compuesto **1120** en metanol (5 ml) y se agregó carbonato de potasio (150 mg) y se agitó durante 30 minutos. La reacción se desactivó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución HCl 1 N, solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron. La purificación mediante LC prep. de fase reversa dio **1121** como un sólido blanco (16 mg) después de la liofilización. HPLC-MS t_R = 3,48 min. ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{24}H_{28}N_4O_5$ 452,2, LCMS observada m/z 453,1(M+H).

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
1122		468,20	469,1
1123		516,10	517,0

Ejemplo 32:



Parte A:

Se disolvió Compuesto **1124** (360 mg, 2,00 mmol) en dietiléter (10 ml) y se enfrió a -70 °C. Se agregó isopropóxido de titanio (624 mg, 2,2 mmol) y se agitó durante 10 minutos. Se agregó cloruro de Etilmagnesio (1M en THF, 4 ml, 4 mmol) gota a gota y la reacción se agitó otros 10 minutos a esta temperatura antes de calentar hasta temperatura ambiente y se agitó un adicional de 30 minutos. se agregó trifluoroeterato de boro (864 mg, 4 mmol) y la solución se agitó durante 2 horas. La reacción se desactivó con HCl 1 N y se lavó con dietiléter. La capa acuosa se hizo básica mediante la adición de solución de NaOH 1N y luego se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera; se secaron sobre sulfato de sodio y se concentraron para dar compuesto **1125** que se usó sin purificación adicional.

Parte B:

Se disolvió Compuesto **1125** en DMF (5 ml) y compuesto **230** (50 mg, 0,140 mmol) y HATU (69 mg, 0,182 mmol) se agregaron y se agitó hasta el día siguiente. La reacción se desactivó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con HCl 1N, solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 50% de acetato de etilo/hexanos) dio

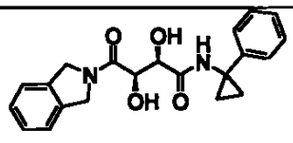
un sólido blanco **1126** (60 mg, 81%). HPLC-MS t_R = 1,928 ($UV_{254\ nm}$); masa calculada para la fórmula $C_{25}H_{25}BrN_2O_6$ 528,0, LCMS observada m/z 529,1 (M+H).

Parte C:

Se disolvió Compuesto **1126** (60 mg, 0,1427 mmol) en MeOH (5 ml) y se agregó carbonato de potasio (100 mg) seguido por agitación durante 30 minutos. La reacción se desactivó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron. La purificación mediante LC prep. de fase reversa dio un sólido blanco **1127** (10 mg, 15,8%) después de la liofilización. HPLC-MS t_R = 4,192 min. ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{21}H_{21}BrN_2O_4$ 444,0, LCMS observada m/z 445,1 (M+H).

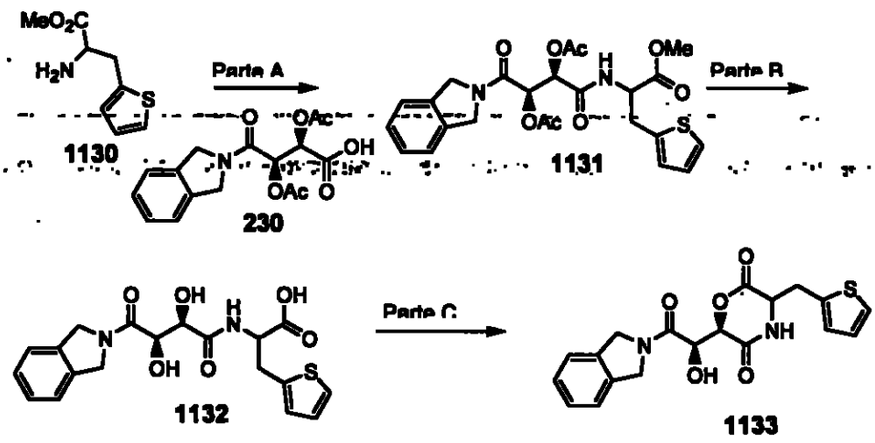
Parte D:

Se disolvió Compuesto **1127** (7,6 mg, 0,017 mmol) en dioxano (2 ml) y $Pd(dba)_3$ (3 mg), trifenilfosfina (4,4 mg, 0,017 mmol), fosfato de potasio (8 mg, 0,0377 mmol), y ácido 2-metilfenilboronico (4,3 mg, 0,034 mmol) se agregaron bajo una atmósfera de nitrógeno. La mezcla de reacción se calentó hasta 90 °C hasta el día siguiente y luego se filtró sobre un lecho de Celite y se concentró. La purificación mediante LC prep. de fase reversa dio un sólido blanco **1128** (5 mg, 65%) después de la liofilización. HPLC-MS t_R = 4,095 min. ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{28}H_{28}N_2O_4$ 456,2, LCMS observada m/z 457,3 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
1129		366,16	367,1

Ejemplo 33: Análogos Forzados

Ejemplo 33A:



Parte A:

A clorhidrato del metil éster del ácido 2-amino-3-tiofen-2-il-propiónico **(1130)** (120 mg, 0,54 mmol) en DMF (2 ml) se agregó **230** (150 mg, 0,45 mmol), DIEA (160 uM, 0,9 mmol) y HATU (205 mg, 0,54 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente, y se diluyó con acetato de etilo y agua. La capa orgánica se lavó con HCl 1N, saturado $NaHCO_3$, y salmuera. Se secó sobre Na_2SO_4, y se concentró, dando compuesto **1131.**

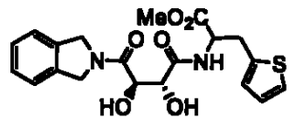
Parte B:

Se disolvió Compuesto **1131** en 5 ml de MeOH, se agregó 10 ml de 10% de solución de K_2CO_3 acuosa. Después de agitar a temperatura ambiente durante 1 h, la mezcla de reacción se concentró en *vacuo*, y luego se acidó con HCl 1N para PH 2. La solución luego se extrajo con EtOAc, la capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4, y se concentró, dando compuesto **1132** como un sólido blanco. Masa calculada para la fórmula $C_{19}H_{20}N_2O_6S$ 404,1, LCMS observada m/z 405,0,0 (M+H).

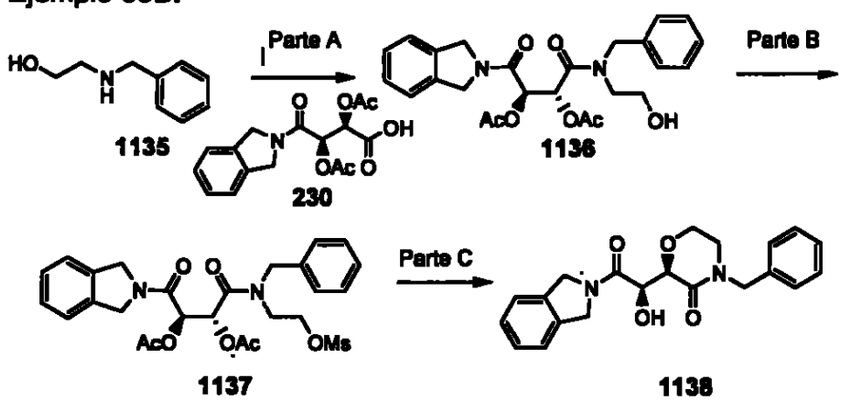
Parte C:

Se agregó Compuesto **1132** (40 mg, 0,1 mmol) en 1 ml de DMF con Resina de PS carbodiimida (117 mg, 1,28 mmol/g de carga, 0,15 mmol) y dimetilaminopiridina (3 mg, 0,024 mmol). Después de agitar hasta el día siguiente a 50 °C, el sólido se filtró, y la solución se concentró en *vacuo*. La purificación

mediante LC prep. de fase reversa dio compuesto **1133** como un sólido blanco. 1515 HPLC-MS t_R = 3,59 min. ($UV_{254\ nm}$, 10 min), Masa calculada para la fórmula $C_{25}H_{26}ClN_3O_4S$ 386,1, LCMS observada m/z 387,0 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
1134		418,1	419,0

Ejemplo 33B:



Parte A:

A 2-bencilamino-etanol (1135) (0,676 g, 4,5 mmol) en DMF (10 ml) se agregó **230** (1,0 g, 3 mmol), y HATU (1,71 g, 4,5 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente, y se diluyó con acetato de etilo y agua. La capa orgánica se lavó con HCl 1N, $NaHCO_3$ saturado y salmuera. Se secó sobre Na_2SO_4, y se concentró, dando el compuesto **1136** (1,1 g, 80%). Masa calculada para la fórmula $C_{25}H_{28}N_2O_7$ 468,2, LCMS observada m/z 469,1 (M+H).

Parte B:

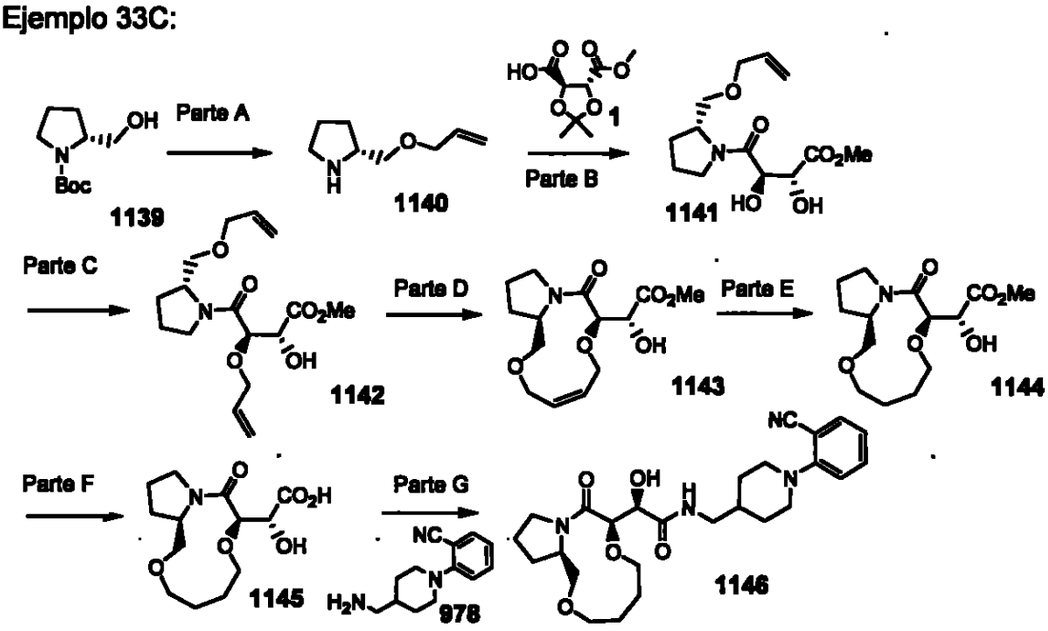
Se agregó gota a gota Compuesto **1136** (468 mg, 1 mmol) y DIEA (261 ml, 1,5 mmol) en CH_2Cl_2 (5 ml) con cloruro de mesilo (116 ml, 1,5 mmol) a 0 °C.

Después de agitar a 0 °C durante 10 min, la mezcla de reacción se dejó en agitación a temperatura ambiente durante 1,5 h, luego se concentró hasta que se secó. El residuo se extrajo con acetato de etilo, se lavó con HCl 1N, saturado $NaHCO_3$, y salmuera. Se secó sobre Na_2SO_4, y se concentró, dando **1137** (511 mg, 93%).

Parte C:

Se agregó Compuesto **1137** (389 mg, 0,71 mmol) en MeOH (20 ml) cn K_2CO_3 sólido (323 mg, 2,34 mmol). Después de agitar a temperatura ambiente durante 2 hrs. Se concentró para eliminar el solvente, luego se disolvió en EtOAc y agua. La capa orgánica se lavó con HCl 1N, saturado $NaHCO_3$, salmuera, y se concentró. La purificación mediante LC prep. de fase reversa dio **1138** como un sólido blanco. HPLC-MS t_R = 3,89 min. ($UV_{254\ nm}$, 10 min), Masa calculada para la fórmula $C_{21}H_{22}N_2O_4$ 366,16, LCMS observada m/z 367,1 (M+H).

Ejemplo 33C:



Parte A:

Paso 1: Se agregó (R)- Boc-prolinol (**1139**) (2,0 g, 9,94 mmol) en THF (5 ml) en NaH (0,437 g, 60% en mineral oil, 10,93 mmol) en 10 ml de THF a 0 oC. Después

de agitar a 0 °C durante 10 min, se agregó bromuro de alilo (1,32 g, 10,93 mmol). Se dejó la mezcla de reacción agitación hasta el día siguiente a temperatura ambiente. Después de la filtración, la solución se concentró hasta que se secó, el residuo se capturó con EtOAc, se lavó con ácido cítrico 1N, $NaHCO_3$ saturado, y salmuera, se secó sobre Na_2SO_4, y se concentró, dando un aceite incoloro (2,30 g, 96%).

Paso 2: Se agregó gota a gota el material anterior en CH_2Cl_2 (10 ml) con 3 ml de TFA a 0 oC. Después de agitar a temperatura ambiente durante 1 h, la solución se concentró. El residuo se disolvió en EtOAc, se lavó con se concentró Na_2CO_3, salmuera, se secó sobre Na_2SO_4, y se concentró, dando el compuesto **1140** como un aceite incoloro (1,06 g, 75% para 2 pasos).

Parte B:

Paso 1: Al compuesto **1140** (500 mg, 3,54 mmol) en DMF (10 ml) se agregó 1 (867 mg, 4,25 mmol) DIEA (1,48 ml, 8,5 mmol) y HATU (1,616 g, 4,25 mmol) a 0 °C. Después de agitar a temperatura ambiente durante 5 h, la mezcla de reacción se diluyó con acetato de etilo y agua. La fase orgánica se lavó con ácido cítrico 1 N, $NaHCO_3$ saturado, y salmuera. Se secó sobre Na_2SO_4, y se concentró. La purificación en columna (SiO_2, EtOAc/hexano 40:60) dio un aceite incoloro (650 mg, 57%).

Paso 2: Se trató el material anterior con 5 ml de TFA/H_2O (80:20) a 0 °C. Después de agitar a temperatura ambiente durante 2 h, Se concentró hasta que se secó. La purificación en columna (SiO_2, EtOAc/hexano 70:30) dio compuesto **1141** (500 mg, 88%) como un aceite incoloro.

Parte C:

Paso 1: Al compuesto **1141** (250 mg, 0,87 mmol) en tolueno (20 ml) se agregó óxido de dibutiltino (217 mg, 0,87 mmol). La mezcla de reacción se reflujó durante 1 h, usando un dispositivo Dean-stark para la remoción azeotrópica de

agua. Después de enfriar hasta temperatura ambiente, el solvente se deshizo hasta que se secó bajo presión reducida. El aceite resultante se secó en *vacuo* durante 2 h.

Paso 2: Al aceite anterior se agregó CsF (198 mg, 1,30 mmol). La mezcla se colocó entonces in *vacuo* durante 2 h. se agregó Bromuro de alilo (220 mg, 1,83 mmol) en DMF (10 ml) a 0 °C. Después de agitar a temperatura ambiente bajo argón durante 30 h, la mezcla de reacción se concentró, y luego se capturó con EtOAc. La solución se lavó con solución saturada de KF, y salmuera, se secó sobre Na_2SO4, y se concentró. La capa orgánica se lavó con HCl 1N, $NaHCO_3$ saturado, salmuera, y se concentró. La cromatografía en columna (SiO_2, EtOAc/hexano 60:40) dio compuesto **1142** como un aceite incoloro (130 mg, 45%). Masa calculada para la fórmula $C_{18}H_{25}NO_6$ 327,17, LCMS observada m/z 328,1 (M+H).

Parte D:

Se agregó Compuesto **1142** (110 mg, 0,33 mmol) en diclorometano (200 ml) con catalizador de segunda generación de Grubbs' (Scholl, M.; Ding, S.; Lee, C.W.; Grubbs, R.H., *Org. Lett*, **1999**, *1*, 953-956,). Después de agitar a temperatura ambiente bajo argón durante 3,5 h, la solución se concentró bajo presión reducida. La cromatografía en columna (SiO_2, EtOAc) dio **1143** como un sólido blanco (60 mg, 60%), Masa calculada para la fórmula $C_{14}H_{21}NO_6$ 299,14, LCMS observada m/z 300,1 (M+H).

Parte E:

To **1143** (60 mg, 0,2 mmol) en EtOAc (10 ml) se agregó 10% de Pd/C (10 mg). La mezcla de reacción se dejó en agitación a temperatura ambiente bajo H_2 durante 2 h, luego se concentró. La cromatografía en columna (SiO_2, EtOAc) dio **1144** como un sólido blanco (50 mg, 83%), Masa calculada para la fórmula $C_{14}H_{23}NO_6$ 301,15, LCMS observada m/z 302,1 (M+H).

Parte F:

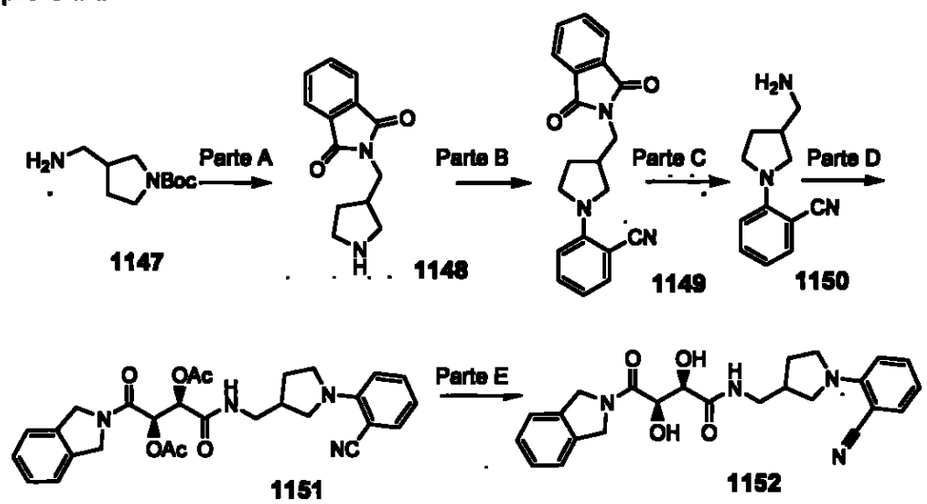
Compuesto **1144** (20 mg, 0,067 mmol) en MeOH (2 ml) se mezcló con K_2CO_3 sólido (20 mg, 0,14 mmol). Después de agitar a temperatura ambiente durante 5 h, la mezcla de reacción se concentró, y se capturó con EtOAc y agua. Se acidó con HCl 1N. La capa orgánica se separó, se lavó con salmuera, se secó sobre Na_2SO_4, y se concentró para dar **1145** como un sólido blanco (12 mg, 63%), Masa calculada para la fórmula $C_{13}H_{21}NO_6$ 287,1, LCMS observada m/z 288,1 (M+H).

Parte G:

Se agitó una mezcla de **1145** (12 mg, 0,042 mmol), **978** (13,5 mg, 0,063 mmol), DIEA (0,018 ml, 0,1 mmol) y HATU (24 mg, 0,063 mmol) en DMF (1 ml) hasta el día siguiente a temperatura ambiente, y luego se diluyó con acetato de etilo y agua. La capa orgánica se lavó con HCl 1N, $NaHCO_3$ saturado, y salmuera. Se secó sobre Na_2SO_4, y se concentró. La purificación mediante LC prep. de fase reversa dio **1146** como un sólido blanco. HPLC-MS t_R = 4,22 min. (UV_{254} nm, 10 min), masa calculada para la fórmula $C_{21}H_{22}N_2O_4$ 484,3, LCMS observada m/z 485,2 (M+H).

Ejemplo 34

Ejemplo 34A:



Parte A

Paso 1: Se agitó una mezcla de 3-(aminometil)-1-N-(*ter*-butoxicarbonil)-pirrolidina (1147) (200 mg, 1,0 mmol), ftalato de monometilo (216 mg, 1,2 mmol), EDC (229 mg, 1,2 mmol), HOBt (162 mg, 1,2 mmol) y trietilamina (0,79 ml, 2,0 mmol) en DCM (4 ml) hasta el día siguiente. La mezcla de reacción se diluyó con DCM y se lavó con HCl 0,1 N, agua, solución de bicarbonato de sodio saturado, agua, y salmuera, se secó sobre sulfato de sodio y se concentró. El residuo se purificó mediante cromatografía en columna (SiO_2, 33% de EtOAc/hexano) para dar un sólido blanco (110 mg, 33%). HPLC-MS t_R = 1,89 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{18}H_{22}N_2O_4$ 330,2, LCMS observada m/z 353,2 (M+Na).

Paso 2: Compuesto **1148** se preparó a partir del material del paso 1 siguiendo el procedimiento según se describe en el Ejemplo 27 Parte A paso 2.

Parte B

Se preparó Compuesto **1149** siguiendo el procedimiento según se describe en el Ejemplo 27 Parte A paso 1, HPLC-MS t_R = 1,96 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{20}H_{17}N_3O_2$ 331,1, LCMS observada m/z 332,2 (M+H).

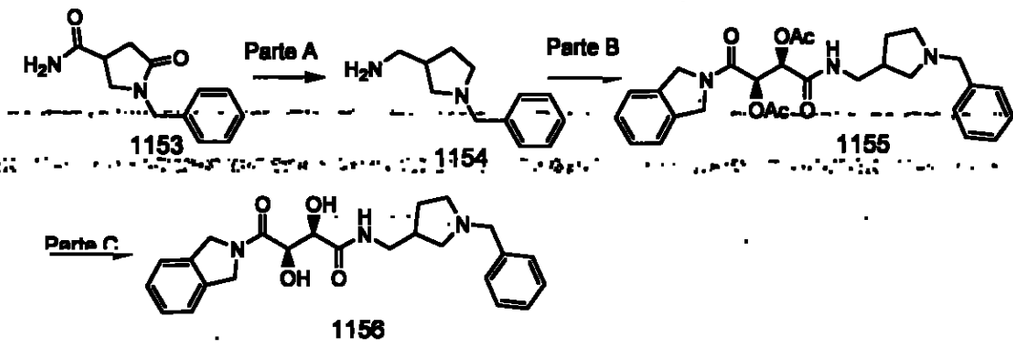
Parte C

Se reflujaron Compuesto **1149** (0,33 mmol) e hidrato de hidracina (65 µl, 1,34 mmol) en etanol (3 ml) durante 2 horas. La mezcla de reacción se enfrió y se filtró. El filtrado se concentró y **1150** se usó sin purificación adicional.

Parte D y E

Se prepararon Compuestos **1151** y **1152** siguiendo los procedimientos descriptos en el Ejemplo 5 Parte D y E. Datos para **1151**: HPLC-MS t_R = 1,78 min. ($UV_{254\ nm}$); masa calculada para la fórmula C28H30N4O6 518,2, LCMS observada m/z 519,2 (M+H). Datos para **1152**: HPLC-MS t_R = 1,52 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{24}H_{26}N_4O_4$ 434,2, LCMS observada m/z 435,2 (M+H).

Ejemplo 34B:



1156

Parte A

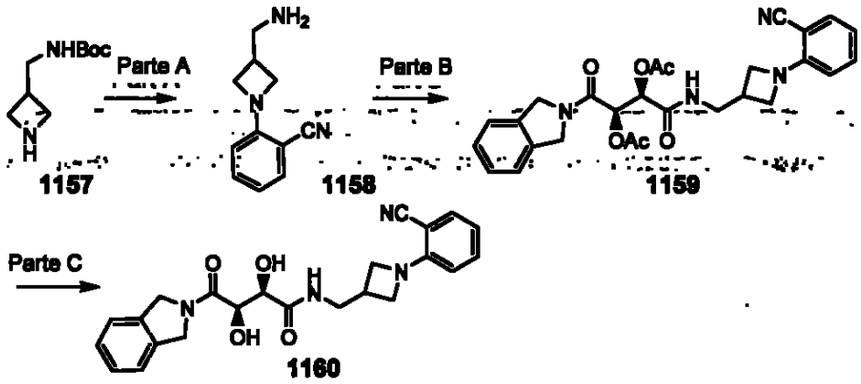
A una solución de 1-bencil-5-oxo-3-pirrolidinacarboxamida (**1153**) (50 mg, 0,23 mmol) en THF (1 ml) se agregó solución 1M de hidruro de litio aluminio en THF (0,69 ml, 0,69 mmol). La mezcla de reacción se agitó a 50 °C durante 3 horas, se enfrió, se desactivó con solución de cloruro de sodio acuoso. Después de la adición de solución de hidróxido de sodio 1N, la mezcla se diluyó con acetato de etilo, se agitó durante 20 minutos, y se filtró a través de un lecho de Celite. El filtrado se lavó con solución de hidróxido de sodio 1N y salmuera, se secó sobre sulfato de sodio y se concentró para dar **1154** como un aceite (14 mg, 32%). HPLC-MS t_R = 0,22 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{12}H_{18}N_2$ 190,2, LCMS observada m/z 191,2 (M+H).

Parte B y C

Se prepararon Compuestos **1155** y **1156** siguiendo los procedimientos descriptos en el Ejemplo 5 Parte D y E. Datos para **1156**: HPLC-MS t_R = 0,91 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{24}H_{29}N_3O_4$ 423,2, LCMS observada m/z 424,1 (M+H).

Ejemplo 35

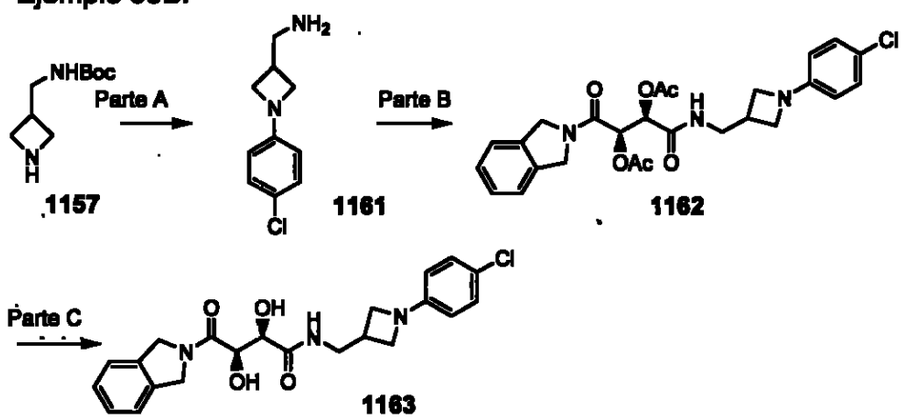
Ejemplo 35A:



Parte A y B y C:

Se prepararon Compuestos **1158, 1159** y **1160** siguiendo los procedimientos descriptos en el Ejemplo 27 Parte A, B y C. Datos para **1158**: HPLC-MS t_R = 0,76 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{11}H_{13}N_3$ 187,1, LCMS observada m/z 188,1 (M+H). Datos para **1159**: HPLC-MS t_R = 1,72 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{27}H_{28}N_4O_8$ 504,2, LCMS observada m/z 505,1 (M+H). Datos para **1160**: HPLC-MS t_R = 1,43 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{23}H_{24}N_4O_4$ 420,2, LCMS observada m/z 421,1 (M+H).

Ejemplo 35B:



Parte A

Paso 1: Se agitó una mezcla de ter-butil éster del ácido azetidin-3-ilmetil-carbámico (**1157**) (20 mg, 0,107 mmol), 4-cloro-1-yodobenceno (38,4 mg, 0,161

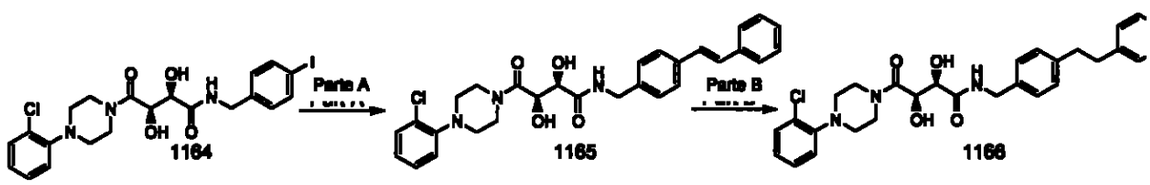
mmol), cobre yoduro (4,0 mg, 0,021 mmol), L-prolina (4,8 mg, 0,042 mmol) y carbonato de potasio (29,6 mg, 0,214 mmol) en DMSO (2 ml) bajo atmósfera de argón a 80 °C hasta el día siguiente. La mezcla de reacción se diluyó con EtOAc, se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró. HPLC-MS t_R = 2,13 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{15}H_{21}ClN_2O_3$ 296,1, LCMS observada m/z 297,2 (M+H).

Paso 2: Compuesto **1161** se preparó a partir del material del paso 1 siguiendo el procedimiento según se describe en el Ejemplo 27 Parte A paso 2.

Parte B y C

Se prepararon Compuestos **1162** y **1163** siguiendo los procedimientos descriptos en el Ejemplo 5 Parte D y E. Datos para **1162**: HPLC-MS t_R = 1,93 min. ($UV_{254\ nm}$); masa calculada para la fórmula C26H28ClN3O6 513,2, LCMS observada m/z 514,2 (M+H). Datos para **1163**: HPLC-MS t_R = 1,63 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{22}H_{24}ClN_3O_4$ 429,2, LCMS observada m/z 430,1 (M+H).

Ejemplo 36:



Se preparó Compuesto **1164** usando procedimientos descriptos en el Ejemplo 2, HPLC-MS t_R = 1,88 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{21}H_{23}ClIN_3O_4$ 543,0, LCMS observada m/z 544,0 (M+H).

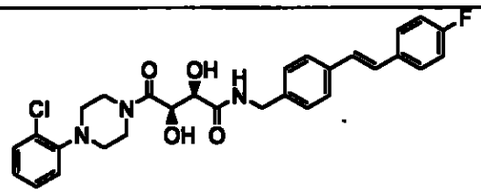
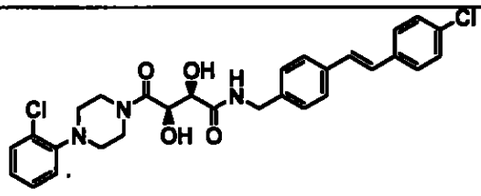
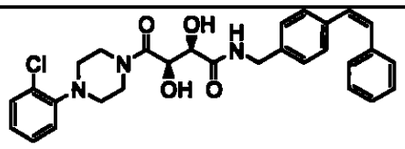
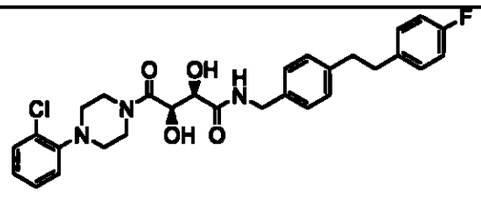
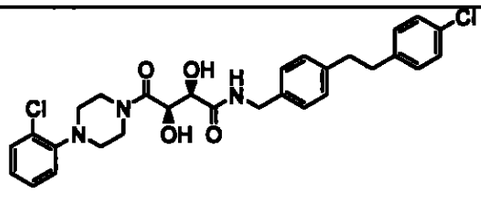
Parte A:

Se preparó Compuesto **1165** a partir de **1164** y ácido estirinil borónico usando las condiciones de acoplamiento descriptas en el Ejemplo 3 Parte F.

HPLC-MS t_R = 2,11 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{29}H_{30}ClN_3O_4$ 519,2, LCMS observada m/z 520,0 (M+H).

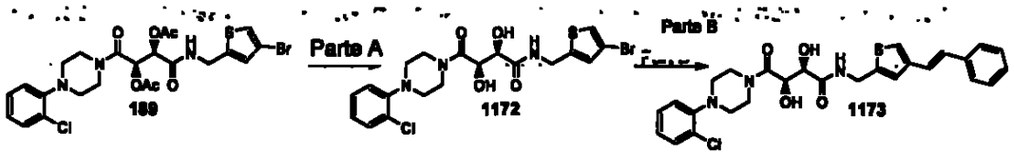
Parte B:

Se agitó una mezcla de **1165** (10 mg, 0,02 mmol) y paladio sobre carbono (10 % en peso, 2 mg) en THF (2 ml) bajo hidrógeno (presión atmosférica) hasta el día siguiente. La mezcla de reacción se filtró a través de Celite y se concentró. La purificación mediante LC prep. dio **1166** como un sólido blancuzco (5 mg). HPLC-MS t_R = 5,42 min. ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{29}H_{32}ClN_3O_4$ 521,2, LCMS observada m/z 522,2 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
1167		537,2	538,1
1168		553,2	554,0
1169		519,2	520,2
1170		539,2	540,2
1171		555,2	556,0

Ejemplo 37: Suzuki alquilo

Ejemplo 37A:



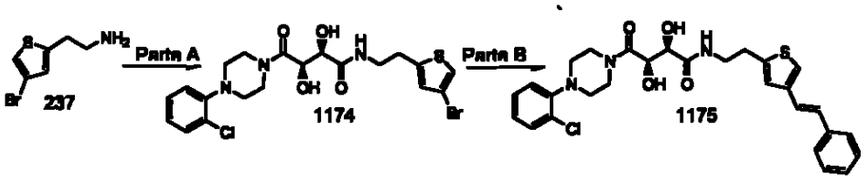
Parte A:

Se preparó Compuesto **1172** a partir de **189** usando los procedimientos descriptos en el Ejemplo 2A Parte B. HPLC-MS t_R = 4,83 min. ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{18}H_{21}BrClN_3O_4S$ 501,0, LCMS observada m/z 502,0 (M+H).

Parte B:

Se preparó Compuesto **1173** usando los procedimientos descriptos en el Ejemplo 36 Parte A. HPLC-MS t_R = 5,37 min. ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{27}H_{28}ClN_3O_4S$ 525,2, LCMS observada m/z 526,2 (M+H).

Ejemplo 37B:



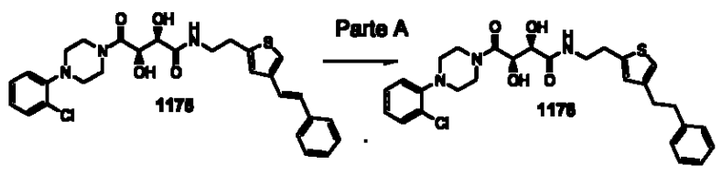
Parte A:

Se preparó Compuesto **1174** a partir de **237** usando los procedimientos descriptos en el Ejemplo 2, HPLC-MS t_R = 4,76 min. ($UV_{254\ nm}$, 10 min); Masa calculada para la fórmula $C_{20}H_{23}BrClN_3O_4S$ 515,0, LCMS observada m/z 516,0 (M+H).

Parte B:

Se preparó Compuesto **1175** usando los procedimientos descriptos en el Ejemplo 36 Parte A. HPLC-MS t_R = 2,29 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{26}H_{30}ClN_3O_4S$ 539,2; LCMS observada m/z 540,2 (M+H).

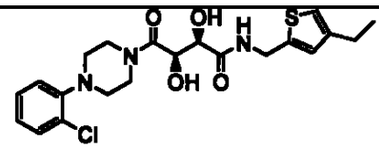
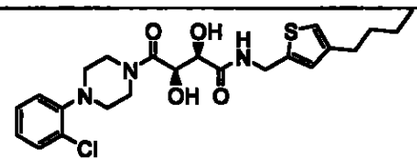
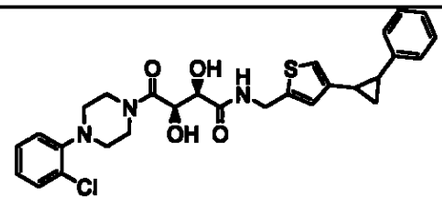
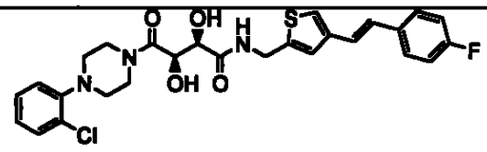
Ejemplo 37C:

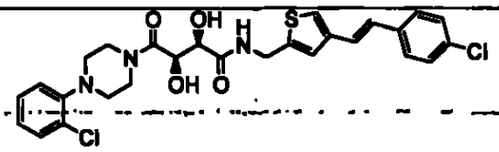
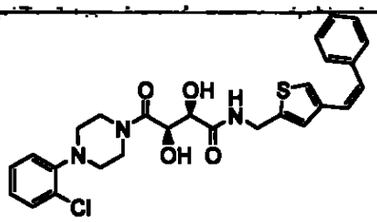
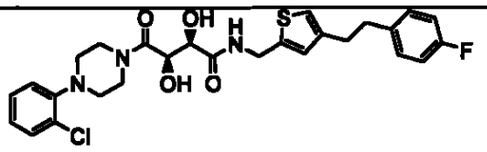
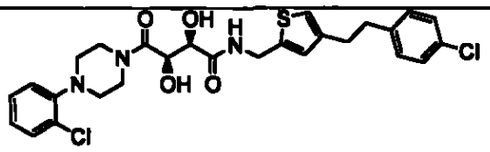
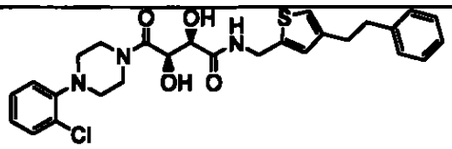
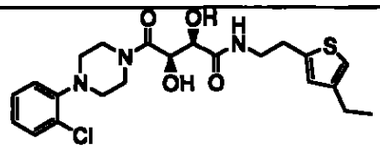
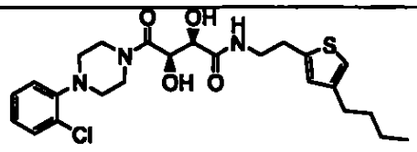
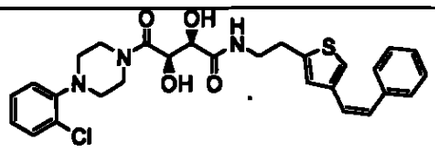


Parte A:

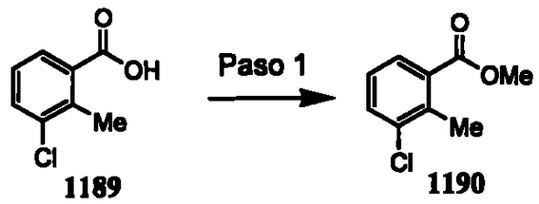
Se preparó Compuesto **1176** usando procedimientos descriptos en el Ejemplo 36 Parte B.

HPLC-MS t_R = 5,50 min. ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{28}H_{32}ClN_3O_4S$ 541,2, LCMS observada m/z 542,2 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
1177		451,1	452,2
1178		479,2	480,2
1179		539,2	540,1
1180		543,1	544,0

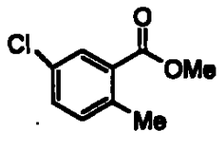
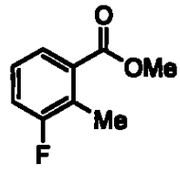
1181		**559,1**	**560,0**
1182		**525,2**	**526,2**
1183		**545,2**	**546,1**
1184		**561,1**	**562,0**
1185		**527,2**	**528,1**
1186		**465,2**	**466,1**
1187		**493,2**	**494,1**
1188		**539,2**	**540,1**

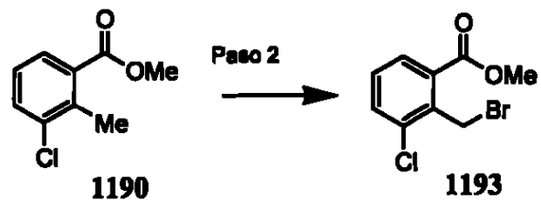
Ejemplo 38: Análogos de Isoindolina



Paso 1

A ácido 3-cloro-2-metilbenzoico **1189** (4,95 g, 0,0290 mol) disuelto en DMF (70 ml) se agregó carbonato de cesio (14,18 g, 0,0435 mol) y metil yoduro (5,35 g, 2,3 ml, 0,0377 mol). La mezcla de reacción se agitó a temperatura ambiente durante 20 h. La mezcla de reacción se concentró, y se agregó EtOAc (200 ml). La solución orgánica se lavó con agua (2 x 100 ml), se secó ($MgSO_4$), se filtró y se concentró para dar 4,43 g (83%) del producto **1190** como un aceite amarillo. MS para M-Cl:149

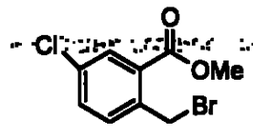
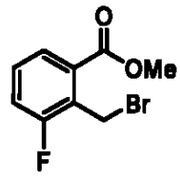
Compuesto #	Estructura	MS
1191		M-Cl: 149
1192		M+1: 169

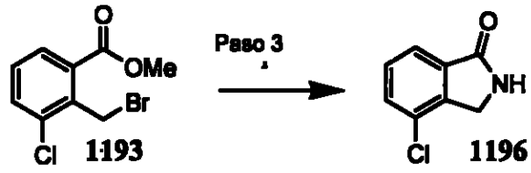


1190 **1193**

Paso 2

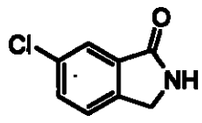
Al compuesto **1190** (4,42 g, 0,0239 mol) disuelto en CCl_4 (100 ml) se agregó n-bromosuccinimida (5,11 g, 0,287 mol) y peróxido de benzoilo (0,58 g, 0,00239 mol). La mezcla de reacción se calentó a reflujo durante 16 h luego se enfrió hasta temperatura ambiente. El sólido se eliminó mediante filtración y se lavó con CH_2Cl_2. El filtrado se concentró para dar 7,80 g del producto **1193** con succinimida como un aceite amarillo y mezcla sólida.

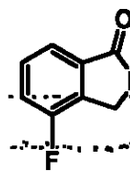
Compuesto #	Estructura
1194	
1195	

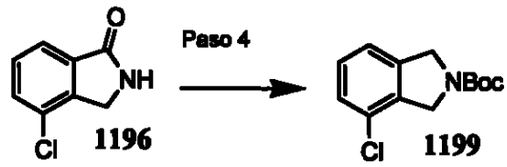


Paso 3

Se disolvió Compuesto **1193** (6,31 g, 0,0239 mol) en NH_3 7 N en MeOH (50 ml) y se agitó a temperatura ambiente durante 3 h luego se calentó a reflujo durante 4 h. La mezcla de reacción se enfrió hasta temperatura ambiente y se concentró. El residuo se suspendió en CH_2Cl_2 (150 ml), y el sólido se eliminó mediante filtración y se lavó con CH_2Cl_2. El filtrado se concentró, y el producto bruto se purificó mediante gel de sílice la cromatografía flash (eluyente: 5% MeOH-CH_2Cl_2 a 10% de MeOH-CH_2Cl_2) para dar 3,68 g (92%) del producto **1196** como un sólido blanco. MS para M+1: 168,

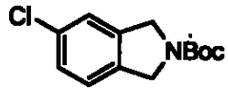
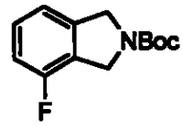
Compuesto #	Estructura	MS (M+1)
1197		168

1198		152

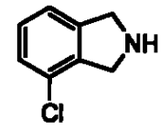
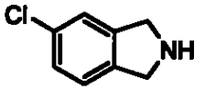
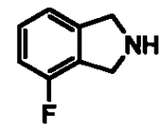


Paso 4

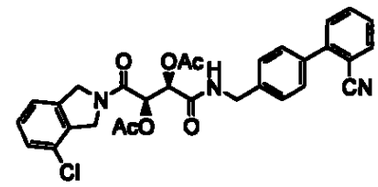
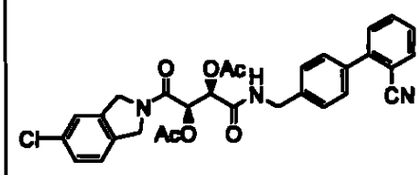
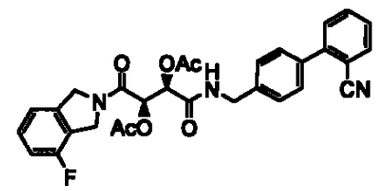
Al compuesto **1196** (1,00 g, 5,97 mmol) suspended en THF seco (15 ml) se agregó boro (1 M en THF, 14,9 ml, 14,0 mmol). La mezcla de reacción se calentó a reflujo durante 5 h luego se enfrió hasta 0°C. Se agregaron cuidadosamente en porciones EtOH (15 ml) y carbonato de potasio (2 g). La mezcla de reacción se calentó a reflujo durante 16 h luego se enfrió hasta 0 °C, y $(tBOC)_2O$ (1,95 g, 8,95 mmol) se agregó. La mezcla de reacción se agitó a temperatura ambiente durante 3 h luego se concentró. Se agregó Agua (30 ml), y la solución acuosa se extrajo con 3 x 30 ml de CH_2Cl_2, Los extractos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se concentraron. El producto bruto se purificó mediante gel de sílice la cromatografía flash (eluyente: 5% de EtOAc-CH_2Cl_2) para dar 0,56 g (37%) del producto **1199** como un aceite amarillo. MS para M+1-tBu: 198.

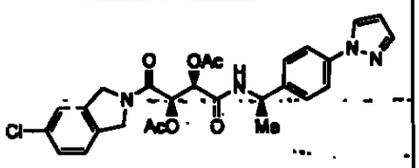
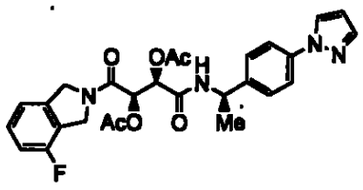
Compuesto #	Estructura	MS
1200		M+2-tBu = 198
1201		M+2-tBu: 182

Se prepararon los siguientes intermediarios de acuerdo con el procedimiento del Ejemplo 11B Parte F...

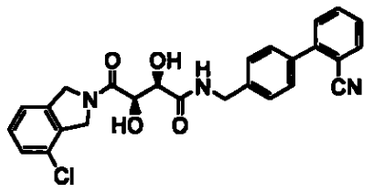
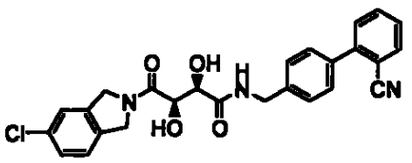
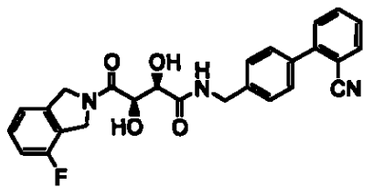
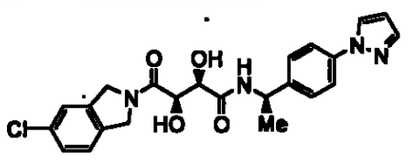
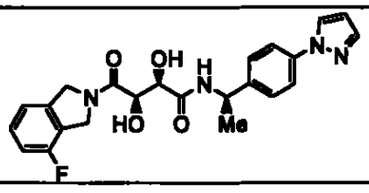
Compuesto #	Estructura	MS (M+1)
1202		154
1203		154
1204		138

Los siguientes intermediarios se prepararon de acuerdo con el procedimiento del Ejemplo 2

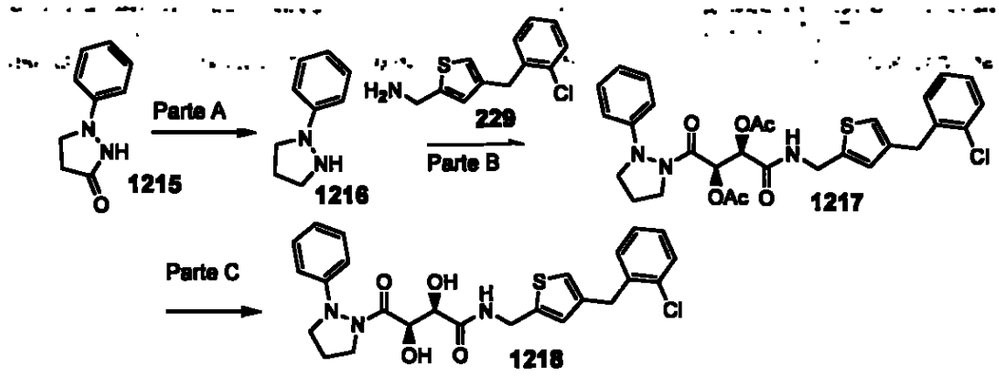
Compuesto #	Estructura	MS (M+1)
1205		560
1206		560
1207		544

1208		539
1209		523

Los siguientes compuestos se prepararon de acuerdo con el procedimiento del Ejemplo 2

Compuesto #	Estructura	MS (M+1)
1210		476
1211		476
1212		460
1213		455
1214		439

Ejemplo 39: Hidrazinoamidas



Parte A:

Se agregó gota a gota 1-fenil-pirazolidin-3-ona (**1215**)(1,0 g, 6,16 mmol) en 15 ml de THF a la mezcla de $AlCl_3$ (0,82 g, 6,16 mmol) y 12 ml de $LiAlH_4$ 1 M (12 mmol) en THF a 0°C bajo argón. La mezcla de reacción se dejó entonces en agitación a temperatura ambiente durante 4 h. Se desactivó con 10 ml de solución de NH4Cl 1N, se diluyó con EtOAc y 15% de solución acuosa de NaOH. Después de la filtración, la capa orgánica se separó, se secó sobre Na_2SO_4, y se concentró. Cromatografía en columna (SiO_2, EtOAc/hexano, 20:80) dio **1216** como un aceite incoloro.

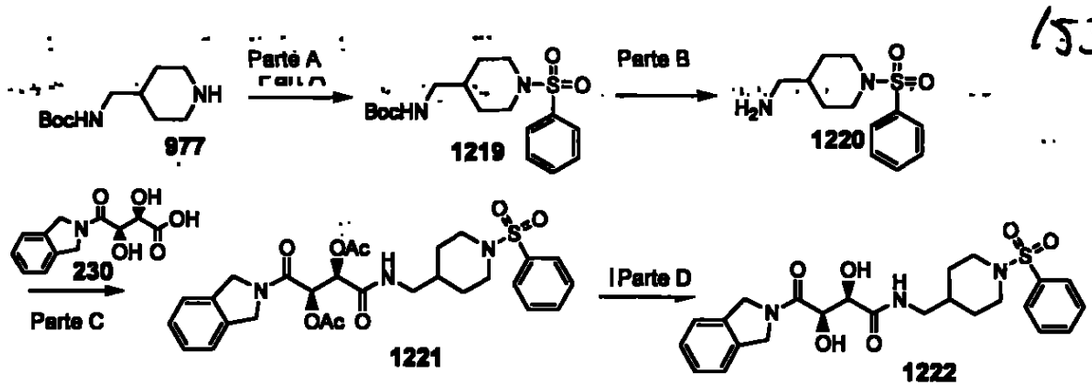
Parte B:

Se preparó Compuesto **1217** de acuerdo con el procedimiento descripto en el Ejemplo 2A Parte A de **1216** (15 mg, 0,1 mmol).

Parte C:

Se disolvió Compuesto **1217** en 1 ml de MeOH, se agregó 0,5 ml de NH_3 7N en MeOH. Después de agitar a temperatura ambiente durante 1 h, la mezcla de reacción se concentró en *vacuo*. La purificación mediante LC prep. de fase reversa dio compuesto **1218** como un sólido blanco. HPLC-MS t_R = 5,09 min. ($UV_{254\ nm}$, 10 min), Masa calculada para la fórmula $C_{25}H_{26}ClN_3O_4S$ 499,1, LCMS observada m/z 500,0 (M+H).

Ejemplo 40: Piperidin Sulfonamidas



Parte A:

Se agregó lentamente cloruro de fenilsulfonilo (212 mg, 1,2 mmol) a una solución de 4-(Boc-aminometil)piperidina (**977**) (214 mg, 1 mmol) en 1,0 ml de piridina a 0 °C. La mezcla de reacción se dejó en agitación a temperatura ambiente hasta el día siguiente, y se diluyó con acetato de etilo y agua. La capa orgánica se lavó con ácido cítrico 1 N, $NaHCO_3$ saturado, y salmuera. Se secó sobre Na_2SO_4, y se concentró, dando **1219** (320 mg, 90%). Masa calculada para la fórmula $C_{17}H_{26}N_2O_4S$ 354,2, LCMS observada m/z 355,2 (M+H), 299,2 (M-55)

Parte B:

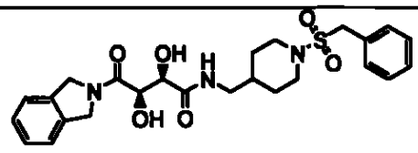
A la solución de **1219** (200 mg, 0,54 mmol) en THF (5 ml) se agregó 2 ml de HCl 4 N en dioxano. La mezcla de reacción se agitó a temperatura ambiente durante 1 h, y se concentró para dar **1220** (105 mg, 66 %).

Parte C:

A **1220** (105 mg, 0,36 mmol) en DMF (2 ml) se agregó **230** (100 mg, 0,3 mmol), DIEA (750 µl, 0,6 mmol) y HATU (137 mg, 0,36 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente, y se diluyó con acetato de etilo y agua. La capa orgánica se lavó con HCl 1 N, $NaHCO_3$ saturado, y salmuera. Se secó sobre Na_2SO_4, y se concentró, dando **1221**.

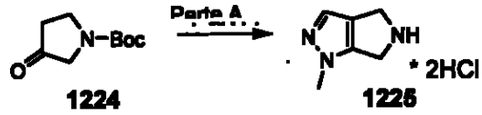
Parte D:

Se disolvió Compuesto **1221** en 4 ml de MeOH, se agregó 2 ml de NH_3 7N en MeOH. Después de agitar a temperatura ambiente durante 1 h, la mezcla de reacción se concentró en *vacuo*. La purificación mediante LC prep. de fase reversa dio **1222** como un sólido blanco. HPLC-MS t_R = 3,59 min. ($UV_{254\ nm}$, 10 min), Masa calculada para la fórmula $C_{24}H_{29}N_3O_6S$ 488,2, LCMS observada m/z 488,1 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
1223		501,2	502,1

Ejemplo 41: Análogos heterocíclicos de isoindolina

Ejemplo 41A:

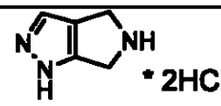
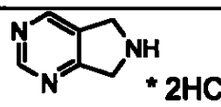


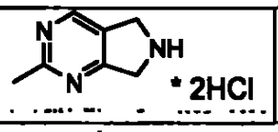
1224 **1225**

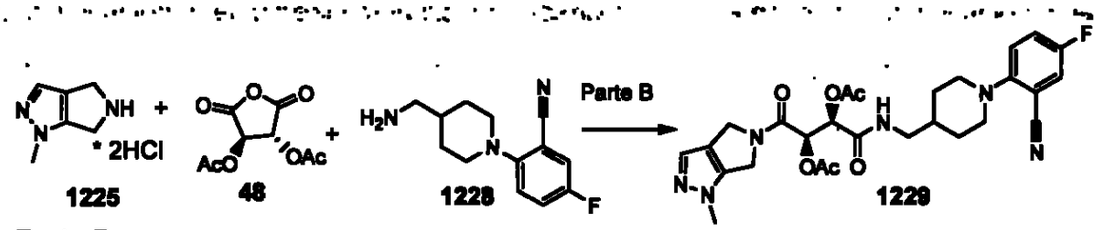
Parte A:

Se preparó Compuesto **1225** (70% de rendimiento global) a partir de **1** de acuerdo con los procedimientos de Fukui, H. *et. al.* (*Heterocycles* **2002**, *56*, 257)

Los siguientes análogos se prepararon de acuerdo con esta referencia:

Compuesto #	Estructura	Rendimiento global
1225		73%
1226		47%

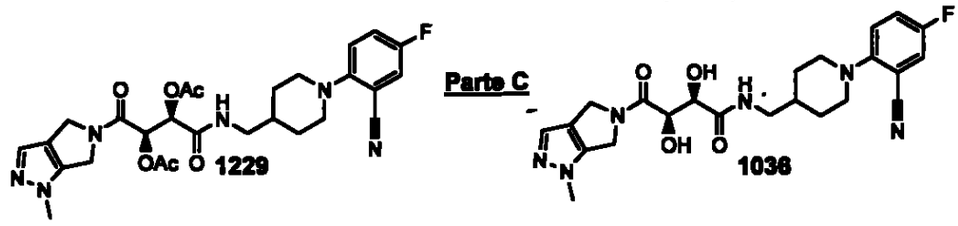
1227		66%



1225 48 1228 1229

Parte B:

Se preparó Compuesto **1228** de acuerdo con procedimientos descriptos en el Ejemplo 27A. HPLC-MS t_R = 0,95 min. (UV_{254nm}); masa calculada para la fórmula C13H16FN3 233,1, LCMS observada m/z 234,2 (M+H). Compuesto **1229** se preparó de acuerdo con los procedimientos descriptos en el Ejemplo 2A Parte A. HPLC-MS t_R = 1,57 min. ($UV_{254\ nM}$); masa calculada para la fórmula $C_{27}H_{31}FN_6O_8$ 554,23, LCMS observada m/z 555,2 (M+H).

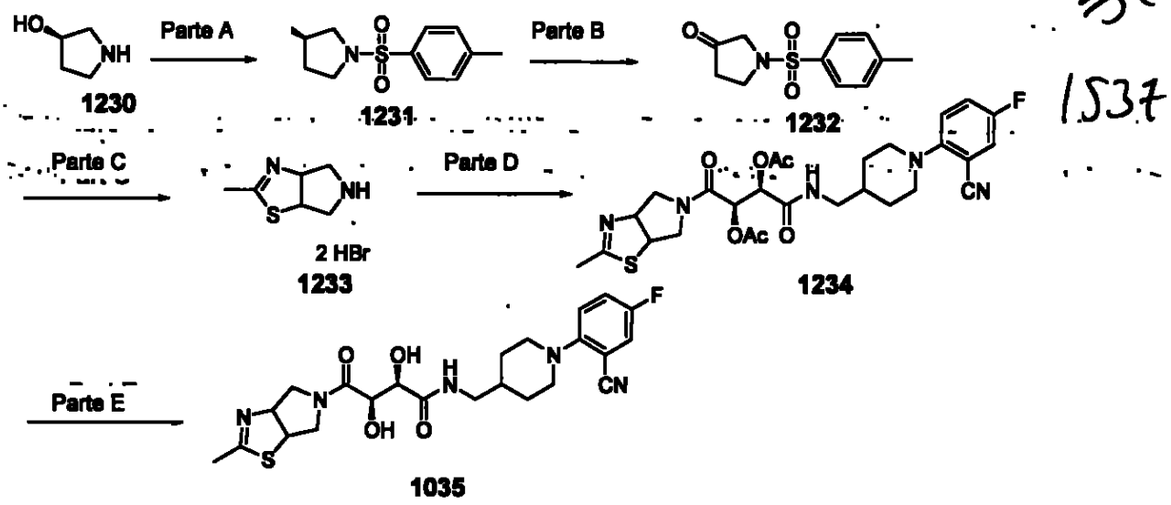


1229 Parte C 1036

Parte C:

Se sintetizó el compuesto **1036** usando el procedimiento que se encuentra en Ejemplo 2A, Parte B. La purificación mediante LC prep. de fase reversa dio un sólido blanco después de la liofilización. HPLC-MS t_R = 3,39 min. ($UV_{254\ nM}$, 10 min); masa calculada para la fórmula $C_{23}H_{27}FN_6O_4$ 470,21, LCMS observada m/z 471,2 (M+H).

Ejemplo 41B:



Parte A:

Se disolvió Compuesto **1230** (2,18 g, 17,7 mmol) en cloruro de metileno (35 ml) y se enfrió en un baño de hielo. Se agregó Trietilamina (5 ml, 35,4 mmol) seguido por cloruro de p-toluensulfonilo (3,35 g, 17,7 mmol) en porciones. La mezcla de reacción se agitó durante 3 horas a temperatura ambiente y luego se desactivó con agua y se extrajo con cloruro de metileno. Las capas orgánicas combinadas se lavaron con solución HCl 1 N, solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron para dar el producto deseado **1231** (3,85 g), que se usó sin purificación adicional. HPLC-MS t_R = 1,26 min. (UV_{254nm}); masa calculada para la fórmula $C_{11}H_{15}NO_3S$ 241,08, LCMS observada m/z 242,2 (M+H).

Parte B:

Se disolvió Compuesto **1231** (3,82 g, 15,78 mmol) en cloruro de metileno (100 ml) y clorocromato de piridinio (6,7 g, 31 mmol) se agregó seguido por tamices moleculares triturados (3,5 g). La reacción se agitó hasta el día siguiente y se agregó luego dietiléter (150 ml) y se continuó la agitación durante una hora adicional. Los sólidos se filtraron y el solvente se evaporó bajo presión reducida. La purificación mediante cromatografía en columna (SiO_2, 50% de acetato de etilo/hexanos) dio un sólido blanco **1232** (3,20 g, 84%). HPLC-MS t_R = 1,43 min.

($UV_{254\ nM}$); masa calculada para la fórmula $C_{11}H_{13}NO_3S$ 239,06, LCMS observada m/z 240,1.(M+H).

Parte C:

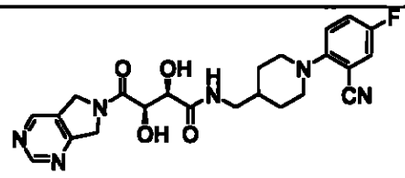
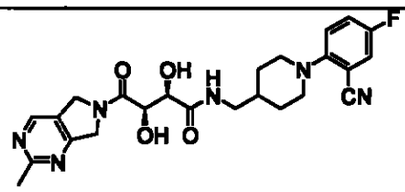
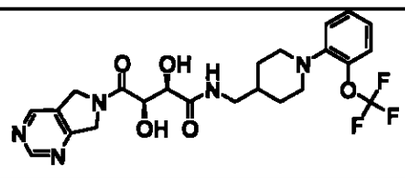
Las reacciones se llevaron a cabo usando procedimientos de Heterocycles, Vol. 41, No. 7, 1995.

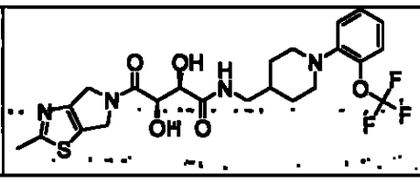
Parte D:

La reacción se llevó a cabo usando el procedimiento que se encuentra en Ejemplo 2A, Parte A. **1234**: HPLC-MS t_R = 1,702 min. ($UV_{254\ nM}$); masa calculada para la fórmula $C_{27}H_{30}FN_5O_6S$ 571,19, LCMS observada m/z 572,2 (M+H).

Parte E:

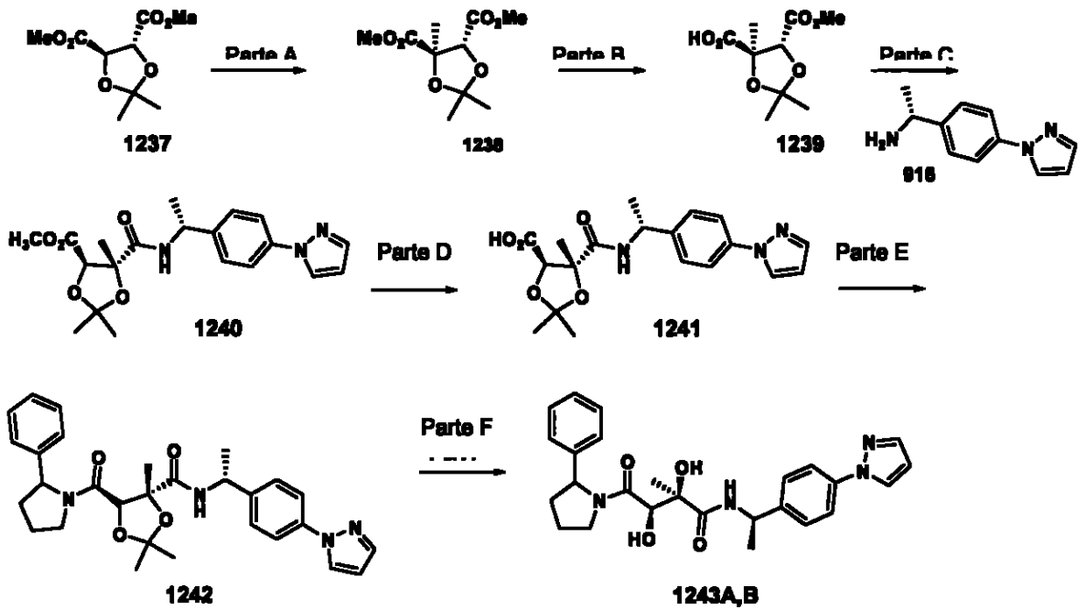
La reacción se llevó a cabo usando el procedimiento que se encuentra en Ejemplo 2A, Parte B. La purificación mediante LC prep. de fase reversa dio un sólido blanco después de la liofilización. **1035**: HPLC-MS t_R = 3,66 min. ($UV_{254\ nM}$, 10 min); masa calculada para la fórmula $C_{23}H_{28}FN_5O_4S$ 487,2, LCMS observada m/z 488,2 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
1235A		468,2	469,2
1235B		482,2	483,2
1236A		509,2	510,2

1236B		528,2	529,2

Ejemplo 42:

Ejemplo 42A:



Parte A:

A una solución de dimetil 2,3-O-isopropiliden-L-tartrato **1237** (10,9 g, 50 mmol) en THF seco (150 ml) y DMPU (25 ml) se agregó metil yoduro (4,7 ml, 75,5 mmol). La mezcla de reacción se enfrió hasta -78 °C y se agregó una solución 1M en THF de $LiN(TMS)_2$ (55ml, 55 mmol) mediante un embudo de goteo en un período de 45 minutos a la mezcla de reacción. La mezcla de reacción de THF se agitó a -78 °C durante 2 horas luego se calentó hasta -20 °C y se desactivó cuidadosamente con agua (20 ml). La mezcla de reacción se vertió en EtOAc (150 ml) y la capa orgánica se separó y se lavó con agua (1 x 50 ml) seguido por salmuera (1 x 50 ml). La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró. La purificación mediante cromatografía en columna (SiO_2, 10% de Et_2O/hexano seguido por 15% de Et_2O/hexano) dio el compuesto deseado **1238**.

como aceite claro (9,7 g, 83%). LCMS m/z: 233,1 (M+H).

Parte B:

Se preparó una solución del buffer de pH 8 buffer por medio de la titulación de una solución de fosfato de sodio 0,1 M (300 ml) con HCl 1M para un pH final de 8. A una mezcla del compuesto **1238** en solución del buffer de pH 8 se agregó esterasa (41 unidades/mg,15 mg, 615 unidades). Se agregó lentamente NaOH ac. 1N (6,5 ml) mediante jeringa durante un período de 3,5 horas a la mezcla de reacción para mantener el pH de la mezcla de reacción en el rango de 7,9-8,2, La mezcla de reacción se extrajo con Et_2O (2 x 50 ml). La capa acuosa se acidó a pH 3 usando HCl 12N luego se extrajo con EtOAc (4 x 25 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron en *vacuo* para dar el compuesto deseado **1239** (1,36 g, 72%). LCMS m/z: 219,1 (M+H).

Parte C:

A una solución de compuesto **916** (0,1 g, 0,535 mmol) en DMF (1,5 ml) se agregó compuesto **1239** (0,092 g, 0,5 mmol), trietil amina (0,2 ml, 1,4 mmol) y HATU (0,365 g, 0,96 mmol). La mezcla de reacción se agitó durante 18 horas y luego se diluyó con CH_2Cl_2 (5 ml) y se lavó con solución ac. NaOH 0,5N (3 ml). La capa orgánica se secó sobre $MgSO_4$ y se concentró. La purificación mediante cromatografía en columna (SiO_2, 30% de EtOAc/hexano seguido por 40% de EtOAc/hexano) dio el compuesto **1240** como una espuma blanca (0,162 g, 67%). LCMS m/z 388,1 (M+H).

Parte D:

A una solución de compuesto **1240** (0,175 g, 0,452 mmol) en THF (2 ml) y MeOH (2 ml) a 0 °C se agregó LiOH ac. 1,0 M (0,91 ml, 0,91 mmol). La mezcla de reacción se calentó hasta temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se acidó con HCl ac. 1N (0,95 ml) y se diluyó con salmuera

(1,5 ml) y se extrajo con EtOAc (2 x 10 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron para dar compuesto **1241** como una espuma blanca (0,182 g, 100%): LCMS m/z: 374,1 (M+H).

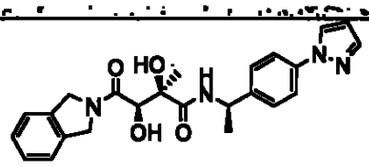
Parte E:

A una solución de compuesto **1241** (0,179 g, 0,48 mmol) en DMF (3 ml) se agregó sal de cloruro de hidrógeno 2-fenilpirrolidina (0,092 g, 0,5 mmol), trietil amina (0,2 ml, 1,4 mmol) y HATU (0,365 g, 0,96 mmol). La mezcla de reacción se agitó durante 4,5 horas y luego se diluyó con EtOAc (10 ml) y se lavó con agua (1,5 ml) seguido por salmuera (1,5 ml). La capa orgánica se secó sobre $MgSO_4$ y se concentró. El residuo se purificó mediante cromatografía de placa prep. (SiO_2, 66% de EtOAc/hexano). Se aislaron dos compuestos diastereoméricos **1242**. EL Compuesto diastereomérico **1242A** (0,067 g, 28%), LCMS m/z 503,1 (M+H) y el compuesto diastereomérico **1242B** (0,095 g, 28%), LCMS m/z 503,1 (M+H).

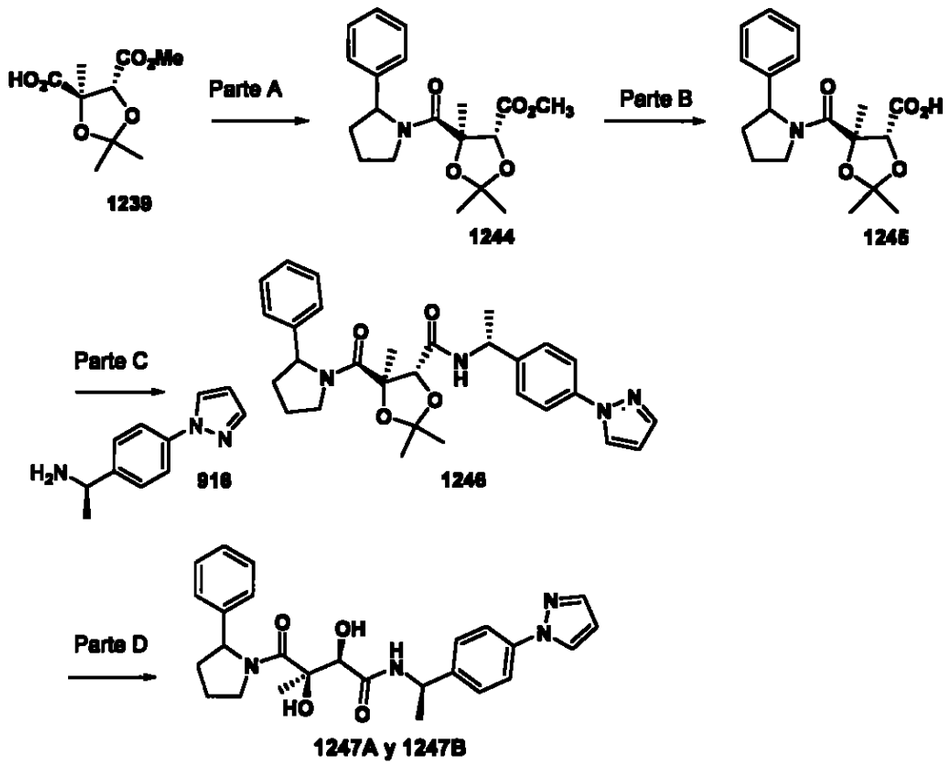
Parte F:

A una solución de compuesto **1242A** (0,06 g, 0,119 mmol) en CH_2Cl_2 (1 ml) se agregó TFA (4 ml) seguido por agua (0,5 ml). La mezcla de reacción se agitó a 80 °C de temperatura durante 3 horas y luego se concentró. El residuo se purificó mediante cromatografía en columna (SiO_2, 5% MeOH/CH_2Cl_2) para dar **1243A** (0,012 g, 22%), LCMS m/z 463,1 (M+H).

A una solución de compuesto **1242B** (0,088 g, 0,18 mmol) en CH_2Cl_2 (1 ml) se agregó TFA (4 ml) seguido por agua (0,5 ml). La mezcla de reacción se agitó a 23 °C de temperatura durante 18 horas y luego se concentró. El residuo se purificó mediante cromatografía en columna (SiO_2, 5% MeOH/CH_2Cl_2) para dar **1243B** (0,05 g, 66%), LCMS m/z 463,1 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
1243C		434,2	435,1

Ejemplo 42B:



Parte A:

A una solución de compuesto **1239** (200 mg, 0,917 mmol) y 2-fenilpirrolidina (177 mg, 0,96 mmol) en CH_2Cl_2 (5 ml) a 23°C se agregó DIEA (0,35 ml, 2,01 mmol) seguido por PyBOP (0,367 g, 1,146 mmol) y la mezcla de reacción se agitó durante 18 horas. La mezcla de reacción se concentró y el residuo se

purificó mediante cromatografía en columna (SiO_2, 20% de EtOAc/hexano seguido por 30% de EtOAc/hexano) para dar el compuesto deseado **1244** como un aceite (0,16 g, 50%). LCMS m/z: 348,1 (M+H).

Parte B:

Se transformó Compuesto **1244** en el compuesto **1245** usando el procedimiento según se describe en el Ejemplo 42A Parte D. LCMS m/z: 374,1 (M+H).

Parte C:

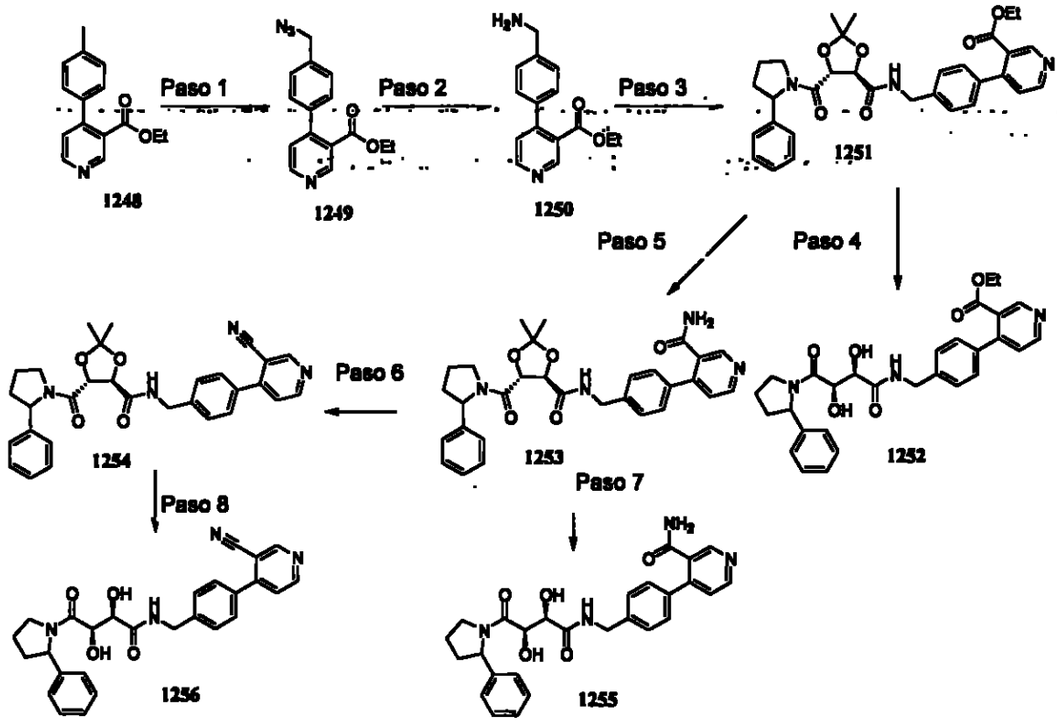
Se transformó Compuesto **1245** en el compuesto **1246** usando el procedimiento según se describe en el Ejemplo 42A Parte E. LCMS m/z: 503,1 (M+H).

Parte D:

Se transformó Compuesto **1246** a **1247A** y **1247B** usando el procedimiento según se describe en el Ejemplo 42A Parte F. Se aislaron dos compuestos diastereoméricos **1247**. El diastereómero **1247A** (16% de producción), LCMS m/z: 463,1 (M+H) y el diastereómero **1247B** (16% de producción), LCMS m/z: 463,1 (M+H).

Ejemplo 43:

Ejemplo 43A:



Paso 1:

Se preparó Compuesto **1248** de acuerdo con el procedimiento de la literatura: Shiao, M.-J.; Liu, K.-H.; Lin, P.-Y *Heterocycles* **1993**, *36*, 3, 507,

Se agitó una solución de **1248** (2,20 g, 9,10 mmol), NBS (1,81 g, 10,20 mmol), 1,1'-azobis(ciclohexancarbonitrilo) (0,113 g, 0,46 mmol) en CCl_4 (40 ml) a 75 °C durante 24 horas. La reacción se enfrió hasta temperatura ambiente, y la mezcla se diluyó con CH_2Cl_2 y Na_2CO_3 sat. La capa orgánica se removió, y la fase acuosa se extrajo con CH_2Cl_2 (4x). Los orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El producto bruto mixture se usó sin purificación adicional.

Se agitó una solución de mezcla del producto bruto preparado anteriormente y azida de sodio (0,75 g, 11,5 mmol) en una mezcla del solvente de MeOH (15 ml)/DMF(15 ml)/DMSO (15 ml) a temperatura ambiente durante 24 horas. La reacción se diluyó con H_2O y EtOAc. La capa orgánica se eliminó, y la fase acuosa se extrajo con EtOAc (1x). Los orgánicos combinados se lavaron con

H_2O (3x), salmuera (1x), se secó (Na_2SO_4), se filtraron y se concentraron. El aceite marrón resultante se purificó mediante cromatografía de gel de sílice para dar **1249** (1,2 g; 4,25 mmol, 47% de producción en dos pasos). MS m/e: 283,1 (M+H).

Paso 2:

A una solución de **1249** (1,2 g, 4,2 mmol) en THF (20 ml) a temperatura ambiente se agregó PPh_3 (1,1g, 4,2 mmol). La reacción se agitó a temperatura ambiente durante 1 hora en dicho momento se agregó H_2O (2 ml). La mezcla resultante se agitó durante 24 horas. Después de la concentración, la mezcla se capturó en Et_2O y HCl 0,25 N. La fase orgánica se eliminó, y la fase acuosa se tornó básica con Na_2CO_3 sat. y se extrajo con EtOAc (4x). Los orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El compuesto se purificó mediante cromatografía de gel de sílice para dar **1250** (0,51 g, 47% de producción). MS m/e: 257,1 (M+H).

Paso 3:

se preparó Compuesto **1251** con **1250** en de manera similar a lo enunciado anteriormente en el Ejemplo 12B.

Paso 4:

Se preparó Compuesto **1252** en un diseño similar a **1251** según se expuso anteriormente en el Ejemplo 12B. MS m/e: 518,1 (M+H).

Paso 5:

A una solución de **1251** (0,20 g, 0,36 mmol) en THF (2 ml)/MeOH (2 ml)/ H_2O (2 ml) se agregó LiOH (0,050 g, 1,2 mmol). La reacción se agitó a temperatura ambiente durante 20 horas. La reacción se acidó a pH ~ 4 con HCl 1N y se diluyó con EtOAc. La capa orgánica se eliminó y la fase acuosa se extrajo con EtOAc (3x). Los orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El compuesto se usó sin purificación adicional.

A la mezcla bruta del producto preparado anteriormente en CH_2Cl_2 (2 ml) se agregó NMM (0,200 ml, 1,82 mmol), EDCI (0,100 g, 0,52 mmol), y HOBt (0,059 g, 0,38 mmol). Esta mezcla se agitó durante 10 minutos en dicho momento se agregó NH_4Cl (0,100 g, 1,86 mmol). Después de 72 horas de agitación, la reacción se desactivó con H_2O y se diluyó con EtOAc. La capa orgánica se eliminó, y la fase acuosa se extrajo con EtOAc (3x). Los orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se purificó mediante cromatografía de gel de sílice para dar **1253** (0,062 g, 61 % de producción en dos pasos). MS m/e: 529,1 (M+H).

Paso 6:

A una solución de **1253** (0,050 g, 0,095 mmol) en CH_2Cl_2 (2 ml) se enfrió hasta 0 °C se agregó DIEA (0,050 ml, 0,28 mmol) seguido por TFAA (0,030 ml, 0,22 mmol). La reacción se agitó a 0 °C durante 3 horas y luego se desactivó con NaOH 1 N. La capa orgánica se eliminó, y la fase acuosa se acidó con HCl 1N a pH ~ 4. La fase acuosa luego se extrajo con EtOAc (3x). Los orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se purificó mediante cromatografía de gel de sílice para dar **1254** (0,042 g, 0,082 mmol, 88% de producción). MS m/e: 511,1 (M+H).

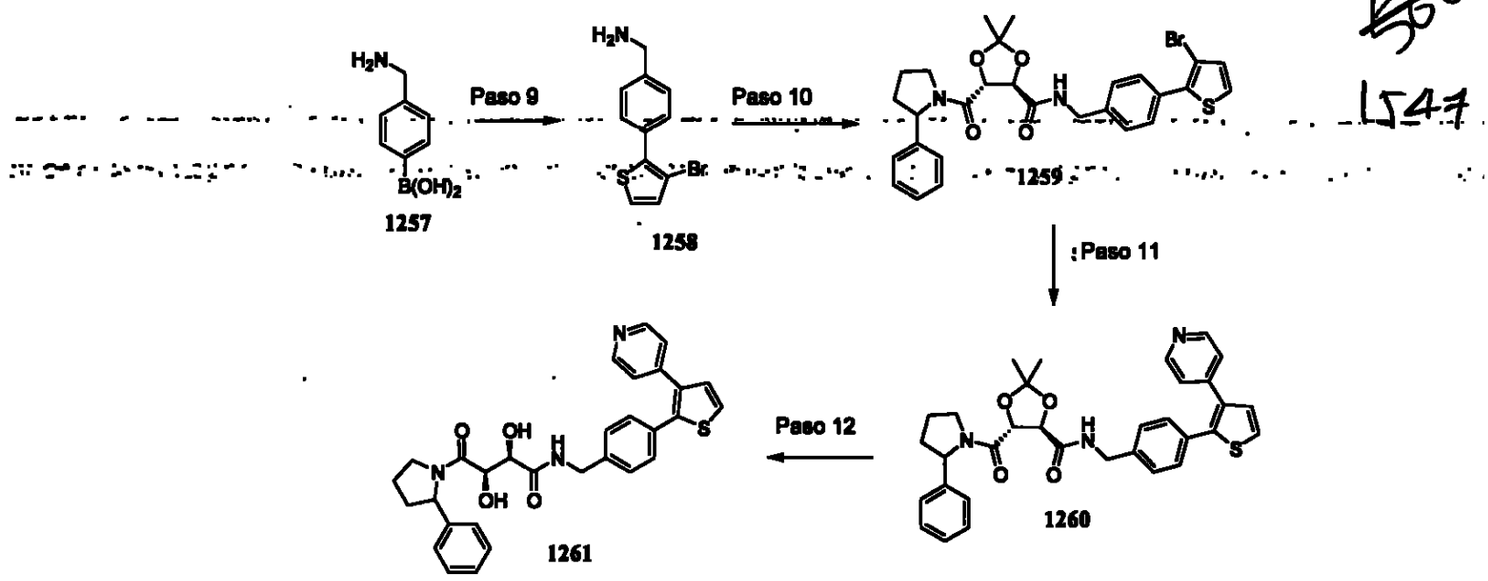
Paso 7:

Se preparó Compuesto **1255** de un modo similar a partir de **1253** según se expuso anteriormente en el Ejemplo 12B. MS m/e: 489,1 (M+H).

Paso 8:

Se preparó Compuesto **1256** de un modo similar a partir de **1254** según se expuso anteriormente en el Ejemplo 12A. MS m/e: 471,1 (M+H).

Ejemplo 43B:



Paso 9:

Una solución de clorhidrato del ácido aminometilfenil borónico (**1257**) (2,0 g, 10,7 mmol), 2,3-dibromotiofeno (2,7 g, 11,0 mmol), y $Pd(dppf)Cl_2$ (0,51 g, 0,69 mmol) en CH_3CN (40 ml)/K_2CO_3 1 M (40 ml) se agitó a 80 °C durante 3 horas. La reacción se enfrió hasta temperatura ambiente y se diluyó con EtOAc. La capa orgánica se eliminó, y la fase acuosa se extrajo con EtOAc (3x). Los orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El aceite marrón se purificó mediante cromatografía de gel de sílice para dar **1258** (1,4 g, 5,3 mmol, 50% de producción) como un aceite marrón. MS m/e: 268,1 (M+H).

Paso 10:

Se preparó Compuesto **1259** de un modo similar a partir de **1258** según se expuso anteriormente en el Ejemplo 12B. MS m/e: 569,1 (M+H).

Paso 11:

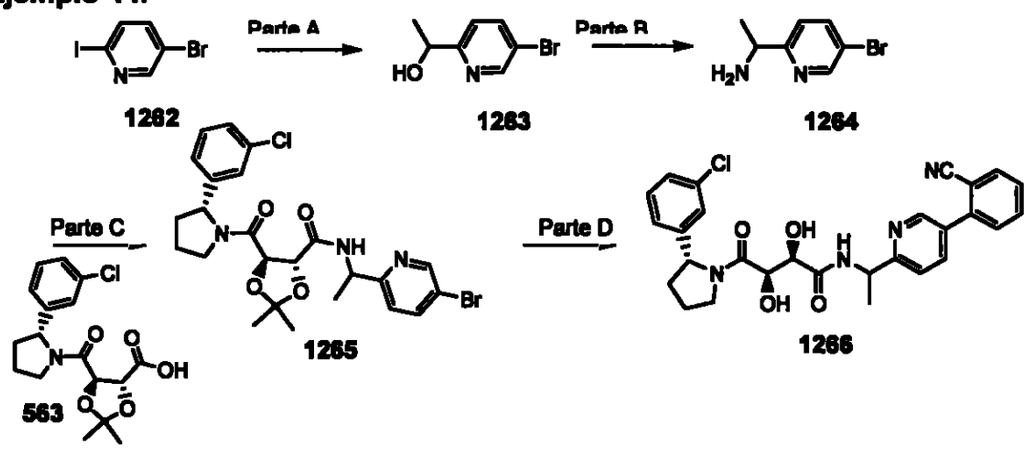
Se calentó una solución de **1259** (0,059 g, 0,10 mmol), ácido piridin-4-yl borónico (0,017 g, 0,14 mmol), y $Pd(dppf)Cl_2$ (0,010 g, 0,014 mmol) en CH_3CN (1 ml)/ K_2CO_3 1 M (1 ml) en un microondas SmithCreator (recipiente de 2-5 ml, 150°C durante 5 minutos). El líquido se concentró, y el residuo se purificó

mediante cromatografía de gel de sílice para dar **1260** (0,057 g, 0,10 mmol, 99% de producción). MS m/e: 568,1 (M+H).

Paso 12:

Se preparó Compuesto **1261** de un modo similar a partir de **1260** según se expuso anteriormente en el Ejemplo 12A MS m/e: 528,1 (M+H).

Ejemplo 44:



Parte A:

Se agregó cloruro de isopropilmagnesio (2,0 M de solución en THF, 5 ml, 10 mmol) gota a gota a la solución de 2-yodo-5-bromopiridina (1262) en THF (20 ml) a –40°C en un baño de acetonitrilo/hielo seco. Después de agitar durante 1 h a esta temperatura durante 1 h, se agregó lentamente acetaldehído (0,615 ml, 1 mmol) en 5 ml de THF. La mezcla de reacción se dejó en agitación a –40 °C durante 0,5 h, luego se desactivó con solución de NH_4Cl 1 N (5 ml), y se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo y agua. Se separó la capa orgánica, se lavó con NH_4Cl 1N, salmuera, se secó sobre Na_2SO_4, y se concentró, dando **1263** como un aceite incoloro (1,95 g, 97%). ^1H RMN ($CDCl_3$, 300 MHz), δ 8,58 (d, J = 2,4 Hz, 1H), 7,80 (dd, J = 8,6, 2,4 Hz, 1H), 7,21 (d, J = 8,6Hz, 1H), 4,87 (br q, J = 6,2 Hz, 1H), 3,79 (br s, 1H), 1,50 (d, J = 6,2 Hz, 3H). Masa calculada para la fórmula C_7H_8BrNO 200,98, LCMS observada m/z 202,0 (M+H).

Parte B:

Se agregó diisopropilazodicarboxilato (1,2 g, 6 mmol) en THF (5 ml) a una solución de **1263** (1,0 g; 5 mmol), ftalimida (0,88 g, 6 mmol) y trifenilfosfina (1,57 g, 6 mmol) en 20 ml de THF. Después de agitar hasta el día siguiente a temperatura ambiente, la mezcla de reacción se concentró hasta que se secó. Luego, se disolvió en 30 ml de etanol, se agregó con monohidrato de hidracina (5 ml), se calentó a reflujo durante 3 h. La mezcla de reacción se filtró y se concentró el filtrado. El residuo se disolvió con acetato de etilo y HCl 1N. La fase acuosa se extrajo con acetato de etilo. El extracto orgánico se desechó. La fase acuosa se agregó con NaOH 1N a pH 12. Se extrajo con EtOAc (30 ml x 3). El extracto del éster se combinó, se lavó con salmuera, se secó sobre Na_2SO_4, y se concentró, dando **1264** (0,61 g, 61%). ^1H RMN ($CDCl_3$, 300 MHz), δ 8,58 (s, 1H), 7,75 (dd, J = 8,1, 2,0 Hz, 1H), 7,23 (d, J = 8,5 Hz, 1H), 4,15 (q, J = 6,5 Hz, 1H), 1,43 (d, J = 6,5 Hz, 3H). Masa calculada para la fórmula $C_7H_9BrN_2$ 199,99, LCMS observada m/z 201,0 (M+H).

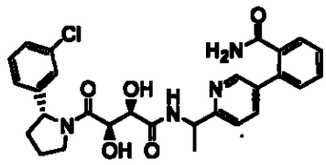
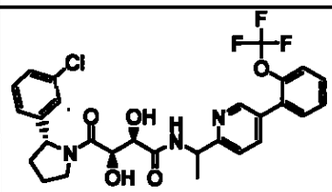
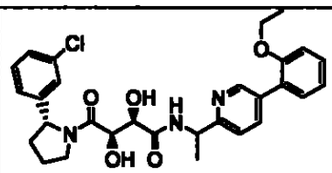
Parte C:

A **1264** (400 mg, 2 mmol) en DMF (5 ml) se agregó **563** (707 mg, 2 mmol), y HATU (912 mg, 2,4 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente, y se diluyó con acetato de etilo y agua. La capa orgánica se lavó con $NaHCO_3$ saturado, y salmuera. Se secó sobre Na_2SO_4, y se concentró, dando **1265** (600 mg, 56%). Masa calculada para la fórmula $C_{24}H_{27}BrClN_3O_4$ 535,09, LCMS observada m/z 534,1 (M+H).

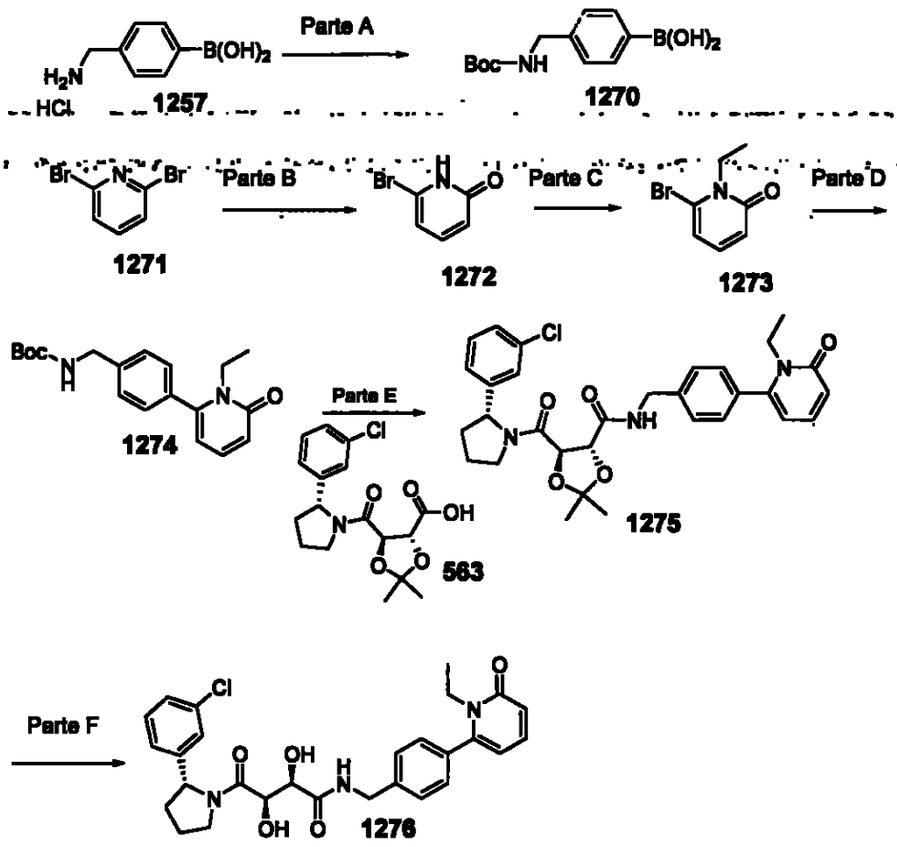
Parte D:

Paso 1: A **1265** (120 mg, 0,22 mmol) en 1 ml de dioxano, agregado con ácido 2-cianofenilboronico (49 mg, 0,33 mmol), fosfato de potasio (142 mg, 0,66 mmol) y $PdCl_2$(dppf) (7,2 mg, 0,0088 mmol, 4 mol%). La mezcla de reacción se agitó

hasta el día siguiente a 80 °C bajo argón, luego se diluyó con EtOAc y agua, se lavó con $NaHCO_3$ saturado, salmuera, se secó sobre Na_2SO_4, y se concentró. Paso 2: El residuo anterior se disolvió en 0,5 ml de TFA/H_2O (80:20) y se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se desactivó con ACN/H_2O (50:50) y se concentró en *vacuo*. La purificación mediante LC prep. de fase reversa dio **1266** como un sólido blanco. HPLC-MS t_R = 4,04 min. ($UV_{254\ nm}$, 10 min), Masa calculada para la fórmula $C_{28}H_{27}ClN_4O_4$ 518,17, LCMS observada m/z 519,1 (M+H).

Compuesto #	Estructura	Masa exacta	MS m/e (M+H)
1267		536,2	537,1
1268		577,2	578,0
1269		537,20	538,2

Ejemplo 45:



Parte A:

Se disolvió Compuesto **1257** (1,00 g, 5,34 mmol) en THF (15 ml) y solución de bicarbonato de sodio saturado (20 ml). Se agregó Di-*t*-butildicarbonato (1,28 g, 5,88 mmol) y la solución se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se desactivó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron para dar un sólido blanco **1270** (560 mg, 42%). HPLC-MS t_R = 1,34 (UV_{254nm}); masa calculada para la fórmula $C_{12}H_{18}BNO_4$ 251,13, LCMS observada m/z 274,1 (M+Na).

Parte B:

Se disolvió Compuesto **1271** (2,0 g, 8,5 mmol) en *t*-butanol (25 ml) y se agregó t-butóxido de potasio (10g) y se agitó a reflujo durante 24 horas. Los solventes se eliminaron bajo presión reducida y la reacción se desactivó con agua

y se extrajo con cloroformo. La capa acuosa se acidó y se extrajo con cloroformo. Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se concentraron para dar un sólido amarillo **1272** (1,10 g, 74%). HPLC-MS t_R = 0,76 min. ($UV_{254\ nm}$); masa calculada para la fórmula C_5H_4BrNO 172,95, LCMS observada m/z 174,0 (M+H).

Parte C:

Se preparó Compuesto **1273** de acuerdo con el procedimiento de Lui, H. et. al. (Tet. Lett. **1995**, 36, 8917). Datos para **1273**: HPLC-MS t_R = 1,12 ($UV_{254\ nm}$); masa calculada para la fórmula C_7H_8BrNO 200,98, LCMS observada m/z 202,0 (M+H).

Parte D:

Se disolvió Compuesto **1273** (50 mg, 0,247 mmol) en dioxano (5 ml) y se agregaron compuesto **1270** (93 mg, 0,370 mmol), fosfato de potasio (108 mg, 0,51 mmol), trifenilfosfina (10 mg), y $Pd(dba)_3$ (5 mg) y se agitó a 90 °C hasta el día siguiente. La reacción se filtró a través de Celite y se purificó mediante cromatografía en columna (EtOAc) para dar el producto deseado **1274** como un sólido blanco (60 mg, 75%). HPLC-MS t_R = 1,64 ($UV_{254\ nm}$); masa calculada para la fórmula $C_{18}H_{24}N_2O_3$ 328,18, LCMS observada m/z 329,2 (M+H).

Parte E:

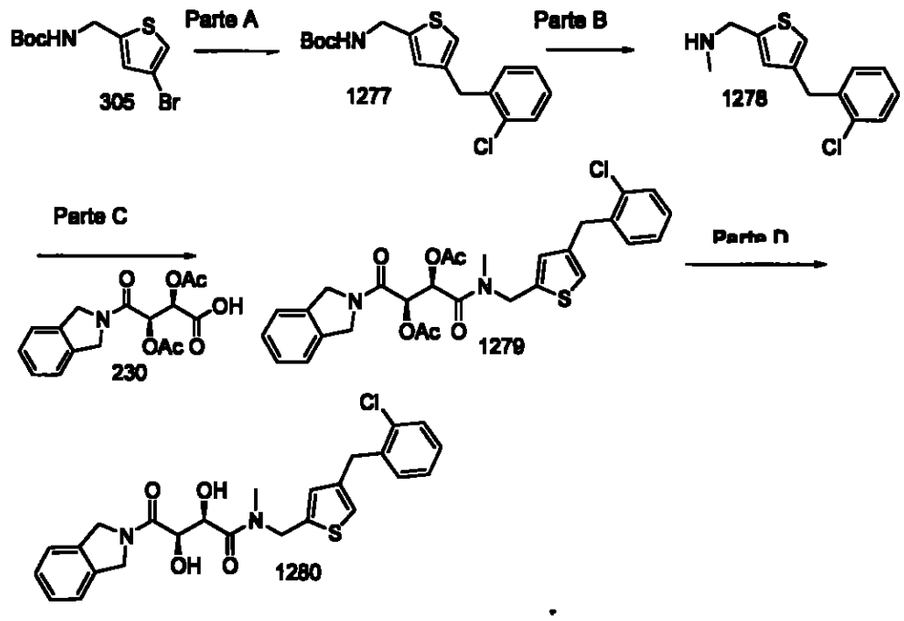
Se disolvió Compuesto **1274** (60 mg, 0,183 mmol) en cloruro de metileno (4 ml) y se agregó TFA (1 ml). La mezcla de reacción se agitó durante 1 hora y luego el solvente se eliminó bajo presión reducida. El residuo se disolvió en DMF (5 ml) y se agregaron compuesto **563** (63,5 mg, 0,183 mmol), HATU (90,5 mg, 0,2379 mmol), y DIEA (0,5 ml) y se agitó hasta el día siguiente. La reacción se desactivó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución HCl 1 N, solución de bicarbonato y salmuera; se secaron sobre sulfato de sodio y se concentraron. La purificación del residuo

mediante cromatografía en columna (EtOAc) dio compuesto **1275** como un sólido blanco (87 mg, 85%). HPLC-MS t_R = 1,81 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{31}H_{34}ClN_3O_5$ 563,22, LCMS observada m/z 564,1(M+H).

Parte F:

Se sintetizó Compuesto **1276** usando procedimientos similares al Ejemplo 1, Parte D. HPLC-MS t_R = 1,48 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{28}H_{30}ClN_3O_5$ 523,19, LCMS observada m/z 524,2(M+H).

Ejemplo 46:



Parte A:

Se preparó Compuesto **1277** a partir de **305** de acuerdo con los procedimientos descriptos en el Ejemplo 4A Parte A.

Parte B:

A **1277** (150 mg, 0,44 mmol) en THF (5 ml) se agregó litio hexametildisilazida (1,0 M, 0,66 ml, 0,66 mmol) a 0 °C. La mezcla de reacción se agitó durante 10 minutos. A la mezcla de reacción se agregó metil yoduro (0,034

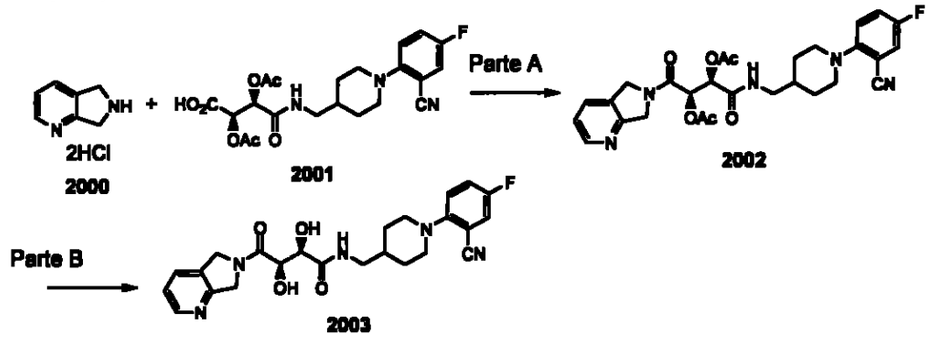
ml, 0,53 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo y se lavó con ácido cítrico 1,0 N, solución saturada de bicarbonato de sodio y salmuera, se secó sobre sulfato de sodio y se concentró. El residuo se disolvió en DCM (5 ml) y se trató con HCl 4N en dioxano (2 ml). La reacción se agitó a temperatura ambiente y se concentró. Se usó Compuesto **1278** sin purificación adicional.

Parte C y D:

Se obtuvo Compuesto **1280** de **1278** y **230** usando los procedimientos descriptos en el Ejemplo 4A Parte D y E. Datos para **1280**: HPLC-MS t_R = 5,05 min. ($UV_{254\ nm}$, 10 min); masa calculada para la fórmula $C_{25}H_{25}ClN_2O_4S$ 484,1, LCMS observada m/z 485,0 (M+H).

Ejemplo 47: Isoindolinas Heterocíclicas

Ejemplo 47A:



Se preparó Compuesto **2000** de acuerdo con el procedimiento en Patente Estadounidense 5.371.090.

Se preparó Compuesto **2001** usando procedimientos descriptos en el Ejemplo 2 y 27, HPLC-MS t_R = min. ($UV_{254\ nm}$); masa calculada para la fórmula C21H24FN3O7 449,2, LCMS observada m/z 450,1 (M+H).

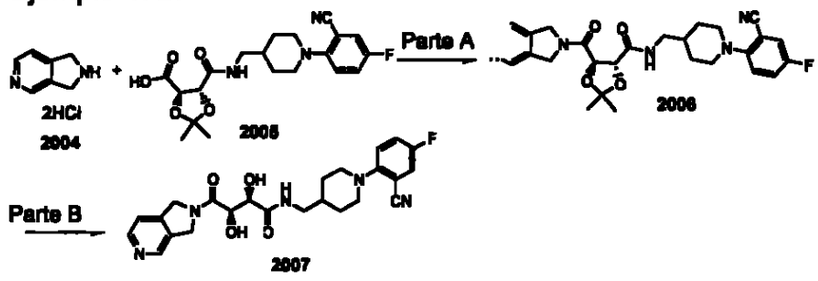
Parte A:

Se preparó Compuesto **2002** usando las condiciones de acoplamiento descriptas en el Ejemplo 2, HPLC-MS t_R = 1,60 min. ($UV_{254\ nm}$); masa calculada para la fórmula C28H30FN5O6 551,2; LCMS observada m/z 552,1 (M+H).

Parte B:

Se disolvió Compuesto **2002** (50 mg) en metanol (2 ml). A esta solución se agregó amoníaco 7,0 M en metanol (2 ml). La mezcla de reacción se agitó durante 1 hora a temperatura ambiente y se concentró. La purificación mediante LC prep.. y la conversión a sal del clorhidrato dio **2003** como un sólido blancuzco (32 mg). HPLC-MS t_R = 1,35 min. ($UV_{254\ nm}$); masa calculada para la fórmula C24H26FN5O4 467,2, LCMS observada m/z 468,1 (M+H).

Ejemplo 47B:



Se preparó Compuesto **2004** de acuerdo con el procedimientos en Patente Estadounidense 5.371.090.

Se preparó Compuesto **2005** usando procedimientos descriptos en el Ejemplo 1 y 27.

Parte A:

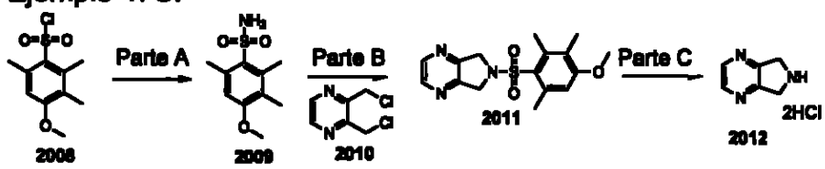
Compuesto **2006** se preparó usando las condiciones de acoplamiento descriptas en el Ejemplo 1, HPLC-MS t_R = 1,40 min. ($UV_{254\ nm}$); masa calculada para la fórmula C27H30FN5O4 507,2, LCMS observada m/z 508,1 (M+H).

Parte B:

El compuesto **2006** (50 mg) se desprotegió usando procedimientos descriptos en el Ejemplo 1. La purificación mediante LC prep. y la conversión a

una sal clorhídrica dio **2007** como un sólido blancuzco (32 mg). HPLC-MS t_R = 1,09 min. ($UV_{254\ nm}$); masa calculada para la fórmula C24H26FN5O4 467,2, LCMS observada m/z 468,1 (M+H). 1556

Ejemplo 47C:



2008 2009 2010 2011 2012

Parte A:

Se disolvió cloruro de sulfonilo **2008** (2,44 g, 9,8 mmol) en dioxano (40 ml) y se enfrió en un baño de hielo. Se hizo burbujear gas amoníaco gas en una mezcla de reacción durante 10 minutos. La mezcla de reacción se calentó hasta temperatura ambiente y se filtró. El filtrado se concentró. El producto bruto se recristalizó a partir de acetato de etilo/hexanos para dar **2009** como un sólido blancuzco (1,74 g). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,09 (s, 2H), 6,74 (s, 1H), 3,80 (s, 3H), 2,57 (s, 3H), 2,48 (s, 3H), 2,08 (s, 3H); HPLC-MS t_R = 1,43 min. ($UV_{254\ nm}$); masa calculada para la fórmula C10H15NO3S 229,1, LCMS observada m/z 230,1 (M+H).

Parte B:

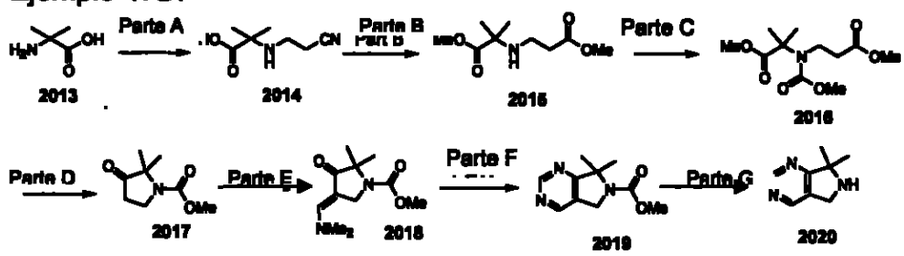
A hidruro de sodio (95%, 131 mg, 5,19 mmol) en DMF (10 ml) se agregó sulfonamida **2009** (596 mg, 2,6 mmol). La mezcla de reacción se calentó hasta 70°C y se agitó durante 45 minutos. A esta mezcla se agregó 2,3-bis(clorometil)pirazina (**2010**) (Yoshiizumi, K. et. al. *Bioorg. Med. Chem.* **2003**, *11*, 433) (448 mg, 2,53 mmol) en DMF (3 ml). La mezcla de reacción se calentó a 70 °C hasta el día siguiente. La mezcla de reacción se enfrió y se vertió en agua. La capa acuosa se saló y se extrajo con cloroformo. Los orgánicos combinados se lavaron con agua, se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 30% de acetato de etilo/hexanos) dio sulfonamida recuperado **2009** (218 mg) y **2011** (245 mg).

HPLC-MS t_R = 1,82 min. ($UV_{254\ nm}$); masa calculada para la fórmula C16H19N3O3S 333,1, LCMS observada m/z 334,1 (M+H).

Parte C:

Se agitó una mezcla de sulfonamida **2011** (245 mg, 0,73 mmol), ácido metansulfónico anhidro (3 ml) y tioanisol: ácido trifluoroacetico 1:9 (3 ml) durante 3 horas a temperatura ambiente. La mezcla de reacción se vertió sobre hielo y se trató con 50% de hidróxido de sodio (10 ml). La capa acuosa se saló y se extrajo con cloroformo. Los orgánicos combinados se secaron sobre sulfato de sodio y se concentraron. El residuo se disolvió en 1,0 M HCl (5 ml) y se extrajo con éter. La capa acuosa se liofilizó para dar **2012** (105 mg) as un sólido marrón. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,27 (s, NH), 8,58 (s, 2H), 4,59 (m, 4H).

Ejemplo 47D:



Parte A:

Se preparó el compuesto **2014** de acuerdo con el procedimiento en *Helv. Chim. Acta.* **1986**, 905-907.

Parte B:

Se agregó cloruro de acetilo (20 ml) gota a gota a metanol (130 ml) se enfrió en un baño de hielo. Esta solución se agregó entonces al compuesto **2014** (5,00 g, 31,8 mmol) y se agitó hasta el día siguiente a reflujo. El solvente se eliminó bajo presión reducida y el residuo se dividió entre acetato de etilo y NaOH 1 N. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio, y se concentró para dar **2015** (5,0 g). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,72 (s, 3H), 3,69 (s, 3H), 2,77 (t, 2H), 2,5 (t, 2H), 1,32 (s, 6H).

Parte C:

El compuesto **2015** (5,00 g, 24 mmol) se disolvió en THF (60 ml) y bicarbonato de sodio saturado (60 ml) y se enfrió en un baño de hielo. Se agregó cloroformoato de metilo (2,93 g, 31,2 mmol) gota a gota y la reacción se agitó a temperatura ambiente hasta el día siguiente. La mezcla de reacción se dividió entre acetato de etilo y agua. La capa orgánica se lavó con HCl 1 N, bicarbonato de sodio saturado, salmuera, se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 20% de acetato de etilo/hexanos) dio **2016** (5,5 g). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,72-3,68 (m, 9H), 3,65-3,6 (t, 2H), 2,66 (t, 2H), 1,5 (s, 6H).

Parte D:

El compuesto **2016** (1,66 g, 6,36 mmol) se disolvió en THF (20 ml) y se enfrió sobre un baño de hielo. Se agregó en porciones hidruro de potasio (35% en oil, 1,12 g, 9,54 mmol) y se continuó revolviendo durante 2 horas a temperatura ambiente. La reacción se desactivó lentamente con agua, se acidó a pH 3, y se extrajo con acetato de etilo. Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se concentraron (1,5 g). Una porción del residuo (350 mg) se disolvió en MeOH (5 ml) y HCl 6N (5 ml) y se agitó a reflujo durante 3 horas y a temperatura ambiente hasta el día siguiente. El solvente se evaporó bajo presión reducida y se dividión entre acetato de etilo y agua. La capa orgánica se lavó con agua, se secó sobre sulfato de sodio, y se concentró para dar **2017** (150 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,72-3,55 (m, 5H), 2,5 (t, 2H), 1,4-1,25 (m, 6H).

Parte E:

De acuerdo con una modificación de un procedimiento de Fukui, H. et al. (*Heterocycles* **2002**, *56*, 257-264) una mezcla de cetona **2017** (200 mg, 1,17 mmol) y N,N-dimetilformamida dimetil acetal (3 ml) se calentó a 100 °C durante

2h, y luego se concentró para dar enamino-cetona **2018** (244 mg, 92%) como un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,32-7,31 (m, 1H), 4,54-4,51 (d, 2H), 3,78-3,22 (d, 3H), 3,12 (s, 6H), 1,48 (s, 3H), 1,40 (s, 3H).

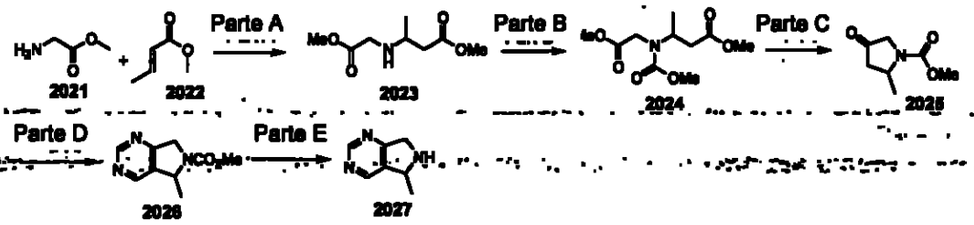
Parte F:

De acuerdo con una modificación de un procedimiento de Fukui, H. et al. (*Heterocycles* **2002**, *56*, 257-264) se calentó a reflujo una mezcla de enamino-cetona **2018** (690 mg, 3,05 mmol) y acetato de formamidina (3,17 g, 30,5 mmol) en etanol (15 ml) durante 3 días, y luego se concentró. El residuo se dividió entre diclorometano y agua, y se extrajo con diclorometano. Los extractos orgánicos combinados se concentraron para dar un aceite que se sometió a cromatografía (SiO_2, 50%-80% de acetato de etilo/hexano) para dar pirimidina **2019** (334 mg, 53%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,15 (s, 1H), 8,67 (s, 1H, amplio), 4,76-4,71 (d, 2H), 3,84-3,77 (d, 3H), 1,75 (s, 3H), 1,67 (s, 3H).

Parte G:

Se calentó una mezcla del compuesto **2019** (235 mg, 1,13 mmol), hidróxido de potasio en polvo (900 mg, 16 mmol) y monohidrato de hidracina (1,36 ml, 28 mmol) en etilén glicol (5 ml) a 100 °C hasta el día siguiente. La mezcla de reacción se enfrió hasta ta, se vertió en salmuera y se extrajo varias veces con diclorometano. Los extractos orgánicos combinados se lavaron con salmuera y se concentraron para dar el compuesto **2020** (121 mg, 72 %). ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,06 (s, 1H), 8,58 (s, 1H), 4,24 (s, 2H), 1,47 (s, 6H). HPLC-MS t_R = 0,2 min. ($UV_{254\ nm}$); masa calculada para la fórmula C8H11N3 149,1, LCMS observada m/z 150,1 (M+H).

Ejemplo 47E:



Parte A:

A una mezcla de crotonato de metilo (**2022**) (2,0 g, 20 mmol) y clorhidrato de metil glicina (**2021**) (5,5 g, 44 mmol) en metanol (27 ml) se agregó trietilamina (6,4 ml, 46 mmol). La mezcla se agitó a temperatura ambiente durante 2 días y se filtró para eliminar el precipitado blanco. El filtrado se concentró y el residuo se disolvió en acetato de etilo, se lavó con solución de bicarbonato de sodio, agua y salmuera, se secó sobre sulfato de sodio y se concentró para dar **2023** como un aceite amarillo claro (2,4 g, 64%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,74 (s, 3H), 3,69 (s, 3H), 3,46 (d, J = 3,2 Hz, 2H), 3,14 (m, 1H), 2,45 (m, 2H), 1,15 (d, J = 7,2 Hz, 3H).

Parte B:

El compuesto **2023** (2,42 g, 13 mmol) se disolvió en THF (20 ml) y bicarbonato de sodio saturado (20 ml) y se enfrió en un baño de hielo. Se agregó gota a gota cloroformiato de metilo (1,2 ml, 15 mmol) y la reacción se agitó a temperatura ambiente hasta el día siguiente. La mezcla de reacción se dividió entre acetato de etilo y agua. La capa orgánica se lavó con HCl 1N, bicarbonato de sodio saturado y salmuera, se secó sobre sulfato de sodio y se concentró para dar **2024** (2,9 g).

Parte C:

El compuesto **2024** (1,30 g, 5,26 mmol) se disolvió en THF (20 ml) y se enfrió sobre un baño de hielo. Se agregó en porciones Hidruro de potasio (35% en oil, 1,12 g, 9,54 mmol) y la mezcla se agitó a temperatura ambiente hasta el día siguiente. La reacción se desactivó lentamente con agua, se acidó a pH 3, y se extrajo con acetato de etilo. Las capas orgánicas combinadas se secaron sobre

sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 25% de acetato de etilo/hexano) dio un aceite (1,27 g). Este aceite (1;27 g) se disolvió en MeOH (5 ml) y HCl 6N (5 ml) y se agitó a reflujo hasta el día siguiente. La mezcla se extrajo con acetato de etilo y las capas orgánicas combinadas se lavaron con solución de bicarbonato de sodio, agua y salmuera, se secaron sobre sulfato de sodio y se concentraron para dar **2025** (663 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,5 (bs, 1H), 3,95 (m, 1H), 3,78 (s, 3H), 3,70 (m, 1H), 2,73 (m, 1H), 2,25 (m, 1H), 1,28 (m, 3H).

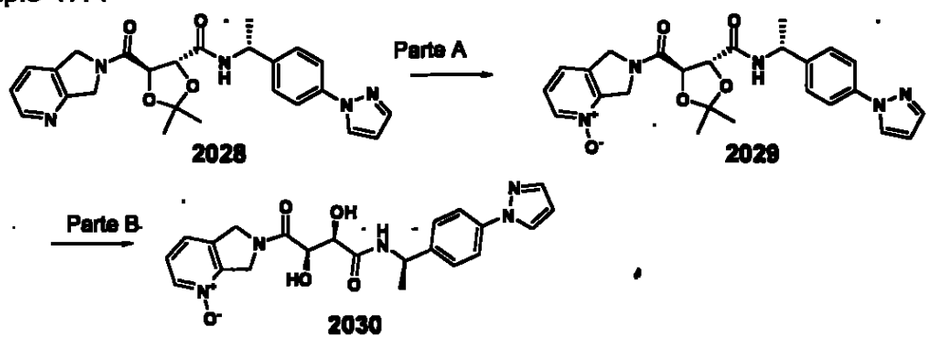
Parte D:

El compuesto **2026** se preparó a partir del material de la parte C de acuerdo con los procedimientos descriptos en el Ejemplo 47D Parte E y Parte F. ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,13 (s, 1H), 8,61 (m, 1H), 5,24 (m, 1H), 4,88 – 4,64 (m, 2H), 3,82 (m, 3H), 1,59 (m, 3H).

Parte E:

Se calentó una mezcla del compuesto **2026** (300 mg, 1,45 mmol), hidróxido de potasio en polvo (600 mg, 10,7 mmol) y monohidrato de hidracina (1,0 ml, 21 mmol) en etilén glicol (5 ml) a 100 °C hasta el día siguiente. La mezcla de reacción se enfrió hasta ta, se vertió en salmuera y se extrajo varias veces con diclorometano. Los extractos orgánicos combinados se lavaron con salmuera y se concentró para dar el compuesto **2027** (105 mg, 54%).

Ejemplo 47F:



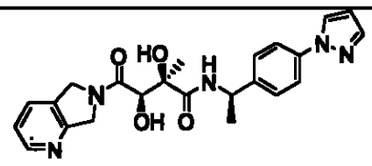
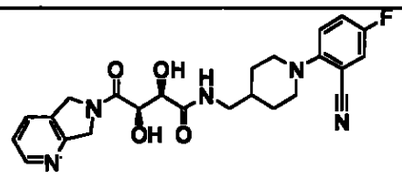
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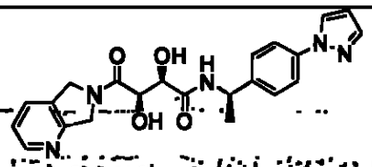
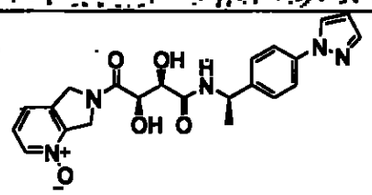
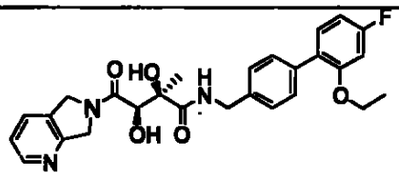
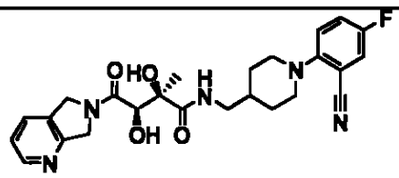
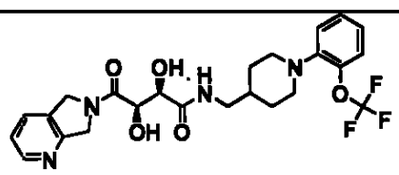
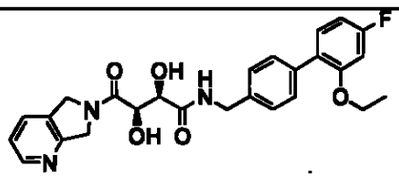
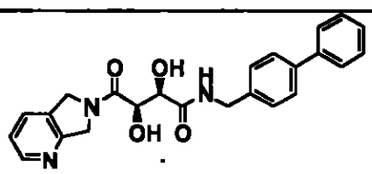
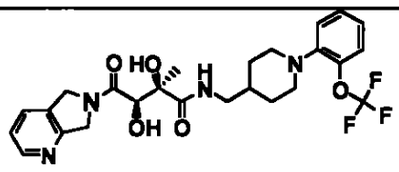
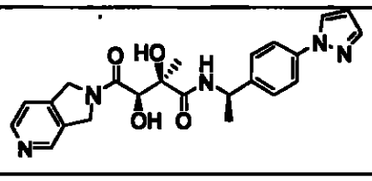
A una solución de compuesto **2028** (0,29 g, 0,63 mmol) en CH_2Cl_2 a 0 °C se agregó 70% m-CPBA (0,31 g, 1,26 mmol) y la mezcla de reacción se calentó hasta temperatura ambiente y se agitó durante 1 hora. Se diluyó con CH_2Cl_2 (5 ml) y se lavó con una solución de agua (6 ml) y se concentró NH_4OH (0,5 ml). La capa acuosa se extrajo con CH_2Cl_2 (3 x 10 ml) y 5% MeOH/CH_2Cl_2 (2 x 5 ml). La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró. La purificación mediante cromatografía en columna (SiO_2, 5% MeOH/CH_2Cl_2) dio el producto deseado con algunas impurezas. Se disolvió el producto impuro en EtOAc (15 ml) y se lavó con NH_4OH 10% (5 ml). La capa acuosa se extrajo con CH_2Cl_2 (3 x 5 ml). Las capas orgánicas combinadas (EtOAc y CH_2Cl_2) se secaron sobre $MgSO_4$, se filtraron y se concentraron para dar el compuesto deseado **2029** (0,25 g, 92%).

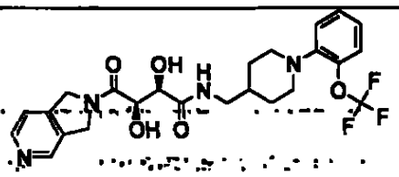
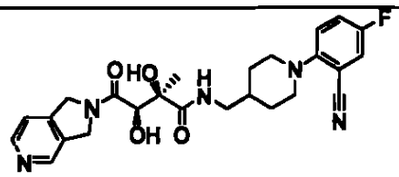
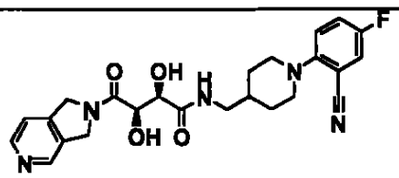
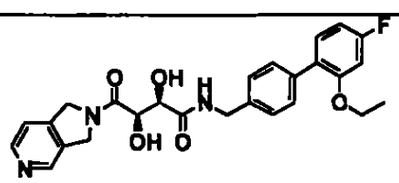
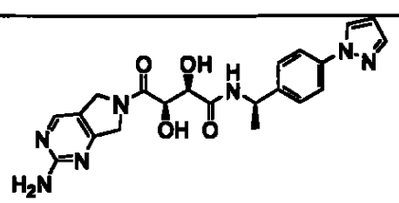
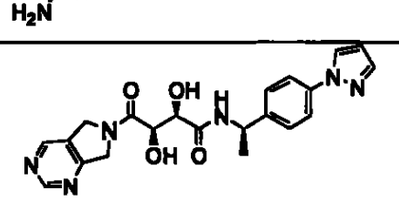
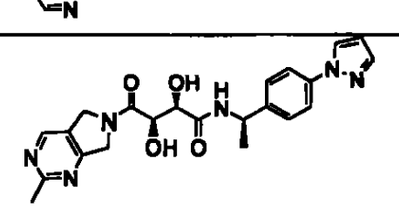
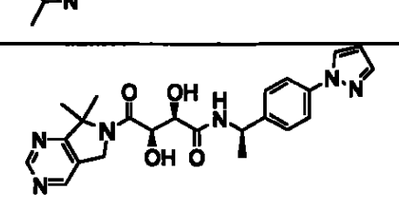
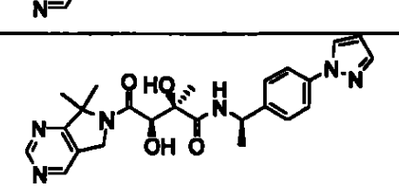
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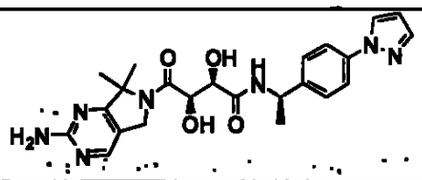
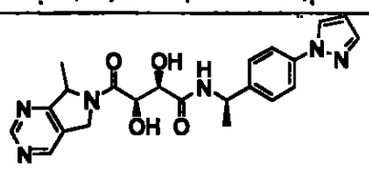
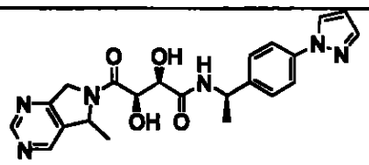
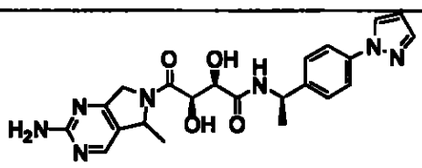
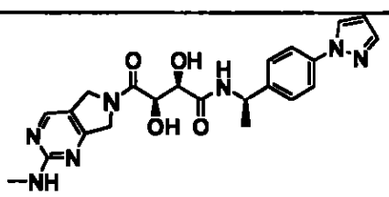
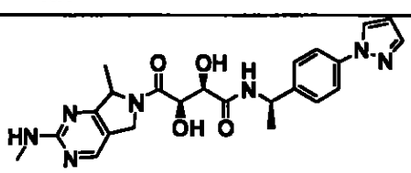
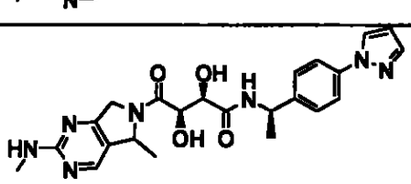
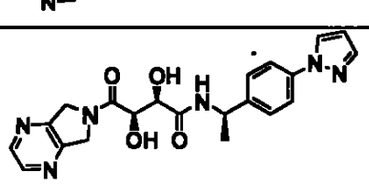
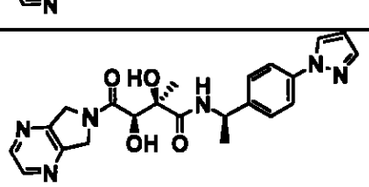
El compuesto **2030** se obtuvo de compuesto **2029** usando el procedimiento de desprotección de TFA según se describe en el Ejemplo 1.

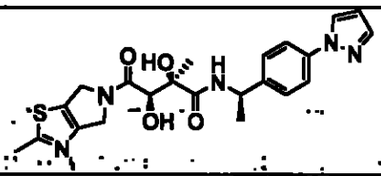
Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
2031		435,2	436,2
2003		467,2	468,1

2032		421,2	422,1
2030		437,2	438,1
2033		493,2	494,1
2034		481,2	482,1
2035		508,2	509,1
2036		479,2	480,1
2037		417,2	418,2
2038		522,2	523,2
2039		435,2	436,1

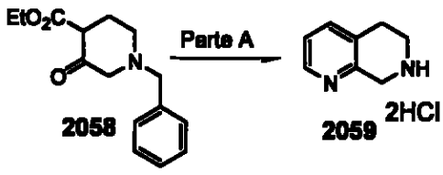
2040		508,2	509,1
2041		481,2	482,2
2007		467,2	468,1
2042		479,2	480,1
2043		437,2	438,1
2044		422,2	423,1
2045		436,2	437,2
2046		450,2	451,1
2047		464,2	465,1

2048		**465,2**	**466,1**
2049		**436,2**	**437,0**
2050		**436,2**	**437,2**
2051		**451,2**	**452,2**
2052		**451,2**	**452,0**
2053		**465,2**	**466,1**
2054		**465,2**	**466,1**
2055		**422,2**	**423,1**
2056		**436,2**	**437,1**

2057		455,2	456,1

Ejemplo 48: Análogos heterocíclicos de tetrahidroisoquinolina

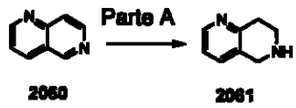
Ejemplo 48A:



Parte A:

EL Compuesto **2059** se sintetizó de acuerdo con los procedimientos de la literatura. (Dow, R.L.; Schneider, S.R. *J. Heterocyclic Chem.* **2001**, *38*, 535).

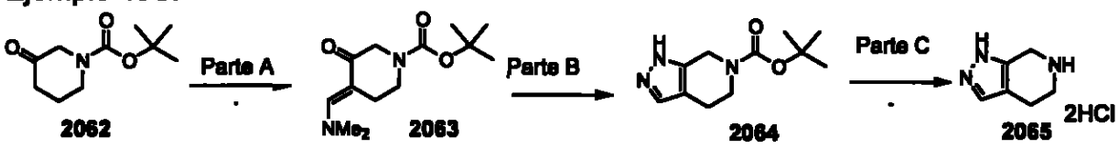
Ejemplo 48B:



Parte A:

Se sintetizó el Compuesto **2061** de acuerdo con los procedimientos de la Patente Estadounidense 5.037.834.

Ejemplo 48C:



Parte A:

De acuerdo con una modificación de un procedimiento de Fukui, H. et al. (*Heterocycles* **2002**, *56*, 257-264) se calentó una mezcla de cetona **2062** (2,5 g, 12,5 mmol) y N,N-dimetilformamida dimetil acetal (21 ml) a 100 °C durante 2h. La mezcla se concentró para un residuo que se pasó a través de una columna corta

de gel de sílice (metanol:trietilamina:diclorometano 9:1:90) para dar enaminocetona **2063** (3,1, 97%) como un aceite marrón viscoso. HPLC-MS t_R = 1,34 min. ($UV_{254\ nm}$); masa calculada para la fórmula C13H22N2O3 254,1, LCMS observada m/z 255,1 (M+H).

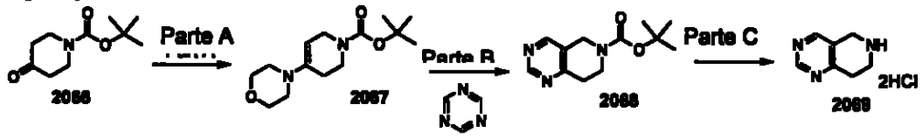
Parte B:

De acuerdo con una modificación de un procedimiento de Fukui, H. et al. (*Heterocycles* **2002**, *56*, 257-264) se calentó a reflujo una mezcla de enaminocetona **2063** (732 mg, 2,88 mmol) y monohidrato de hidracina (0,28 ml, 5,76 mmol) en etanol (8 ml) hasta el día siguiente, y luego se concentró. El residuo se dividió entre diclorometano y agua, y se extrajo con diclorometano. Los extractos orgánicos combinados se concentraron para dar un aceite que se sometió a cromatografía (SiO_2, 80% de acetato de etilo/hexano) para dar el compuesto **2064** como un aceite (isómero principal, 300 mg, 46%). HPLC-MS t_R = 1,39 min. ($UV_{254\ nm}$); masa calculada para la fórmula C11H17N3O2 223,1, LCMS observada m/z 224,2 (M+H).

Parte C:

El Compuesto **2064** (300 mg, 1,34 mmol) se desprotegió de acuerdo con un procedimiento descripto por Fukui, H. et al. (*Heterocycles* **2002**, *56*, 257-264) para dar el compuesto **2065** (57 mg, 22 %). ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,9 (s, 1H, amplio), 9,4 (s, 1H, amplio), 7,57 (s, 1H), 4,19 (t, 2H), 3,30-3,26 (m, 2H), 2,78 (t, 2H). HPLC-MS t_R = 0,2 min. ($UV_{254\ nm}$); masa calculada para la fórmula C6H9N3 123,1, LCMS observada m/z 124,2 (M+H).

Ejemplo 48D:



Parte A:

Se calentó a reflujo una mezcla de cetona **2066** (4,0 g, 20 mmol), morfolina (7,5 ml, 85 mmol) y monohidrato del ácido p-toluensulfónico (160 mg, 0,84 mmol) en benceno (30 ml) durante 3 días usando una trampa Dean-Stark. La mezcla luego se lavó con solución de bicarbonato de sodio saturado y se concentró para dar **2067** como un aceite amarillo (4,36 g, 65%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,58 (s, 1H, amplio), 3,96-3,95 (m, 2H), 3,77-3,73 (m, 4H), 3,55 (t, 2H), 2,83-2,80 (m, 4H), 2,18 (t, 2H), 1,49 (s, 9H).

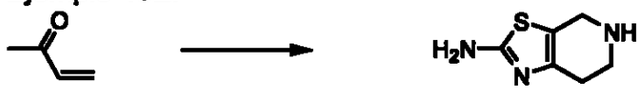
Parte B:

De acuerdo con una modificación de un procedimiento de Gündisch, D. et. al. (*Bioorg. Med. Chem.* **2002**, *10*, 1-9) se calentó una mezcla de enamina **2067** (2,27 g, 8,48 mmol) y 1,3,5-triazina (688 mg, 8,48 mmol) en 1,4-dioxano (10 ml) a 100 °C en un tubo sellado hasta el día siguiente. La mezcla de reacción se concentró y se sometió a cromatografía (SiO_2, 50-65% de acetato de etilo/hexano) para dar pirimidina **2068** como un aceite amarillo (665 mg, 35%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,01 (s, 1H), 8,49 (s, 1H), 4,64 (s, 2H), 3,80 (t, 2H), 3,00 (t, 2H), 1,54 (s, 9H). HPLC-MS t_R = 1,32 min. ($UV_{254\ nm}$); masa calculada para la fórmula C12H17N3O2 235,1, LCMS observada m/z 236,1 (M+H).

Parte C:

Se desprotegió el Compuesto **2068** (100 mg) usando procedimientos descriptos en el Ejemplo 48C para dar amina **2069** como un sólido amarillo (68 mg, 78%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,67 (s, 2H, amplio), 9,01 (s, 1H), 8,67 (s, 1H), 4,33 (t, 2H), 3,50-3,45 (m, 2H), 3,09 (t, 2H). HPLC-MS t_R = 0,18 min. ($UV_{254\ nm}$); masa calculada para la fórmula C7H9N3 135,1, LCMS observada m/z 136,2 (M+H).

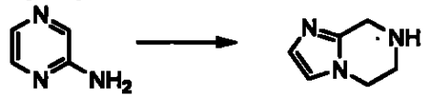
Ejemplo 48E:



2070

Se preparó Compuesto **2070** a partir de metil vinil cetona en 6 pasos siguiendo procedimientos descriptos en la Patente Estadounidense 5.037.834/1991.

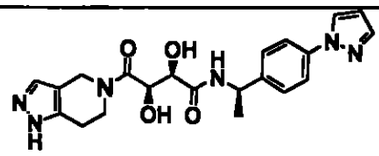
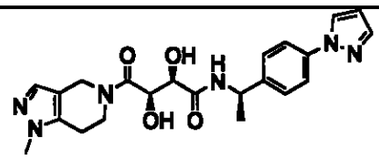
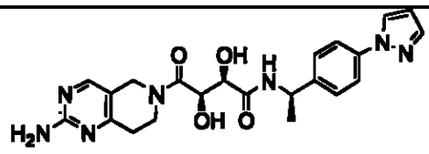
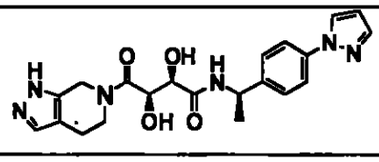
Ejemplo 48F:

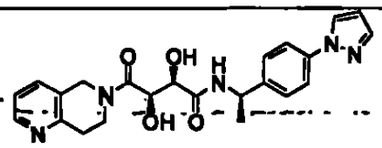
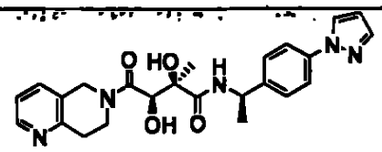
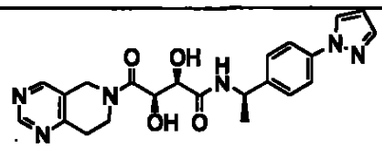
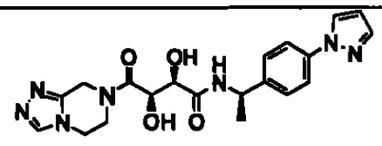
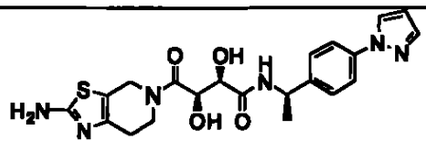
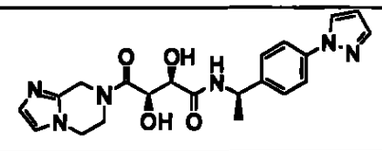
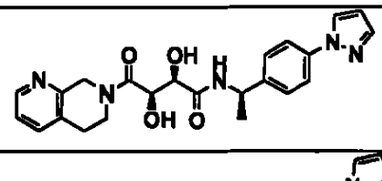
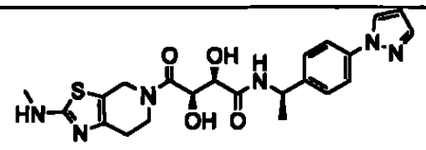


2071 **2072**

El Compuesto **2072** se preparó a partir de 2-aminopirazina (**2071**) en 2 pasos siguiendo procedimientos descriptos por Sablayrolles, C. et. al. (*J. Med. Chem.* **1984**, *27*, 206-212) y Bonnet, P. A. et. al. (*J. Chem. Res. Miniprint FR* **1984**, *2*, 0468-0480).

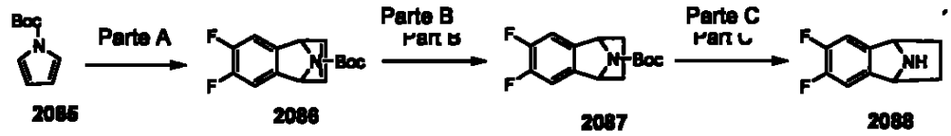
Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
2073		424,2	425,0
2074		438,2	439,1
2075		451,2	452,0
2076		424,2	425,1

2077		**435,2**	**436,1**
2078		**449,2**	**450,1**
2079		**436,2**	**437,1**
2080		**425,2**	**426,1**
2081		**456,2**	**457,1**
2082		**424,2**	**425,1**
2083		**435,2**	**436,1**
2084		**470,2**	**471,1**

Ejemplo 49:

Ejemplo 49A:



2085 2086 2087 2088

Parte A:

El Compuesto **2086** se preparó de acuerdo con el procedimiento en *Org. Lett.* **2002**, *4*, 24, 4353-4356,

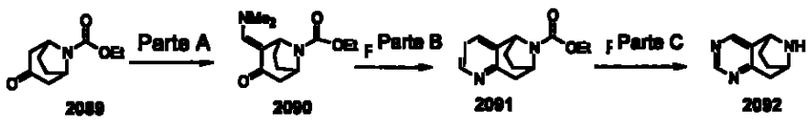
Parte B:

El Compuesto **2087** se preparó de acuerdo con el procedimiento en *Org. Lett.* **2002**, *4*, 24, 4353-4356, ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,05 (t, 2H), 5,1 (bs, 2H), 2,15 (m, 2H), 1,4 (s, 9H), 1,3 (m, 2H).

Parte C:

El Compuesto **2087** (80 mg, 0,30 mmol) se disolvió en HCl 4 M en dioxano (2 ml) y se agitó a temperatura ambiente durante 1 hr. La reacción se diluyó con dietil éter (5 ml) y el sólido resultante se filtró para dar **2088** como una sal de HCl (45 mg).

Ejemplo 49B:



Parte A:

El Compuesto **2090** se preparó de acuerdo con el procedimiento en *Bioorg. Med. Chem.* **2002**, *10*, 5, 1197-1206.

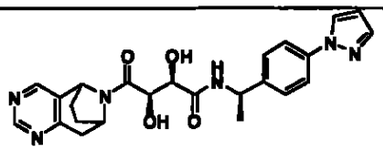
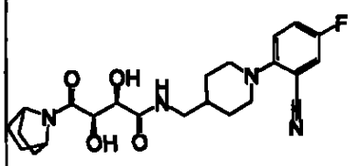
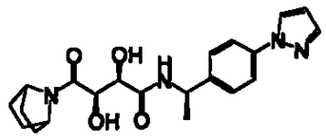
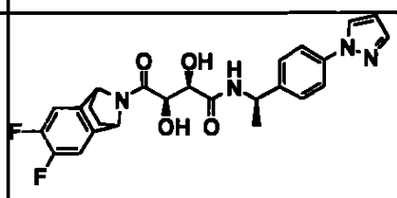
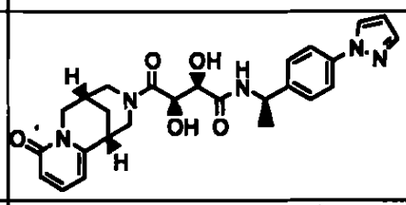
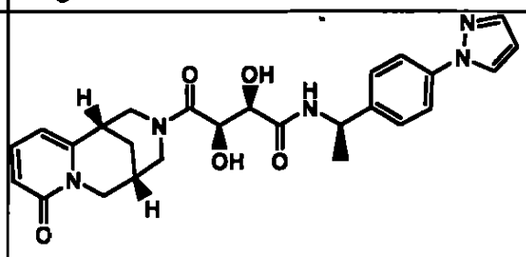
Parte B:

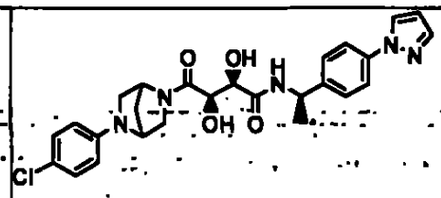
El Compuesto **2091** se preparó de acuerdo con el procedimiento en *Bioorg. Med. Chem.* **2002**, *10*, 5, 1197-1206, ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,00 (s, 1H), 8,40 (s, 1H), 5,10 (bs, 1H), 4,70 (bs, 1H), 4,10 (m, 2H), 3,40 (bs, 1H), 2,50 (s, 1H), 2,40-2,30 (m, 2H), 1,80 (m, 2H), 1,75 (m, 2H), 1,25 (m, 3H).

Parte C:

El Compuesto **2091** (350 mg, 1,5 mmol) se disolvió en etilén glicol (4 ml) y se agregaron KOH (0,5 g) y monohidrato de hidracina (1 ml) y se agitó a 100 °C durante 12 horas. La mezcla de reacción se vertió en salmuera y se extrajo con cloruro de metileno. Las capas orgánicas combinadas se lavaron con agua, se secaron sobre sulfato de sodio y se concentraron para dar **2092** (150 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,00 (s, 1H), 8,40 (s, 1H), 4,30 (d, 1H), 4,00 (t, 1H), 3,20 (m, 1H), 2,80 (m, 1H), 2,20-2,10 (m, 2H), 2,00-1,90 (m, 2H), 1,80-1,60 (m, 2H).

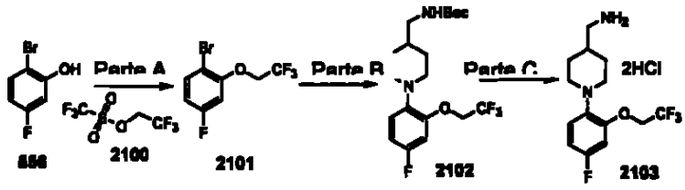
Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
2093		462,2	463,1
2094		444,2	445,1
2095		398,2	399,3
2096		482,2	483,1
2097		491,2	492,1
2098		491,2	492,1

2099		509,2	510,1

Ejemplo 50: Piperidin-aril compuestos

Ejemplo 50A:



Parte A:

Se agitó una mezcla de 2-bromo-5-fluorofenol (**556**) (0,111 ml, 1 mmol), 2,2,2-trifluoroetil trifluorometanosulfonato (**2100**) (279 mg, 1,2 mmol) y carbonato de cesio (358 mg, 1,1 mmol) en NMP (5 ml) a temperatura ambiente hasta el día siguiente. La mezcla de reacción se vertió en agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua (2x) y salmuera, se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, hexanos a 2% de acetato de etilo/hexanos) dio **2101** (232 mg) como un aceite. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,53 (m, 1H), 6,70 (m, 2H), 4,40 (q, 2H, J = 8,0 Hz).

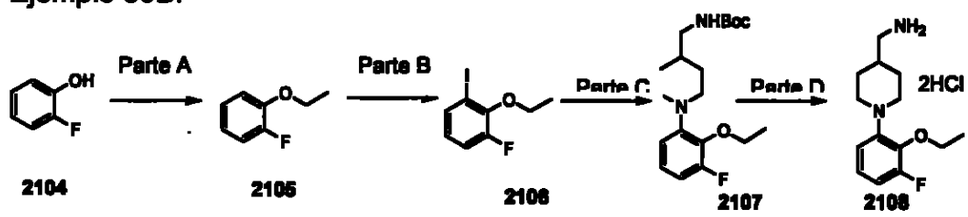
Parte B:

El Compuesto **2102** se preparó de acuerdo con los procedimientos en el Ejemplo 27B Parte A. HPLC-MS t_R = 2,10 min. ($UV_{254\ nm}$); masa calculada para la fórmula C19H26F4N2O3 406,2, LCMS observada m/z 407,2 (M+H).

Parte C:

El Compuesto **2102** (8 mg, 0,02 mmol) se disolvió en DCM:TFA 3:1 (4 ml) y se agitó durante 1 hora a temperatura ambiente. El solvente se eliminó en *vacuo*. El residuo se disolvió en éter y se trató con 1;0 M HCl en éter (1 ml). Los solventes se concentraron para dar **2103** como un sólido blanco (8 mg).

Ejemplo 50B:



Parte A:

Una mezcla de 2-fluorofenol (**2104**) (1,0 ml, 10,7 mmol), etil yoduro (1,05 ml, 13 mmol) y carbonato de potasio (1,66 g, 12 mmol) en acetona (20 ml) se agitó a temperatura ambiente hasta el día siguiente. Se agregó etil yoduro adicional (0,24 ml, 3 mmol) a la reacción y la mezcla se agitó durante 24 horas. La mezcla se filtró y se concentró. El residuo se dividió entre agua y acetato de etilo. Las capas se separaron. La capa orgánica se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró para dar **2105** (1,23 g) como un aceite. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,07 (m, 2H), 6,96 (m, 1H), 6,87 (m, 1H), 4,12 (q, 2H, J = 7,1 Hz), 1,48 (t, 3H, J = 7,1 Hz).

Parte B:

Al areno **2105** (1,23 g, 8,8 mmol) y TMEDA (1,32 ml, 8,8 mmol) en THF (20 ml) a –78 °C bajo argón se agregó s-Buli (1,4 M, 6,3 ml, 8,8 mmol). La mezcla de reacción se agitó durante 2 horas a –78 °C. A la mezcla de reacción se agregó yoduro (2,23 g, 8,8 mmol) en THF (10 ml) a –78 °C. La reacción se agitó durante 10 minutos luego se calentó hasta 0 °C. La mezcla de reacción se vertió en agua y se extrajo con dietil éter. Los orgánicos combinados se lavaron con agua (2x), 5% de sulfito de hidrógeno de sodio y salmuera, se secaron sobre sulfato de sodio y se concentraron. El producto bruto **2106** (1,70 g) como una mezcla de

producto:material de partida 75:25 por ^{1}H RMN. se usó sin purificación adicional. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,28 (m, 1H), 6,94 (m, 1H), 6,81 (m, 1H), 4,11 (q, 2H, J = 7,1 Hz), 1,47 (t, 3H, J = 7,1 Hz).

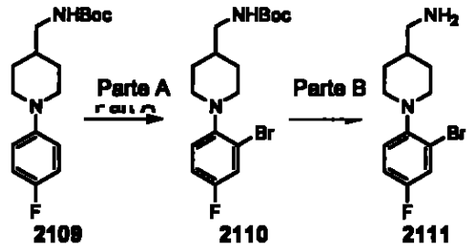
Parte C:

El Compuesto **2107** se preparó de acuerdo con los procedimientos en el Ejemplo 27B Parte A. HPLC-MS t_R = 2,15 min. ($UV_{254\ nm}$); masa calculada para la fórmula C19H29FN2O3 352,2, LCMS observada m/z 353,2 (M+H).

Parte D:

El Compuesto **2107** (276 mg, 0,78 mmol) se disolvió en DCM:TFA 3:1 (4 ml) y se agitó durante 1 hora a temperatura ambiente. El solvente se eliminó en *vacuo*. El residuo se disolvió en éter y se trató con 1,0 M HCl en éter (1 ml). Los solventes se concentraron para dar **2108** como un sólido blanco (241 mg). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,89 (bs, NH), 6,97 (m, 1H), 6,75 (m, 1H), 6,63 (m, 1H), 4,04 (q, 2H, J = 6,9 Hz), 3,33 (m, 2H), 2,76 (m, 2H), 2,62 (m, 2H), 1,80 (m, 2H), 1,70 (m, 1H), 1,38 (m, 2H), 1,32 (t, 3H, J = 7,1 Hz).

Ejemplo 50C:



El Compuesto **2109** se preparó usando procedimientos descriptos en el Ejemplo 27, ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,00 – 6,80 (m, 4H), 4,64 (m, 1H), 3,55 (m, 2H), 3,09 (m, 2H), 2,65 (m, 2H), 1,82 (m, 2H), 1,60-1,50 (m, 2H), 1,49 (s, 9H), 1,42 (m, 1H).

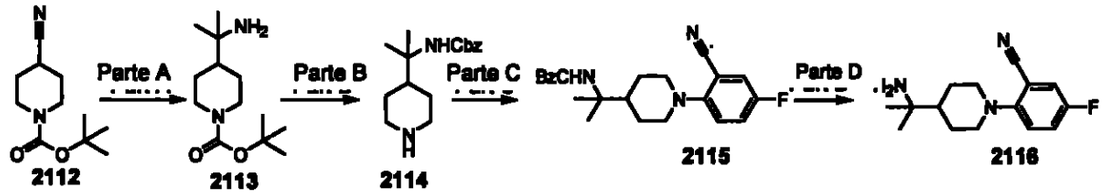
Parte A:

Al Compuesto **2109** (100 mg, 0,32 mmol) y piridina (0,026 ml, 0,32 mmol) en DMF (2 ml) se agregó NBS (115 mg, 0,64 mmol). La mezcla se agitó a temperatura ambiente durante 2 horas y se diluyó con acetato de etilo. La mezcla se lavó con solución de carbonato de sodio, agua y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 5% de acetato de etilo/hexano) dio **2110** como un sólido blanco (88 mg). ^1H RMN (400 MHz, $CDCl_3$) δ 7,3 (m, 1H), 7,0 (m, 2H), 4,65 (bs, 1H), 3,28 (m, 2H), 3,10 (m, 2H), 2,61 (m, 2H), 1,8 (m, 2H), 1,65 – 1,4 (m, 12 H).

Parte B:

A **2110** (21 mg, 0,055 mmol) en diclorometano (2 ml) a 0 °C se agregó TFA (1 ml). La mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla se desactivó con acetonitrilo y se concentró. El Compuesto **2111** se usó sin purificación adicional.

Ejemplo 50D:



Parte A:

El Compuesto **2113** se preparó a partir de 1-N-(*t*-butoxicarbonil)-4-ciano-piperidina (**2112**) de acuerdo con un procedimiento descripto en *J. Org. Chem.* **1992**, *57*, 4521-4527.

Parte B:

Paso 1: A **2113** (100 mg, 0,41 mmol) en THF (2 ml) se agregaron cloroformoato de bencilo (0,089 ml, 0,619 mmol) y carbonato de potasio (114 mg, 0,82 mmol). La mezcla se agitó a temperatura ambiente hasta el día siguiente, se diluyó con acetato de etilo, se lavó con agua, salmuera, se secó sobre sulfato de sodio y se

concentró. El producto se purificó mediante cromatografía en columna (SiO_2, 10% de acetato de etilo/hexano a 25% de acetato de etilo/hexano) para dar una aceite amarillo pálido (80 mg). HPLC-MS t_R = 2,14 min. ($UV_{254\ nm}$). Masa calculada para C21H32N2O4 376,5, LSMS observada m/z 399,2 (M+Na).

Paso 2: El material del paso 1 (80 mg) se agitó en HCl 4 N en 1,4-dioxano (2ml) durante 1 hora. El solvente se eliminó en vacío y **2114** se usó sin purificación adicional.

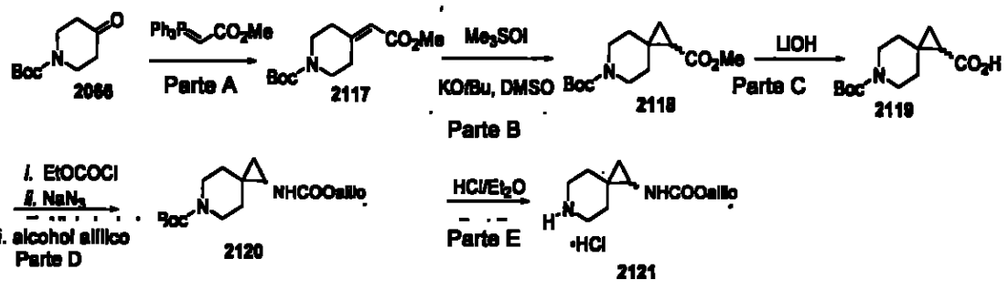
Parte C:

Una mezcla de **2114**, 2,5-difluorobenzonitrilo (32,5 mg, 0,234 mmol) y DIEA (0,113 ml, 0,637 mmol) en NMP (2 ml) bajo atmósfera de argón se agitó hasta el día siguiente a 100°C. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 25% de acetato de etilo/hexano) dio **2115** como un aceite amarillo (26 mg). ^1H RMN (400 MHz, $CDCl_3$) δ 7,3 – 7,2 (m, 6H), 7,2 (m, 1H), 7,0 (m, 1H), 5,05 (s, 2H), 4,7 (m, 1H), 3,52 (m, 2H), 2,77 (m, 2H), 2,15 (m, 1H), 1,8 (m, 2H), 1,63 (m, 2H), 1,32 (s, 6H).

Parte D:

Una mezcla de **2115** (26 mg) y 10% de Paladio sobre carbono (5 mg) en etanol (4 ml) bajo atmósfera de hidrógeno se agitó durante 3 horas. La mezcla se filtró a través de un lecho de Celite y el filtrado se concentró para dar **2116** como un residuo amarillo (20 mg), que se usó sin purificación adicional.

Ejemplo 50E:



Parte A:

Se agregó acetato de metil (trifenilfosforanilideno) (104,5 g, 0,31 mmol) a una solución de *N*-Boc-piperidinona (2066) (49,79 g, 0,25 mol) en tolueno (625 ml). La mezcla de reacción resultante se calentó hasta reflujo y se agitó durante 17 h. La mezcla de reacción luego se enfrió hasta temperatura ambiente y se concentró en vacío. El residuo resultante se pre-adsorbió luego sobre gel de sílice y se purificó mediante la elusión a través de un tapón de gel de sílice con 50% de acetato de etilo/hexanos, para dar éster no saturado **2117** (62,16 g, 0,243 mol) como un sólido blanco.

Parte B:

Se agregó Ter-butóxido de potasio (450 g, 0,41 mol) a una solución de yoduro de trimetilsulfoxonio (90,0 g, 0,41 mol) en DMSO (700 ml), en una porción. La mezcla se agitó a temperatura ambiente durante 3 h. El éster no saturado **2117** (59,64 g, 0,23 mol) se disolvió en DMSO (0,26 L) y se agregó a la mezcla de reacción. La mezcla de reacción se agitó durante 20 h a temperatura ambiente y luego se agregó a salmuera (1 L). Se agregó luego NH_4Cl acuoso saturado a la mezcla de reacción para regular el pH a aproximadamente 7. La mezcla de reacción se extrajo luego varias veces con éter, se combinaron los extractos de éter, se lavaron con agua y salmuera, se secaron con $MgSO_4$ anhidro, se filtraron y se concentraron en vacío para dar éster **2118** (53,5 g, 0,20 mol) como un aceite.

Parte C:

Se agregó una solución acuosa de LiOH (2N, 200 ml) a una solución del éster **2118** (53,5 g, 0,20 mol) en THF (200 ml). La mezcla luego se agitó a temperatura ambiente durante 17 h, se diluyó con agua (750 ml) y se lavó con éter. La fase de éter se desechó, y la fase acuosa se acidó a un pH de 3-4 con HCl 6N. la fase acuosa ácida luego se extrajo con éter en varias oportunidades. Los lavados de éter se combinaron, se lavaron con agua y salmuera, se secaron con $MgSO_4$

anhidro, se filtraron y se concentraron en vacío para dar carboxílico ácido **2119** (49,25 g, 0,19 mol) como un sólido blanco.

Parte D:

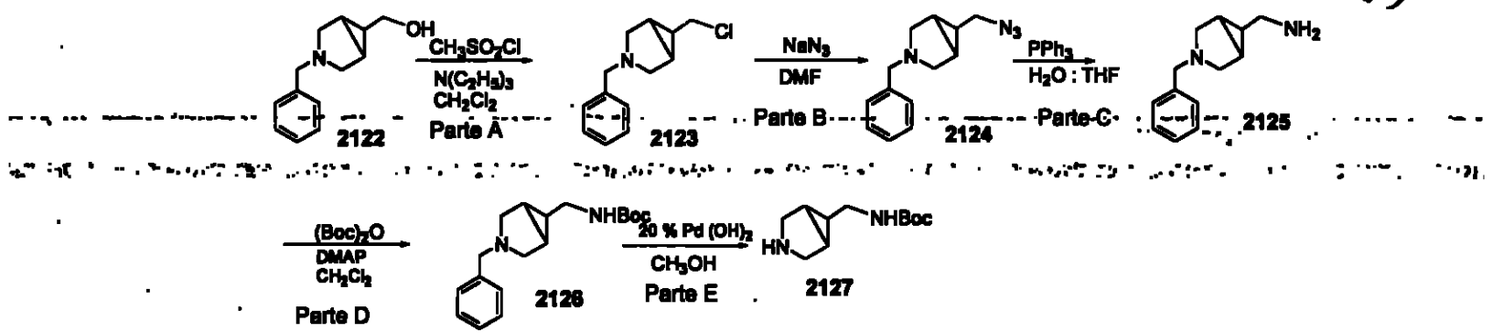
Se agregó Trietilamina (8,7 g, 0,086 mol) seguida por cloroformoato de etilo (9,4 g, 0,086 mol) a una solución de carboxílico ácido **2119** (20,0 g, 0,078 mol) en acetona (78 ml) a 0 °C. La mezcla resultante se agitó a 0 °C durante 40 minutos. Luego se agregó azida de sodio (10,2 g, 0,15 mol) en agua (50 ml) a la mezcla. La mezcla luego se dejó calentar hasta temperatura ambiente y se agitó durante 4 h. Más tarde, se agregó agua, y luego la mezcla se extrajo en varias oportunidades con CH_2Cl_2. Los extractos orgánicos se combinaron y se lavó con agua y salmuera, se secó sobre sulfato de magnesio y se concentró en vacío para dar un aceite. El aceite se tomó en tolueno (200 ml), se agregó cloruro de alilo (5,5 g, 0,094 mol), y la mezcla se calentó hasta reflujo y se agitó a reflujo durante 17 h. La mezcla de reacción luego se enfrió hasta temperatura ambiente y se agregó EtOAc (250 ml). Luego, la mezcla se lavó con agua y salmuera, se secó sobre sulfato de magnesio y se concentró en vacío. El residuo resultante se purificó mediante cromatografía de gel de sílice (35% de acetato de etilo/hexanos) para dar el carbamato **2120** (24,4 g, 0,061 mol).

Parte E:

Se agregó una solución de HCl/Et_2O (2 N, 50 ml) a una solución de el carbamato **2120** (24,4 g, 0,061 mol) en CH_2Cl_2 (100 ml). La mezcla de reacción se agitó hasta el día siguiente y luego se concentró en vacío para dar **2121** como una espuma higroscópica (17,4 g, 0,052 mol).

Ejemplo 50F:

1580 [illegible]



Se preparó alcohol de partida **(2122)** (1α, 5α, 6α)-3-bencil-6-hidroximetil-3-azabiciclo[3,1,0]hexano mediante métodos conocidos (i.e., Brighty, K. E; Castaldi, M. J *Synlett*, **1996**, 1097).

Parte A:

Se disolvieron alcohol **2122** (11 g, 54 mmol) y trietilamina (38 ml, 27 mmol) en CH_2Cl_2 (200 ml) y se enfrió a 0 °C. La solución fría se agitó, y se agregó gota a gota CH_3SO_2Cl (como una solución CH_2Cl_2; 6 ml, 78 mmol, 25 ml CH_2Cl_2), y se continuó revolviendo durante 3-4 h. La mezcla de reacción se lavó luego dos veces con 100 ml de agua y dos veces con 100 ml de salmuera. Las fases orgánica y acuosa se separaron, y la fase orgánica se secó, y se concentró para dar un producto bruto. El producto bruto se purificó mediante cromatografía de gel de sílice (eluída con acetato de etilo:hexano 1:6). Las fracciones apropiadas se recolectaron de la cromatografía en columna y se concentraron para dar cloro puro, Compuesto **2123** como un aceite (7 g, 59%).

Parte B:

El compuesto clorado **2123** se disolvió en DMF (100 ml) y se trató con NaN_3 (10,3 g, 157 mmol), y la mezcla se agitó vigorosamente durante 36-48 h. La mezcla de reacción luego se diluyó con 100 ml agua y se extrajo con acetato de etilo (2 x 100 ml). Los extractos orgánicos se combinaron, se secaron y se concentraron para dar azida pura **2124** (6,2 g, 87%).

Parte C:

1581/6002

Se disolvieron la azida **2124** (6,2 g, 27 mmol) y trifenilfosfina (15 g, 57 mmol) en 100 ml de THF, y luego se agregó agua (6 ml, 333 mmol). La mezcla resultante se agitó vigorosamente durante 16-24 h. El solvente se eliminó y la amina bruta **2125** se obtuvo sin purificación adicional.

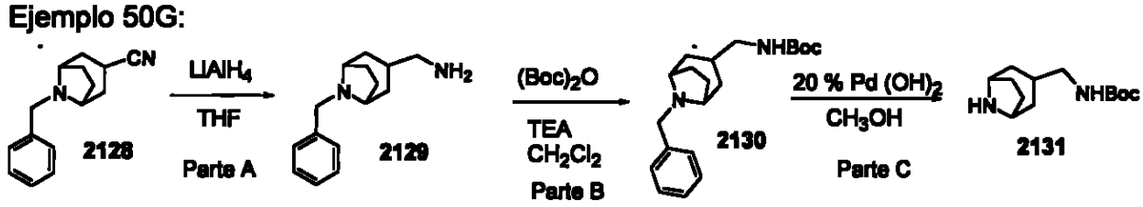
Parte D:

Se disolvieron la amina bruta **2125** y N, N-dimetilaminopiridina (0,66 g, 5,4 mmol) en CH_2Cl_2 (100 ml). A esta solución se agregó di-ter-butildicarbonato (7 g, 33 mmol), en porciones, y la mezcla de reacción se agitó durante 16 h. La mezcla de reacción se lavó luego dos veces (50 ml) con agua y once con salmuera (50 ml). La fase orgánica se aisló y se secó, y el solvente se eliminó bajo presión reducida. El producto bruto se sometió a cromatografía de gel de sílice usando 1:3 acetato de etilo:hexano como el solvente eluyente. Las fracciones eluidas se combinaron y se concentraron para dar 6,9 g de carbamato puro **2126** (84%).

Parte E:

El carbamato **2126** (1,9 g, 6,3 mmol) se disolvió en metanol (100 ml) y se mezcló con hidróxido de paladio (20%, 0,4 g). La mezcla se transfirió a una botella de Parr, que luego se cargó con hidrógeno (20 psi). La botella de Parr se agitó durante 10 h. El hidrógeno remanente se eliminó de la botella Parr en vacío, y la reacción se filtró a través de Celite. El filtrado luego se concentró para dar amina pura **2127** (1,4 g).

Ejemplo 50G:



Se preparó N-benciltropinancarbonitrilo **2128** usando procedimientos conocidos (ver, por Ejemplo: Montzka, T. A.; Matiskella, J. D.; Partyka, R. A. *Tetrahedron Letters* **1974**, *14*, 1325; Lowe, J. A.; Drozda, S. E.; McLean, S.;

Bryce, D. K.; Crawford, R.T.; Snider, R. M.;Tsuchiya, M. *J. Med. Chem.* **1994**, *37*, 2831).

Parte A:

Se agregó $LiAlH_4$ a THF seco (40 ml) y la mezcla se enfrió entonces hasta 0 °C. Luego se agregó carbonitrilo **2128** (0,9 g, 3,8 mmol, en a 10 ml THF solución) a la mezcla gota a gota. La mezcla de reacción se dejó calentar hasta temperatura ambiente y se agitó durante 48 h, luego se enfrió de vuelta a 0 °C y se desactivó mediante la adición en secuencia de 1 ml de agua, 2 ml de NaOH ac. 0,5 N, y 1 ml de agua. La mezcla resultante se agitó vigorosamente durante 2 h y luego se filtró a través de Celite. El filtrado se concentró para dar **2129** puro como un aceite (0,9 g, 100%).

Parte B:

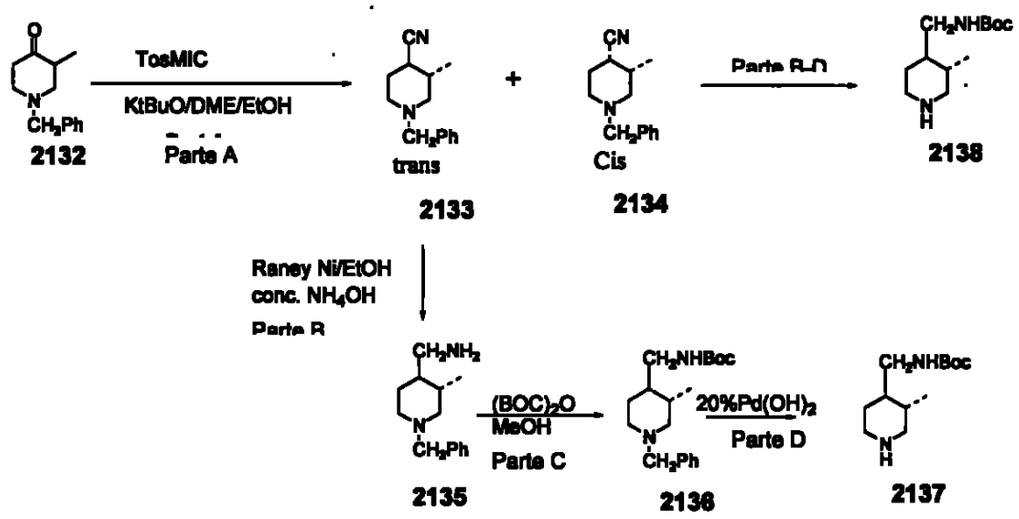
El producto bruto **2129** y trietilamina (TEA) (0,6 ml, 4,3 mmol) se disolvieron en CH_2Cl_2 (50 ml). Se agregó di-ter-butildicarbonato (0,85 g, 3,9 mmol) a esta solución en porciones, y la mezcla de reacción se agitó durante 16 h. La mezcla de reacción se lavó luego dos veces con 50 ml de agua y una vez con 50 ml de salmuera. La fase orgánica se secó y el solvente se eliminó bajo presión reducida. El producto bruto se sometió a cromatografía de gel de sílice usando 2,5% de amoníaco saturado metanol en CH_2Cl_2 como el solvente eluyente. Las fracciones eluidas se combinaron y se concentró para dar 0,78 g del producto de carbamato puro **2130** (61%).

Parte C:

El carbamato **2130** (0,8 g, 2,3 mmol) se disolvió en metanol (60 ml) y se trató con hidróxido de paladio (20%, 0,08 g). La mezcla se transfirió a una botella de Parr, que luego se cargó con hidrógeno (20 psi). La botella de Parr se agitó durante 10 h. El hidrógeno se eliminó de la botella de Parr en vacío, y la mezcla de reacción

se filtró a través de Celite. El filtrado luego se concentró para dar amina pura **2131** (0,6 g).

Ejemplo 50H:



Parte A:

Se agregó isocianuro de tosilmetilo (TosMIC) (7,2 g, 37 mmol) a 3-metil-N-bencil piperidona (**2132**) (4,25 g, 20,93 mmol) en DME (150 ml) y se enfrió hasta 0 °C. Se agregaron alcohol Etilo (2,9 ml) y ter-butóxido de potasio (7 g, 62,4 mmol) a la mezcla de reacción y se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se vertió en hielo y se extrajo con acetato de etilo (2 x 50 ml). La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$ anhídrido y se concentró en vacío. El residuo resultante se purificó mediante cromatografía de gel de sílice (20% de acetato de etilo/hexano) para dar primero **2133** (trans isomer, 1,85 g, 41%), y segudno **2134** (cis isómero, 1,05 g, 22%).

Parte B:

El intermediario trans **2133** (2,0 g, 9,34 mmol) se disolvió en alcohol etílico (50 ml) y Raney Nickel (wet, 5,0 g) se agregó bajo N_2, seguido por la adición de hidróxido de amonio conc. (1,0 ml). La mezcla se sometió a atmósfera de H_2 a 50 p.s.i. durante 16 horas con agitación vigorosa. La reacción se filtró a través de Celite

bajo N_2 y el filtrado se concentró en vacío para dar 1,8 g (88%) del intermediario **2135.**

Parte C:

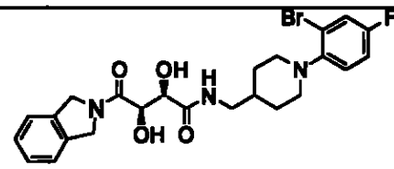
El intermediario **2135** (1,0 g, 4,6 mmol) se disolvió en alcohol metílico (35 ml). Se agregó gota a gota una solución de BOC-anhídrido (1,2 g, 5,5 mmol) en alcohol metílico (15 ml) a 0 °C. La mezcla resultante se agitó a 0 °C durante una hora, luego a temperatura ambiente durante una hora adicional. El solvente se eliminó en vacío para dar un producto bruto que se purificó mediante cromatografía en columna de gel de sílice usando acetato de etilo como el solvente eluyente. Se recolectaron las fracciones relevantes y se concentró bajo presión reducida para dar 1,1 g (76%) del intermediario **2136.**

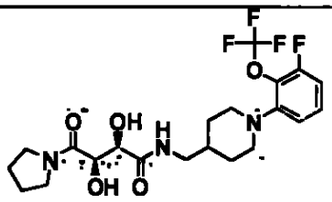
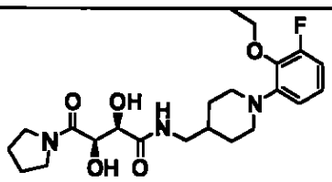
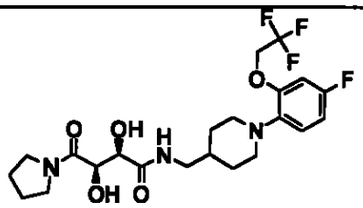
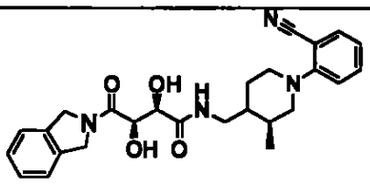
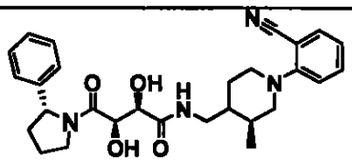
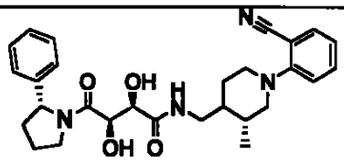
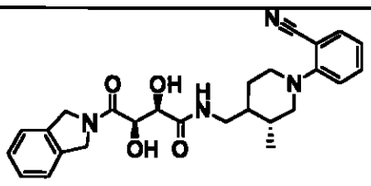
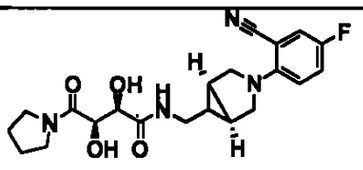
Parte D:

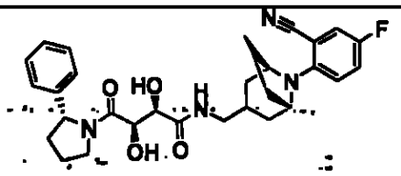
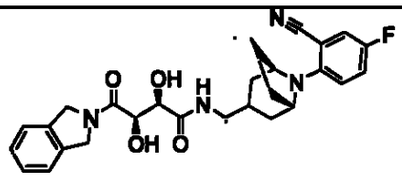
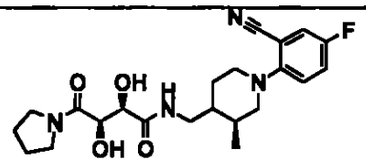
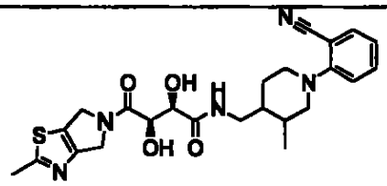
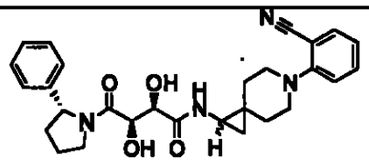
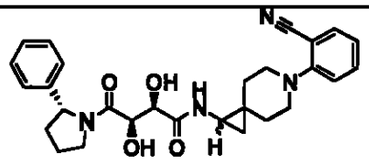
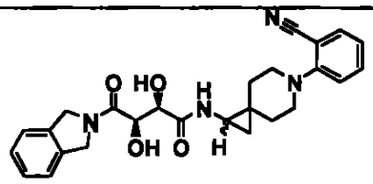
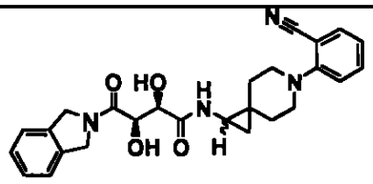
El intermediario **2136** (0,5 g, 1,57 mmol) se disolvió en alcohol metílico (25 ml). Se agregó hidróxido de paladio (20 % en peso de Pd, 0,1 g) bajo N_2, La mezcla resultante se expuso a atmósfera de H_2 a 20 p.s.i. durante 16 horas con agitación vigorosa. La mezcla de reacción se filtró a través de Celite y se lavó con alcohol metílico (1 X 25 ml). El filtrado se concentró en vacío para dar intermediario **2137** (0,38 g) como un aceite que se usó en el paso siguiente sin purificación adicional.

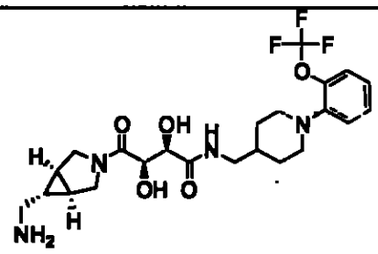
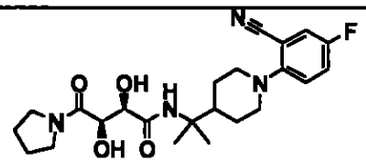
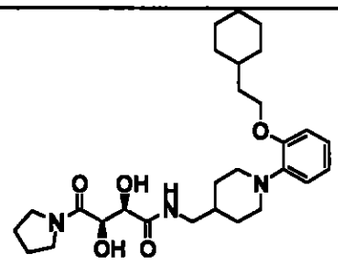
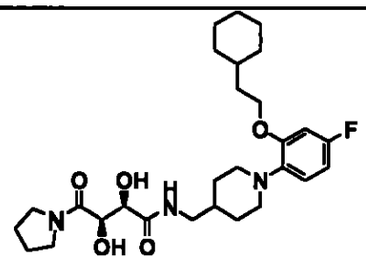
El intermediario **2138** se preparó usando métodos similares a los usados en la Parte B-D.

Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
2139		519,1	520,1

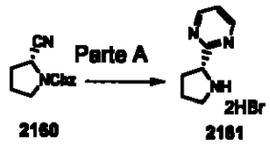
2140		477,2	478,1
2141		437,2	438,1
2142		491,2	492,1
2143		462,2	463,1
2144		490,3	491,1
2145		490,3	491,3
2146		462,2	463,3
2147		416,2	417,2

2148		**520,2**	**521,1**
2149		**492,2**	**493,3**
2150		**432,2**	**433,2**
2151		**483,2**	**484,1**
2152		**488,2**	**489,1**
2153		**488,2**	**489,1**
2154		**460,2**	**461,1**
2155		**460,2**	**461,3**

2156		**500,2**	**500,1**
2157		**446,2**	**447,3**
2158		**501,3**	**502,3**
2159		**519,3**	**520,3**

Ejemplo 51:

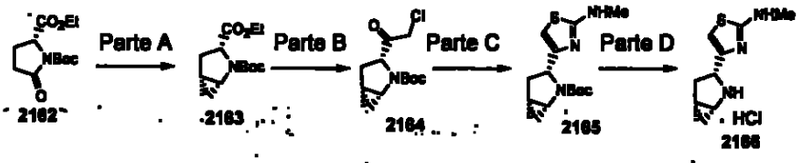
Ejemplo 51A:



Parte A:

El Compuesto **2161** se sintetizó de acuerdo con los procedimientos de WO02060894A2. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,58 (bs, NH), 8,89 (m, 2H), 7,57 (m, 1H), 4,88 (m, 1H), 3,80 (m, 2H), 2,06 (m, 4H).

Ejemplo 51B:



Parte A:

El Compuesto **2163** se sintetizó a partir del Compuesto **2162** (preparado de acuerdo con los procedimientos de WO2004/052850) de acuerdo con los procedimientos de Hanessian et. al.(*Bioorg. Med. Chem Lett.* **1998**, *8*, 2123 y las referencias en el mismo.) HPLC-MS t_R = 1,90 min. ($UV_{254\ nm}$); masa calculada para la fórmula C13H21NO4 255,2, LCMS observada m/z 278,2 (M+Na).

Parte B:

El Compuesto **2164** se sintetizó de acuerdo con los procedimientos de Ejemplo 10B Parte A. HPLC-MS t_R = 1,79 min. ($UV_{254\ nm}$); masa calculada para la fórmula C12H18ClNO3 259,1, LCMS observada m/z 282,1 (M+Na).

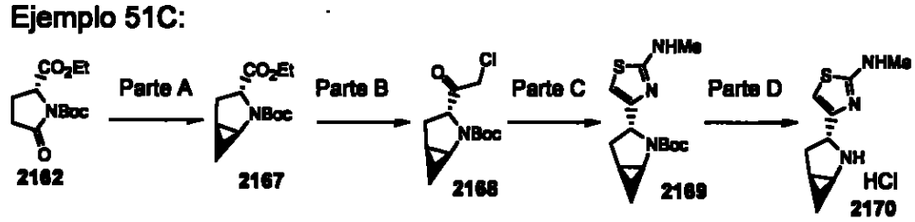
Parte C:

El Compuesto **2164** (190 mg) se ciclizó con N-metiltiourea en DMF (2 ml) para dar **2165** (81 mg) de acuerdo con los procedimientos de Ejemplo 10B Parte B. HPLC-MS t_R = 1,27 min. ($UV_{254\ nm}$); masa calculada para la fórmula C14H21N3O2S 295,1, LCMS observada m/z 296,2 (M+H).

Parte D:

Al Compuesto **2165** (81 mg) en metanol (2 ml) se agregó 4,0 M HCl/dioxano (1 ml) con enfriamiento de baño de hielo. La mezcla de reacción se agitó durante 1,5 horas y se concentró. El residuo se suspendió en DCM (5 ml) y se concentró para dar **2166** impuro. El material se usó sin purificación.

Ejemplo 51C:



Parte A:

El Compuesto **2167** se sintetizó a partir del Compuesto **2162** (made de acuerdo con los procedimientos de WO2004/052850) de acuerdo con los procedimientos de Hanessian et. al. *Bioorg. Med. Chem Lett.* **1998**, *8*, 2123 y las referencias en el mismo. HPLC-MS t_R = 1,83 min. (MS); masa calculada para la fórmula C13H21NO4 255,2, LCMS observada m/z 278,2 (M+Na).

Parte B:

El Compuesto **2168** se sintetizó de acuerdo con los procedimientos de Ejemplo 10B Parte A. HPLC-MS t_R = 1,78 min. (MS); masa calculada para la fórmula C12H18ClNO3 259,1, LCMS observada m/z 282,1 (M+Na).

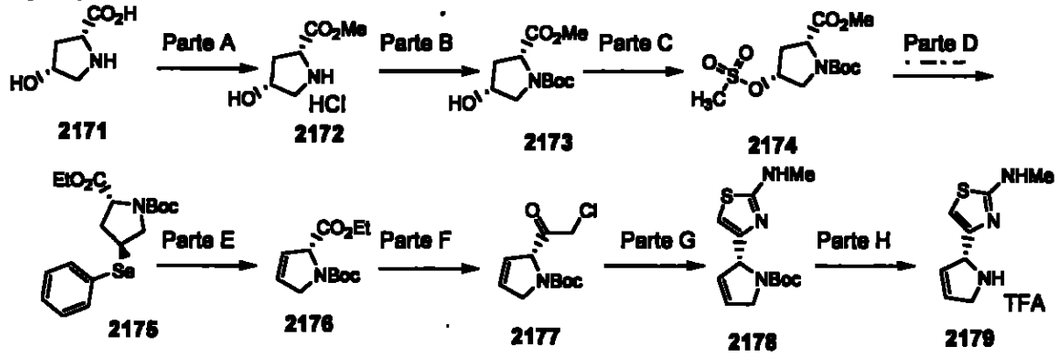
Parte C:

El Compuesto **2168** (117 mg) se ciclizó con N-metiltiourea en DMF (2 ml) para dar **2169** (35 mg) de acuerdo con los procedimientos de Ejemplo 10B Parte B. HPLC-MS t_R = 1,16 min. ($UV_{254\ nm}$); masa calculada para la fórmula C14H21N3O2S 295,1, LCMS observada m/z 296,2 (M+H).

Parte D:

Al Compuesto **2169** (35 mg) en metanol (2 ml) se agregó HCl/dioxano 4,0 M (1 ml) con enfriamiento de baño de hielo. La mezcla de reacción se agitó durante 1,5 horas y se concentró. El residuo se suspendió en DCM (5 ml) y se concentró para dar **2170** impuro. El material se usó sin purificación.

Ejemplo 51D:



Parte A:

A hidroxiprolina **2171** (1,52 g, 11,6 mmol) en metanol (25 ml) en un baño de hielo se agregó cloruro de tionilo (0,95 ml, 13 mmol). El baño de hielo se eliminó y la mezcla de reacción se calentó hasta reflujo hasta el día siguiente. La mezcla de reacción se enfrió y se concentró. El residuo se disolvió en metanol y se concentró. El residuo se disolvió en dietil éter y se concentró para dar **2172** de manera cuantitativa. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,25 (bs, 1H), 8,95 (bs, 1H), 4,50 (d, 1H, J = 7,0 Hz), 4,36 (m, 1H), 3,75 (s, 3H), 3,16 (m, 2H), 2,31 (m, 1H), 2,13 (m, 1H).

Parte B:

Al Compuesto **2172** (2,11 g, 11,6 mmol) en DCM (25 ml) se agregó DIEA (4,2 ml, 24 mmol) y una solución de BOC-anhídrido (3,03 g, 13, 9 mmol) en DCM (25 ml) con enfriamiento de baño de hielo. La mezcla de reacción se calentó lentamente hasta temperatura ambiente y se agitó hasta el día siguiente. La mezcla de reacción se lavó con agua, HCl 0,1 N, solución de bicarbonato y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, cargado con acetato de etilo y eluyó con 30% de acetato de etilo/hexano a acetato de etilo) dio **2173** (2,66 g) como un aceite. ^{1}H RMN (400 MHz, $CDCl_3$) δ rotómeros 4,40-4,29 (m, 2H), 3,81 y 3,80 (s, 3H), 3,75 – 3,64 (m, 1H), 3,57-3,50 (m, 1H), 2,35 (m, 1H), 2,11 (m, 1H), 1,48 y 1,44 (s, 9H).

Parte C:

Al Compuesto **2173** (2,66 g, 10,8 mmol) en DCM (50 ml) en un baño de hielo se agregó gota a gota trietil amina (1,66 ml, 11,9 mmol) y cloruro de metansulfonilo (1,09 ml, 14,1 mmol). La mezcla de reacción se calentó lentamente hasta temperatura ambiente y se agitó hasta el día siguiente. La mezcla de reacción se desactivó con hielo agua y las capas se separaron. La capa acuosa se extrajo con DCM. Las capas orgánicas combinadas se lavaron con HCl 0,1 N y

salmuera, se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 50% de acetato de etilo/hexanos) dio **2174** (3,36 g) como un aceite. HPLC-MS t_R = 1,49 min. (ELSD); masa calculada para la fórmula C12H21NO7S 323,1, LCMS observada m/z 346,1 (M+Na).

Parte D:

A difenilseleniuro (1,97 g, 6,3 mmol) en etanol (20 ml) en un baño de hielo se agregó borohidruro de sodio (472 mg, 12,5 mmol) en porciones. La mezcla de reacción se agitó durante 10 minutos una vez que se detuvo el burbujeo. La solución anterior se agregó al Compuesto **2174** (3,36 g, 10, 4 mmol) en etanol (10 ml). La mezcla de reacción se calentó hasta reflujo durante 2 horas. La reacción se enfrió y los solventes removed en *vacuo*. El residuo se dividió entre agua (50 ml) y acetato de etilo (50 ml). Las capas se separaron. La capa orgánica se lavó con agua y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 5al to 20% de acetato de etilo/hexanos) dio **2175** (2,91 g) como un aceite. HPLC-MS t_R = 2,32 min. ($UV_{254\ nm}$); masa calculada para la fórmula C18H25NO4Se 399,1, LCMS observada m/z 422,0 (M+Na).

Parte E:

A **2175** (481 mg, 1,21 mmol) en DCM (5 ml) en un baño de hielo se agregó gota a gota piridina (0,162 ml, 2,0 mmol) y 50% de peróxido de hidrógeno (0,161 ml, 2,63 mmol). El baño de hielo se eliminó y la mezcla de reacción se agitó a temperatura ambiente durante 1,25 horas. La mezcla de reacción se diluyó con acetato de etilo (50 ml), se lavó con HCl 0,1 N, solución de bicarbonato y salmuera, se secó sobre sulfato de sodio y se concentró para dar **2176** (272 mg) como un aceite amarillo. HPLC-MS t_R = 1,81 min. (MS); masa calculada para la fórmula C12H19NO4 241,1, LCMS observada m/z 264,1 (M+Na).

Parte F:

El Compuesto **2177** (123 mg) se preparó a partir de **2176** (202 mg, 0,84 mmol) de acuerdo con el procedimiento descripto en el Ejemplo 10B. Parte B. HPLC-MS t_R = 1,70 min. (MS); masa calculada para la fórmula C11H16ClNO3 245,1; LCMS observada m/z 264,1 (M+Na).

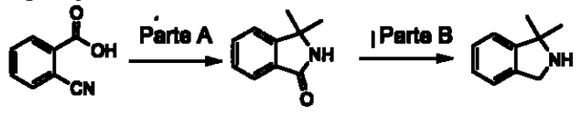
Parte G:

El Compuesto **2178** (48 mg) se preparó según se describe en el Ejemplo 51B Parte C del compuesto **2177** (123 mg, 0,5 mmol). HPLC-MS t_R = 1,12 min. ($UV_{254\ nm}$); masa calculada para la fórmula C13H19N3O2S 281,1, LCMS observada m/z 282,1 (M+H).

Parte H:

Se agitaron una mezcla del compuesto **2178** (48 mg, 0,17 mmol), TFA (2 ml) y DCM (2 ml) a temperatura ambiente durante 1 hora. Los solventes se eliminaron y el residuo se disolvió en DCM (5 ml) y se concentró para dar **2179** (70 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,58 (bs, NH), 6,75 (s, 1H), 6,26 (d, 1H, J = 6,3 Hz), 5,92 (d, 1H, J = 7,5 Hz), 5,77 (m, 1H), 4,43 (d, 1H, J =17,2 Hz), 4,28 (d, 1H, J =17,2 Hz), 3,11 (s, 3H).

Ejemplo 51E:



2180 **2181** **2182**

Parte A:

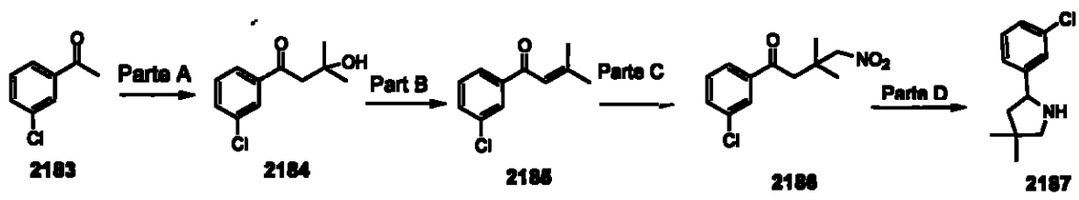
El Compuesto **2180** se preparó usando un procedimiento de modificación en *J. Org. Chem.* **1998**, *63*, 8, 2451-2455, El Compuesto **2180** (0,400 g, 2,72 mmol) se disolvió en THF (60 ml) y se enfrió en un baño de hielo seco/acetona. Una solución de metillitio (1,6 M en dietiléter, 18 ml) se agregó gota a gota y la solución se calentó hasta temperatura ambiente. La reacción se desactivó con salmuera después de 10 minutos. La mezcla de reacción se vertió en agua y se

extrajo con acetato de etilo. Los orgánicos combinados se lavaron con HCl 1N, bicarbonato de sodio saturado y agua, se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 50% de acetato de etilo/hexanos) dio **2181** (0,200 g). HPLC-MS t_R = 1,126 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{10}H_{11}NO$ 161,1, LCMS observada m/z 162 (M+H).

Parte B:

El Compuesto **2181** (0,200 g, 1,24 mmol) se disolvió en THF (10 ml) y se agregó gota a gota una solución de boro (2,5 M en THF, 3 ml) y la solución se agitó a reflujo hasta el día siguiente. La reacción se desactivó con una solución de hidróxido de sodio 1 M (2 ml) y metanol (2 ml) y se continuó el reflujo durante 5 horas. La mezcla de reacción se vertió en agua y se extrajo con acetato de etilo. Los orgánicos combinados se lavaron con bicarbonato de sodio saturado, agua, se secaron sobre sulfato de sodio y se concentraron para dar **2182** (65 mg). HPLC-MS t_R = 0,595 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{10}H_{11}N$ 147,1, LCMS observada m/z 148 (M+H).

Ejemplo 51F:



Parte A:

El Compuesto **2184** se preparó usando un procedimiento de modificación en *J. Med.Chem.*. **1994**, *37*, 23, 3878-3881. El Compuesto **2183** (2,0 g, 12,9 mmol) se disolvió en cloruro de metileno y se enfrió en un baño de hielo. Se agregó Trietilamina (3,61 ml, 26 mmol) seguida por la adición gota a gota de TMSOTf (2,81 ml, 15,5 mmol). La reacción se calentó hasta temperatura ambiente y se

agitó durante 30 minutos. Se agregó lentamente bicarbonato de sodio saturado para desactivar la reacción y la capa acuosa se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera; se secaron sobre sulfato de sodio. En una matraz se agregó $TiCl_4$ (1M en tolueno, 20 ml) a cloruro de metileno (80 ml) a –78 °C. Se agregó acetona (1,2 g, 22 mmol) y se agitó durante 2 minutos. El éter de silil enol del anterio se agregó y la reacción se agitó durante 4 horas. Después de calentar hasta temperatura ambiente, la reacción se desactivó con bicarbonato de sodio saturado y se extrajo con cloruro de metileno. Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se evaporó. La purificación mediante cromatografía en columna (SiO_2, 33% de acetato de etilo/hexanos) dio **2184** (600 mg). ^1H RMN (400 MHz, $CDCl_3$) δ 7,90 (d, 1H), 7,80 (d, 1H), 7,55 (d, 1H), 7,40 (t, 1H), 3,15 (s, 2H), 1,40 (s, 6H).

Parte B:

El Compuesto **2184** (600 mg; 2,84 mmol) se disolvió en cloruro de metileno (2 ml) y piridina (2 ml) y se enfrió en un baño de hielo. Se agregó gota a gota TFAA (0,894 g, 4,26 mmol) y se agitó 1 hora a temperatura ambiente. La mezcla de reacción se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con HCl 1N, bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio, y se concentró. El residuo se disolvió en cloruro de metileno (5 ml) y se agregó DBU (0,5 ml) y se agitó durante 1 hora a temperatura ambiente. La mezcla de reacción se dividió entre cloruro de metileno y agua. Las capas orgánicas se lavaron con HCl 1N, bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio, y se concentró. La purificación mediante cromatografía en columna (SiO_2, 10% de acetato de etilo/hexanos) dio **2185** (460 mg). ^1H RMN (400 MHz, $CDCl_3$) δ 7,90 (d, 1H), 7,80 (d, 1H), 7,50 (d, 1H), 7,40 (t, 1H), 6,70 (m, 1H), 2,20 (d, 3H), 2,05 (d, 3H).

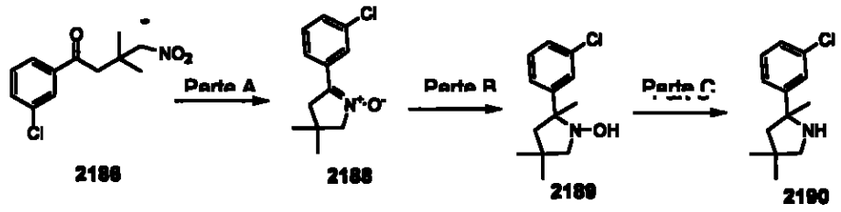
Parte C:

El Compuesto **2185** (460 mg, 2,38 mmol) se disolvió en nitrometano (295 mg, 4,76 mmol) y benciltrimetilhidróxido de amonio (40% en peso en MeOH, 200 mg) y se agitó durante 2 horas a temperatura ambiente. La reacción se desactivó con ácido acético (1 ml) y se dividió entre dietil éter y agua. La capa orgánica se secó sobre sulfato de sodio y se concentró para dar **2186** (550 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,90 (d, 1H), 7,80 (d, 1H), 7,58 (d, 1H), 7,40 (t, 1H), 4,70 (s, 2H), 3,10 (s, 2H), 1,30 (s, 6H).

Parte D:

El Compuesto **2187** se preparó de acuerdo con el procedimiento en *Chem. Ber.* **1958**, *91*, 1978-1980, ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,38 (m, 1H), 7,22 (m, 2H), 7,18 (m, 1H), 4,30 (m, 1H), 2,90-2,80 (dd, 2H), 2,00 (m, 1H), 1,50 (m, 1H), 1,15 (d, 6H).

Ejemplo 51G:



Parte A:

El Compuesto **2186** (500 mg, 1,96 mmol) y cloruro de amonio (104 mg, 1,96 mmol) se disolvieron en THF (5 ml) y agua (5 ml) y se enfrió en un baño de hielo. Se agregó Zn en polvo (637 mg, 9,8 mmol) en porciones y se agitó hasta el día siguiente. La mezcla de reacción se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio, y se concentró. El residuo se disolvió en cloruro de metileno (10 ml) y se agregó m-CPBA (510 mg, 2,94 mmol) y se agitó durante 2 horas. La mezcla de reacción se dividió entre cloruro de metileno y agua. Las capas orgánicas se lavaron con bicarbonato de sodio saturado, salmuera, se secó

sobre sulfato de sodio, y se concentró para dar **2188** (300 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,80 (m, 1H), 7,65 (m, 2H), 7,40-7,30 (m, 2H), 3,80 (t, 2H), 2,80 (t, 2H), 1,20 (s, 6H).

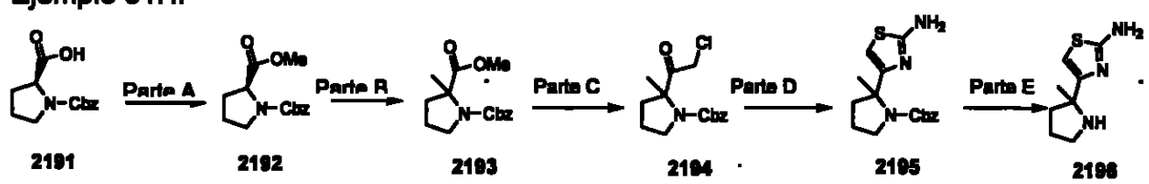
Parte B:

El Compuesto **2188** (300 mg, 1,35 mmol) se disolvió en THF (10 ml) y se agregó gota a gota MeMgBr (3M en THF, 5 ml). Después de agitar durante 30 minutos a temperatura ambiente la mezcla de reacción se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con bicarbonato de sodio saturado, salmuera, se secaron sobre sulfato de sodio, y se concentraron para dar **2189** (280 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,53 (t, 1H), 7,42 (m, 1H), 7,30-7,20 (m, 2H), 3,20 (m, 2H), 2,00 (m, 2H), 1,55 (s, 3H), 1,20 (s, 3H), 1,15 (s, 3H).

Parte C:

El Compuesto **2189** (280 mg, 1,26 mmol) se disolvió en HCl 1N (10 ml) y se agregó polvo de Zn (0,5 g). La mezcla de reacción se agitó a 60 °C durante 12 horas. La mezcla de reacción se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio, y se concentró para dar **2190** (110 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,53 (bs, 1H), 7,38 (m, 1H), 7,30-7,20 (m, 2H), 2,85 (m, 1H), 2,75 (m, 1H), 2,05 (m, 1H), 1,85 (m, 1H), 1,50 (s, 3H), 1,20 (s, 3H), 0,95 (s, 3H).

Ejemplo 51H:



2191 **2192** **2193** **2194** **2195** **2196**

Parte A:

El Compuesto **2191** (2,8 g, 11,2 mmol) se disolvió en tolueno (10 ml) y MeOH (10 ml) y se enfrió en un baño de hielo. Se agregó gota a gota una solución de TMS diazometano en hexanos (2M, 8,4 ml) hasta que presisitió un color amarillo. La

reacción se desactivó con ácido acético hasta que el color se aclaró y el solvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica se lavó con HCl 1N, bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio y se concentró para dar **2192** (3,1 g). El producto se usó sin purificación.

Parte B:

Se disolvió diisopropilamina (3,9 ml, 28 mmol) en THF (20 ml) y se enfrió hasta –40 °C. Se agregó gota a gota una solución de n-Buli (2,5M en hexanos, 8,9 ml) y la reacción se agitó durante 30 minutos. El Compuesto **2192** (3,1 g, 11,2 mmol) disuelto en THF (10 ml) se agregó gota a gota a –78 °C y se agitó durante otros 30 minutos. Se agregó gota a gota yodometano (3,1 g, 22,4 mmol) y la reacción se agitó durante una hora adicional. La reacción se calentó hasta temperatura ambiente y se desactivó con salmuera y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua, salmuera, se secaron sobre sulfato de sodio y se concentraron para dar **2193** (2,5 g). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,40-7,20 (m, 5H), 5,20-5,00 (m, 2H), 3,70-3,40 (d, 3H), 3,70-3,60 (m, 2H), 2,20 (m, 1H), 1,90 (m, 3H), 1,60 (d, 3H).

Parte C:

Se disolvió diisopropilamina (1,24 ml, 8,85 mmol) en THF (10 ml) y se enfrió hasta –40 °C. Se agregó gota a gota una solución de n-Buli (2,5M en hexanos, 3,5 ml) y la reacción se agitó durante 30 minutos. Esta solución se agregó gota a gota a una solución de compuesto **2193** (450 mg, 1,61 mmol) y cloroyodometano (1,12 g, 6,44 mmol) en THF (10 ml) a –78 °C. La reacción se agitó durante 30 minutos y luego se desactivó mediante la adición gota a gota de ácido acético (1 ml) en THF (5 ml). Después de revolver durante 10 minutos, la mezcla de reacción se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con bicarbonato de sodio saturado, salmuera, se secaron sobre sulfato de sodio y se concentraron.

La purificación mediante cromatografía en columna (SiO_2, 25% de acetato de etilo/hexanos).dio **2194**.(330 mg). ^1H RMN (400 MHz, $CDCl_3$) δ 7,40-7,20 (m, 5H), 5,20-5,00 (m, 2H), 4,40-4,00 (m, 2H), 3,80-3,60 (m, 2H), 2,20 (m, 1H), 2,00-1,80 (m, 3H), 1,60-1,40 (m, 3H).

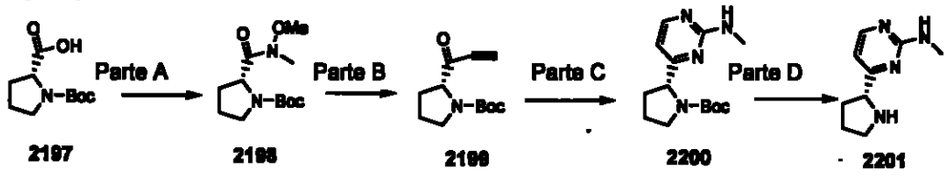
Parte D:

El Compuesto **2194** (175 mg, 0,59 mmol) se disolvió en DMF (5 ml) y se agregó tiourea (91 mg, 1,2 mmol) y se agitó a temperatura ambiente hasta el día siguiente. La mezcla de reacción se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con bicarbonato de sodio saturado, salmuera, se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 50% de acetato de etilo/hexanos) dio **2195** (115 mg). HPLC-MS t_R = 1,17 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{16}H_{19}N_3O_2S$ 317,1, LCMS observada m/z 318,1 (M+H).

Parte E:

El Compuesto **2195** (115 mg, 0,36 mmol) se disolvió en 30% de HBr/AcOH (2 ml) y se agitó durante 2 horas. El solvente se eliminó bajo presión reducida y el residuo se disolvió en agua y se lavó con dietil éter. La capa acuosa se liofilizó para dar **2196** as a di-HBr salt (100 mg).

Ejemplo 51l:



Parte A:

Se disolvieron El Compuesto **2197** (2,3 g, 10,6 mmol), 4-cloro-2,6-dimetoxitriazina (2,4 g, 13,9 mmol) y NMM (7,3 ml, 53 mmol) en THF (50 ml) y se agitó durante 1 hora. Se agregó clorhidrato de N,O- dimetilhidroxilamina (2,05 g, 21,2 mmol) y la mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La

mezcla de reacción se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con HCl 1N, bicarbonato de sodio saturado, salmuera, se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 50% de acetato de etilo/hexanos) dio **2198** (2,0 g). ^1H RMN (400 MHz, $CDCl_3$) δ 4,70-4,60 (m, 1H), 3,75 (m, 3H), 3,60-3,40 (m, 2H), 3,20 (s, 3H), 2,20 (m, 1H), 2,00-1,80 (m, 3H), 1,50-1,40 (m, 9H).

Parte B:

El Compuesto **2198** (550 mg, 2,13 mmol) se disolvió en THF (10 ml) y se agregó gota a gota una solución de litio (trimetilsilil)acetiluro (0,5 M en THF, 12 ml) y se agitó hasta el día siguiente. La mezcla de reacción se dividió entre acetato de etilo y HCl 1N. La capa orgánica se lavó con HCl 1N, bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 20% de acetato de etilo/hexanos) dio **2199** (370 mg). HPLC-MS t_R = 1,69 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{12}H_{17}NO_3$ 223,1, LCMS observada m/z 168,1 (M-(t-butyl)).

Parte C:

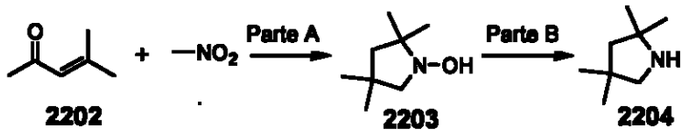
Se disolvieron el Compuesto **2199** (350 mg, 1,56 mmol) y dietilamina (228 mg, 3,13 mmol) en EtOH (1,5 ml) y agua (1,5 ml) y se agitó durante 3 horas. La mezcla de reacción se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con bicarbonato de sodio saturado, salmuera, se secaron sobre sulfato de sodio y se concentraron. El residuo se combinó con clorhidrato de metil guanidina (756 mg, 7,8 mmol) y carbonato de sodio (826 mg, 7,8 mmol) en EtOH (6 ml) y se reflujó durante 48 horas. La mezcla de reacción se dividió entre acetato de etilo y agua. La capa orgánica se lavó con bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 80% de acetato de

etilo/hexanos) dio **2200** (210 mg). HPLC-MS t_R = 1,26 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{14}H_{22}N_4O_2$ 278,1, LCMS observada m/z 279,1 (M+H).

Parte D:

El Compuesto **2200** (105 mg, 0,377 mmol) se disolvió en HCl 4 M en dioxano (2 ml) y metanol (0,5 ml) y se agitó a temperatura ambiente durante 1 hr. La mezcla de reacción se concentró y se trituró con dietil éter para dar **2201** (74 mg) como una sal de HCl. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,00 (bs, 1H), 8,70 (bs, 1H), 8,30 (s, 1H), 6,70 (d, 1H), 4,60 (bs, 1H), 3,40 (m, 2H), 2,75 (s, 3H), 2,40 (m, 1H), 2,00-1,80 (m, 3H).

Ejemplo 51J:



2202 **2203** **2204**

Parte A:

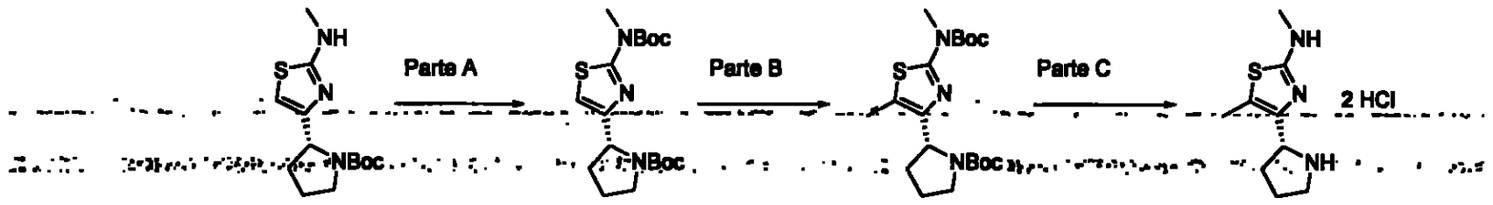
El Compuesto **2203** se preparó de acuerdo un procedimiento descripto en *J. Org. Chem.* **1991**, *57*, 7034-7038,

Parte B:

Se agitó a reflujo una mezcla de **2203** (200 mg, 1,42 mmol) y polvo de cinc (278 mg, 4,25 mmol) en ácido clorhídrico concentrado (1,4 ml) y agua (5,8 ml) hasta el día siguiente. La mezcla se tornó básica con pellets de hidróxido de potasio, se decantó y la solución acuosa se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio y se concentraron para dar **2204** como un sólido pegajoso amarillo (95 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,35 (m, 2H), 1,88 (s, 2H), 1,66 (s, 6H), 1,30 (s, 6H).

Ejemplo 51K:

1601 620



2205 **2206** **2207** **2208**

El Compuesto **2205** se preparó usando procedimientos descriptos en el Ejemplo 10B.

Parte A:

A la solución de 2-metilaminotiazol **2205** (100 mg, 0,35 mmol) y DMAP (135 mg, 1,0 mmol) en THF (5 ml), se agregó Boc_2O (218 mg, 1,0 mmol) a temperatura ambiente. La mezcla resultante se agitó hasta el día siguiente y luego se diluyó con acetato de etilo (30 ml). Los orgánicos se lavaron con agua, salmuera y se secaron sobre sulfato de sodio y se concentraron. El residuo que se purificó mediante cromatografía en columna (SiO_2, 20% de acetato de etilo/hexanos) dio el producto protegido **2206** (130 mg) como un semi aceite. HPLC-MS t_R = 2,42 min. ($UV_{254\ nm}$); masa calculada para la fórmula C18H29N3O4S 383,2, LCMS observada m/z 384,1 (M+H).

Parte B:

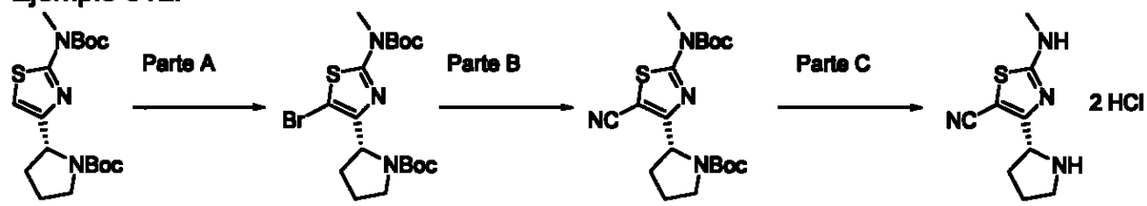
La solución de tiazol **2206** (150 mg, 0,39 mmol) en THF (5 ml) se enfrió hasta –78°C, y se agregó lentamente *n*-Buli (2,5 M en hexano, 0,19 ml, 0,47 mmol). La mezcla resultante se agitó a –78 °C durante 30 min, y luego se agregó yodometano (0,1 ml, 1,55 mmol). La mezcla se agitó durante otros 30 min. seguido por la adición de solución de NH_4Cl saturado (15 ml). La capa acuosa se extrajo con acetato de etilo. Los orgánicos combinados se lavaron con agua, salmuera, se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 10% de acetato de etilo/hexanos) dio tiazol recuperado **2206** (36 mg) y **2207** (100 mg). HPLC-MS t_R = 2,51 min. (UV_{254}

$_{nm}$); masa calculada para la fórmula C19H31N3O4S 397,2, LCMS observada m/z 398,2 (M+H).

Parte C:

A una solución de 5-metiltiazol **2207** (100 mg, 0,25 mmol) en dioxano (2 ml) se agregó HCl (4N en dioxano, 4 ml) seguido por agua (0,5 ml). La mezcla se agitó a temperatura ambiente durante 1 hora y se concentró. El residuo resultante **2208** (72 mg) se secó en vacío y se usó en el siguiente paso sin purificación adicional.

Ejemplo 51L:



2206 **2209A** **2209B** **2210**

Parte A:

A la solución del tiazol **2206** (190 mg, 0,5 mmol) en cloroformo (5 ml), se agregó NBS (107 mg, 0,6 mmol). La mezcla se calentó hasta 50 °C y se agitó durante 1 hora. Después de enfriar hasta temperatura ambiente, la mezcla se concentró y se purificó mediante cromatografía en columna (SiO_2, 10% de acetato de etilo/hexanos) para dar 5-bromotiazol **2209A** (221 mg). HPLC-MS t_R = 2,65 min. ($UV_{254\ nm}$); masa calculada para la fórmula C18H28BrN3O4S 461,1, LCMS observada m/z 462,1 (M+H).

Parte B:

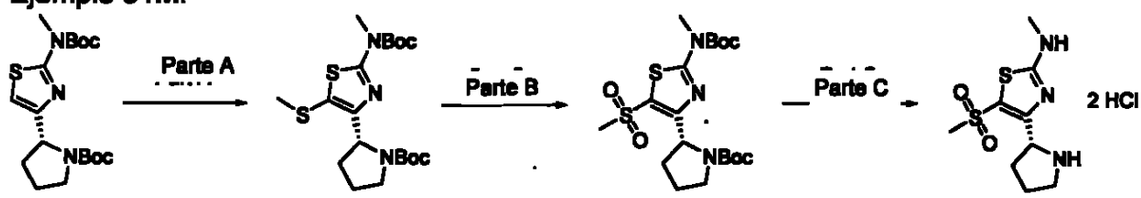
Se saturó una mezcla de 5-bromotiazol **2209A** (221 mg, 0,48 mmol), $Zn(CN)_2$ (117 mg, 1,0 mmol), $Pd_2(dba)_3$ (45 mg, 0,05 mmol) y DPPF (55 mg, 0,1 mmol) en un balón de 25-ml con argón durante 3 min. Bajo argón, se agregó DMA (3 ml) y la matraz se selló bajo la atmósfera de argón. La mezcla se calentó hasta 85 °C y se agitó hasta el día siguiente. Después de enfriar hasta temperatura ambiente, acetato de etilo (30 ml) se agregó una la mezcla de reacción diluida y la solución

se filtró a través de Celite. El filtrado se concentró y se purificó mediante cromatografía en columna (SiO_2, 10% de acetato de etilo/hexanos) para dar 5-cianotiazol **2209B** (167 mg) as oil. HPLC-MS t_R = 2,39 min. ($UV_{254\ nm}$); masa calculada para la fórmula C19H28N4O4S 408,2, LCMS observada m/z 409,2 (M+H).

Parte C:

El Compuesto **2210** (110 mg) se preparó a partir de **2209B** (167 mg, 0,41 mmol) de acuerdo con el procedimiento descripto en el Ejemplo 51K Parte C. HPLC-MS t_R = 0,62 min. ($UV_{254\ nm}$); masa calculada para la fórmula C9H12N4S 208,1, LCMS observada m/z 209,1 (M+H).

Ejemplo 51M:



2206 **2211** **2212** **2213**

Parte A:

Se agregó lentamente una solución de *n*-Buli (2,5 M en hexano, 0,24 ml, 0,6 mmol) a una solución de tiazol **2206** (190 mg, 0,5 mmol) en THF (5 ml) a -78 °C. La mezcla resultante se agitó a -78 °C durante 1 hora, y luego se agregó disulfuro de metilo (94 mg, 1,0 mmol). La mezcla se agitó durante otra hora, y luego calentó hasta temperatura ambiente lentamente. Luego se agregó solución de NH_4Cl saturado para desactivar la reacción. La mezcla se extrajo con acetato de etilo (30 ml x 3). Los orgánicos combinados se secaron sobre sulfato de sodio, se concentraron y se purificaron mediante cromatografía en columna (SiO_2, 10% de acetato de etilo/hexanos) para dar 5-metilsulfidetiazol **2211** (137 mg) y se recuperó tiazol **2206** (38 mg). HPLC-MS t_R = 2,62 min. ($UV_{254\ nm}$); masa calculada para la fórmula C19H31N3O4S2 429,2, LCMS observada m/z 430,1 (M+H).

1604

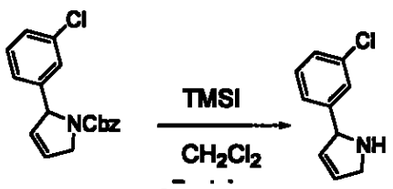
Parte B:

Se agitó a temperatura ambiente una mezcla de sulfuro **2211** (137 mg, 0,32 mmol) y m-CPBA (~77%, 230 mg, 1,0 mmol) en diclorometano (10 ml) hasta el día siguiente. Se agregó acetato de etilo (80 ml) a la mezcla diluida y los orgánicos se lavaron con solución de bicarbonato de sodio saturado dos veces seguido por salmuera, se secaron sobre sulfato de sodio, se concentraron. El residuo se purificó mediante cromatografía en columna (SiO_2, 20% de acetato de etilo/hexanos) dio 5-metilsulfonetiazol **2212** (141 mg). HPLC-MS t_R = 2,62 min. ($UV_{254\ nm}$); masa calculada para la fórmula C19H31N3O6S2 461,2, LCMS observada m/z 406,1 (M+H- *t*-Bu).

Parte C:

El Compuesto **2213** (110 mg) se preparó a partir de **2212** (141 mg, 0,30 mmol) de acuerdo con el procedimiento descripto en el Ejemplo 51K Parte C. HPLC-MS t_R = 0,63 min. ($UV_{254\ nm}$); masa calculada para la fórmula C9H15N3O2S2 261,1, LCMS observada m/z 262,0 (M+H).

Ejemplo 51N:



2214 Parte A **2215**

Se preparó derivado de partida de pirrolina **2214** mediante métodos conocidos (Billet, M; Schoenfelder, A; Klotz, P.; Mann, A.. *Tetrahedron Letters*, 2002, 1453).

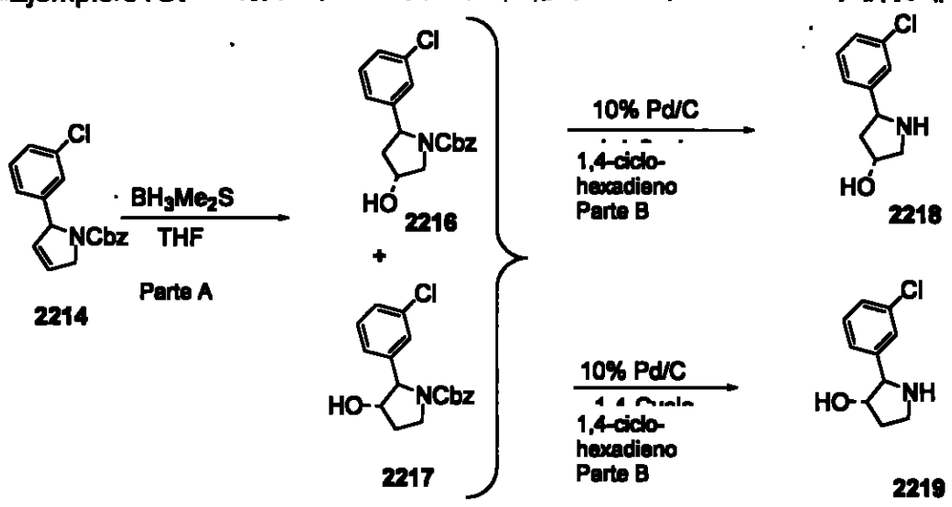
Parte A:

Se agregó gota a gota yoduro de trimetilsililo (0,44 g, 2,24 mmol) a una solución de **2214** (0,47 g, 1,5 mmol; 20 ml CH_2Cl_2) a temperatura ambiente y se agitó durante 3 horas. La mezcla se enfrió hasta 0 °C antes de desactivar con metanol

1605-24

(5 ml). El solvente se eliminó bajo presión reducida para dar amina bruta **2215**, que se usó sin purificación adicional.

Ejemplo 510:



Parte A:

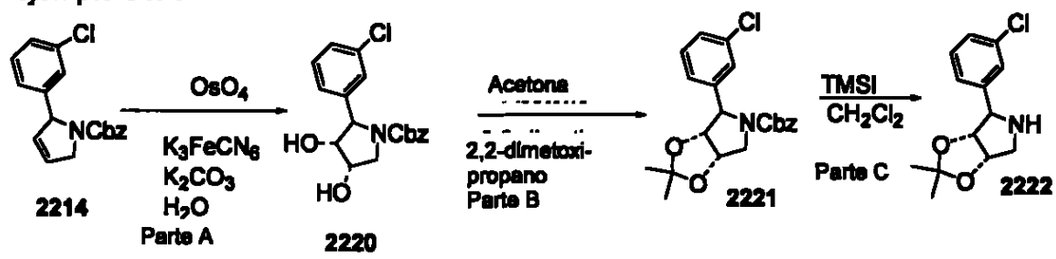
Se agregó gota a gota dimetil sulfuro de borano (2,0 M solución en tolueno, 1,45 ml, 2,9 mmol) a una solución de intermediario **2214** (0,65 g, 2 mmol) en THF (10 ml) a 0 °C. Después de la adición, la mezcla se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se desactivó con la adición gota a gota de agua (1,0 ml) y NaOH 3N (3,0 ml). La mezcla resultante se agitó durante 5 minutos y luego se enfrió hasta 0 °C antes de agregar 30% de H_2O_2 (6,0 ml) gota a gota. La mezcla se agitó a temperatura ambiente durante 2 horas y luego se trató con 5% de $Na_2S_2O_3$ (25 ml) y se agitó durante media hora adicional. La mezcla de reacción se diluyó con acetato de etilo (100 ml), y los orgánicos se lavaron con salmuera, se secó (Na_2SO_4), se filtraron y se concentraron en vacío para dar un residuo bruto que se purificó mediante cromatografía en columna de gel de sílice (1:3 a 1:2 acetato de etilo / hexano) para dar un primer intermediario **2217** (0,3 g, 44%) seguido por intermediario **2216** (0,2 g, 29%).

Parte B:

Se disolvió Intermediario **2216** (0,075 g, 0,22 mmol) en alcohol etílico (1,5 ml). Luego se agregó 1,4-ciclohexadieno (0,21 ml, 2,24 mmol), seguido por la adición de 10% de Pd/C bajo N_2. La mezcla de reacción se agitó a t.a. durante 2 horas, se filtró a través de Celite y se concentró en vacío para dar intermediario **2218** (0,035 g, 80%).

El Compuesto **2219** se preparó mediante el uso de métodos similares a aquellos descriptos en las Partes A-B para el intermediario **2218.**

Ejemplo 51P:



Parte A:

Se disolvió Intermediario **2214** (0,1 g, 0,3 mmol) en *t*-butanol (3 ml) y agua (3 ml). Se agregaron hexacianoferrato de potasio (0,31 g, 0,94 mmol) y carbonato de potasio (0,13 g, 0,94 mmol) y se agitó durante 15 minutos. A esta mezcla se agregó tetróxido de osmio (0,005 g, 0,02 mmol) y se agitó durante 16 h. La reacción se diluyó con acetato de etilo (50 ml) y los orgánicos se lavaron una vez con salmuera (10 ml), se secaron (Na_2SO_4), se filtraron y se concentraron bajo presión reducida para dar intermediario **2220** (0,1 g, 91%).

Parte B:

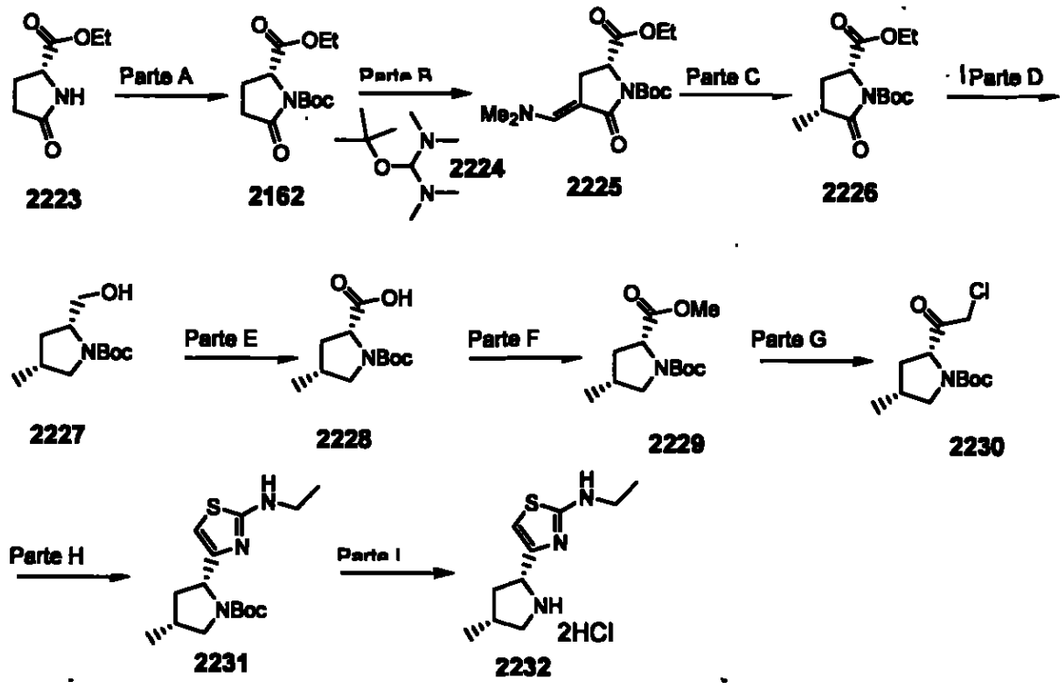
Se disolvió Diol **2220** (0,1 g, 0,28 mmol) en acetona (5 ml) y se agregó 2,2-dimetoxipropano (0,045 g, 0,43 mmol), seguido por la adición de una cantidad catalítica de ácido p-toluensulfónico (0,06 g, 0,03 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 14 h. El solvente se eliminó en vacío para dar un producto bruto que se purificó mediante cromatografía preparativa de

gel de sílice usando acetato de etilo/hexano (1/3) como el solvente eluyente para dar 2221 (0,075 g, 68%).

Parte C:

Se disolvió intermediario **2221** (0,06 g, 0,15 mmol) en CH_2Cl_2 (0,5 ml), seguido por la adición de yoduro de trimetilsililo (0,034 ml, 0,24 mmol) a 0 °C. La mezcla se agitó a t.a. durante 2 horas. La reacción se desactivó con metanol (5 ml) y se agitó durante otras 2 horas. La mezcla de reacción se concentró para dar la amina bruta **2222**, que se usó sin purificación adicional.

Ejemplo 51Q:



Parte A:

El Compuesto **2223** (2,2 g, 13,9 mmol) se disolvió en cloruro de metileno (25 ml) y se agregaron trietilamina (3,9 ml, 27,8 mmol), DMAP (100 mg), y di-*t*-butildicarbonato (3,33 g, 15,3 mmol). La mezcla de reacción se agitó durante 5 horas a temperatura ambiente y luego se diluyó con agua y cloruro de metileno. Las capas orgánicas se lavaron con HCl 1N, bicarbonato de sodio saturado, agua,

salmuera, se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 33% de acetato de etilo/hexanos) dio el producto deseado (3,0 g). ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,60 (m, 1H), 4,20 (q, 2H), 2,70-2,60 (m, 1H), 2,50 (m, 1H), 2,40-2,30 (m, 1H), 2,05 (m, 1H), 1,50 (s, 9H), 1,20 (t, 3H).

Parte B:

El Compuesto **2162** (630 mg, 2,44 mmol) se agregó a *t*-butoxi-bis(dimetilamino)metano (**2224**) (0,705 ml, 3,42 mmol) y se agitó a 80 °C hasta el día siguiente. El reactivo de exceso se eliminó bajo presión reducida para dar **2225** que se usó sin purificación adicional (750 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,10 (m, 1H), 4,50 (m, 1H), 4,30-4,20 (m, 2H), 3,30 (m, 1H), 3,00 (s, 6H), 2,80 (m, 1H), 1,50 (s, 9H), 1,30 (m, 3H).

Parte C:

El Compuesto **2225** (750 mg, 2,4 mmol) se disolvió en acetato de etilo (12 ml) y se agregó 10% de Pd-C (200 mg) bajo una atmósfera de argón. La mezcla de reacción se colocó bajo atmósfera de hidrógeno y se agitó durante 96 horas a temperatura ambiente. La reacción se filtró y el solvente se evaporó. La purificación mediante cromatografía en columna (SiO_2, 33% de acetato de etilo/hexanos) dio el producto deseado (350 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,50 (m, 1H), 4,25 (q, 2H), 2,60 (m, 2H), 1,65 (m, 1H), 1,50 (s, 9H), 1,32 (t, 3H), 1,28 (d, 3H).

Parte D:

El Compuesto **2226** (200 mg, 0,73 mmol) se disolvió en THF (2 ml) y sulfuro de dimetil boro (2M en THF, 1,5 ml) se agregó. La mezcla de reacción se agitó durante 40 horas y luego se enfrió en un baño de hielo y se desactivó lentamente con metanol. El solvente se evaporó y el residuo se purificó mediante cromatografía en columna (SiO_2, 33% de acetato de etilo/hexanos) para dar el

producto deseado (80 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,95 (m, 1H), 3,75-3,50 (m, 3H), 2,75 (t, 1H), 2,25 (m, 2H), 1,50 (s, 9H), 1,20 (m, 1H), 1,00 (d; 3H).

Parte E:

El Compuesto **2227** (70 mg, 0,32 mmol) se disolvió en acetona (3 ml) y se agregó gota a gota reactivo Jones (1 ml). La mezcla de reacción se agitó hasta el día siguiente y luego se desactivó con metanol. La mezcla luego se filtró y se concentró. El residuo se disolvió en bicarbonato de sodio saturado y se lavó con dietil éter. La capa acuosa se acidó a pH 2 y luego se extrajo con acetato de etilo. La capa de acetato de etilos se secaron sobre sulfato de sodio y se concentraron para dar el producto deseado (55 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,30-4,20 (m, 1H), 3,80-3,70 (m, 1H), 2,95 (m, 1H), 2,50-2,30 (m, 1H), 2,25 (m, 1H), 1,80-1,60 (m, 1H), 1,50 (d, 9H), 1,05 (m, 3H).

Parte F:

El Compuesto **2228** (370 mg, 1,62 mmol) se disolvió en tolueno (2 ml) y metanol (2 ml) y se enfrió en un baño de hielo. Una solución de trimetilsilil diazometano (2M en hexanos, 1,5 ml) se agregó gota a gota. La solución se agitó durante 1 hora y luego se concentró. El residuo se disolvió en acetato de etilo y agua. La capa orgánica se lavó con HCl 1N, bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio, y se concentró para dar el metil éster **2229** (310 mg).

Parte G:

En un matraz separado se disolvió diisopropilamina (1,0 ml) en THF (10 ml) y se enfrió hasta -78°C. Una solución de *n*-butyl litio (2,5 M en hexanos, 2,55 ml) se agregó gota a gota y se agitó durante 30 minutos. Esta solución se agregó gota a gota a una solución del metil éster **2229** (310 mg, 1,27 mmol) y cloroyodometano (0,9 g, 5,08 mmol) en THF (5 ml) a -78°C. Después de 30 minutos la reacción se desactivó gota a gota con ácido acético (1 ml) en THF (5 ml). La mezcla de reacción se calentó hasta temperatura ambiente y se diluyó con agua y acetato de

etilo. La capa orgánica se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 25% de acetato de etilo/hexanos) dio la cetona deseada alfa-cloro **2230** (150 mg).

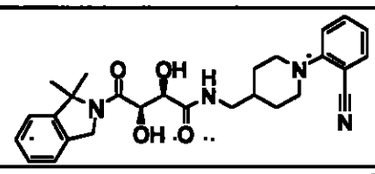
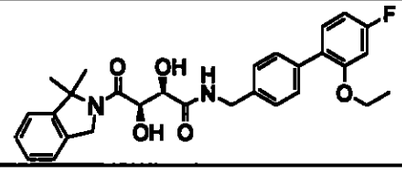
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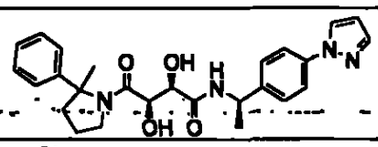
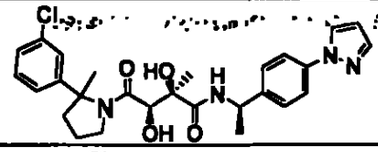
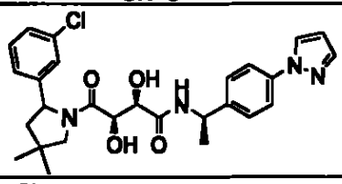
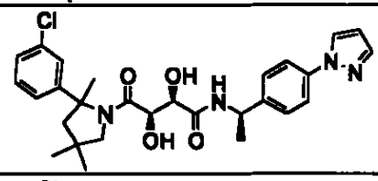
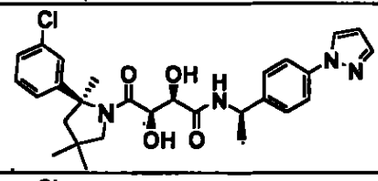
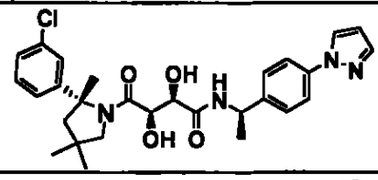
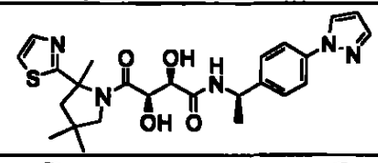
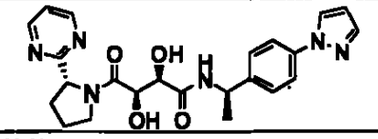
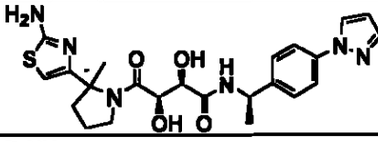
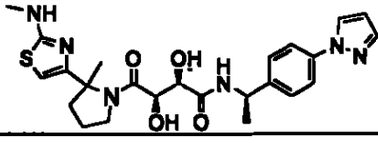
Se disolvió la alpha-cloro cetona **2230** (150 mg, 0,575 mmol) en DMF (5 ml) y se agregó etil tiourea (134 mg, 1,15 mmol) y se agitó a 80 °C hasta el día siguiente. La mezcla de reacción se dividió entre acetato de etilo y agua. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, acetato de etilo) dio el producto deseado **2231** (85 mg). HPLC-MS t_R = 1,35 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{15}H_{25}N_3O_2S$ 311,1, LCMS observada m/z 312,1 (M+H).

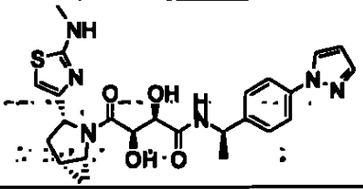
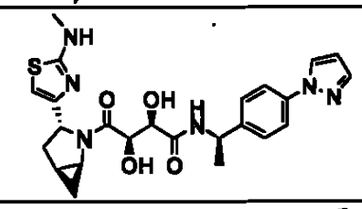
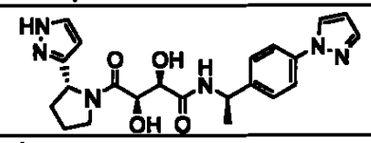
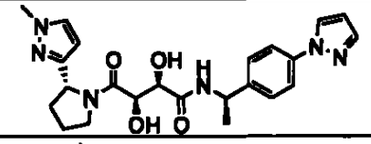
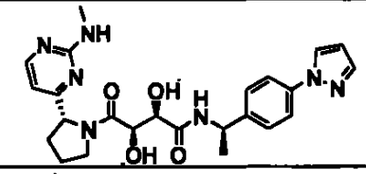
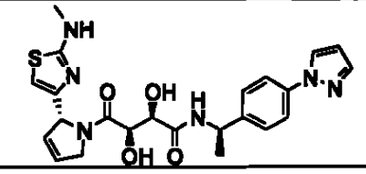
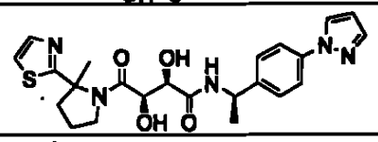
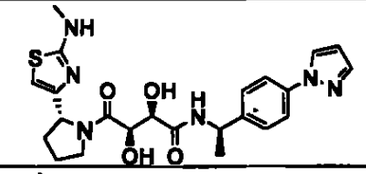
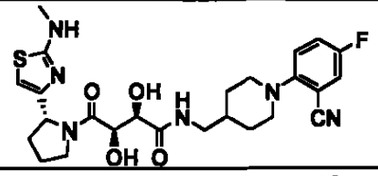
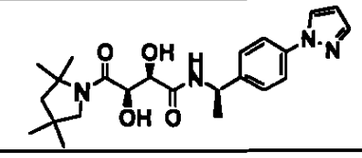
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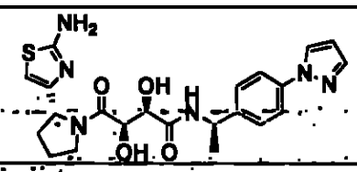
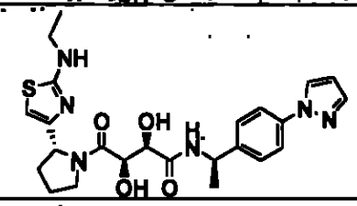
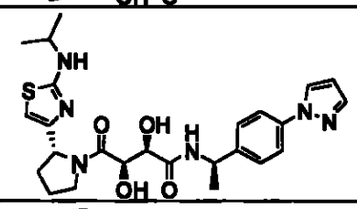
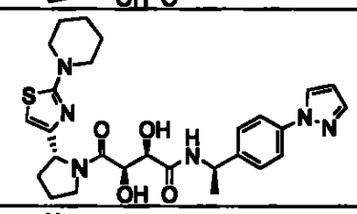
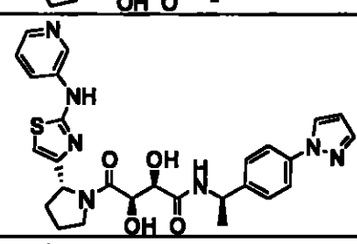
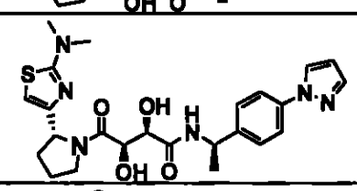
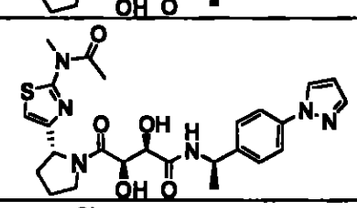
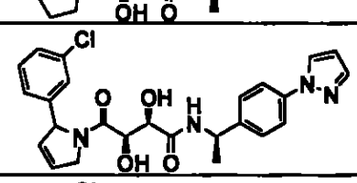
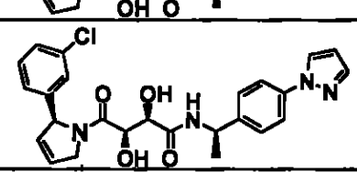
El Compuesto **2231** (85 mg, 0,30 mmol) se disolvió en HCl 4M en dioxano (2ml) y metanol (0,5 ml) y se agitó durante 30 minutos. Los solventes se eliminaron para dar **2232** as a di-HCl salt (65 mg). ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,50 (bs, 1H), 8,70 (bs, 1H), 7,80 (bs, 1H), 6,70 (s, 1H), 4,50 (m, 1H), 3,30-3,20 (m, 2H), 2,75-2,65 (m, 2H), 2,40 (m, 2H), 1,70 (m, 1H), 1,15 (t, 3H), 1,10 (d, 3H).

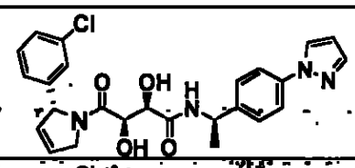
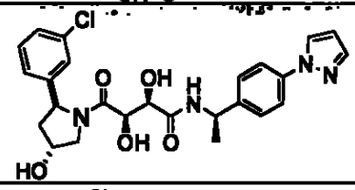
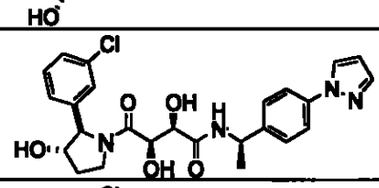
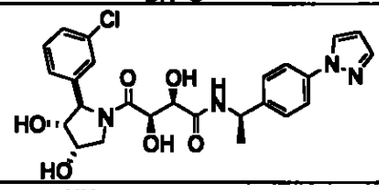
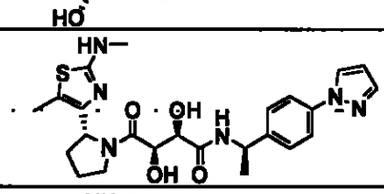
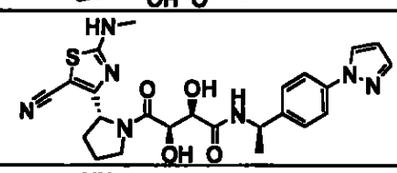
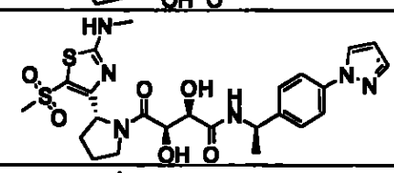
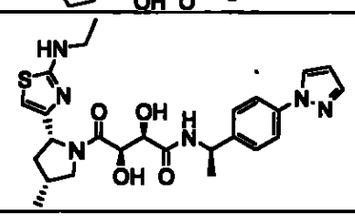
Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
2233		494,2	495,2
2234		506,2	507,1

2235		462,2	463,1
2236		510,2	511,1
2237		510,2	511,1
2238		524,2	525,1
2239		524,2	525,1
2240		524,2	525,1
2241		497,2	498,1
2242		450,2	451,1
2243		484,1	485,0
2244		498,2	499,1

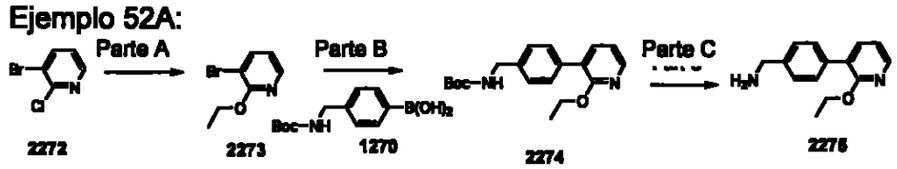
2245		496,2	497,1
2246		496,2	497,1
2247		438,2	439,1
2248		452,2	453,1
2249		479,2	480,1
2250		482,2	483,1
2251		469,2	470,0
2252		484,2	485,1
2253		530,2	531,1
2254		428,2	429,2

2255		470,2	471,1
2256		498,2	499,1
2257		512,2	513,1
2258		538,2	539,2
2259		547,2	548,2
2260		498,2	499,1
2261		526,2	527,1
2262		480,2	481,1
2263		480,2	481,1

2264		**480,2**	**481,3**
2265		**498,2**	**499,1**
2266		**498,2**	**499,1**
2267		**514,2**	**515,1**
2268		**498,2**	**499,1**
2269		**509,2**	**510,1**
2270		**562,2**	**563,0**
2271		**512,2**	**513,1**

Ejemplo 52:

Ejemplo 52A:



Parte A:

Se disolvieron pellets de sodio (1,0 g, 43 mmol) en etanol (35 ml). El Compuesto **2272** (1,4 g, 7,2 mmol) se agregó a la solución y la reacción se reflujó hasta el día siguiente. El solvente se eliminó bajo presión reducida y el residuo se dividió entre acetato de etilo y agua. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio y se concentraron para dar **2273** (1,3 g). El producto se usó sin purificación adicional. HPLC-MS t_R = 1,92 min. ($UV_{254\ nm}$); masa calculada para la fórmula C_7H_8NOBr 201,0, LCMS observada m/z 202,1 (M+H).

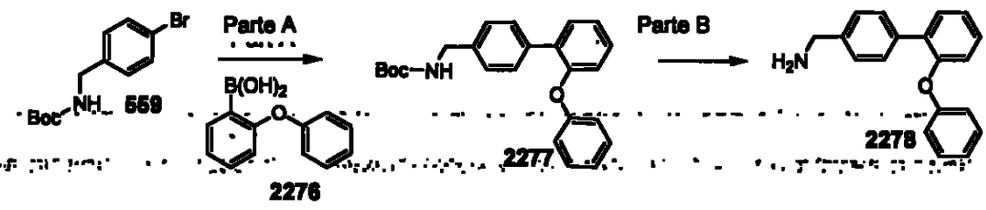
Parte B:

El Compuesto **2273** (171 mg, 0,8592 mmol) se disolvió en tolueno (10 ml). Se agregaron el ácido borónico **1270** (409 mg, 1,69 mmol), $Pd_2(dba)_3$ (38 mg, 0,0423 mmol), S-PHOS (34 mg, 0,084 mmol), fosfato de potasio (358 mg, 1,69 mmol) a la solución y se agitó a reflujo hasta el día siguiente. La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró y se eliminó el tolueno bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se concentraron para dar **2274** (190 mg). El material se usó sin purificación adicional. HPLC-MS t_R = 2,21 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{19}H_{24}N_2O_3$ 328,2, LCMS observada m/z 329,2 (M+H).

Parte C:

El Compuesto **2274** (190 mg, 0,584 mmol) se disolvió en cloruro de metileno (4 ml) y TFA (1 ml) y se agitó durante 30 minutos. Los solventes se eliminaron para dar **2275** como la sal de TFA (190 mg).

Ejemplo 52B:



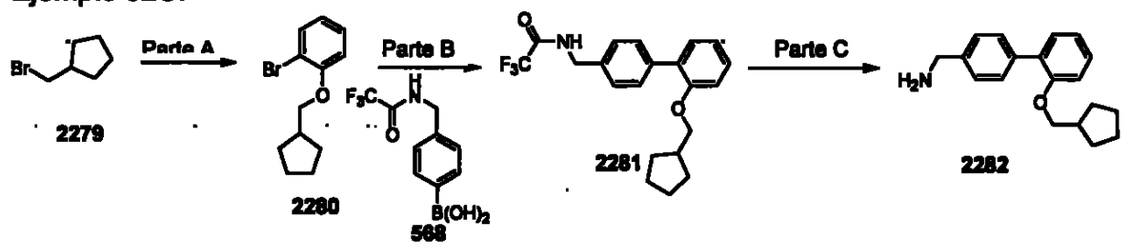
Parte A:

El Compuesto **559** (100 mg, 0,35 mmol) se disolvió en dioxano (5 ml). Luego se agregaron ácido borónico **2276** (113 mg, 0,52 mmol), $Pd_2(dba)_3$ (27 mg, 0,03 mmol), trifenilfosfina (13,7 mg, 0,052 mmol), fosfato de potasio (148 mg, 0,70 mmol) a la solución y se agitó a reflujo hasta el día siguiente. La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró y el tolueno se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 25% de acetato de etilo/hexanos) dio **2277** (80 mg). ^1H RMN (400 MHz, $CDCl_3$) δ 7,50 (d, 1H), 7,45 (m, 2H), 7,30-7,15 (m, 5H), 7,20-7,10 (m, 2H), 7,00-6,90 (m, 3H), 4,30 (d, 2H), 1,45 (s, 9H).

Parte B:

El Compuesto **2277** (80 mg, 0,21 mmol) se disolvió en HCl 4 M en dioxano (2 ml) y se agitó a temperatura ambiente durante 1 hr. La reacción se diluyó con dietil éter (5 ml) y **2278** (60 mg) se recolectó mediante filtración.

Ejemplo 52C:



Parte A:

Se disolvieron el Compuesto **2279** (500 mg, 3,08 mmol), carbonato de cesio (3,0 g, 9,25 mmol), y 2-bromofenol (527 mg, 3,08 mmol) en DMF (15 ml) y se agitó a 60 ºC durante 2 horas. La mezcla de reacción se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con bicarbonato de sodio saturado, salmuera, se secaron sobre sulfato de sodio, y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 10% de acetato de etilo/hexanos) dio **2280** (400 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,50 (m, 1H), 7,20 (m, 1H), 6,85 (d, 1H), 6,80 (t, 1H), 3,90 (d, 2H), 2,40 (m, 1H), 1,85 (m, 2H), 1,60-1,45 (m, 4H), 1,40 (m, 2H).

Parte B:

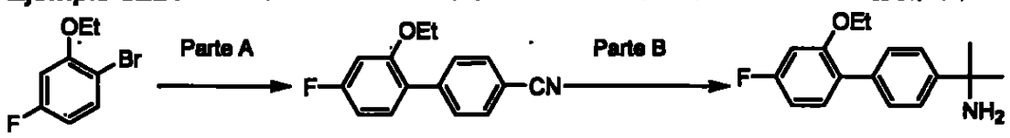
Se disolvieron el Compuesto **2280** (157 mg, 0,50 mmol), compuesto **568** (250 mg, 1,02 mmol), $Pd_2(dba)_3$ (9,1 mg, 0,01 mmol), S-PHOS (8,3 mg, 0,02 mmol), fluoruro de potasio (350 mg, 3,0 mmol) en dioxano (8 ml) y se agitó a reflujo hasta el día siguiente. La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró y el tolueno se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 10% de acetato de etilo/hexanos) dio **2281** (200 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,60 (m, 2H), 7,40 (m, 2H), 7,30 (m, 2H), 7,00 (m, 2H), 4,60 (d, 2H), 3,85 (d, 2H), 2,35 (m, 1H), 1,80 (m, 2H), 1,60 (m, 4H), 1,30 (m, 2H).

Parte C:

El Compuesto **2281** (100 mg, 0,317 mmol) se disolvió en MeOH (5 ml) y se agregó una solución de carbonato de potasio saturado (1 ml) y la reacción se agitó durante 3 horas. La mezcla de reacción se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con bicarbonato de sodio saturado, salmuera, se secaron sobre sulfato de sodio, y se concentraron para dar **2282** (40

mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,55 (d, 2H), 7,40 (m, 4H), 7,00 (m, 2H), 4,60 (d, 2H), 3,85 (d, 2H), 2,35 (m, 1H), 1,80 (m, 2H), 1,60 (m, 4H), 1,35 (m, 2H):

Ejemplo 52D:



567 **2283** **2284**

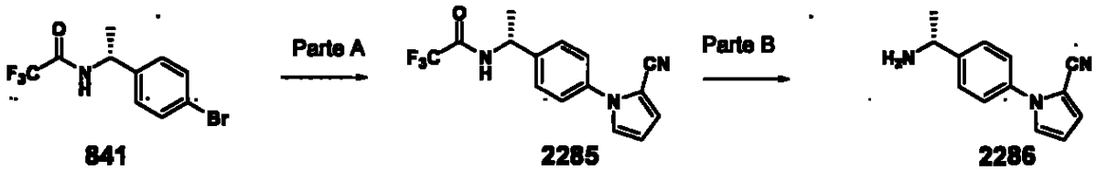
Parte A:

Se disolvieron el Compuesto **567** (500 mg, 2,29 mmol), 4-cianofenilácido borónico (483 mg, 3,43 mmol), $Pd_2(dba)_3$ (70 mg, 0,08 mmol), trifenilfosfina (70 mg, 0,26 mmol), fosfato de potasio (970 mg, 4,58 mmol) en dioxano (15 ml) y se agitó a reflujo hasta el día siguiente. La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró y el dioxano se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 5% de acetato de etilo/hexanos) dio **2283** (240 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,70-7,58 (m, 4H), 7,27-7,23 (m, 1H), 6,75-6,70 (m, 2H), 4,05 (q, 2H), 1,38 (t, 3H).

Parte B:

El Compuesto **2284** se preparó de acuerdo con el procedimiento en *J. Org. Chem.* **1992**, *57*, 4521-4527.

Ejemplo 52E:



841 **2285** **2286**

Parte A:

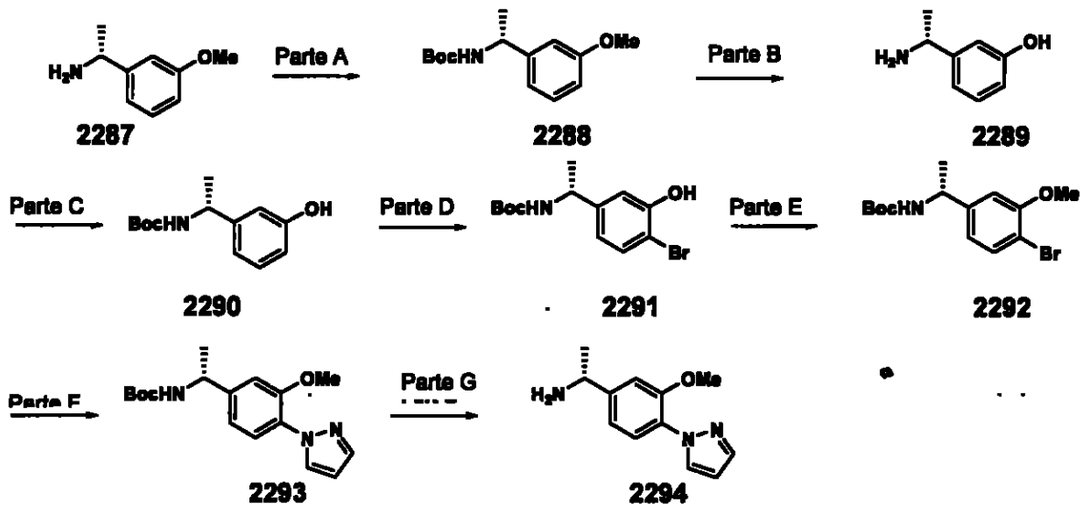
A una mezcla del compuesto **841** (2,96 g, 10 mmol), pirrol-2-carbonitrilo (1,1 g, 12 mmol) y 1,10-fenantrolina (1,17 g, 6,5 mmol) en DMA (10 ml) se agregó carbonato

de cesio (6,52 g, 20 mmol) y CuI (0,42 g, 2,2 mmol) y la mezcla se calentó a 150 °C durante 18 horas. La mezcla se filtró y se enjuagó con EtOAc (100 ml). El filtrado se lavó con agua (2 x 10 ml) y salmuera (10 ml); se secó sobre $MgSO_4$ y se concentró. La purificación mediante cromatografía en columna (SiO_2, 10% de EtOAc/hexano seguido por 20% de EtOAc/hexano) dio compuesto **2285** como un aceite (0,17 g, 5,7%).

Parte B:

Se agitó una mezcla del compuesto **2285** (0,17 g, 0,57 mmol) y LiOH ac. 1M (1 ml, 1 mmol) en dioxano (3 ml) a temperatura ambiente durante 18 horas. La mezcla de reacción se concentró y se agregó agua (2 ml) y se extrajo con CH_2Cl_2 (2 x 10 ml). La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró. La purificación mediante cromatografía en columna (SiO_2, 1% MeOH/ CH_2Cl_2 seguido por 5% MeOH/ CH_2Cl_2) dio compuesto **2286** como un aceite (0,085 g, 71%).

Ejemplo 52F:



Parte A:

A una solución de compuesto **2287** (20,6 g, 136,4 mmol) en CH_2Cl_2 (200 ml) se

agregó trietilamina (27,5 g, 272,8 mmol) y la mezcla de reacción se enfrió hasta 0 °C, y $(Boc)_2O$ (32,7 g, 150 mmol) se agregó. La mezcla se agitó a 0 °C durante 10 minutos y luego se calentó hasta temperatura ambiente y se agitó durante 4 horas. La mezcla de reacción se lavó con NH_4Cl ac. sat. (100 ml) y se secó sobre $MgSO_4$, se filtró y se concentró. La purificación mediante cromatografía en columna (SiO_2, 10% de EtOAc/hexano seguido por 15% de EtOAc/hexano) dio el Compuesto **2288** como sólido blanco (32,7 g, 95%).

Parte B:

A una solución de compuesto **2288** (3,95 g, 15,7 mmol) en CH_2Cl_2 (200 ml) a -78 °C se agregó una solución de BBr_3/CH_2Cl_2 1M (37 ml) gota a gota mediante un embudo de goteo durante 15 minutos. La mezcla de reacción se agitó a -78 °C durante 2 horas, luego se vertió cuidadosamente en MeOH (100 ml) y se concentró a un tostado un alquitrán marrón (3,6 g). La trituración con éter (3 x 20 ml) y la concentración dio compuesto **2289** como un alquitrán marrón que se usó en la siguiente reacción sin purificación adicional.

Parte C:

El compuesto bruto **2289** se suspendió en CH_2Cl_2 (100 ml) y se agregó trietilamina (8,8 ml, 63 mmol). La mezcla de reacción se enfrió hasta 0 °C y se agregó $(Boc)_2O$ (3,77 g, 17,3 mmol). La mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción luego se lavó con agua (100 ml), $NaHCO_3$ sat. (25 ml) y salmuera (10 ml). La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró. La purificación mediante cromatografía en columna (SiO_2, 10% de EtOAc/hexano seguido por 15% de EtOAc/hexano y 20% de EtOAc/hexano) dio compuesto **2290** como un aceite (1,85 g, 62% en dos pasos).

Parte D:

A una solución de compuesto **2290** (0,45 g, 1,9 mmol) en CH_2Cl_2 (10 ml) se agregó una solución de NBS (0,34 g, 1,9 mmol) en CH_2Cl_2 (10 ml) mediante un

embudo de goteo. Se agitó a temperatura ambiente durante 3,5 horas y luego se lavó con 10% de H_2SO_4 ac. (10 ml). La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró. La purificación mediante cromatografía en columna (SiO_2, 100% de CH_2Cl_2 seguido por 1% de EtOAc/CH_2Cl_2) dio compuesto **2291** (0,13 g, 21%).

Parte E:

A una solución de compuesto **2291** (0,22 g, 0,7 mmol) en acetona (6 ml) se agregó K_2CO_3 (0,288 g, 2,1 mmol) seguido por una solución de metil yoduro (0,065 ml, 1,05 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La mezcla se filtró y se concentró hasta que se secó. El residuo se disolvió en EtOAc (20 ml) y se lavó con agua (2 ml) seguido por salmuera (2 ml). La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró para dar el compuesto **2292** (0,2 g, 86%).

Parte F:

El Compuesto **2293** se preparó siguiendo el procedimiento descripto en el Ejemplo 52E, Parte A.

Parte G:

El compuesto **2294** se preparó a partir de compuesto **2293** mediante la desprotección de TFA según se describe en el Ejemplo 1.

Ejemplo 52G:

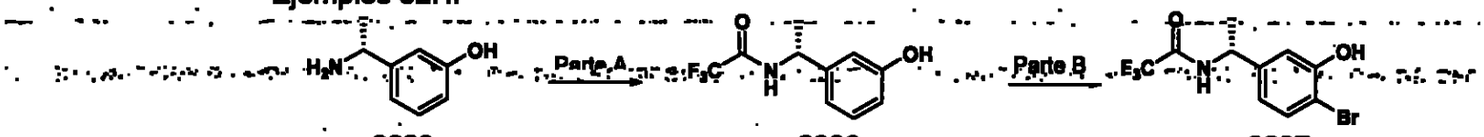


2292 **2295**

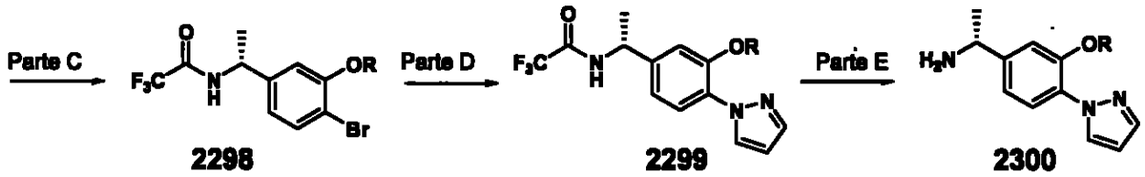
Parte A:

El Compuesto **2295** se preparó a partir de compuesto **2292** **2293** mediante TFA según se describe en el Ejemplo 1,.

Ejemplos 52H:



2289 2296 2297



2298 2299 2300

R = Bn, H_2C— 

Parte A:

El Compuesto **2289** se transformó en el compuesto **2296** mediante el procedimiento descripto en el Ejemplo 52F Parte C y usando anhídrido trifluoroacético en lugar de Boc_2O.

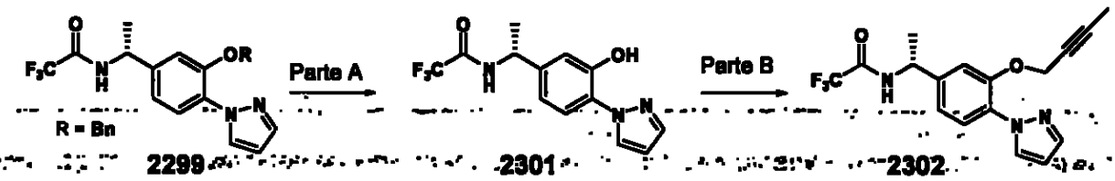
Parte B,C,D:

Los Compuestos **2297, 2298 y 2299** se prepararon siguiendo los procedimientos descriptos en el Ejemplo 52F, Parte D, E y F usando bromuro de bencilo y bromuro de ciclopropilo en lugar de yoduro de metilo.

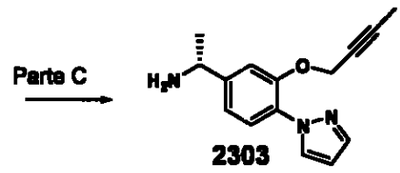
Parte E:

El Compuesto **2300** se preparó a partir del compuesto **2299** siguiendo los procedimientos descriptos en el Ejemplo 52E, Parte B.

Ejemplo 52I:



2299 2301 2302



2303

Parte A:

Se agitó una mezcla del compuesto **2299** (0,27 g, 0,69 mmol), Pd-C 10% (0,18 g) y EtOH (25 ml) bajo una atmósfera de hidrógeno a 3,45 x 10^5 Pa (55 psi) durante 18 horas. Se filtró a través de Celite y se enjuagó con CH_2Cl_2 y se concentró para dar el compuesto deseado **2301** (0,21 g, 100%).

Parte B, C:

Los Compuestos **2302** y **2303** se prepararon siguiendo los procedimientos descriptos en el Ejemplo 52H, Parte C y E y usando 1-bromo-2-butino como el reactivo alquilante .

Ejemplo 52J:

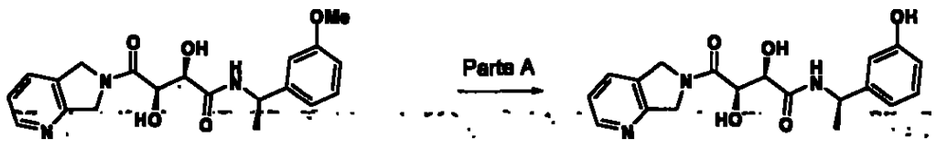


2304 2305

Parte A:

Se agitó Una mezcla del compuesto **2304** (60 mg), 10% de Pd-C (30 mg) y MeOH (10 ml) a temperatura ambiente bajo atmósfera de hidrógeno durante 18 horas. Se filtró y se enjuagó con CH_2Cl_2 y se concentró para dar el producto deseado **2305** (50 mg).

Ejemplo 52K:



2306 **2307**

Parte A:

El Compuesto **2307** se preparó a partir de compuesto **2306** siguiendo el procedimiento descripto en el Ejemplo 52F, Parte B.

Ejemplo 52L:

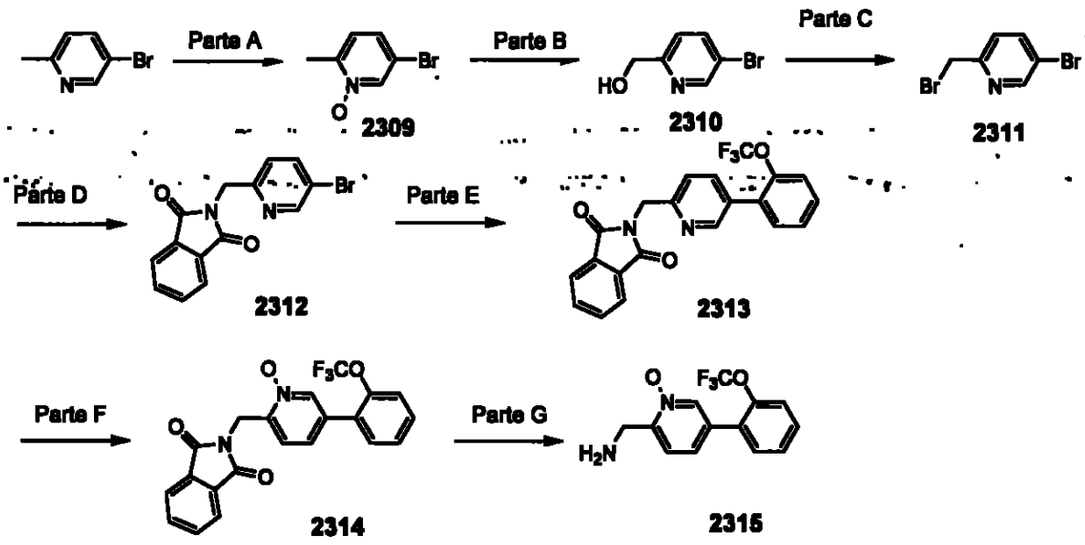


2307 **2308**

Parte A:

A una mezcla de **2307** (0,065 g, 0,18 mmol) en acetona (10 ml) se agregó K_2CO_3 (0,082 g, 0,59 mmol) seguido por bromuro de bencilo (0,022 ml, 0,19 mmol) y la mezcla de reacción se reflujó durante 18 horas. Se agregó DMF (0,5 ml) a la mezcla de reacción y se calentó a 70 °C durante 18 horas. La mezcla de reacción se enfrió hasta temperatura ambiente y EtOAc (5 ml) se agregó, luego se lavó con agua (2 x 1 ml) seguido por salmuera (1 ml). La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró. La purificación mediante cromatografía en columna (SiO_2, 5% MeOH (NH_3)/CH_2Cl_2) dio **2308** (0,019 g, 23%).

Ejemplo 52M:



Parte A:

A una solución de 5-bromopicolina (20 g, 116 mmol) en cloroformo (100 ml) a 0 °C se agregó en porciones mCPBA 77% (28,7 g, 128 mmol) durante 20 min. La mezcla de reacción se dejó en agitación a temperatura ambiente hasta el día siguiente, después de ese tiempo el sólido se filtró, el filtrado se lavó con saturado Na_2CO_3, se secó sobre Na_2SO_4, y se concentró para dar **2309** (17,83 g, 82%) como un sólido blanco. ^1H RMN (400 MHz, $CDCl_3$) δ 8,39 (s, 1H), 7,29 (d, J = 8,0 Hz, 1H), 7,12 (d, J = 8,3 Hz, 1H), 2,47 (s, 3H).

Parte B:

El Compuesto **2309** (15 g, 80 mmol) se enfrió hasta 0 °C, y se agregó anhídrido trifluoroacético (35 ml, 250 mmol) lentamente bajo argón. La mezcla se dejó en agitación a temperatura ambiente durante 30 min, luego a 55 °C.durante 30 min. después se enfrió hasta 0 °C en un baño de hielo. Se agregó solución acuoso de $NaHCO_3$ (10%, 150 ml) lentamente con cuidado. Una vez completada la adición, la mezcla se dejó en agitación a temperatura ambiente durante 6 h. La solución se extrajo con diclorometano, se secó sobre Na_2SO_4, y se concentró. El residuo se purificó mediante cromatografía flash en columna sobre gel de sílice (EtOAc/hexano 50:50), dando el producto **2310** como un sólido blanco (9,2 g,

61%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,61 (d, *J* = 1,9 Hz, 1H), 7,80 (dd, *J* = 7,9, 2,4 Hz, 1H), 7,19 (dd, *J* = 8,3, 0,9 Hz, 1H), 4,73 (s, 2H), 3,37 (br s, 1H).

Parte C:

A una solución de **2310** (9,0 g, 47,86 mmol) en tolueno (40 ml) se agregó PBr_3 (5 ml, 52,6 mmol) gota a gota. Una vez completada la adición, la mezcla se agitó a 100 °C durante 2 h. Se enfrió hasta temperatura ambiente; el sólido se recolectó mediante filtración para dar **2311** como un sólido amarillo (HBr salt, 14,83 g, 93%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,74 (br, 1H), 8,66 (d, *J* = 1,8 Hz, 1H), 8,06 (dd, *J* = 8,4, 1,4 Hz, 1H), 7,19 (dd, *J* = 8,3, 0,9 Hz, 1H), 4,67 (s, 2H).

Parte D:

A una solución de **2311** (14,83 g, 44,7 mmol) en DMF a 0 °C se agregó lentamente Cs_2CO_3 (29,1 g, 89,4 mmol) y ftalimida de potasio (9,1 g, 49,2 mmol). La mezcla de reacción se dejó en agitación a temperatura ambiente durante 6h después de este tiempo, el solvente se evaporó hasta que se secó. El sólido resultante se lavó con H_2O. La torta sólida se recristalizó en EtOH caliente, dando compuesto **2312** (7,64 g, 54%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,54 (d, *J* = 1,9 Hz, 1H), 8,00 (dd, *J* = 8,4, 2,3 Hz, 1H), 7,90-7,83 (m, 4H), 7,41 (d, *J* = 7,8 Hz, 1H), 4,88 (s, 2H).

Parte E:

Se cargó una mezcla de $Pd(OAc)_2$ (45 mg, 0,2 mmol), 2-bis(ter-butil)fosfino-bifenil (120 mg, 0,4 mmol), compuesto **2312** (3,17 g, 10 mmol), ácido 2-trifluorometoxifenil borónico (2,47 g, 12 mmol) y KF (2,1 g, 36 mmol) en un balón de 250-ml. Luego se agregó THF (30 ml) bajo argón, y la mezcla de reacción se dejó en agitación a 50 °C hasta el día siguiente, después de dicho tiempo se enfrió hasta temperatura ambiente, se filtró a través de Celite y se concentró. La cromatografía flash en columna sobre gel de sílice (EtOAc/hexano (5:95) dio compuesto **2313** (3,27 g, 82%) como un sólido blanco. ^{1}H RMN (400 MHz,

$CDCl_3$) δ 8,59 (d, *J* = 1,5 Hz, 1H), 7,91-7,89 (m, 2H), 7,77-7,73 (m, 3H), 7,44-7,34 (m, 5H), 5,08 (s, 2H).

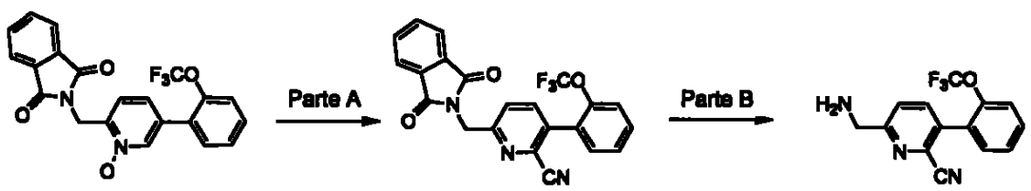
Parte F:

El Compuesto **2314** se preparó de acuerdo con el mismo procedimiento que en el Ejemplo 52M Parte A. HPLC-MS t_R = 1,74 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{21}H_{13}F_3N_2O_4$ 414,1, LCMS observada m/z 415,0 (M+H).

Parte G:

A una solución de compuesto **2314** (210 mg, 0,51 mmol) en EtOH (10 ml) se agregó con hidracina (0,5 ml). La solución se reflujó durante 3 h, luego se enfrió hasta temperatura ambiente. Después de la remoción del precipitado mediante filtración, la solución se concentró. El residuo resultante se extrajo con Et_2O y se concentró, dando compuesto **2315** como un aceite amarillo pálido (160 mg, 91%). HPLC-MS t_R = 1,74 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{13}H_{11}F_3N_2O_2$ 284,1, LCMS observada m/z 285,1 (M+H).

Ejemplo 52N:



2314 **2316** **2317**

Parte A:

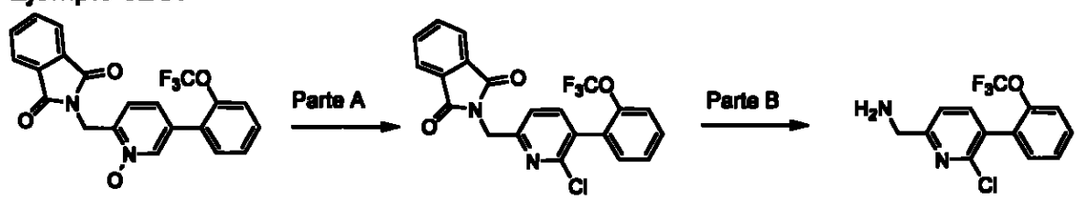
Al compuesto **2314** (200 mg, 0,48 mmol) en acetonitrilo (1 ml) se agregó Et_3N (0,094 ml, 0,672 mmol) y Me_3SiCN (0,225 ml, 1,69 mmol) posteriormente bajo argón. La mezcla de reacción se agitó a 80 °C durante 48 h, después de dicho tiempo se enfrió hasta temperatura ambiente y se concentró en *vacuo*. El residuo se disolvió en EtOAc, se lavó con $NaHCO_3$ saturado, salmuera, se secó (Na_2SO_4), y se concentró. Cromatografía flash en columna (EtOAc/hexano 40:60) dio compuesto **2316** (130 mg, 64%). HPLC-MS t_R = 2,06 min. ($UV_{254\ nm}$); masa

calculada para la fórmula $C_{22}H_{12}F_3N_3O_3$ 423,1, LCMS observada m/z 424,0 (M+H).

Parte B:

El Compuesto **2317** se preparó usando el procedimiento descripto en el Ejemplo 52M Parte G. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,77 (d, *J* = 8,1 Hz, 1H), 7,60 (d, *J* = 8,0 Hz, 1H), 7,47-7,42 (m, 4H), 4,12 (s, 2H). 1,98 (br s, 2H).

Ejemplo 52O:



2314 **2318** **2319**

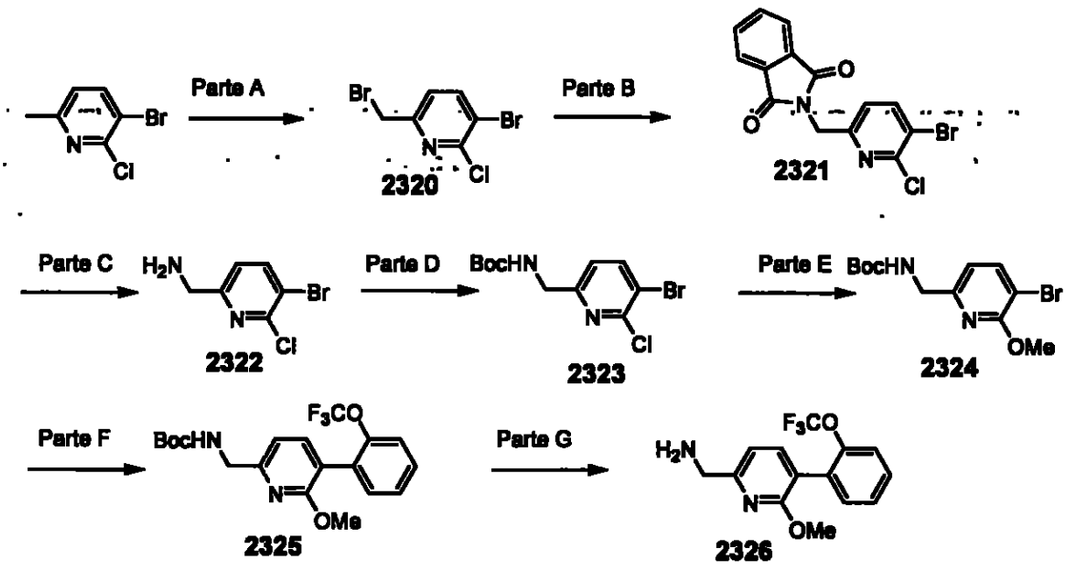
Parte A:

Se agregó tricloruro de fósforo (0,330 ml, 3,62 mmol) a una solución de **2314** (300 mg, 0,72 mmol) en $CHCl_3$ (1 ml). La mezcla de reacción se agitó a 60 °C hasta el día siguiente, después de dicho tiempo se enfrió hasta temperatura ambiente y se concentró en *vacuo*. El residuo se disolvió en EtOAc, se lavó con $NaHCO_3$ saturado, salmuera, se secó (Na_2SO_4), y se concentró. Cromatografía flash en columna (EtOAc/hexano 30:70) dio **2318** (180 mg, 58%). HPLC-MS t_R = 2,33 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{21}H_{12}ClF_3N_2O_3$ 432,1, LCMS observada m/z 433,0 (M+H).

Parte B:

El Compuesto **2319** se preparó usando el procedimiento descripto en el Ejemplo 52M Parte G. HPLC-MS t_R = 1,26 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{13}H_{10}ClF_3N_2O$ 302,0, LCMS observada m/z 303,0 (M+H).

Ejemplo 52P:



Parte A:

Se disolvieron 3-Bromo-2-cloro-6-picolina (1,0 g, 4,84 mmol) y NBS (1,20 g, 6,78 mmol) en CCl_4 (20 ml). La solución se saturó brevemente con argón, luego se agregó AIBN (16 mg, 0,097 mmol). La mezcla se agitó a temperatura ambiente hasta el día siguiente, después de eso el solvente se evaporó en *vacuo*. El residuo se purificó mediante cromatografía flash en columna (EtOAc/hexano 5:95) dando el compuesto **2320** como un sólido blanco (1,28 g, 92%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,01 (d, *J* = 8,2 Hz, 1H), 7,65 (d, *J* = 8,2 Hz, 1H), 4,19 (s, 2H).

Parte B:

El Compuesto **2321** se preparó de acuerdo con el procedimiento descripto en el Ejemplo 52M, Parte D. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,19 (d, *J* = 8,0 Hz, 1H), 7,92-7,84 (m, 4H), 7,41 (d, *J* = 8,0 Hz, 1H), 4,86 (s, 2H).

Parte C:

El Compuesto **2322** se preparó de acuerdo con el procedimiento descripto en el Ejemplo 52M, Parte G. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,87 (d, *J* = 8,0 Hz, 1H), 7,41 (d, *J* = 8,1 Hz, 1H), 3,93 (s, 2H), 1,78 (br s, 2H).

Parte D:

El Compuesto **2322** (370 mg, 1,67 mmol) en THF (10 ml) se agregó gota a gota en una solución de Boc_2O (437 mg, 2,0 mmol) en THF (10 ml), seguido por DIEA (300 ml). La mezcla se agitó a temperatura ambiente hasta el día siguiente y se concentró. Cromatografía en columna sobre gel de sílice (EtOAc/hexano 20:80) dio el Compuesto **2323** (450 mg, 84%) como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,89 (d, *J* = 7,5 Hz, 1H), 7,12 (d, *J* = 8,2 Hz, 1H), 5,35 (br s, 1H), 4,37 (d, *J* = 5,9 Hz, 2H), 1,47 (s, 9H).

Parte E:

Se disolvió sodio (4 pellets) en MeOH (15 ml). La mezcla se agitó a temperatura ambiente durante 10 min. Hasta que todo el sodio reaccionó. A esta solución se agregó compuesto **2323** (450 mg, 1,4 mmol) en MeOH (5 ml) mediante jeringa. La mezcla de reacción se agitó a 60 °C durante 48 h y se concentró. El residuo se disolvió con EtOAc y solución NH_4Cl 1N, se lavó con salmuera, se secó sobre Na_2SO_4, y se concentró. Cromatografía en columna (SiO_2, EtOAc/hexano 20:80) dio compuesto **2324** como un sólido blanco (350 mg, 79%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,43 (d, *J* = 7,3 Hz, 1H), 6,73 (d, *J* = 7,5 Hz, 1H), 5,26 (br s, 1H), 4,32 (d, *J* = 5,1 Hz, 2H), 4,02 (s, 3H),

1,48 (s, 9H).

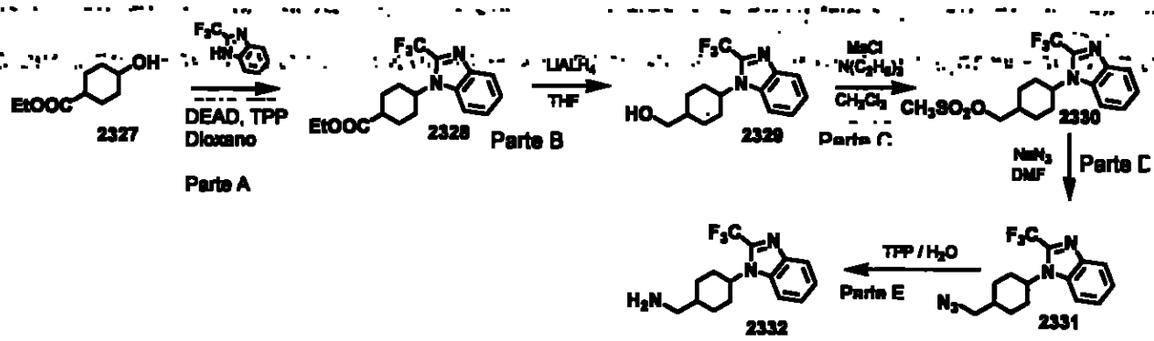
Parte F:

El Compuesto **2325** se preparó de acuerdo con el mismo procedimiento que en Ejemplo 52M Parte E para el acoplamiento de Suzuki. HPLC-MS t_R = 2,35 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{19}H_{21}F_3N_2O_4$ 398,2, LCMS observada m/z 399,1 (M+H).

Parte G:

El Compuesto **2325** se desprotegió con TFA en CH_2Cl_2, HPLC-MS t_R = 1,12 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{14}H_{13}F_3N_2O_2$ 298,1, LCMS observada m/z 299,0 (M+H).

Ejemplo 52Q:



Parte A:

Se disolvieron etil-4-hidroxiciclohexilcarboxilato (2327) (mezcla cis/trans) (4,3 g, 25 mmol), 2-trifluorometilbenzimidazol (4,65 g, 25 mmol), y trifenilfosfina (9,8 g, 37,5 mmol) en dioxano (60 ml). La solución resultante se trató con dietildiazodicarboxilato (6,5 g, 37,5 mmol), gota a gota, durante un período de 1h y se agitó durante 16h. La mezcla de reacción se diluyó con acetato de etilo (200 ml) y se lavó en secuencia con agua (2 X 100 ml) y salmuera (1 X 100 ml). Los orgánicos se secaron y se concentró para dar un bruto que se sometió a cromatografía en columna de gel de sílice (10% de acetato de etilo/hexano) para dar **2328** puro (0,2 g, 0,6 mmol).

Parte B:

Se agregó $LiAlH_4$ a THF seco (40 ml) y la mezcla se enfrió entonces hasta 0 °C. Luego se agregó gota a gota el éster **2328** (0,2 g, 0,6 mmol) en THF (5 ml) a la mezcla. La mezcla de reacción se dejó calentar hasta temperatura ambiente y se agitó durante 48 h, luego se enfrió de vuelta a 0 °C y se desactivó mediante la adición en secuencia de 1 ml de agua, 2 ml de NaOH 0,5 N, y 1 ml de agua. La mezcla resultante se agitó vigorosamente durante 2 h y luego se filtró a través de Celite. El filtrado se concentró para dar **2329** puro como un aceite (0,2 g, 0,6 mmol).

Parte C:

Se disolvieron alcohol **2329** (0,2 g, 0,6 mmol) y trietilamina (0,18 g, 1,8 mmol) en CH_2Cl_2 (200 ml) y se enfrió hasta 0 °C. La solución fría se agitó, y se agregó gota a gota CH_3SO_2Cl (como una solución CH_2Cl_2; 0,2 g, 1,8 mmol, 5 ml CH_2Cl_2), y se continuó revolviendo durante 24 h. La mezcla de reacción se lavó luego dos veces con 50 ml de agua y dos veces con 50 ml de salmuera. Las fases orgánica y acuosa se separaron, y la fase orgánica se secó, y se concentró para dar producto puro **2330** como un aceite (0,21 g).

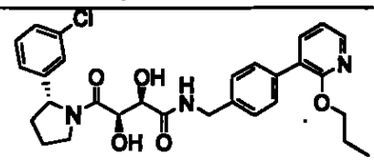
Parte D:

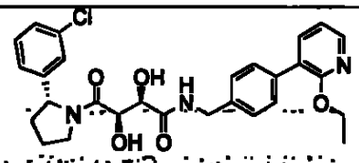
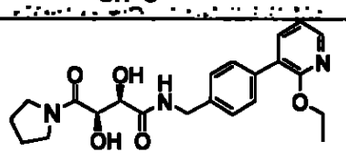
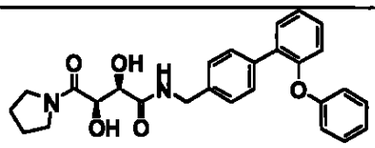
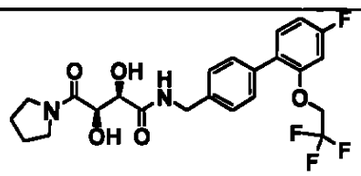
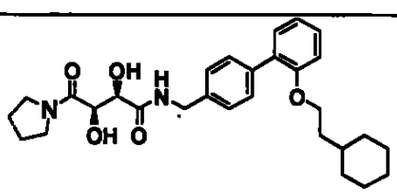
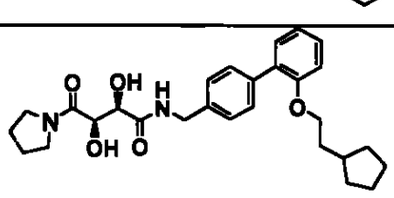
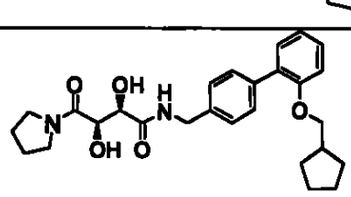
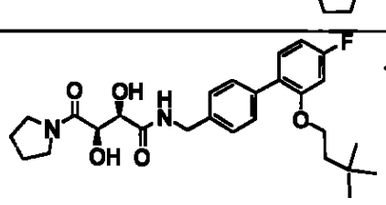
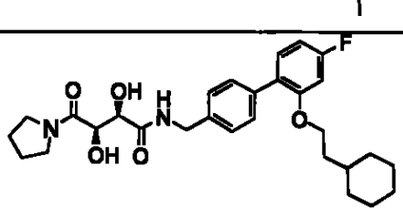
El mesilato **2330** se disolvió en DMF (10 ml) y se trató con NaN_3 (0,23 g, 1,8 mmol), y la mezcla se agitó vigorosamente durante 36-72 h. La mezcla de reacción luego se diluyó con 100 ml agua y se extrajo con acetato de etilo (2 x 100 ml). Las fases orgánicas se combinaron, se secaron y se concentraron para dar azida pura **2331** (0,19 g, 87%).

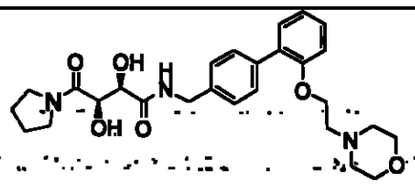
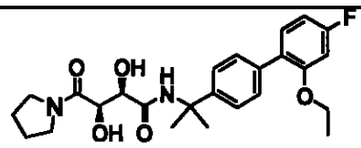
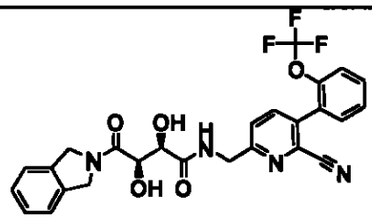
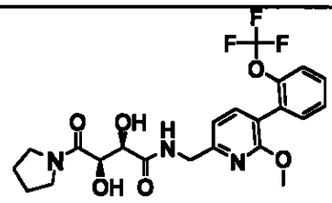
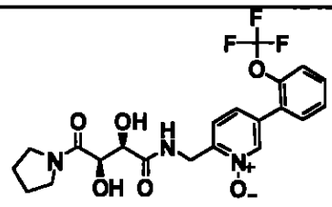
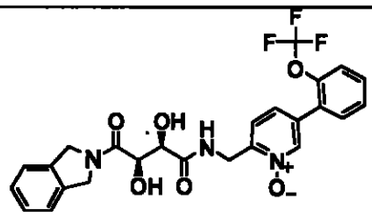
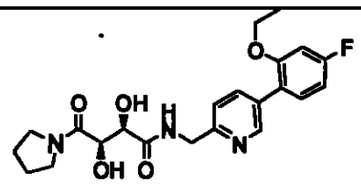
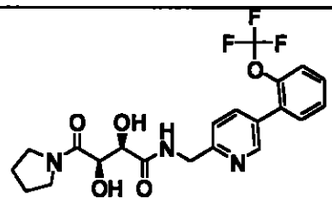
Parte E:

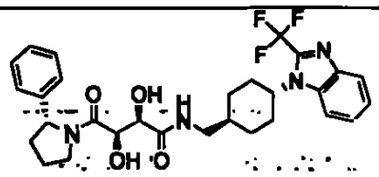
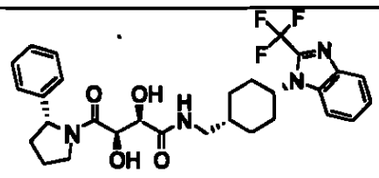
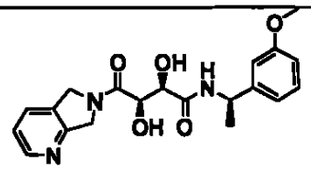
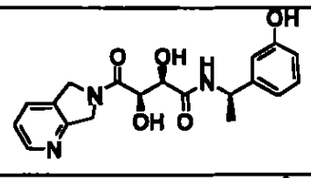
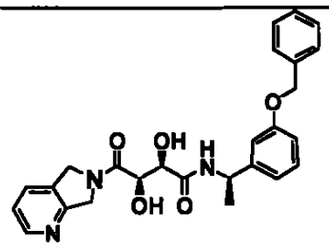
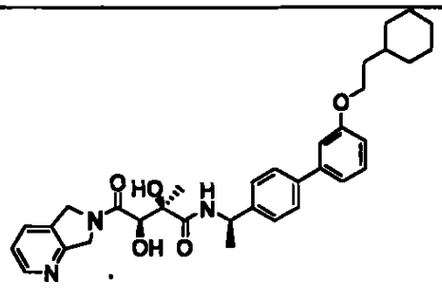
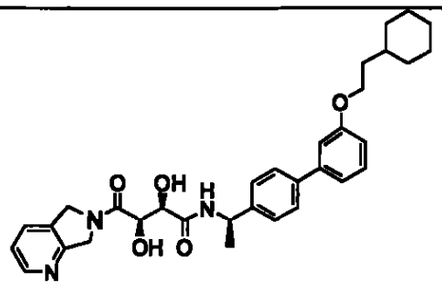
Se disolvieron la azida **2331** (0,19 g, 0,6 mmol)) y trifenilfosfina (0,15 g, 0,6 mmol) en 5 ml de THF, y luego se agregó agua (0,6 ml, 33,3 mmol). La mezcla resultante se agitó vigorosamente durante 16-24 h. El solvente se eliminó y la amina bruta **2332** se tomó para el siguiente paso sin purificación adicional.

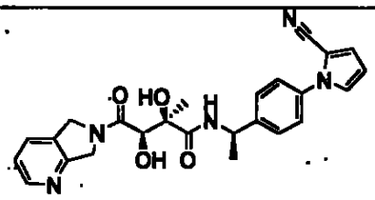
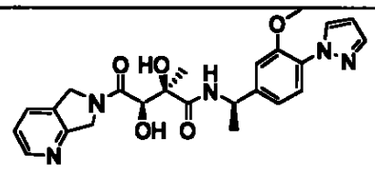
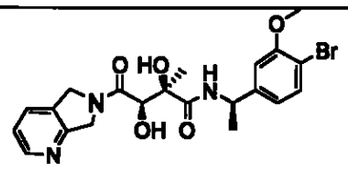
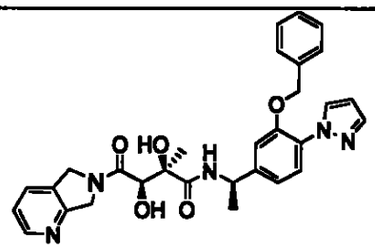
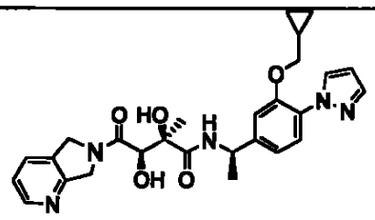
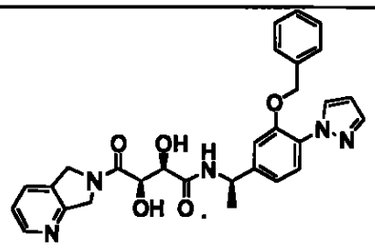
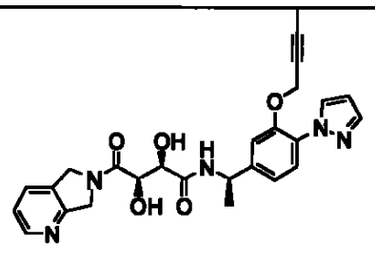
Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente.

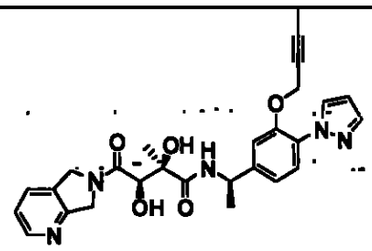
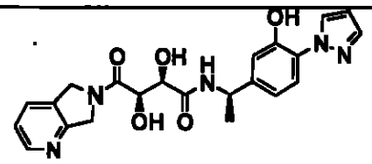
Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
2333		537,2	538,1

2334		523,2	524,1
2335		413,2	414,2
2336		460,2	461,0
2337		484,2	485,2
2338		494,3	495,2
2339		480,3	481,1
2340		466,3	467,2
2341		486,3	487,2
2342		512,3	513,2

2343		**497,3**	**498,2**
2344		**458,2**	**459,2**
2345		**526,2**	**527,0**
2346		**483,2**	**484,0**
2347		**469,2**	**470,0**
2348		**517,2**	**518,0**
2349		**431,2**	**432,1**
2350		**453,2**	**454,1**

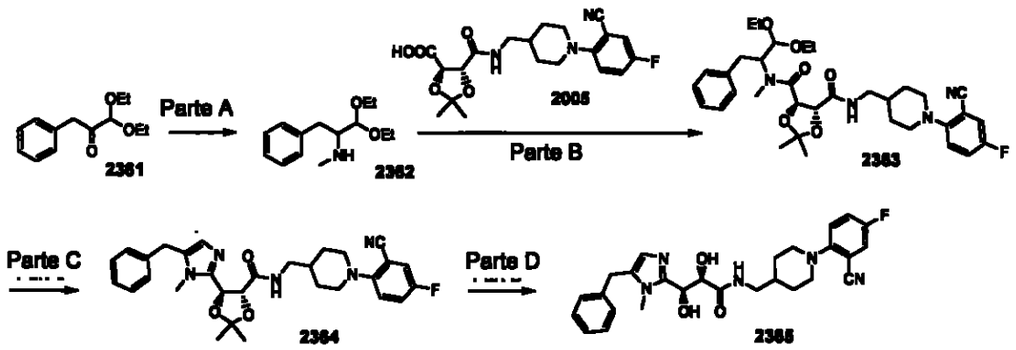
2351		**558,2**	**559,1**
2352		**558,2**	**559,1**
2306		**385,2**	**386,1**
2307		**371,2**	**372,1**
2308		**461,2**	**462,1**
2353A		**571,3**	**572,3**
2353B		**557,3**	**558,1**

2354		459,2	460,1
2355		465,2	466,3
2356		477,1	478,3
2357		541,2	542,3
2358		505,2	506,3
2304		527,2	528,3
2359		489,2	490,3

2360		503,2	504,3
2305		437,2	438,1

Ejemplo 53:

Ejemplo 53A:



Parte A:

El Compuesto **2361** se preparó usando procedimientos descriptos en Adamczyk, M. et al. *Synth. Commun.* **2002**, *32*, 3199-3205.

De acuerdo con una modificación de un procedimiento de Neidigh, K. A. et al. *(J. Chem. Soc. Perkin Trans. 1* **1998**, 2527-2531) se agitó una mezcla de cetona **2361** (1,56 g, 7 mmol), isopropóxido de titanio (IV) (4,1 ml, 14 mmol), clorhidrato de metilamina (0,94 g, 14 mmol) y trietilamina (1,95 ml, 14 mmol) en etanol (15 ml) a ta hasta el día siguiente. Luego se agregó borohidruro de sodio (0,4 g, 10,5 mmol) y la mezcla resultante se agitó a ta durante 8 h. La mezcla de reacción luego se vertió en hidróxido de amonio acuoso (40 ml), el precipitado blanco inorgánico se filtró y se lavó en varias oportunidades con diclorometano. La capa orgánica se separó, y la fase acuosa se extrajo con diclorometano. Los

extractos combinados de diclorometano se lavaron con salmuera, se concentraron y se sometieron a cromatografía (SiO_2, 5% metanol/diclorometano) para dar **2362** (1,03 g, 62%). ^1H RMN (400 Mhz, $CDCl_3$): δ 7,30-7,17 (m, 5H), 4,31-4,30 (d, 1H), 3,78-3,62 (m, 2H), 3,57-3,47 (m, 2H), 2,97-2,70 (m, 3H), 2,43 (s, 3H), 1,27-1,20 (m, 6H).

Parte B:

El Compuesto **2005** se preparó usando procedimientos descriptos en el Ejemplo 27.

El Compuesto **2363** se preparó usando las condiciones de acoplamiento descriptas en el Ejemplo 1, HPLC-MS t_R = 2,42 min. ($UV_{254\ nm}$); masa calculada para la fórmula C34H45FN4O6 624,3, LCMS observada m/z 625,2 (M+H).

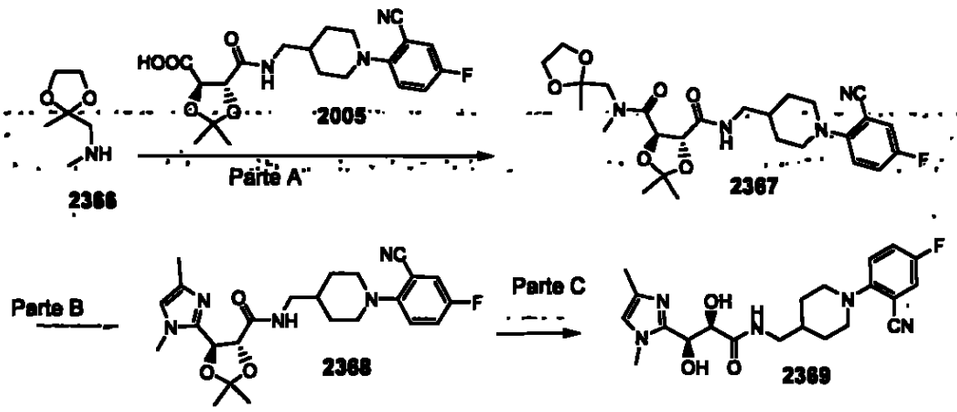
Parte C:

El Compuesto **2364** se preparó usando las condiciones de ciclación descriptas en el Ejemplo 29, HPLC-MS t_R = 1,66 min. ($UV_{254\ nm}$); masa calculada para la fórmula C30H34FN5O3 531,3, LCMS observada m/z 532,2 (M+H).

Parte D:

El Compuesto **2364** se desprotegió usando procedimientos descriptos en el Ejemplo 29. La purificación mediante LC prep. y la conversión a una sal clorhídrica dio **2365** como un sólido blancuzco. HPLC-MS t_R = 3,54 min. (10 min; $UV_{254\ nm}$); masa calculada para la fórmula C27H30FN5O3 491,2, LCMS observada m/z 492,1 (M+H).

Ejemplo 53B:



Parte A:

El Compuesto **2366** se preparó usando procedimientos descriptos en Waldvogel, E. et al. *Helv. Chim. Acta*. **1997**, *80*, 2084-2099.

El Compuesto **2367** se preparó usando las condiciones de acoplamiento descriptas en el Ejemplo 1, HPLC-MS t_R = 1,88 min. ($UV_{254\ nm}$); masa calculada para la fórmula C26H35FN4O6 518,2, LCMS observada m/z 519,2 (M+H).

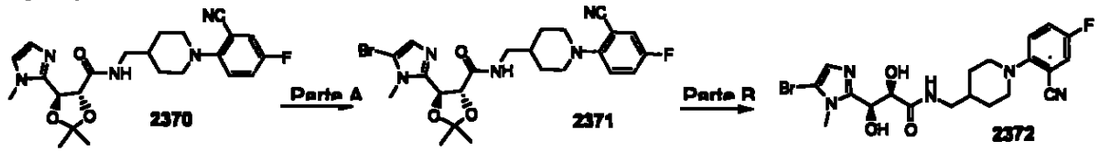
Parte B:

El Compuesto **2368** se preparó usando las condiciones de ciclación descriptas en el Ejemplo 29. HPLC-MS t_R = 1,40 min. ($UV_{254\ nm}$); masa calculada para la fórmula C24H30FN5O3 455,2, LCMS observada m/z 456,1 (M+H).

Parte C:

El Compuesto **2368** se desprotegió usando procedimientos descriptos en el Ejemplo 29.La purificación mediante LC prep. y la conversión a una sal clorhídrica dio **2369** como un sólido blancuzco. HPLC-MS t_R = 2,99 min. (10 min; $UV_{254\ nm}$); masa calculada para la fórmula C21H26FN5O3 415,2, LCMS observada m/z 416,2 (M+H).

Ejemplo 53C:



Parte A:

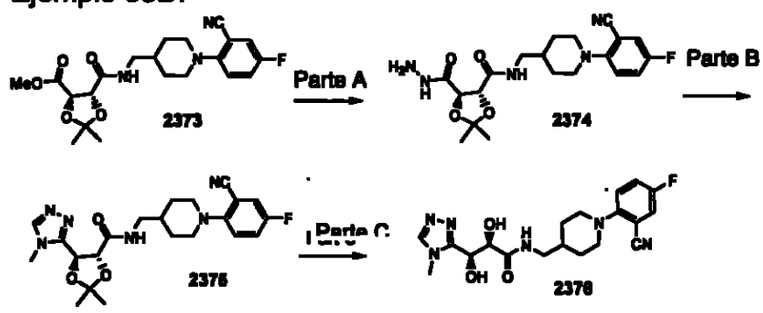
El Compuesto **2370** se preparó usando los procedimientos descriptos anteriormente en Ejemplo 29. HPLC-MS t_R = 1,30 min. ($UV_{254\ nm}$); masa calculada para la fórmula C23H28FN5O3 441,2; LCMS observada m/z 442,1 (M+H).

De acuerdo con una modificación de un procedimiento de Miller, R. D. et al. *(Chem. Mater.* **1994**, *6*, 1023-1032) se agregó gota a gota a una solución helada del compuesto **2370** (104 mg, 0,23 mmol) y piridina (0,039 ml, 0,48 mmol) en diclorometano (3 ml) una solución de bromo (0,016 ml, 0,31 mmol) en diclorometano (1 ml) y la solución resultante se agitó a 0 °C durante 20 min. La mezcla de reacción se desactivó con 10% de solución de tiosulfato de sodio y se extrajo con diclorometano. Los extractos combinados orgánicos se secaron, se concentraron y se sometieron a cromatografía (SiO_2, elusión de gradiente 50% a 80% de acetato de etilo/hexano, acetato de etilo seguido por 5% metanol/acetato de etilo) para dar **2371** como un sólido blanco (35 mg, 37% basado en material de partida reaccionado). HPLC-MS t_R = 1,94 min. ($UV_{254\ nm}$); masa calculada para la fórmula C23H27BrFN5O3 519,1, LCMS observada m/z 520,0 (M+H).

Parte B:

El Compuesto **2371** se desprotegió usando procedimientos descriptos en el Ejemplo 29, La purificación mediante LC prep. y la conversión a una sal clorhídrica dio **2372** como un sólido blanco. HPLC-MS t_R = 3,1 min. (10 min; $UV_{254\ nm}$); masa calculada para la fórmula C20H23BrFN5O3 479,1, LCMS observada m/z 480,0 (M+H).

Ejemplo 53D:



Parte A:

El Compuesto **2373** se preparó usando los procedimientos descriptos anteriormente en Ejemplos 1 y 27:

A una solución de **2373** (300 mg, 0,71 mmol) en metanol (7 ml) se agregó monohidrato de hidracina (0,35 ml, 7,1 mmol) y la mezcla resultante se calentó a 70°C en un tubo sellado hasta el día siguiente. La mezcla luego se enfrió hasta ta, se concentró, se diluyó con acetato de etilo, se lavó con agua, salmuera y se concentró para dar **2374** (220 mg, 73%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,27-7,24 (m, 1H), 7,22-7,17 (m, 1H), 7,00 (t, 1H, NH), 6,99-6,96 (m, 2H), 4,62-4,57 (dd, 2H), 3,51-3,48 (d, 2H), 3,38-3,24 (m, 2H), 2,80-2,74 (m, 2H), 1,88-1,84 (d, 2H), 1,79-1,69 (m, 1H), 1,61-1,50 (m, 2H), 1,53 (s, 3H), 1,52 (s, 3H). HPLC-MS t_R = 1,49 min. ($UV_{254\ nm}$); masa calculada para la fórmula C20H26FN5O4 419,2 LCMS observada m/z 420,1 (M+H).

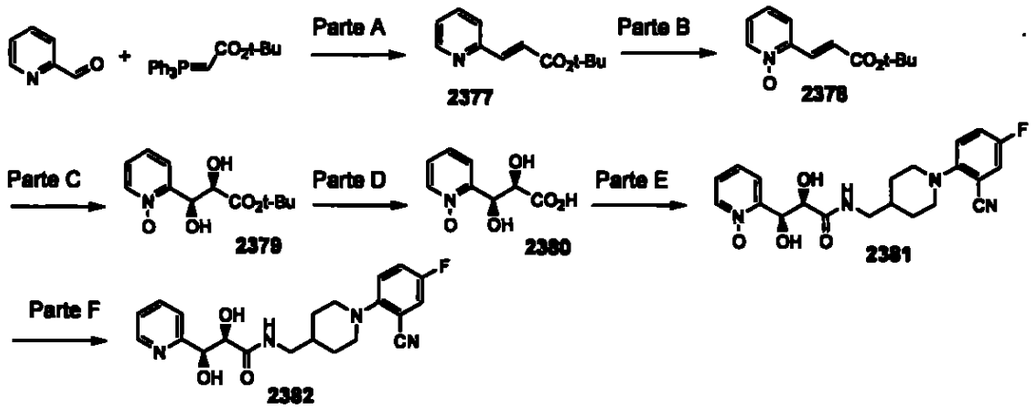
Parte B:

De acuerdo con una modificación de un procedimiento de Stocks, M. J. et al. *(Org. Lett.* **2004**, *17*, 2969-2971) a una solución de hidracida **2374** (110 mg, 0,26 mmol) en acetonitrilo (1 ml) se agregó dimetil acetal N,N-dimetilformamida (0,035 ml, 0,26 mmol) y la mezcla se calentó a 50 °C durante 50 min. Luego se agregó metilamina (0,18 ml de 2 M solución en THF, 0,36 mmol), seguida por ácido acético (1 ml) y la mezcla resultante se calentó a 80 °C hasta el día siguiente. La mezcla de reacción luego se concentró y se sometió a cromatografía (SiO_2, metanol:trietilamina:diclorometano 9:1:90) para dar **2375**, ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,42 (s, 1H), 7,27-7,24 (m, 1H), 7,21-7,18 (m, 1H), 7,02-6,97 (m, 1H), 6,92 (t, 1H, NH), 5,48-5,37 (dd, 2H), 3,51-3,47 (m, 2H), 3,36-3,23 (m, 2H), 2,80-2,74 (m, 2H), 1,88-1,81 (m, 2H), 1,76-1,70 (m, 1H), 1,58-1,54 (m, 2H), 1,58 (s, 3H), 1,43 (s, 3H). HPLC-MS t_R = 1,58 min. ($UV_{254\ nm}$); masa calculada para la fórmula C22H27FN6O3 442,2 LCMS observada m/z 443,2 (M+H).

Parte C:

El Compuesto **2375** se desprotegió con HCl 4 M en dioxano (3 ml) y agua (0,3 ml) a 55°C durante 1 hora. La purificación mediante LC prep. y la conversión a una sal clorhídrica dio **2376** como un sólido blancuzco (20 mg). HPLC-MS t_R = 1,23 min. ($UV_{254\ nm}$); masa calculada para la fórmula C19H23FN6O3 402,2, LCMS observada m/z 403,1 (M+H).

Ejemplo 53E:



Parte A:

Se agregó (*ter*-Butoxicarbonilmetilen)trifenilfosforano (15,1 g, 40 mmol) en porciones a una solución de 2-piridincarboxaldehído (4,28 g, 40 mmol) en THF (60 ml) a 0°C durante un período de 5 min. La mezcla de reacción se dejó en agitación a temperatura ambiente hasta el día siguiente. La solución se concentró, se extrajo con hexano (120 ml). Después de la filtración para eliminar el sólido, el filtrado se concentró para dar un aceite amarillo. La purificación mediante la cromatografía flash sobre gel de sílice (EtOAc/hexano 15:85) dio el producto deseado **2377** (4,5 g, 55%) como un líquido levemente amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,62 (d, *J* = 4,9 Hz, 1H), 7,69 (td, *J* = 6,6, 1,7 Hz, 1H), 7,58 (d, *J* = 15,5 Hz, 1H), 7,41(dd, *J* = 7,8, 0,6 Hz, 1H), 7,23 (m, 1H), 6,82 (d, *J* = 16,1 Hz, 1H), 1,54 (s, 9H).

Parte B:

El Compuesto **2377** (4,5 g, 21,92 mmol) se disolvió en DCM seco (40 ml) y se enfrió hasta 0°C, luego se agregó 77% de *m*-CPBA (5,41 g, 24,12 mmol) en tres porciones durante 5 min. La mezcla de reacción se dejó en agitación hasta el día siguiente a temperatura ambiente. Se vertió en $NaHCO_3$ acuoso saturado (100 ml) y el producto se extrajo en DCM. La capa orgánica se lavó con agua y salmuera y se secó (Na_2SO_4). La cromatografía flash sobre gel de sílice (MeOH/DCM 5:95) dio compuesto **2378** como un sólido amarillo pálido (3,2 g, 66%). ^1H RMN (400 MHz, $CDCl_3$) δ 8,24 (m, 1H), 7,96 (d, *J* = 16,0 Hz, 1H), 7,51 (m, 1H), 7,22 (m, 1H), 6,85 (d, *J* = 16,0 Hz, 1H), 1,55 (s, 1H).

Parte C:

Un balón de 250-ml relleno con H_2O (30 ml) se enfrió hasta 0 °C en un baño de hielo. Posteriormente se agregaron los reactivos $K_3[Fe(CN)_6]$ (9,88 g, 30 mmol), K_2CO_3 (6,91 g, 50 mmol), y $MeSO_2NH_2$ (0,95 g, 10 mmol), seguido por $K_2[OsO_2(OH)_4]$ (14,7 mg, 0,04 mmol), (DHQ)PHAL (233,7 mg, 0,3 mmol), compuesto **2378** (2,21 g, 10 mmol) y *t*-BuOH (20 ml). La mezcla de reacción se agitó a 0 °C durante 24 h. El sólido se filtró y se lavó con EtOAc exceso. La capa orgánica se separó. La solución acuosa se concentró hasta que se secó, y el sólido resultante se extrajo con CH_2Cl_2. Las soluciones anteriores de EtOAc y CH_2Cl_2 se combinaron y se concentraron. La cromatografía flash sobre gel de sílice (MeOH/CH_2Cl_2 10:90) dio compuesto **2379** como un sólido blanco (2,2 g, 86%). La recristalización a partir de EtOAc dio material puro analíticamente (1,51 g, 52% de producción). ^1H RMN (400 MHz, $CDCl_3$), δ 8,24 (d, *J* = 6,5 Hz, 1H), 7;54 (dd, *J* = 7,7, 2,0 Hz, 1H), 7,39 (t, *J* = 7,5 Hz, 1H), 7,30 (m, 1H), 5,41 (d, *J* = 2,6 Hz, 1H), 4,69 (d, *J* = 2,7 Hz, 1H), 1,54 (s, 9H).

Parte D:

El Compuesto **2379** (1,0 g, 3,9 mmol) en CH_2Cl_2 (10 ml) se trató con TFA (4 ml). La solución se dejó en agitación a temperatura ambiente durante 2 h, y luego se

concentró para dar compuesto **2380** como un sólido blanco (750 mg, 96%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,20 (dd, *J* = 6,3, 1,2 Hz, 1H), 7,54 (dd, *J* = 6,4, 2,2 Hz, 1H), 7,37 – 7,32 (m, 2H), 5,38 (d, *J* = 2,1 Hz, 1H), 4,62 (d, *J* = 2,3 Hz, 1H).

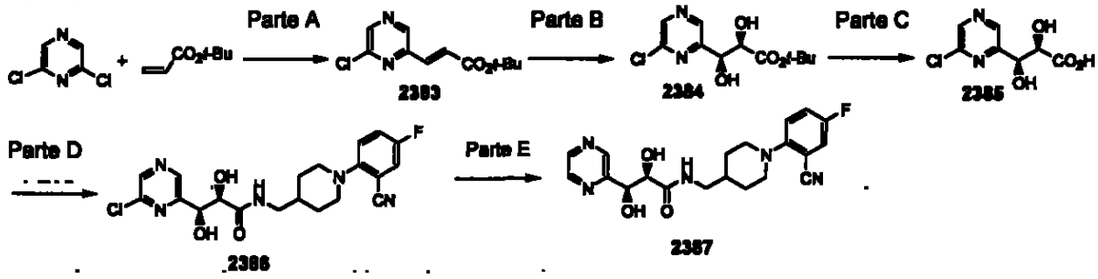
Parte E:

El Compuesto **2381** se preparó usando las condiciones de acoplamiento descriptas en el Ejemplo 1. La purificación mediante LC prep. dio **2381** como un sólido blanco (63 mg). HPLC-MS t_R = 1,30 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{21}H_{23}FN_4O_4$, 414,2, LCMS observada m/z 415,1 (M+H).

Parte F:

Al compuesto **2381** (25 mg, 0,06 mmol) en EtOH (5 ml) se agregó con solución NH_4Cl acuoso saturado (5 ml) e indio (16,6 mg, 0,072 mmol). La mezcla de reacción se dejó a reflujo durante 24 h. Después de enfriar hasta temperatura ambiente, se concentró y se extrajo con DCM. El extracto de DCM se filtró y se concentró. La purificación mediante cromatografía en columna sobre gel de sílice (Et_3N / MeOH / EtOAc 5:5:95) dio compuesto **2382** como un sólido blanco (8,5 mg, 35%). HPLC-MS t_R = 1,16 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{21}H_{23}FN_4O_3$, 398,2, LCMS observada m/z 399,1 (M+H).

Ejemplo 53F:



Parte A:

Bajo argón, a una mezcla de $Pd_2(dba)_3$ (384 mg, 0,42 mmol), se agregaron secuencialmente tetrafluoroborato de tri(t-butil)fosfinio (243 mg, 0,84 mmol), y 2,6-dicloropirizina (5,0 g, 33,56 mmol) NMP (10 ml), *t*-butil acrilato de (2,46 ml, 16,78

mmol) y Et_3N (3,51 ml, 25,17 mmol). La mezcla de reacción se dejó en agitación a 50 °C durante 12 h. Después de enfriar hasta temperatura ambiente; la mezcla se diluyó con EtOAc y agua, se filtró a través de un lecho de Celite, se lavó con agua, salmuera, se secó (Na_2SO4), y se concentró. La cromatografía flash en columna sobre gel de sílice (EtOAc / hexano 15:85) dio compuesto **2383** como un sólido amarillo pálido (2,32 g, 57%). ^1H RMN (400 MHz, acetona-d_6) δ 8,84 (s, 1H), 8,68 (s, 1H), 7,61 (d, *J* = 15,7 Hz, 1H), 6,92 (d, *J* = 15,5 Hz, 1H), 1,55 (s, 9H).

Parte B:

Un balón de 50-ml lleno con H_2O (9 ml) se enfrió hasta 0°C en un baño de hielo. Posteriormente se agregaron secuencialmente los reactivos $K_3[Fe(CN)_6]$ (1,29 g, 3,93 mmol), K_2CO_3 (905 mg, 6,55 mmol), y $MeSO_2NH_2$ (124,6 mg, 1,31 mmol), seguidos por $K_2[OsO_2(OH)_4]$ (2,0 mg, 0,005 mmol), (DHQ)PHAL (31,0 mg, 0,04 mmol), compuesto **2383** (315 mg, 1 mmol) y *t*-BuOH (6 ml). La mezcla de reacción se agitó a 0 °C durante 36 h. Luego se agregaron EtOAc y H_2O para disolver el sólido. La capa orgánica se separó y la capa acuosa se extrajo de vuelta con EtOAc. Los extractos de EtOAc se combinaron, se lavaron con agua y salmuera, se secaron (Na_2SO_4), y se concentraron. La cromatografía flash sobre gel de sílice (EtOAc/hexano 40:60) dio compuesto **2384** como un sólido blanco (285 mg, 79%). ^1H RMN (400 MHz, $CDCl_3$) δ 8,68 (s, 1H), 8,54 (s, 1H), 5,13 (d, *J* = 2,3 Hz, 1H), 4,55 (d, *J* = 2,9 Hz, 1H), 1,55 (s, 9H). HPLC-MS t_R = 1,73 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{11}H_{15}ClN_2O_4$, 274,1, LCMS observada m/z 275,0 (M+H).

Parte C:

El Compuesto **2384** (285 mg, 1,04 mmol) en dioxano (5 ml) se trató con HCl 4N en dioxano (5 ml). Después de agitar a temperatura ambiente durante 2 h, la solución se concentró para dar compuesto **2385** (200 mg, 88%). ^1H RMN (400

MHz, $CDCl_3$) δ 8,70 (s, 1H), 8,66 (s, 1H), 5,00 (d, *J* = 2,6 Hz, 1H), 4,31 (d, *J* = 2,2 Hz, 1H), 1,55 (s, 9H).

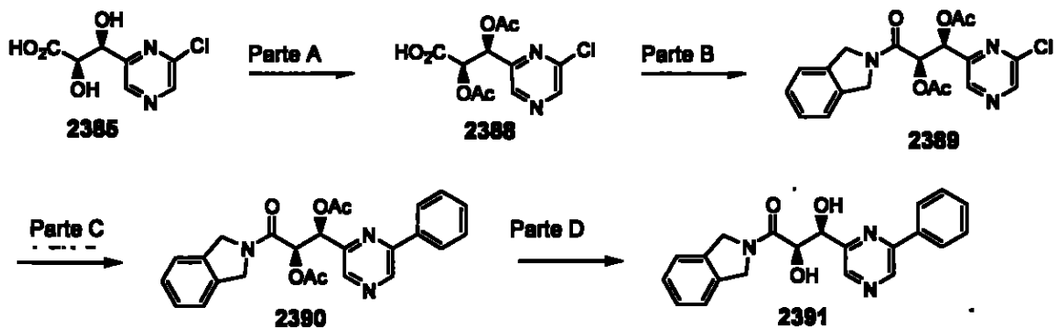
Parte D:

El Compuesto **2386** se preparó usando las condiciones de acoplamiento descriptas en el Ejemplo 1. La purificación mediante LC prep. dio **2386** como un sólido blanco (42 mg). HPLC-MS t_R = 1,55 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{20}H_{21}ClFN_5O_3$, 433,1, LCMS observada m/z 434,0

Parte E:

El Compuesto **2386** (20 mg, 0,046 mmol) junto con 10% de Pd/C (20 mg) en EtOAc (10 ml) se agitó a temperatura ambiente durante 12 h bajo atmósfera de hidrógeno (1 atm). La solución se filtró a través de Celite y se concentró. La purificación mediante LC prep. dio **2387** como un sólido blanco (15 mg, 81%). HPLC-MS t_R = 1,35 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{20}H_{22}FN_5O_3$, 399,2, LCMS observada m/z 400,1

Ejemplo 53G:



Parte A:

Al compuesto **2385** (150 mg, 0,69 mmol) en ácido acético (2 ml) se agregó anhídrido acético (0,5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, y luego se concentró. El residuo se disolvió en EtOAc, se lavó con H_2O, salmuera, se secó sobre Na_2SO_4, y se concentró, dando el compuesto **2388** como sólido aceitoso (180 mg, 86%). HPLC-MS t_R = 1,10 min.

($UV_{254\ nm}$); masa calculada para la fórmula $C_{11}H_{11}ClN_2O_6$ 302,0, LCMS observada m/z 303,0 (M+H).

Parte B:

Al compuesto **2388** (180 mg, 0,59 mmol) y HATU (269 mg, 0,71 mmol) en DMF (4 ml) se agregó isoindolina (84 mg, 0,71 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 12 h, y se concentró. El residuo se disolvió con EtOAc y agua, se lavó con solución de bicarbonato saturado, y salmuera, se secó sobre Na_2SO_4, y se concentró. La purificación mediante cromatografía en columna sobre gel de sílice (EtOAc/hexano 60:40) dio el producto deseado **2389** como un sólido amarillo pálido (150 mg, 63%). ^1H RMN (400 MHz, CDCl3) δ 8,67 (s, 1H), 8,51 (s, 1H), 7,29 (m, 4H), 6,39 (d, *J* = 7,1 Hz, 1H), 5,93 (d, *J* = 6,7 Hz, 1H), 5,21 (d, *J* = 5,4 Hz, 1H), 5,05 (d, *J* = 4,1 Hz, 1H), 4,78 (d, *J* = 5,6 Hz, 1H), 4,52 (d, *J* = 4,7 Hz, 1H), 2,18 (s, 3H), 2,16 (s, 3H). HPLC-MS t_R = 1,70 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{19}H_{18}ClN_3O_5$ 403,1, LCMS observada m/z 404,0 (M+H).

Parte C:

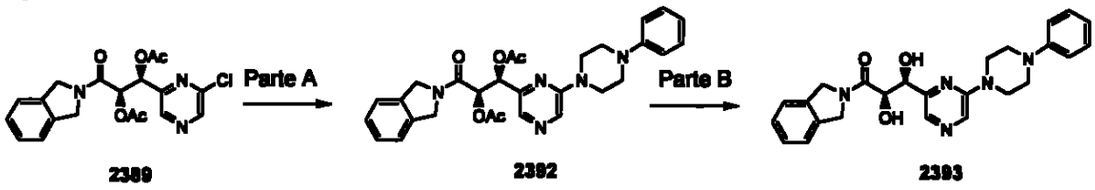
Un vial de 4 ml se cargó con $Pd_2(dba)_3$ (2,3 mg, 0,0025 mmol), tetrafluoroborato de tri(t-butil)fosfonio (1,5 mg, 0,0025 mmol), compuesto **2389** (20 mg, 0,05 mmol), fenilácido borónico (9,1 mg, 0,075 mmol) y fluoruro de potasio (13 mg, 0,225 mmol). Bajo argón, se agregó dioxano (1 ml) mediante jeringa. El vial se selló con una tapa a rosca recubierta con Teflon y se colocó en un baño de aceite precalentado a 80°C. La mezcla de reacción se dejó en agitación a 80 °C durante 12 h. la LC-MS indicó que se completó la reacción. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se filtró a través de Celite con la ayuda de EtOAc. El filtrado se lavó con NaHCO3 saturado, salmuera, se secó sobre Na2SO4, y se concentró. El sólido resultante (21 mg) se usó para el paso

siguiente sin purificación. HPLC-MS t_R = 1,89 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{25}H_{23}N_3O_5$ 445,1, LCMS observada m/z 446,0 (M+H).

Parte D:

El Compuesto **2390** (21 mg) se desprotegió usando procedimientos descriptos en el Ejemplo 2. La purificación mediante LC prep. dio **2391** como un sólido blancuzco (8,3 mg). HPLC-MS t_R = 4,02 min. (10 min. method) ($UV_{254\ nm}$); masa calculada para la fórmula $C_{21}H_{19}N_3O_5$ 361,1, LCMS observada m/z 362,0 (M+H).

Ejemplo 53H:



2389 2392 2393

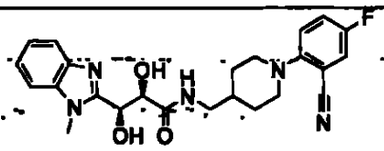
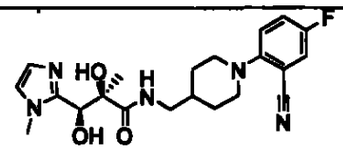
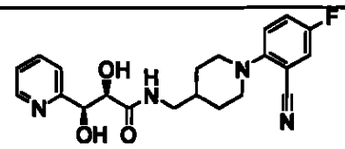
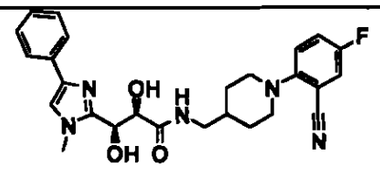
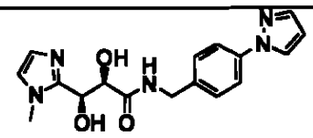
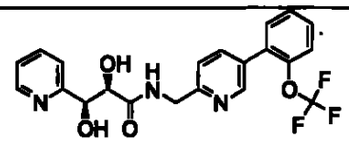
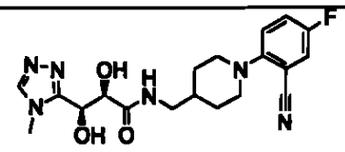
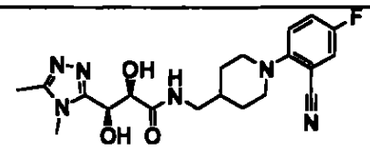
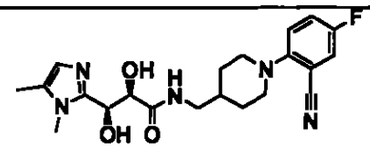
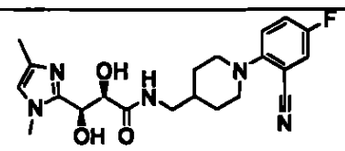
Parte A:

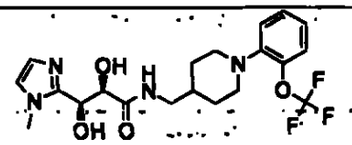
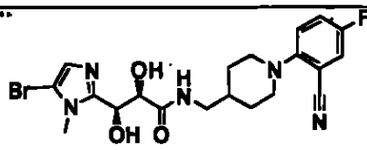
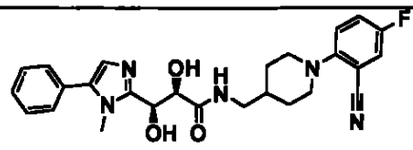
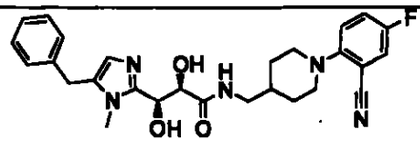
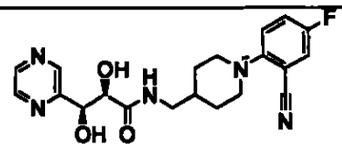
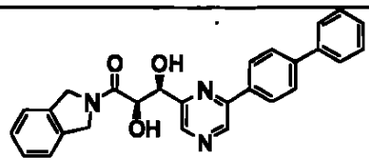
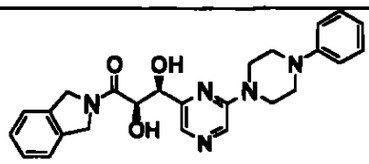
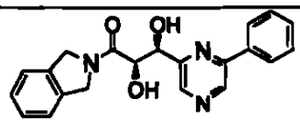
Al compuesto **2389** (50 mg, 0,12 mmol) en NMP (1 ml) se agregó 4-N-fenilpipizina (29 mg, 0,18 mmol) y DIEA (0,032 ml, 0,18 mmol). La mezcla de reacción se dejó en agitación a 80 °C durante 16 h. Después de enfriar hasta temperatura ambiente, la solución se diluyó con EtOAc, se lavó con agua y salmuera, se secó sobre Na2SO4, y se concentró. El sólido aceitoso resultante (52 mg) se usó para el paso siguiente sin purificación adicional. HPLC-MS t_R = 1,96 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{29}H_{31}N_5O_5$ 529,2, LCMS observada m/z 530,2 (M+H).

Parte B:

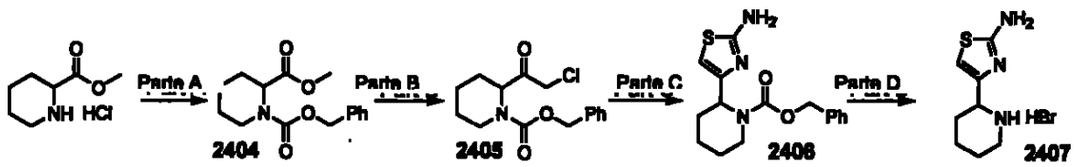
El Compuesto **2392** (52 mg) se desprotegió usando procedimientos descriptos en el Ejemplo 2. La purificación mediante LC prep. dio **2393** como un sólido blancuzco (15 mg). HPLC-MS t_R = 1,60 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{25}H_{27}N_5O_3$ 445,2, LCMS observada m/z 446,1 (M+H).

Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
2394		451,2	452,2
2395		415,2	416,2
2382		398,2	399,1
2396		477,2	478,2
2397		341,2	342,1
2398		433,1	434,0
2376		402,2	403,1
2399		416,2	417,1
2400		415,2	416,2
2369		415,2	416,2

2401		442,2	443,2
2372		479,1	480,0
2402		477,2	478,1
2365		491,2	492,1
2387		399,2	400,1
2403		437,2	438,0
2393		445,2	446,1
2391		361,1	362,0

Ejemplo 54:



Parte A:

Se disolvió clorhidrato de metil pipecolinato (2,0 g, 11 mmol) en THF (20 ml) y bicarbonato de sodio saturado (20 ml) y se enfrió en un baño de hielo. Se agregó gota a gota cloroformiato de bencilo (1,5 ml, 11 mmol) y la reacción se agitó a temperatura ambiente hasta el día siguiente. La mezcla de reacción se dividió entre acetato de etilo y agua. La capa orgánica se lavó con HCl 1N, bicarbonato de sodio saturado, agua y salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 10% de acetato de etilo/hexano a 15% de acetato de etilo/hexano) dio **2404** como un aceite claro (2,9 g, 93%).

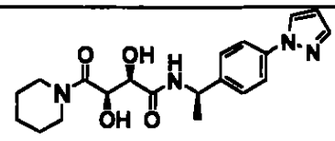
Parte B y C:

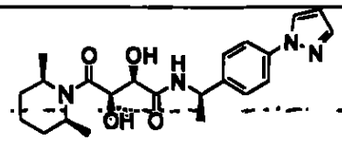
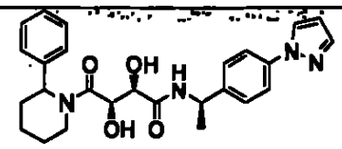
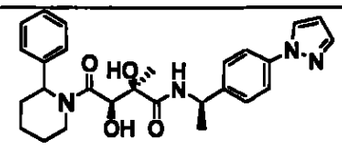
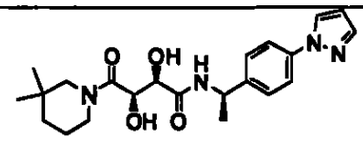
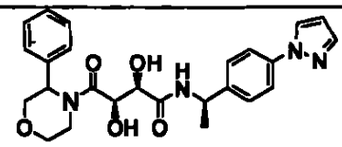
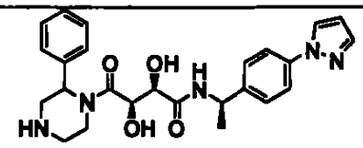
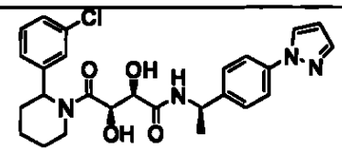
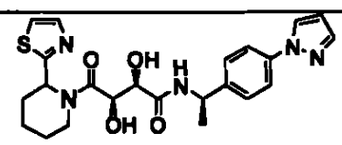
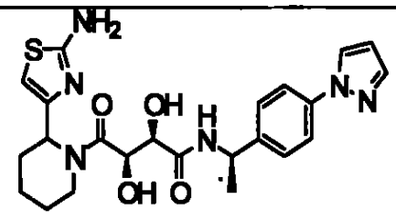
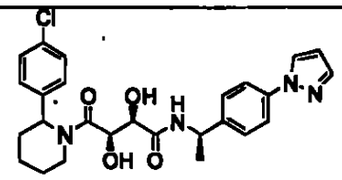
Los Compuestos **2405** y **2406** se prepararon siguiendo los procedimientos descriptos en el Ejemplo 10B parte A y parte B. Compuesto **2406**: ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,40 – 7,30 (m, 5H), 6,11 (s, 1H), 5,36 (m, 1H), 5,18 (s, 2H), 3,72 (m, 1H), 3,00 (m, 1H), 2,33 (m, 1H), 1,90 – 1,40 (m, 7H). HPLC-MS t_R = 1,34min. ($UV_{254\ nm}$); Masa calculada para C16H19N3O2S 317,4, LSMS observada m/z 318,1 (M+H).

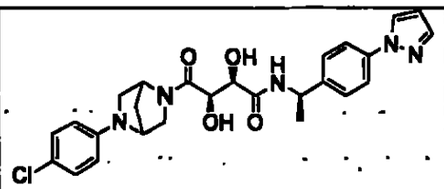
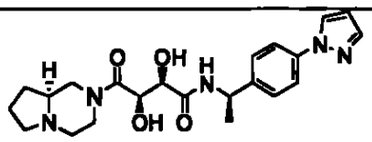
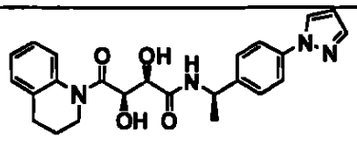
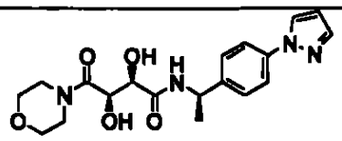
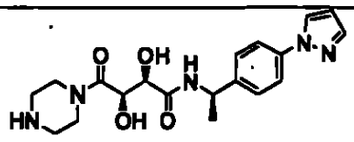
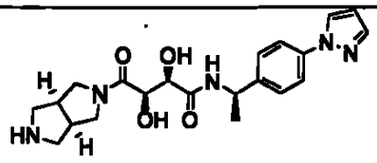
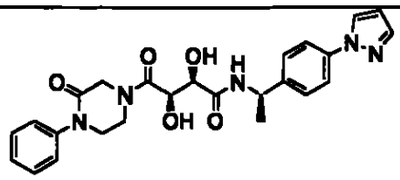
Parte D:

El Compuesto **2406** (75 mg, 0,24 mmol) se agitó en 30% de HBr en ácido acético (2 ml) durante 1 hora a temperatura ambiente. El solvente se evaporó y el residuo se disolvió en agua y se liofilizó para dar **2407** (66 mg) como un sólido rojo.

Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente.

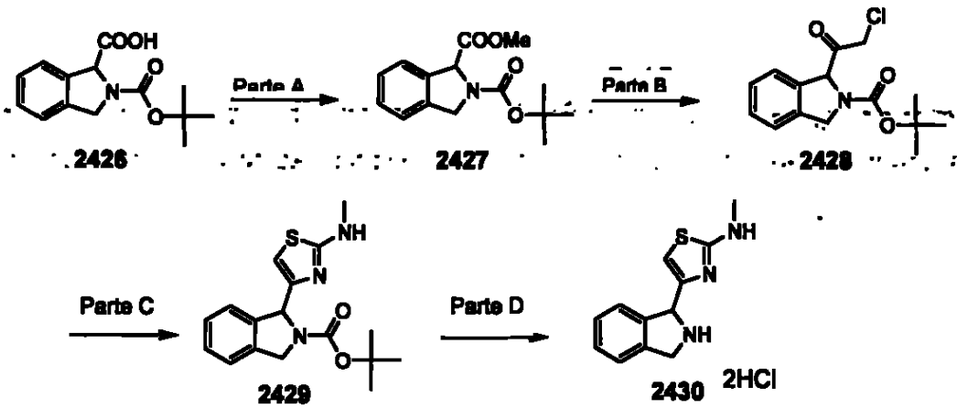
Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
2408		386,2	387,1

2409		414,2	415,1
2410		462,2	463,1
2411		476,2	477,1
2412		414,2	415,1
2413		464,2	465,1
2414		463,2	464,2
2415		496,2	497,0
2416		469,2	470,0
2417		484,2	485,0
2418		496,2	497,0

2419		509,2	510,1
2420		427,2	428,2
2421		434,2	435,1
2422		388,2	389,1
2423		387,2	388,1
2424		413,2	414,1
2425		477,2	478,1

Ejemplo 55:

Ejemplo 55A:



Parte A:

A una solución helada de ácido **2426** (1,0 g, 3,8 mmol) en metanol:tolueno 1:1 (10 ml) se agregó gota a gota TMS-diazometano (3,2 ml de 2 M solución en hexano, 6,4 mmol) y la solución resultante se agitó a ta durante 1 h. La mezcla de reacción se concentró, se dividió entre acetato de etilo y agua y se extrajo con acetato de etilo. Los extractos orgánicos combinados se lavaron con solución de bicarbonato de sodio saturado, salmuera, se secó y se evaporó para dar éster **2427** como un sólido blancuzco (0,907 g, 86%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,43-7,28 (m, 4H), 5,53-5,46 (dd, 1H), 4,86-4,69 (m, 2H), 3,77-3,75 (d, 3H), 1,54-1,49 (d, 9H).

Parte B:

Se preparó Clorocetona **2428** usando procedimientos descriptos en el Ejemplo 10, ^{1}H RMN (400 MHz, CDCl3) δ 7,46-7,30 (m, 4H), 5,65-5,48 (d de d, 1H), 4,90-4,71 (m, 2H), 4,42-4,06 (m, 2H), 1,57-1,52 (d, 9H).

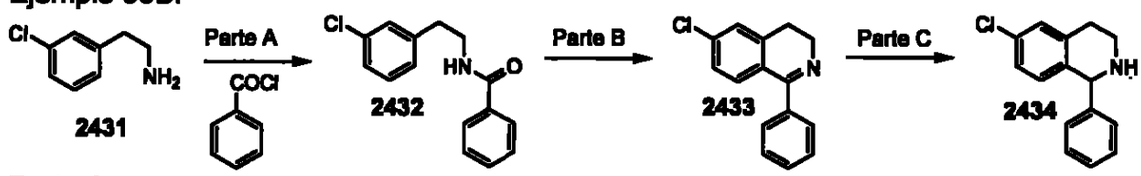
Parte C:

El Compuesto **2429** se preparó usando procedimientos descriptos en el Ejemplo 10, HPLC-MS t_R = 1,51 min. ($UV_{254\ nm}$); masa calculada para la fórmula C17H21N3O2S 331,1, LCMS observada m/z 332,1 (M+H).

Parte D:

El Compuesto **2430** se preparó usando procedimientos descriptos en el Ejemplo 10. HPLC-MS t_R = 0,80 min. ($UV_{254\ nm}$); masa calculada para la fórmula C12H13N3S 231,1, LCMS observada m/z 232,1 (M+H).

Ejemplo 55B:



Parte A:

De acuerdo con una modificación de un procedimiento de Mach, U. R. et al. (*ChemBioChem* **2004**, *5*, 508-518) a una mezcla de 3-clorophenetilamina **2431** (3,89 g, 25 mmol) y solución 2 M de hidróxido de potasio (35 ml) se agregó gota a gota cloruro de benzoilo (3,48 ml, 30 mmol). En unos minuto, se formó un precipitado, se filtró y y se lavó cuidadosamente con agua, se secó (aire) y se recristalizó (etanol) para dar amida **2432** como un sólido blanco (4,22 g, 65%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,53 (t, 1H, NH), 7,78-7,76 (d, 2H), 7,50-7,17 (m, 7H), 3,50-3,46 (m, 2H), 2,85 (t, 2H). HPLC-MS t_R = 1,81 min. ($UV_{254\ nm}$); masa calculada para la fórmula C15H14ClNO 259,1, LCMS observada m/z 260,0 (M+H).

Parte B:

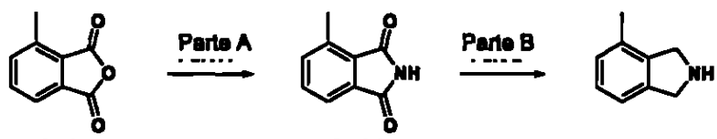
De acuerdo con una modificación de un procedimiento de Mach, U. R. et al. (*ChemBioChem* **2004**, *5*, 508-518) a una mezcla de amida **2432** (1,79 g, 6,9 mmol) y cloruro de zinc en polvo (3,29 g, 24,1 mmol) en tolueno (30 ml) se agregó gota a gota oxicloruro de fósforo (4,4 ml, 48,3 mmol) y la mezcla se calentó a reflujo durante 2 h, durante ese tiempo se formó un residuo similar al polímero,. La mezcla de reacción se enfrió en un baño de hielo, se desactivó mediante el agregado de solución de hidróxido de sodio 2 M, se extrajo y se sonicó con diclorometano (el residuo se disolvió). Los extractos combinados de diclorometano se concentraron para un residuo sólido que luego se trituró con

THF. El sólido blanco resultante se filtró y se secó para dar el compuesto **2433** (1,23 g, 74%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,82-7,67 (m, 6H), 7,58-7,55 (dd, 1H), 7,41-7,39 (d, 1H), 3,98 (t, 2H), 3,23 (t, 2H). HPLC-MS t_R = 0,96 min. ($UV_{254\ nm}$); masa calculada para la fórmula C15H12ClN 241,1, LCMS observada m/z 242,1 (M+H).

Parte C:

De acuerdo con una modificación de un procedimiento de Mach, U. R. et al. (*ChemBioChem* **2004**, *5*, 508-518) a una solución de imina **2433** (760 mg, 3,14 mmol) en etanol (50 ml) se agregó borohidruro de sodio en porciones (300 mg, 7,86 mmol) y la mezcla resultante se calentó a reflujo hasta el día siguiente. La mezcla de reacción se enfrió, se desactivó con agua, se concentró, se dividió entre acetato de etilo y agua, y se extrajo con acetato de etilo. Los extractos orgánicos combinados se secaron y se concentró para dar amina **2434** (418 mg, 55%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,33-7,04 (m, 7H), 6,62-6,60 (d, 1H), 5,00 (s, 1H), 3,36-3,26 (m, 1H), 3,11-3,06 (m, 1H), 2,98-2,73 (m, 2H). HPLC-MS t_R = 1,14 min. ($UV_{254\ nm}$); masa calculada para la fórmula C15H14ClN 243,1, LCMS observada m/z 244,1 (M+H).

Ejemplo 55C:



2435 **2436** **2437**

Parte A:

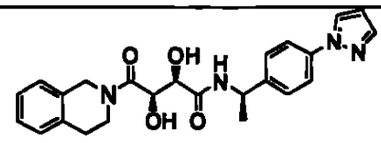
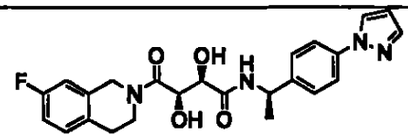
Una mezcla del compuesto **2435** (6 g, 36,5 mmol) y urea (1,95 g, 32,5 mmol) se calentó sobre un baño de arena a 350 °C durante 30 minutos. La brea negra resultante se enfrió a 100 °C y se agregó agua cuidadosamente (25 ml). Esta mezcla se agitó durante 1 hora. El sólido se recolectó mediante filtración, se disolvió en DMF (40 ml) y se agitó con Darco (1 g) durante 1 hora. La mezcla se

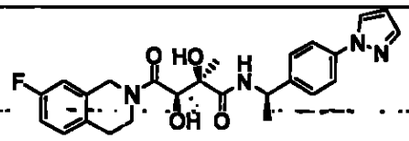
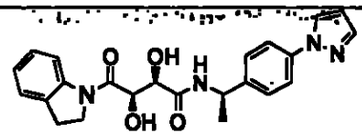
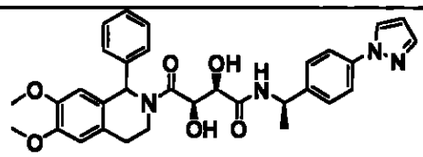
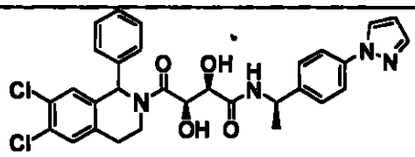
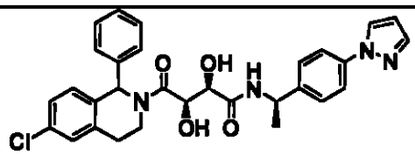
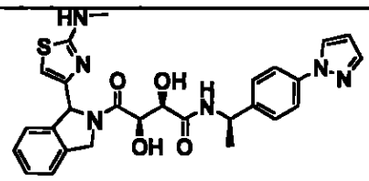
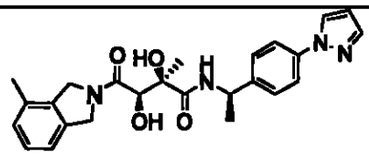
filtró y agua (100 ml) se agregó a el filtrado para precipitar un sólido marrón. El sólido se recolectó mediante filtración y se secó con aire. El sólido se disolvió en MeOH en ebullición (120 ml) con Darco (1 g). La mezcla se filtró y el filtrado se concentró hasta que se secó. El residuo se suspendió en EtOAc y se filtró para dar el compuesto deseado **2436** como un sólido marrón (2,5 g, 43%).

Parte B:

El Compuesto **2436** (1 g, 6,2 mmol) se agregó a una solución de boro/THF 1M (21 ml, 21 mmol) a 0 °C y la mezcla se calentó hasta temperatura ambiente y luego se reflujó durante 18 horas. La mezcla de reacción se enfrió hasta temperatura ambiente y se agregó gota a gota HCl 6N (50 ml). La mezcla de reacción se concentró para eliminar THF y luego se enfrió hasta 0 °C y se agregaron cuidadosamente pellets de hidróxido de sodio (13 g) a la mezcla de reacción. La mezcla de reacción se extrajo con CH_2Cl_2 (1 x 50 ml, 1 x 20 ml). La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró. La purificación mediante cromatografía en columna (SiO_2, 3% MeOH(NH_3)/CH_2Cl_2, seguido por 5% MeOH(NH_3)/CH_2Cl_2) dio el compuesto deseado **2437** como sólido color tostado (64 mg, 7,7%).

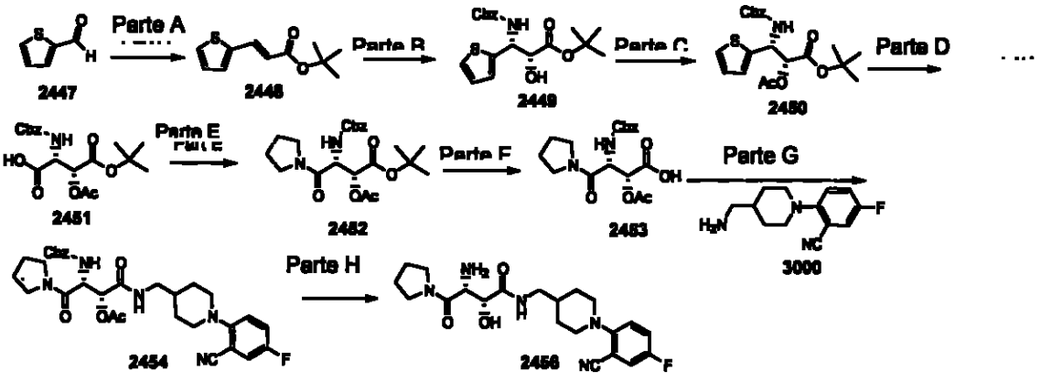
Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
2438		434,2	435,1
2439		452,2	453,1

2440		**466,2**	**467,0**
2441		**420,2**	**421,1**
2442		**570,2**	**571,1**
2443		**578,2**	**579,1**
2444		**544,2**	**545,0**
2445		**532,2**	**533,0**
2446		**448,2**	**449,1**

Ejemplo 56:

Ejemplo 56A:



Partes A-D:

Los Compuestos **2448-2451** se prepararon de acuerdo con los procedimientos en *Syn. Lett.* **1999**, 12, 1907-1910.

Parte E:

Se disolvieron el Compuesto **2451** (200 mg, 0,52 mmol), HATU (260 mg, 0,68 mmol), pirrolidina (0,052 ml, 0,624 mmol), y DIEA (0,1 ml) en DMF (5 ml). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente y luego se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con HCl 1 M, bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio, y se concentró. La purificación mediante cromatografía en columna (SiO_2, 50% de acetato de etilo/hexanos) dio el producto deseado (200 mg). HPLC-MS t_R = 1,91 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{22}H_{30}N_2O_7$ 434,21, LCMS observada m/z 435,1 (M+H).

Parte F:

El Compuesto **2452** (200 mg, 0,46 mmol) se disolvió en cloruro de metileno (4 ml) y ácido trifluoro acético (1 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas. El solvente se evaporó y el material se usó sin purificación adicional (160 mg). HPLC-MS t_R = 1,31 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{18}H_{22}N_2O_7$ 434,21, LCMS observada m/z 379,1 (M+H).

Parte G:

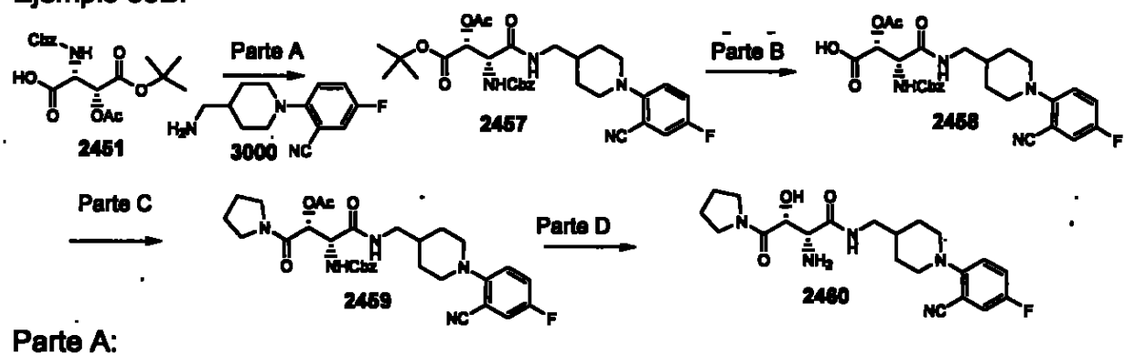
Se disolvieron Compuesto **2453** (160 mg, 0,423 mmol), compuesto **3000** (preparado según se describe en el Ejemplo 27A) (122 mg, 0,423 mmol), HATU (210 mg, 0,55 mmol), y DIEA (0,5 ml) en DMF (10 ml). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente y luego se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con HCl 1 M, bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio, y se concentró. La purificación mediante cromatografía en columna (SiO_2, 25% de acetato de

etilo/hexanos a 100% de acetato de etilo) dio el producto deseado (175 mg). HPLC-MS t_R = 1,94 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{31}H_{36}FN_5O_6$ 593,2, LCMS observada m/z 594,2 (M+H).

Parte H:

El Compuesto **2454** (50 mg, 0,084 mmol) se disolvió en amoníaco 7 M en MeOH (0,5 ml) y MeOH (2 ml) y se agitó durante 30 minutos. El solvente se eliminó bajo presión reducida. El residuo se disolvió en MeOH (5 ml) y ácido acético (0,3 ml) y se agregó Pd-C (100 mg) bajo una atmósfera de argón. La reacción se agitó bajo a atmósfera de hidrógeno durante 3 horas y luego se filtró a través de un lecho de Celite. El solvente se evaporó y el residuo se dividió entre acetato de etilo y agua. Las capas orgánicas combinadas se lavaron con bicarbonato de sodio saturado, salmuera, se secaron sobre sulfato de sodio y se concentraron. El residuo se disolvió en acetato de etilo (2 ml) y se trató con HCl 4 M en dioxano (0,1 ml). Los sólidos se filtraron y se lavaron en varias oportunidades con acetato de etilo para obtener el producto deseado como una sal de HCl (23 mg). HPLC-MS t_R = 1,15 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{21}H_{28}FN_5O_3$ 417,2, LCMS observada m/z 418,1 (M+H).

Ejemplo 56B:



Parte A:

Se disolvieron el Compuesto **2451** (200 mg, 0,52 mmol), compuesto **3000** (194 mg, 0,68 mmol), HATU (260 mg, 0,68 mmol), y DIEA (0,5 ml) en DMF (5 ml). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente y luego

se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con HCl 1 M, bicarbonato de sodio saturado, salmuera, se secaron sobre sulfato de sodio, y se concentraron. La purificación mediante cromatografía en columna (SiO_2; 33% de acetato de etilo/hexanos a 100% de acetato de etilo) dio el producto deseado (230 mg). HPLC-MS t_R = 2,20 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{31}H_{37}FN_4O_7$ 596,2, LCMS observada m/z 597,2 (M+H).

Parte B:

El Compuesto **2457** (230 mg, 0,386 mmol) se disolvió en cloruro de metileno (4 ml) y ácido trifluoro acético (1 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas. El solvente se evaporó y **2458** (190 mg) se usó sin purificación adicional. HPLC-MS t_R = 1,77 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{27}H_{29}FN_4O_7$ 540,2, LCMS observada m/z 541,2 (M+H).

Parte C:

El Compuesto **2458** (190 mg, 0,32 mmol), HATU (160 mg, 0,416 mmol), pirrolidina (0,035 ml, 0,416 mmol), y DIEA (0,5 ml) se disolvieron en DMF (5 ml). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente y luego se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con HCl 1 M, bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio, y se concentró. La purificación mediante cromatografía en columna (SiO_2, 25% de acetato de etilo/hexanos a 100% de acetato de etilo) dio el producto deseado (200 mg). HPLC-MS t_R = 1,92 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{31}H_{36}FN_5O_6$ 593,2, LCMS observada m/z 594,2 (M+H).

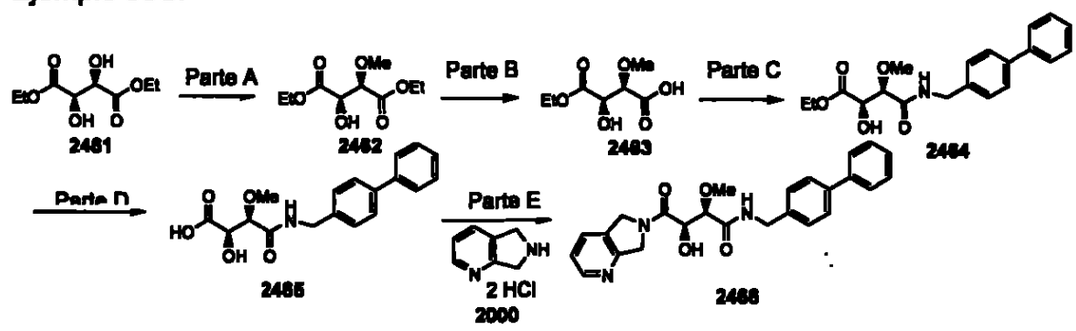
Parte D:

El Compuesto **2459** (55 mg, 0,092 mmol) se disolvió en amoníaco 7 M en MeOH (0,5 ml) y MeOH (2 ml) y se agitó durante 30 minutos. El solvente se eliminó bajo presión reducida. El residuo se disolvió en MeOH (5 ml) y ácido acético (0,3 ml) y se agregó Pd-C (100 mg) bajo una atmósfera de argón. La reacción se agitó bajo

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a atmósfera de hidrógeno durante 3 horas y luego se filtró sobre un lecho de Celite. El solvente se evaporó y el residuo se dividió entre acetato de etilo y agua. Las capas orgánicas combinadas se lavaron con bicarbonato de sodio saturado, salmuera, se secaron sobre sulfato de sodio y se concentraron. El residuo se disolvió en acetato de etilo (2 ml) y se trató con HCl 4 M en dioxano (0,1 ml). Los sólidos se filtraron y se lavaron en varias oportunidades con acetato de etilo para dar **2460** como una sal de HCl (29 mg). HPLC-MS t_R = 1,15 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{21}H_{28}FN_5O_3$ 417,2, LCMS observada m/z 418,1 (M+H).

Ejemplo 56C:



Parte A:

El Compuesto **2462** se preparó usando un procedimiento de modificación en *Chem. Pharm. Bull.* **1991**, 39, 8, 1972-1982. Se disolvieron Compuesto **2461** (1,06 g, 5,14 mmol) y Bu_2SnO (1,28 g, 5,14 mmol) en tolueno (20 ml) y se agitó a reflujo durante 1,5 horas usando una trampa de Dean-Stark para azeotropicar el agua formada en la reacción. El solvente se evaporó bajo presión reducida y se colocó en vacío durante 1 hr. Se agregó fluoruro de cesio (1,08 g, 6,68 mmol) al residuo y se colocó en vacío durante 2 horas adicionales. La mezcla se disolvió luego en DMF (20 ml) y yodometano (2,99 g, 22,1 mmol) y se agitó hasta el día siguiente a temperatura ambiente. La mezcla de reacción se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con HCl 1N, bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio, y se concentró. La

purificación mediante cromatografía en columna (SiO_2, 33% de acetato de etilo/hexanos) dio el producto deseado (800 mg). ^1H RMN (400 MHz, $CDCl_3$) δ 4,60 (d, 1H); 4,30 (m, 4H); 4,15 (d, 1H); 3,50 (s, 3H), 1,35 (t, 6H).

Parte B:

El Compuesto **2463** se preparó usando una modicación a un procedimiento que se encuentra en *Tetrahedron* **1993**, 49, 37, 8381-8396. El diéster **2462** (0,837 g, 3,6 mmol) se suspendió en buffer de fosfato de pH 8 (75 ml) y el pH se monitoreó a 8,33. Se agregó esterasa de hígado de cerdo (20 mg) a la suspensión y la mezcla de reacción se agitó a temperatura ambiente. El pH de la reacción se mantuvo entre 7,9-8,2 mediante la adición gota a gota de NaOH 1M (3,27 ml, 3,24 mmol) durante 1,5 horas. La mezcla de reacción se dividió entre dietil éter y agua. La capa acuosa se acidó a pH 2 y se extrajo con acetato de etilo. Las capas combinadas de acetato de etilo se secaron sobre sulfato de sodio y se evaporó para dar el producto deseado como una mezcla 4,5:1 de ácidos inseparables (275 mg). ^1H RMN (400 MHz, $CDCl_3$) δ 4,60 (d, 1H), 4,40 (m, 2H), 4,25 (d, 1H), 3,50 (s, 3H), 1,35 (t, 3H).

Parte C:

Se disolvieron el Compuesto **2463** (130 mg, 0,65 mmol), HATU (322 mg, 0,845 mmol), 4-fenilbencilamina (153 mg, 0,845 mmol), y DIEA (0,2 ml) en DMF (6 ml). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente y luego se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con HCl 1 M, bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio, y se concentró. La recristalización a partir de acetato de etilo dio producto puro (50 mg) y producto levemente impuro (150 mg). HPLC-MS t_R = 1,70 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{20}H_{23}NO_5$ 357,1, LCMS observada m/z 358,1 (M+H).

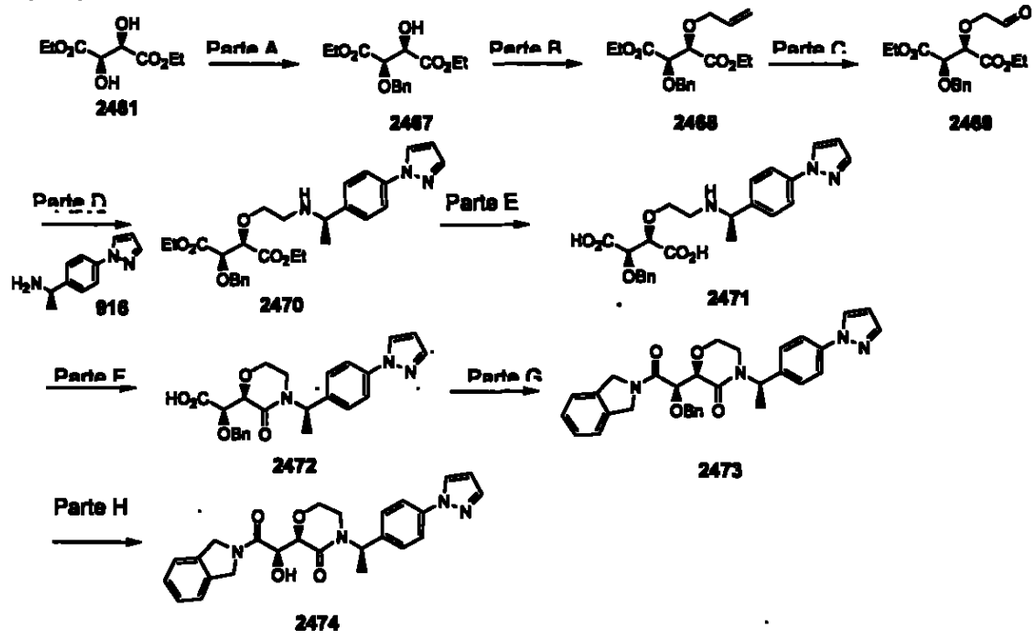
Parte D:

El Compuesto **2464** (50 mg, 0,140 mmol) se disolvió en LiOH 1 M (0,151 ml, 0,151 mmol) y THF (5 ml) y se agitó durante 1 hora. La mezcla de reacción se dividió entre acetato de etilo y agua y la capa acuosa se acidó a pH 2 usando HCl 1N. Las capas orgánicas se secaron sobre sulfato de sodio y se concentraron para dar el producto deseado (46 mg). HPLC-MS t_R = 1,43 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{18}H_{19}NO_5$ 329,1, LCMS observada m/z 330,1 (M+H).

Parte E:

El Compuesto **2465** (46 mg, 0,140 mmol), HATU (70 mg, 0,182 mmol), compuesto **2000** (35 mg, 0,182 mmol), y DIEA (0,12 ml) se disolvieron en DMF (6 ml). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente y luego se dividió entre acetato de etilo y agua. Las capas orgánicas se lavaron con bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio, y se concentró. La recristalización a partir de acetato de etilo dio el producto puro (30 mg). HPLC-MS (10 min) t_R = 3,51 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{25}H_{25}N_3O_4$ 431,2, LCMS observada m/z 432,1 (M+H).

Ejemplo 56D:



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Parte A:

El Compuesto **2467** se preparó de acuerdo con un procedimiento modificado de la literatura (Nagashima, N. y Ohno, M., *Chem. Pharm. Bull.*, **1991**, *39*, 1972-1982). Se calentó L-dietil tartrato (2461) (6,18 g, 30 mmol) y dibutiltino óxido (7,47 g, 30 mmol) en tolueno (100 ml) bajo reflujo durante 1h, eliminando el agua formada como la mezcla azotrópica. La solución se evaporó hasta que se secó por completo en *vacuo* para dar un sólido blanco. A este sólido se agregó CsF seco (8,66 g, 59 mmol) y DMF (60 ml). La mezcla resultante se enfrió hasta 0 °C, y se agregó gota a gota bromuro de bencilo (6 ml, 51 mmol) mediante una jeringa. Una vez completada la adición, la mezcla de reacción se dejó en agitación vigorosamente a temperatura ambiente durante 12 h. El solvente se eliminó en vacío y el residuo obtenido se disolvió en EtOAc y H_2O. La capa orgánica se lavó con solución acuosa de $NaHCO_3$, salmuera, se secó sobre Na_2SO_4, y se concentró. La purificación mediante cromatografía flash en columna sobre gel de sílice (EtOAc / hexano 30:70) dio compuesto **2467** como líquido incoloro (8,10 g, 91%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,37-7,25 (m, 5H), 4,87 (d, *J* = 12,0 Hz, 1H), 4,58 (br s, 1H), 4,02 (d, *J* = 12,0 Hz, 1H), 4,34 – 4,25 (m, 3H), 4,23-4,21 (m, 1H), 4,08 – 4,03 (m, 1H), 3,12 (br s, 1H), 1,35 (t, *J* = 7,0 Hz, 3H), 1,19 (t, *J* = 6,9 Hz, 3H).

Parte B:

Al compuesto **2467** (2,96 g, 10 mmol) en tolueno (10 ml) se agregó con Ag_2O (4,63 g, 20 mmol) y bromuro de alilo (1,31 ml, 15 mmol). La mezcla de reacción se dejó en agitación a 110°C durante 16 h y se enfrió hasta temperatura ambiente. Después de la filtración a través de un lecho de Celite, la solución se concentró. La cromatografía flash en columna sobre gel de sílice (EtOAc / hexano 20: 80) dio el producto deseado **2468** (2,65 g, 79%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,33-7,25 (m, 5H), 4,87 (d, *J* = 12,0 Hz, 1H), 5,89-5,79 (m, 1H), 5,26-5,15 (m, 2H), 4,87 (d, *J*

= 11,4 Hz, 1H), 4,46 (d, *J* = 11,7 Hz, 1H), 4,41-4,38 (m, 2H), 4,34 – 3,92 (m, 6H), 1,32 (t, *J* = 7,2 Hz, 3H), 1,19 (t, *J* = 7,2 Hz, 3H).

Parte C:

A una mezcla helada del compuesto **2468** (1,0 g, 3 mmol) y N-metilmorfolina monohidrato (703 mg, 6 mmol) en THF / H_2O 3:1 (20 ml) se agregó OsO_4 (2,5 % en peso en *t*-BuOH, 610 mg, 0,06 mmol). Después de agitar durante 30 min, el baño de hielo se eliminó y la mezcla de reacción se agitó a temperatura ambiente hasta el día siguiente. Se agregó $NaHSO_3$ sólido (750 mg, 7,2 mmol), y la mezcla se agitó durante 30 minutos adicionales. La mezcla se filtró a través de un lecho de sílice y la solución se concentró en *vacuo* dando un aceite. Este material se disolvió en THF/H_2O 3:1 (20 ml) y se agregó $NaIO_4$ (1,28 g, 6 mmol). La mezcla se dejó en agitación a temperatura ambiente durante 1 h. Se filtró a través de sílice, y el solvente se evaporó. La cromatografía flash en columna sobre gel de sílice (EtOAc/hexano 50:50) dio el aldehído **2469** (760 mg, 75%) como un aceite incoloro). ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,72 (s, 1H), 7,35-7,26 (m, 5H), 4,89 (d, *J* = 11,8 Hz, 1H), 4,52-4,48 (m, 2H), 4,45 – 4,04 (m, 7H), 1,34 (t, *J* = 7,7 Hz, 3H), 1,19 (t, *J* = 7,4 Hz, 3H).

Parte D:

El Compuesto **2469** (340 mg, 1 mmol) y amina **916** (187 mg, 1 mmol) en 1,2-dicloroetano (5 ml) se agitaron a temperatura ambiente durante 5 min, después se agregó lentamente tri(acetoxil)borohidruro de sodio (254 mg, 1,2 mmol). La mezcla de reacción se dejó en agitación a temperatura ambiente hasta el día siguiente. La solución se concentró, el residuo bruto se purificó mediante la cromatografía flash en columna sobre gel de sílice (MeOH/EtOAc 10:90), dando el producto deseado **2470** (350 mg, 69%) como un aceite incoloro. HPLC-MS t_R = 1,49 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{28}H_{35}N_3O_6$ 509,2, LCMS observada m/z 510,1 (M+H).

Parte E:

A una solución de compuesto **2470** (170 mg, 0,33 mmol) en dioxano / agua 1:1 (10 ml) se agregó LiOH (1M, 1,32 ml, 1,32 mmol) gota a gota. La mezcla se agitó a temperatura ambiente durante 2h después se neutralizó con HCl 1 M y se concentró. El residuo se usó para el paso siguiente sin purificación adicional. HPLC-MS t_R = 1,12 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{24}H_{27}N_3O_6$ 453,2, LCMS observada m/z 454,1 (M+H).

Parte F:

El compuesto bruto **2471** se disolvió en DMF (10 ml) y se enfrió hasta 0 °C en un baño de hielo, se agregó lentamente HATU (304 mg, 0,8 mmol) y la mezcla de reacción se agitó a 0 °C durante 2h. LC-MS indicó la desaparición del diácido y la formación del producto ciclado **2472**, HPLC-MS t_R = 1,65 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{24}H_{25}N_3O_5$ 435,2, LCMS observada m/z 436,1 (M+H).

Parte G:

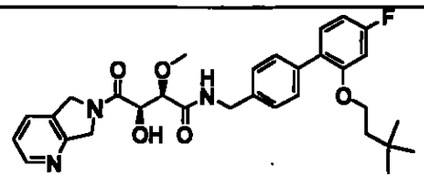
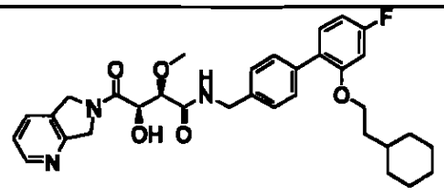
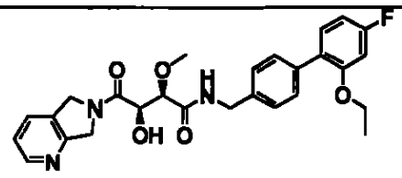
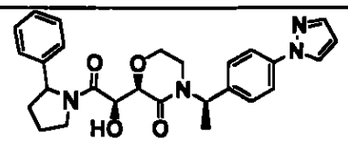
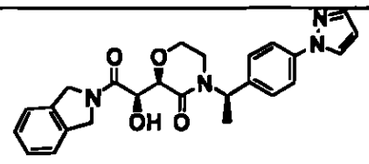
A la solución anterior a 0 °C se agregó isoindolina (48 mg, 0,4 mmol) y la mezcla de reacción se agitó a temperatura ambiente hasta el día siguiente. El DMF se evaporó, el residuo se disolvió en EtOAc y agua, se lavó con HCl 1N, NaHCO3 saturado y salmuera, se secó sobre Na2SO4 y se concentró para dar **2437** como un sólido aceitoso (85 mg, 47% de producción en tres pasos). HPLC-MS t_R = 2,00 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{32}H_{32}N_4O_4$ 536,1, LCMS observada m/z 537,1 (M+H).

Parte H:

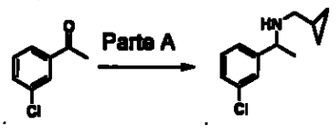
El compuesto bruto **2473** se disolvió en EtOH (20 ml), y se agregó paladio sobre carbono (10%, 40 mg). La mezcla se hidrogenó (presión atmosférica) a temperatura ambiente hasta el día siguiente. La suspensión se filtró a través de Celite y se concentró. El residuo resultante se purificó mediante LC preparativa

dando **2474** como un sólido blanco (9,4 mg). HPLC-MS t_R = 3,57 min. (método de 10 min., $UV_{254\ nm}$); masa calculada para la fórmula $C_{25}H_{26}N_4O_4$ 446,2, LCMS observada m/z 447,1 (M+H).

Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
2475		549,3	550,2
2476		575,3	576,1
2477		493,2	494,2
2478		474,2	475,1
2474		446,2	447,1

Ejemplo 57:

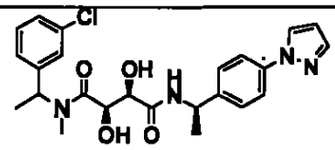
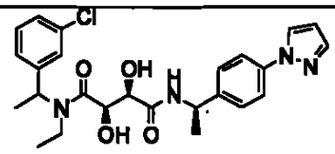
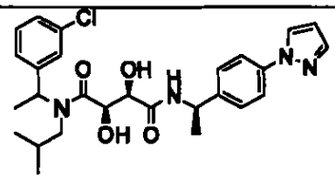
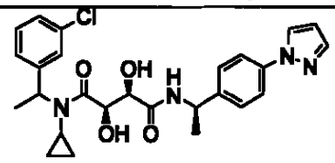
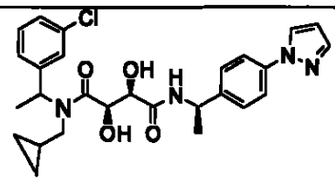


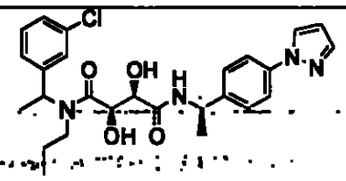
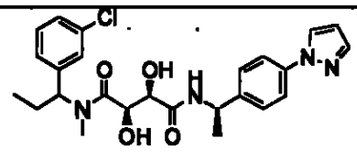
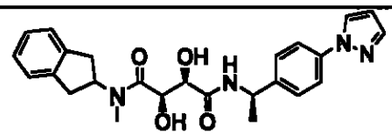
2183 2478

Parte A:

El Compuesto **2183**(200 mg, 1,3 mmol) y ciclopropilmetil amina (0,16 ml) se disolvieron en MeOH (5 ml) y se agitaron a 50 °C hasta el día siguiente. Luego se agregó borohidruro de sodio (42 mg, 1,3 mmol) y la mezcla se agitó durante 2 horas. El solvente se eliminó bajo presión reducida y el residuo se dividió entre dietil éter y HCl 1N. La capa acuosa se tornó básica y se extrajo con acetato de etilo. Las capas combinadas de acetato de etilo se secaron sobre sulfato de sodio y se concentraron para dar el producto deseado **2479** (130 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,32 (m, 1H), 7,28-7,18 (m, 3H), 3,79 (m, 1H), 2,50-2,25 (m, 2H), 1,38 (d, 3H), 1,00-0,90 (m, 1H), 0,50-0,45 (m, 2H), 0,10-0,00 (m, 2H).

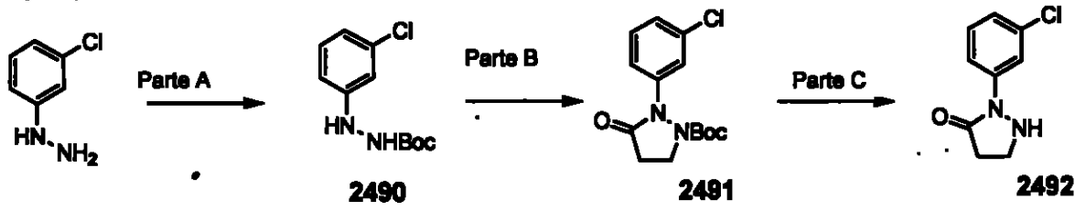
Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
2480		470,2	471,1
2481		484,2	485,0
2482		512,2	513,1
2483		496,2	497,0
2485		510,2	511,1

2486		**498,2**	**499,1**
2487		**484,2**	**485,0**
2489		**448,2**	**449,1**

Ejemplo 58:

Ejemplo 58A:



Parte A:

A una solución de Boc_2O (6,1 g, 28 mmol) y Et_3N (7,8 ml, 56 mmol) en DMF (20 ml) a 0°C se agregó en porciones clorhidrato de 3-clorofenilhidrazina (5,0 g, 28 mmol) en DMF (20 ml). La mezcla de reacción se dejó en agitación a temperatura ambiente durante 2 h y se concentró. El residuo se disolvió en EtOAc y H_2O, se lavó con cítrico ácido 1N y $NaHCO_3$ saturado, se secó sobre Na_2SO_4 y se concentró, dando **2490** (17,83 g, 97%) como un sólido blancuzco. ^1H RMN (400 MHz, $CDCl_3$) δ 7,13 (t, *J* = 8,3 Hz, 1H), 6,86-6,81 (m, 2H), 6,70-6,66 (m; 1H), 6,36 (br s, 1H), 1,48 (s, 10H).

Parte B:

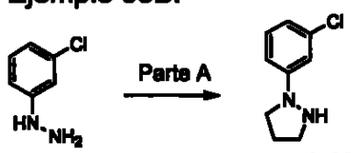
Se agregó gota a gota cloruro de 3-cloropropionilo (0,400 ml, 4,12 mmol) en una solución de compuesto **2490** (1,0 g, 4,12 mmol) y K_2CO_3 (1,14 g, 8,24 mmol) en DMF (10 ml) a 0 °C. La mezcla de reacción se dejó en agitación a 80°C hasta el día siguiente y se concentró. El residuo se disolvió en EtOAc y H_2O, se lavó con

cítrico ácido 1N y $NaHCO_3$ saturado, se secó sobre Na_2SO_4, y se concentró. La cromatografía en columna (EtOAc/hexano 25:75) dio compuesto **2491** (600 mg, 49%) como un sólido blancuzco. ^1H RMN (400 MHz, $CDCl_3$) δ 7,57 (t, *J* = 2,3 Hz, 1H), 7,51-7,48 (m, 1H), 7,27 (t, *J* = 8,3 Hz, 1H), 7,12-7,09 (m, 1H), 4,16 (t, *J* = 7,2 Hz, 2H), 2,77 (t, *J* = 7,3 Hz, 2H), 1,34 (s, 9H).

Parte C:

El Compuesto **2491** se desprotegió con TFA en CH_2Cl_2. El material se usó sin purificación adicional.

Ejemplo 58B:



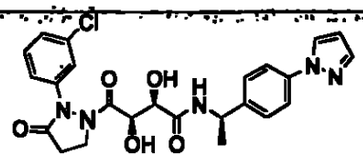
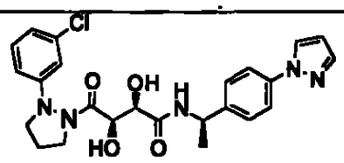
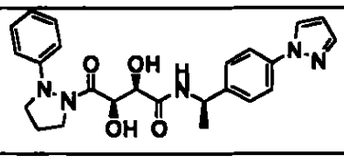
2493

Parte A:

A una suspensión de NaH (60% en aceite mineral, 1,56 g, 39 mmol) en benceno (40 ml) a 0 °C se agregó con 3-clorofenilhirazina (2,13 g, 15 mmol). La mezcla se agitó a 80 °C durante 1 h, después se agregó lentamente 1,3-dibromopropano (2,0 g, 10 mmol) mediante jeringa. Se agitó a 80 °C hasta el día siguiente y se desactivó mediante la adición de agua (20 ml). La capa orgánica se separó, se lavó con agua y salmuera, se secó sobre Na_2SO_4, y se concentró. Cromatografía en columna (DCM) dio compuesto **2493** (850 mg, 47%) como un aceite amarillo pálido. ^1H RMN (400 MHz, $CDCl_3$) δ 7,12 (t, *J* = 8,2 Hz, 1H), 7,04 (t, *J* = 2,3 Hz, 1H), 6,84-6,81 (m, 1H), 6,74-6,71 (m, 1H), 3,75 (bs, 1H), 3,35 (t, *J* = 7,5 Hz, 2H), 3,00 (t, *J* = 6,7 Hz, 2H), 2,16-2,11 (m, 2H).

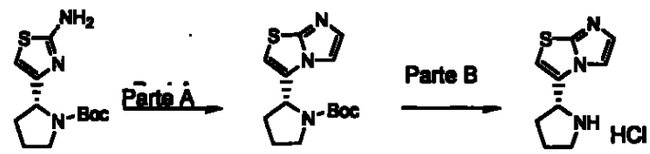
Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente.

1672 SAT

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
2494		497,2	498,1
2495		483,2	484,1
2496		449,2	450,1

Ejemplo 59:

Ejemplo 59A:



471 2500 2501

Parte A:

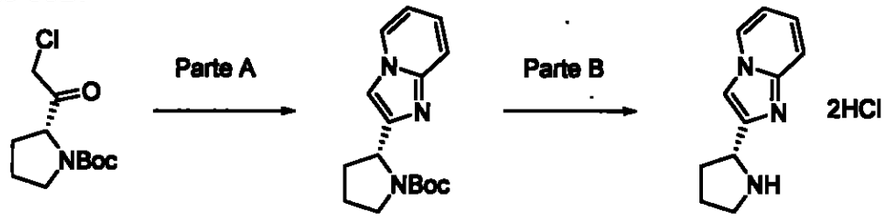
Al compuesto **471** (100 mg, 0,37 mmol) en EtOH (2 ml) se agregó cloroacetaldehído (50 % en peso en agua, 233 mg, 1,48 mmol). La mezcla de reacción se dejó en agitación a 90°C hasta el día siguiente y se concentró. El residuo se disolvió en EtOAc, se lavó con agua y salmuera, se secó (Na_2SO_4) y se concentró. El producto bruto **2500** (90 mg, 82%) se usó sin purificación adicional. HPLC-MS t_R = 1,10 min; Masa calculada para la fórmula $C_{14}H_{19}N_3O_2S$ 293,1, observado m/z 294,1(M+H).

Parte B:

El Compuesto **2500** (90 mg) se disolvió en 2 ml de HCL 4 N en dioxano/H2O (1:1). Después de agitar a temperatura ambiente durante 1 h, la solución se

concentró, dando un sólido marrón (80 mg, 90%). HPLC-MS t_R = 0,22 min; Masa calculada para la fórmula $C_9H_{11}N_3S$ 193,1, m/z observado 194,1(M+H).

Ejemplo 59B:



470 **2502** **2503**

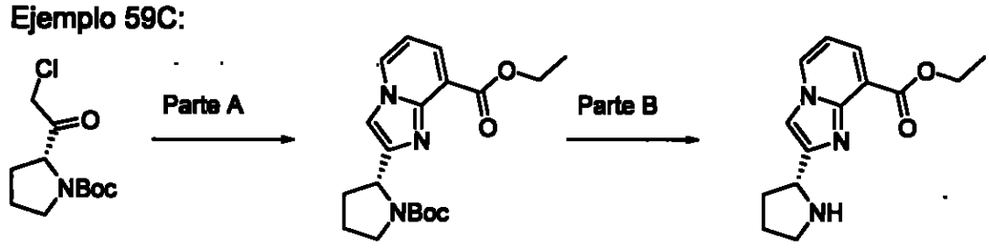
Parte A:

Una mezcla de la clorocetona **470** (200 mg, 0,81 mmol) y 2-aminopiridina (77 mg, 0,82 mmol) en etanol (5 ml) se calentó hasta reflujo y se agitó hasta el día siguiente. La mezcla de reacción se concentró y se purificó mediante HPLC prep. para dar **2502** (103 mg). HPLC-MS t_R = 1,00 min. ($UV_{254\ nm}$); masa calculada para la fórmula C16H21N3O2 287,2, LCMS observada m/z 288,3 (M+H).

Parte B:

A una solución de imidazopiridina **2502** (103 mg, 0,56 mmol) en dioxano (2 ml) se agregó HCl (4N en dioxano, 4 ml) y agua (0,5 ml). La mezcla se agitó a temperatura ambiente durante 1 hora y se concentró. El residuo resultante **2503** (81 mg) se secó en vacío y se usó en el siguiente paso sin purificación adicional. HPLC-MS t_R = 0,19 min. ($UV_{254\ nm}$); masa calculada para la fórmula C11H13N3 187,1, LCMS observada m/z 188,1 (M+H).

Ejemplo 59C:



470 **2504** **2505**

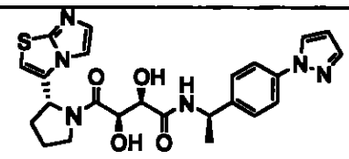
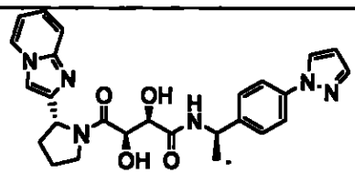
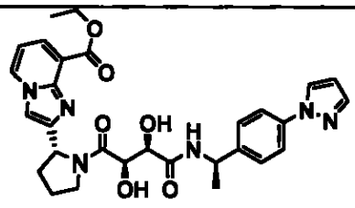
Parte A:

Una mezcla de la clorocetona **471** (200 mg, 0,81 mmol) y 2-aminopiridina (140 mg, 0,81 mmol) en etanol (5 ml) se calentó up a reflujo y se agitó hasta el día siguiente. La mezcla de reacción se concentró y se purificó mediante HPLC prep. para dar **2504** (119 mg). HPLC-MS t_R = 1,22 min. ($UV_{254\ nm}$); masa calculada para la fórmula C19H25N3O4 359,2, LCMS observada m/z 360,1 (M+H).

Parte B:

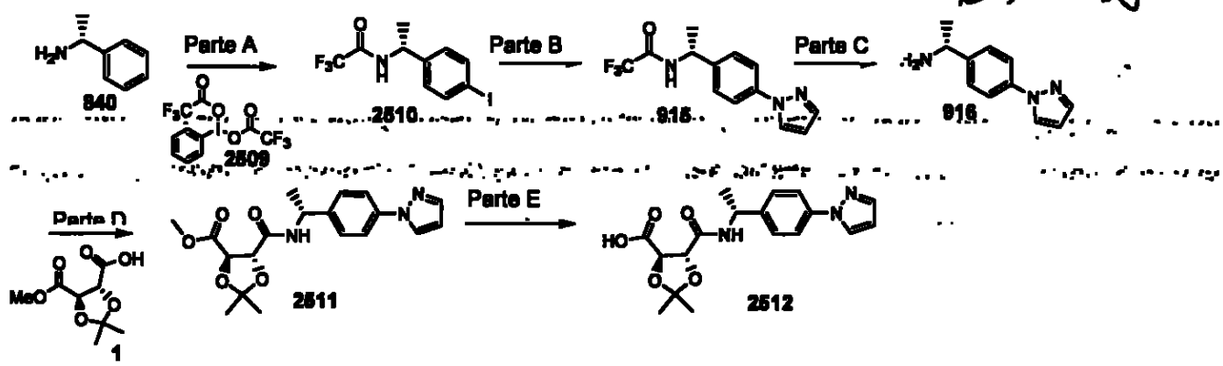
A una solución de imidazopiridina **2504** (119 mg, 0,33 mmol) en dioxano (2 ml) se agregó HCl (4N en dioxano, 4 ml) y agua (0,5 ml). La mezcla se agitó a temperatura ambiente durante 1 hora y se concentró. El residuo resultante **2505** (83 mg) se secó en vacío y se usó en el siguiente paso sin purificación adicional. HPLC-MS t_R = 0,70 min. ($UV_{254\ nm}$); masa calculada para la fórmula C14H17N3O2 259,1, LCMS observada m/z 260,1 (M+H).

Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
2506		494,2	495,1
2507		488,2	489,1
2508		560,2	561,2

Ejemplo 60:

675



Parte A:

Se disolvió anhídrido trifluoroacético (16 ml, 115,1 mmol) en cloruro de metileno (60 ml) y se enfrió en un baño de hielo. El Compuesto **840** (10,0 g, 82,6 mmol) se agregó gota a gota en cloruro de metileno (40 ml) y se agitó a temperatura ambiente durante una hora. La solución se enfrió en un baño de hielo y se agregaron yoduro (11,0 g, 43,2 mmol) y compuesto **2509** (9,8 g, 22 mmol) y se agitó durante 12 horas en la oscuridad (cubrir matraz con tapa de aluminio). Se agregó compuesto adicional **2509** (9,5 g, 20 mmol) y se continuó revolviendo durante 12 horas. La mezcla de reacción se agregó a una solución enfriada de cloruro de metileno y 5% de bisulfuro de sodio y se agitó durante una hora. La capa orgánica se lavó con bicarbonato de sodio saturado, se filtró a través de un lecho de sílice y se concentró. El residuo se suspendió en dietil éter (30 ml) y hexanos (90 ml) y se agitó durante 30 minutos. La mezcla se filtró para dar compuesto **2510** como un sólido blanco (15,5 g). El producto se almacenó en la oscuridad a temperatura ambiente. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7.70 (d, 2H), 7,06 (d, 2H), 5,10 (m, 1H), 1,60 (d, 3H).

Parte B:

Se combinaron el Compuesto **2510** (4,0 g, 11,66 mmol), pirazol (0,953 g, 14 mmol), yoduro de cobre (I) (444 mg, 2,33 mmol), carbonato de cesio (7,6 g, 23,3 mmol), 1,10-fenantrolina (844 mg, 4,66 mmol) y dimetilacetamida (40 ml) en a 80 ml de vial tapado a rosca y se agitó en la oscuridad a 120 °C durante 12 horas. La mezcla de reacción se vertió en acetato de etilo (200 ml) y se filtró. La capa

orgánica se lavó con agua en varias oportunidades seguido por solución de ácido cítrico 1N. La capa orgánica se secó sobre sulfato de sodio y se concentró. El residuo se recristalizó a partir de acetato de etilo y hexanos para dar 2,45 g del compuesto **915**, ^{1}H RMN (400 MHz, $CDCl_3$) δ7,92 (m, 1H), 7,70 (m, 2H), 7,40 (d, 1H), 6,45 (t, 1H), 5,20 (m, 1H), 1,65 (d, 3H).

Parte C:

El Compuesto **915** (2,43 g, 9,13 mmol) se disolvió en metanol (20 ml) y hidróxido de litio 1N (20 ml) y se agitó durante 6 horas. La mezcla de reacción se vertió en acetato de etilo y agua. La capa acuosa se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre sulfato de sodio, y se concentró para dar compuesto **916** (1,45 g). ^{1}H RMN (400 MHz, $CDCl_3$) δ7,90 (d, 1H), 7,70 (d, 1H), 7,64 (d, 2H), 7,43 (d, 2H), 6,46 (t, 1H), 1,44 (d, 3H).

Parte D:

El Compuesto **916** (1,45 g, 7,7 mmol), compuesto **1** (1,5 g, 7,35 mmol), HATU (3,63 g, 9,55 mmol), y diisopropiletilamina (1,28 ml, 7,35 mmol) se disolvieron en DMF (20 ml) a 0 °C. La mezcla de reacción se agitó durante 12 horas y luego se diluyó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con HCl 1N, bicarbonato de sodio saturado, salmuera y agua, se secaron sobre sulfato de sodio y se concentraron. El residuo se purificó mediante cromatografía en columna (2:1 hexanos/acetato de etilo) para dar compuesto **2511** (2,15 g). ^{1}H RMN (400 MHz, $CDCl_3$) δ7,90 (d, 1H), 7,72 (m, 1H), 7,66 (d, 2H), 7,40 (d, 2H), 6,75 (d, 1H), 6,49 (d, 1H), 5,20 (m, 1H), 4,82-4,75 (dd, 2H), 3,83 (s, 3H), 1,57 (d, 3H), 1,54 (s, 3H), 1,50 (s, 3H).

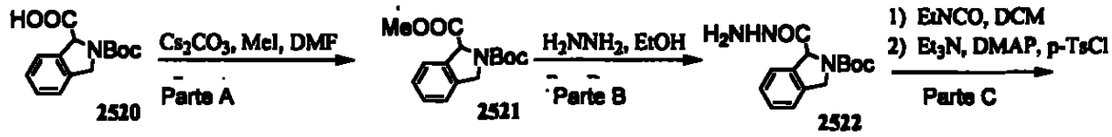
Parte E:

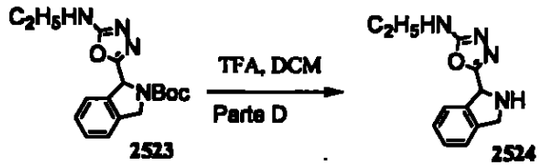
El Compuesto **2511** (2,15 g, 5,76 mmol) se disolvió en THF (20 ml) y hidróxido de litio 1N y se agitó durante 2 horas. Se agregó dietil éter y la capa acuosa se acidó

a pH 2 con HCl 1N y se extrajo con acetato de etilo. Las capas combinadas de acetato de etilo se secaron sobre sulfato de sodio y se concentraron para dar compuesto **2512** como un sólido blanco (1,95 g). 1H NMP (400MHz, $CDCl_3$) δ7,9 (d, 1H), 7,74 (m, 1H), 7,70 (d, 2H), 7,42 (d, 2H), 6,96 (d, 1H), 6,49 (t, 1H), 5,2 (m, 1H), 4,60-4,50 (dd, 2H), 1,64 (d, 3H), 1,54 (d, 3H).

Ejemplo 61:

Ejemplo 61A:





Parte A:

Se agitaron juntos ácido (R,S)-BOC-1,3-dihidro-2H-Isoindol carboxílico **2520** (3,0 g, 11,39 mmol) y carbonato de cesio (4,05 g, 12,43 mmol) en DMF (25ml) a ta durante una hora. Se agregó yodometano (1,05 ml, 16,86 mmol) y la mezcla de reacción se agitó a temperatura ambiente hasta el día siguiente. La mezcla de reacción se diluyó con acetato de etilo luego, se lavó en varias oportunidades con agua, salmuera (1 x 50 ml), se secó sobre Na_2SO_4 y se concentró para dar un aceite amarillo claro. La purificación mediante cromatografía en columna (SiO2, 25% de acetato de etilo / hexano) dio **2521** (2,66 g, 84 %) as sólido blanco.

Parte B:

Se calentó una mezcla de **2521** (0,2 g, 0,72 mmol) e hidracina (0,22 ml, 7,0 mmol) en etanol (20 ml) a 70 °C durante 5 horas. El solvente se eliminó bajo presión reducida y el residuo resultante se disolvió en acetato de etilo, se lavó con agua (2 x 30ml), salmuera (1 x 20 ml), se secó sobre Na_2SO_4 y se concentró para dar

2522 (0,18 g, 86%) como un aceite amarillo, que se usó en el paso siguiente sin purificación adicional.

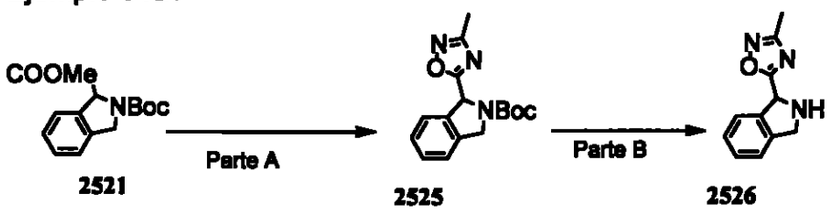
Parte C:

Se agitó a t.a. una mezcla de **2522** (0,2 g, 0,72 mmol) y etil isocianato (0,077 g, 1,083 mmol) en DCM (5 ml) durante 16 horas. Se agregó etil isocianato adicional (0,077 g, 1,083 mmol) y la reacción se agitó durante otras dos horas. El solvente se eliminó bajo presión reducida para dar el producto bruto como una goma blanca. Se disolvió en DCM (20 ml) y se trató trietil amina (0,5 ml, 3,6 mmol) , DMAP (0,017 g, 0,139 mmol) y cloruro de *p*-toluen sulfonilo (0,16 g, 0,83 mmol). La mezcla se agitó a temperatura ambiente durante 64 horas y el solvente se eliminó. El residuo se purificó mediante cromatografía preparativa usando MeOH/CH_2Cl_2 5%, para dar el producto que se purificó nuevamente usando acetato de etilo/hexano (3/1) para dar intermediario **2523** (0,1 g, 44%) como un sólido marrón claro.

Parte D:

Se disolvió Intermediario **2523** (0,05 g, 0,15 mmol) en DCM (10 ml) luego se agregó ácido trifluoro acético (0,06 ml, 0,77 mmol). La reacción se agitó a temperatura ambiente durante 3 horas y luego se concentró. El residuo se disolvió en DCM y se lavó con solución de bicarbonato de sodio saturado (1 x 0,8 ml), salina (1 x 0,8 ml), se secó sobre sulfato de sodio y se concentró en vacío para dar amina **2524** (0,03 g, 86%) como un aceite marrón. Se usó en el siguiente paso sin purificación adicional.

Ejemplo 61B:



2521 2525 2526

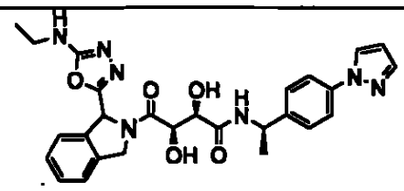
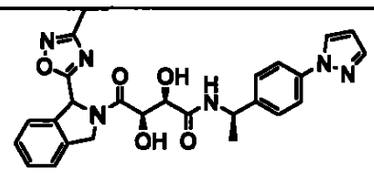
Parte A:

Se preparó Intermediario **2525** mediante métodos conocidos (Showell , G.A.; Gibbons, T.L.; Kneen, C.O.; Macleod, A.M.; Merchant, K.; Saunders, J.; Freedman, S.B.; Patel, S; Baker, R.. *J.Med.Chem.* **1991**, *34*:(3), 1086-1094):

Parte B:

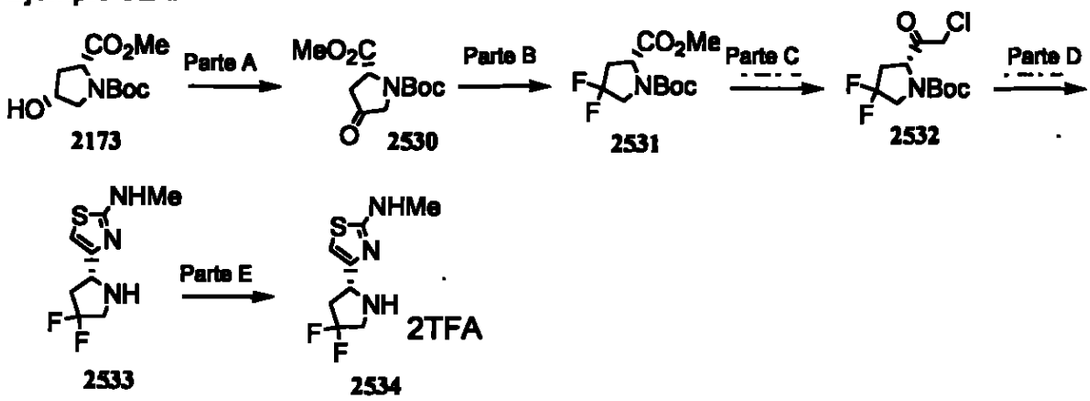
Se preparó Intermediario **2526** usando el método descripto en el Ejemplo 61A Parte D.

Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente.

Compuesto #	SCH	Estructura	Masa exacta	MS m/z (M+H)
2527	786656		531,2	532,2
2528	7867566		502,2	503,2

Ejemplo 62:

Ejemplo 62A:



Parte A:

Se agitó Una mezcla de **2173** (1,54 g, 6,28 mmol) y periodinano Dess-Martin (2,72 g, 6,41 mmol) en DCM (30 ml) a temperatura ambiente hasta el día siguiente. A la mezcla de reacción se agregó solución de bicarbonato de sodio saturado y la mezcla se agitó durante 2 horas. Los sólidos se eliminaron mediante filtración. El filtrado se separó y la capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 30% de acetato de etilo / hexano) dio **2530** (939 mg, 61%) como un aceite. HPLC-MS t_R = 1,10 min. (MS); Masa calculada para la fórmula C11H17NO5 243,1, m/z observado 266,1 (M+Na).

Parte B:

A cetona **2530** (939 mg, 3,86 mmol) en DCM (30 ml) a -78 oC bajo argón se agregó trifloruro de (dietilamino)azufre (2,53 ml, 19,3 mmol). El baño se calentó lentamente hasta temperatura ambiente mientras la mezcla se agitó hasta el día siguiente. La mezcla de reacción se vertió en bicarbonato de sodio saturado y las capas se separaron. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio y se concentró. La purificación mediante cromatografía en columna (SiO_2, 10% a 30% de acetato de etilo / hexano) dio **2531** (751 mg, 74%) como un aceite. HPLC-MS t_R = 4,72 min. (10 min, MS); Masa calculada para la fórmula C11H17F2NO4 265,1, m/z observado 288,1 (M+Na).

Parte C:

El Compuesto **2531** (751 mg, 2,83 mmol) se transformó en **2532** (418 mg, 52 %) usando los procedimientos descriptos en el Ejemplo 10 Parte A. HPLC-MS t_R = 1,85 min. (MS); Masa calculada para la fórmula C11H16ClF2NO3 283,1, m/z observado 228,1 (M-55).

Parte D:

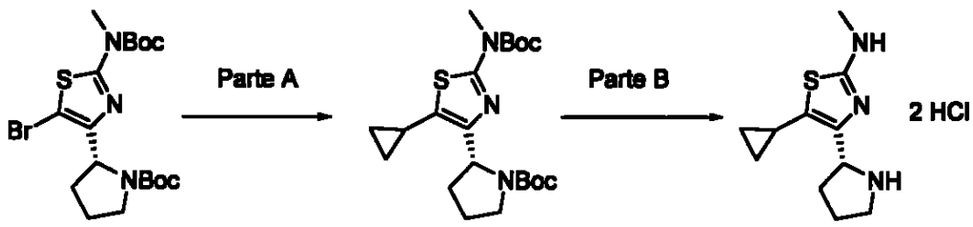
El Compuesto **2532** (418 mg, 1,47 mmol) se cicló con N-metiltiourea de acuerdo con los procedimientos descriptos en el Ejemplo 51B Parte C para dar **2533** (200

mg, 42%). HPLC-MS t_R = 1,38 min. (UV $_{254\ nm}$); Masa calculada para la fórmula C8H11E2N3S 319,1, m/z observado 320,1 (M+H).

Parte E:

El Compuesto **2534** se sintetizó en rendimiento cuantitativo usando el procedimiento descripto en el Ejemplo 51D Parte H. ^{1}H RMN (400 MHz, $CDCl_3$) δ 6,89 (s, 1H), 4,98 (dd, 1H, J = 7,2, 11,7 Hz), 3,89 (m, 1H), 3,72 (m, 1H), 3,13 (s, 3H), 3,09-2,85 (m, 2H).

Ejemplo 62B:



2209A **2535** **2536**

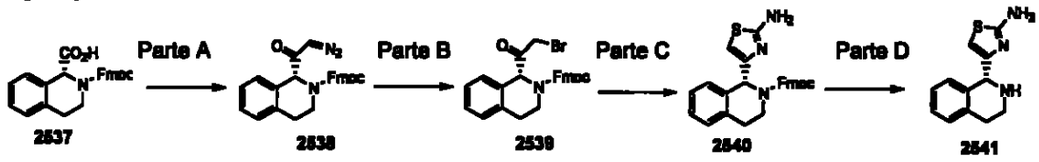
Parte A:

La mezcla de 5-bromotiazol **2209A** (210 mg, 0,45 mmol), ácido ciclopropil borónico (80 mg, 1,0 mmol), $Pd(dppf)Cl_2$ (41 mg, 0,05 mmol) y K_3PO_4 (424 mg, 2,0 mmol) en 20-ml vial se saturó con argón durante 3 min. Bajo argón, se agregó dioxano (5 ml) y el vial se selló bajo la atmósfera de argón. La mezcla se calentó hasta 80 °C y se agitó hasta el día siguiente. Después de enfriar hasta temperatura ambiente, se agregó acetato de etilo (30 ml) a la mezcla de reacción y la solución se filtró a través de Celite. El filtrado se concentró y se purificó mediante cromatografía en columna (SiO_2, 10% de acetato de etilo/hexanos) para dar 5-ciclopropiltiazol **2535** (166 mg) as oil. HPLC-MS t_R = 2,65 min. (UV$_{254\ nm}$); masa calculada para la fórmula C21H33N3O4S 423,2, LCMS observada m/z 424,1 (M+H).

Parte B:

A la solución de 5-ciclopropiltiazol **2535** (166 mg, 0,39 mmol) en dioxano (2 ml), se agregó HCl (4N en dioxano, 4 ml) seguido por la adición de agua (0,5 ml). La mezcla se agitó a temperatura ambiente durante 1 hora y se concentró. El residuo resultante **2536** (111 mg) se secó en vacío y se usó en el siguiente paso sin purificación adicional. HPLC-MS t_R = 0,86 min. ($UV_{254\ nm}$); masa calculada para la fórmula C11H17N3S 223,1, LCMS observada m/z 224,1 (M+H).

Ejemplo 62C:



Parte A:

Se agregó un Fmoc-D-Tiq-OH (**2537**) (1,0 g, 2,5 mmol) en diclorometano (20 ml) a 0°C $(COCl)_2$ (0,262 ml, 3,0 mmol) y DMF (2 gotas, catalítico) bajo argón. La mezcla de reacción se agitó a 0 °C durante 2 hr y se concentró hasta que se secó en *vacuo*. La jalea resultante se disolvió en THF seco (20 ml) y se enfrió hasta 0 °C. Se agregó gota a gota trimetilsilildiazometano (2,0 M en Et2O, 5 ml, 10 mmol) bajo argón durante un período de 30 min. Una vez completada la adición, la solución se agitó a 0 °C durante 3 hr y se concentró bajo presión reducida. Cromatografía flash en columna sobre sílice (EtOAc/hexano 25:75) dio **2538** (630 mg, 60%) como un aceite amarillo sólido. HPLC-MS t_R = 2,23 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{28}H_{21}N_3O_3$ 423,2, LCMS observada m/z 446,2 (M+Na).

Parte B:

El Compuesto **2538** (630 mg, 1,49 mmol) en Et_2O (20 ml) se enfrió hasta 0 °C. A esta solución se agregó ácido hidrobromuro 2,15 M en Et_2O (830 □L, 1,79 mmol) gota a gota. La mezcla de reacción se agitó durante 20 min. a 0 °C y se concentró. El residuo se disolvió en EtOAc, la solución se lavó entonces con solución de bicarbonato saturado, salmuera, se secó (Na_2SO_4) y se concentró en

vacuo para dar **2539** (630 mg, 89%) como un sólido blancuzco. HPLC-MS t_R = 2,40 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{28}H_{22}BrNO_3$ 475,1, LCMS observada m/z 476,0 (M+H).

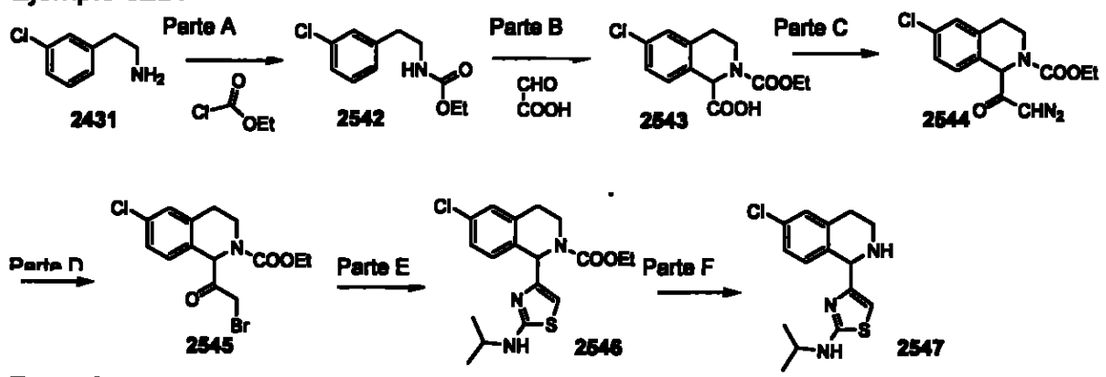
Parte C:

El Compuesto **2539** (150 mg, 0,31 mmol) y tiourea (36 mg, 0,47 mmol) en DMF (2 ml) se dejaron en agitación a temperatura ambiente durante 3 hr. La solución se concentró y el residuo se disolvió con EtOAc y solución de $NaHCO_3$ saturado. La fase orgánica se lavó con H_2O, salmuera, se secó sobre Na_2SO_4, y se concentró. Cromatografía flash en columna sobre sílice (EtOAc / hexano 60:40) dio **2540** (120 mg, 84%) como un sólido blanco. HPLC-MS t_R = 1,96 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{27}H_{23}N_3O_2S$ 453,2, LCMS observada m/z 454,1 (M+H).

Parte D:

El Compuesto **2540** (150 mg, 0,26 mmol) se trató con 20% de Piperidina en DMF (10 ml). La solución se agitó a temperatura ambiente durante 2 hr y se concentró. LC-MS indicó la desprotección del grupo Fmoc. HPLC-MS t_R = 0,72 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{12}H_{13}N_3S$ 231,1, LCMS observada m/z 232,1 (M+H).

Ejemplo 62D:



Parte A:

De acuerdo con una modificación de un procedimiento de Ortwine, D. F. et al. (*J. Med. Chem.* **1992**, 35, 1345-1370) a una solución helada del 3-clorofenetilamina

2431 (10 g, 64,6 mmol) y trietilamina (6,46 ml, 67,8 mmol) en DCM (200 ml) se agregó gota a gota cloroformiato de etilo (9,45 ml, 67,8 mmol), y la solución resultante se agitó a 0 °C durante 1 h, y luego a ta durante 1,5 h. La mezcla de reacción se lavó con solución de bicarbonato de sodio saturado, salmuera, se secó y se concentró para dar carbamato de etilo **2542** como un aceite incoloro (14,36 g, 98%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,24-7,19 (m, 3H), 7,09-7,07 (d, 1H), 4,66 (s, amplio, NH), 4,12 (q, 2H), 3,44 (q, 2H), 2,81 (t, 2H), 1,25 (t, 3H).

Parte B:

De acuerdo con una modificación de un procedimiento de Ortwine, D. F. et al. (*J. Med. Chem.* **1992**, 35, 1345-1370) a una mezcla helada del carbamato **2542** (6,81 g, 29,9 mmol) y se agregó ácido acético glacial 3:1: ácido sulfúrico (64 ml) (en dos porciones) monohidrato de ácido glicoxílico (3,03 g, 32,9 mmol) y la mezcla se agitó a ta hasta el día siguiente. La mezcla de reacción se vertió en hielo, y se extrajo con diclorometano (5 veces). Los extractos combinados de diclorometano se secaron y se concentraron para un residuo aceitoso que luego se tomó en tolueno y se concentró (3 times) y se secó en vacío hasta el día siguiente para dar el compuesto **2543** (7,91 g, 93%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 12,9 (s, amplio, COOH), 7,50-7,12 (m, 3H), 5,42 (s, 1H), 4,12-4,03 (m, 2H), 3,77-3,50 (m, 2H), 2,89-2,79 (m, 2H), 1,24-1,16 (m, 3H). HPLC-MS t_R = 1,68 min. ($UV_{254\ nm}$); masa calculada para la fórmula C13H14ClNO4 283,1, LCMS observada m/z 284,0 (M+H).

Parte C:

Se preparó diazocetona **2544** usando procedimientos descriptos en el Ejemplo 62C Parte A. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,23-7,18 (m, 3H), 5,60-5,41 (m, 2H), 4,26-4,22 (m, 2H), 3,90-3,65 (m, 2H), 2,97-2,82 (m, 2H), 1,36-1,32 (m, 3H). HPLC-MS t_R = 1,8 min. ($UV_{254\ nm}$); masa calculada para la fórmula C14H14ClN3O3 307,1, LCMS observada m/z 280,1 (M-N2+H), y 330,1 (M+Na).

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Parte D:

Se preparó bromocetona **2545** usando procedimientos descriptos en el Ejemplo 62C Parte B. ^{1}H RMN (400 MHz, CDCl3) δ 7,31-7,20 (m, 3H); 5,87-5,81 (m, 1H), 4,25-4,04 (m, 4H), 3,90-3,82 (m, 1H), 3,60-3,51 (m, 1H), 2,98-2,79 (m, 2H), 1,34-1,31 (m, 3H). HPLC-MS t_R = 2,07 min. ($UV_{254\ nm}$); masa calculada para la fórmula C14H15BrClNO3 359,0, LCMS observada m/z 360,0 (M+H).

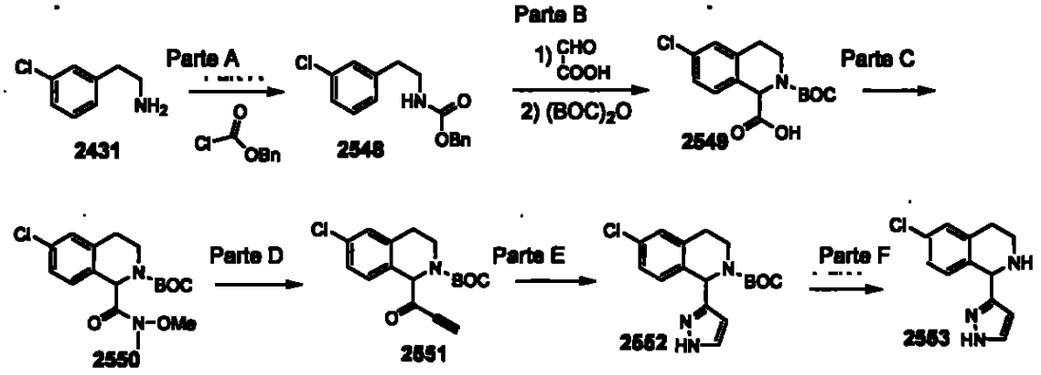
Parte E:

Se preparó el tiazol **2546** usando procedimientos descriptos en el Ejemplo 10, HPLC-MS t_R = 2,05 min. ($UV_{254\ nm}$); masa calculada para la fórmula C18H22ClN3O2S 379,1, LCMS observada m/z 380,1 (M+H).

Parte F:

A una solución de tiazol **2546** (117 mg, 0,31 mmol) en cloroformo (1,5 ml) se agregó yodotrimetilsilano (0,32 ml, 2,24 mmol) y la mezcla resultante se calentó a 50 °C durante 2 h. La mezcla de reacción se diluyó con diclorometano, se lavó con bicarbonato de sodio saturado, salmuera y se concentró para dar amina **2547** como un sólido amarillo oscuro (93 mg, 97%). ^{1}H RMN (400 MHz, CDCl3) δ 7,12-6,97 (m, 3H), 6,01(s, 1H), 5,26 (s, amplio, 1H), 5,15 (s, 1H), 3,60-3,53 (m, 1H), 3,18-2,80 (m, 4H), 1,28-1,26 (d de d, 6H). HPLC-MS t_R = 1,24 min. ($UV_{254\ nm}$); masa calculada para la fórmula C15H18ClN3S 307,1, LCMS observada m/z 308,2 (M+H).

Ejemplo 62E:



1686 645

Parte A:

De acuerdo con una modificación de un procedimiento de Ortwine, D. F. et al. (*J. Med. Chem.* **1992**, *35*, 1345-1370) a una solución helada del 3-clorophenetilamina **2431** (11,6 g, 75 mmol) y trietilamina (10,9 ml, 78,7 mmol) en DCM (300 ml) se agregó gota a gota cloroformoato de bencilo (11,1 ml, 78,1 mmol), y la solución resultante se agitó a 0 °C durante 30 min, y luego a ta hasta el día siguiente. La mezcla de reacción se lavó con solución de bicarbonato de sodio saturado, salmuera, se secó y se concentró para dar carbamato de bencilo **2548** como un aceite incoloro (21,4 g, 99%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,38-7,30 (m, 5H), 7,23-7,05 (m, 4H), 5,1 (s, 2H), 4,75 (s, amplio, NH), 3,46 (q, 2H), 2,82 (t, 2H).

Parte B:

De acuerdo con una modificación de un procedimiento de Ortwine, D. F. et al. (*J. Med. Chem.* **1992**, *35*, 1345-1370) a una mezcla helada de carbamato de bencilo **2548** (8,6 g, 31,4 mmol) y se agregó ácido acético glacial: ácido sulfúrico 3:1 (64 ml) (en dos porciones) monohidrato del ácido glicoxílico (3,0 g, 32,6 mmol) y la mezcla se agitó a ta hasta el día siguiente. La mezcla de reacción se vertió en ice, y se lavó con diclorometano (4 times). La fase acuosa se concentró, se diluyó con tetrahidrofurano (200 ml), y se trató con solución NaOH 6M (130 ml) a pH 12-13, seguido por dicarbonato de di-ter-butilo (7,94 g, 36,4 mmol), y luego se agitó a ta hasta el día siguiente. La mezcla de reacción se concentró, se diluyó con agua, se acidó con solución de HCl 2 M a pH 2, y se extrajo con acetato de etilo. Los extractos orgánicos combinados se concentraron y se sometieron a cromatografía (SiO_2, 5% metanol/diclorometano) para dar el compuesto **2549** (0,95 g, 15% basado en material de partida reaccionado). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,54-7,27 (m, 3H), 5,67-5,50 (d, 1H), 3,87-3,79 (m, 2H), 3,01-2,88 (m, 2H), 1,61-1,57 (9H).

Parte C:

1687

Se preparó amida de Weinreb **2550** usando procedimientos descriptos en el Ejemplo 51I. Parte A. ^{1}H RMN (400 MHz, CDCl3) δ 7,37-7,14 (m, 3H), 6,1-5,88 (d, 1H), 4,0 (s, 3H), 3,84-3,67 (m, 2H), 3,21 (s, 3H), 3,17-3,09 (m, 1H), 2,79-2,72 (m, 1H), 1,5 (s, 9H). HPLC-MS t_R = 2,15 min. ($UV_{254\ nm}$); masa calculada para la fórmula C17H23ClN2O4 354,1, LCMS observada m/z 255,1 (M-BOC+H).

Parte D:

Se preparó acetileno **2551** usando procedimientos descriptos en el Ejemplo 51I. Parte B. HPLC-MS t_R = 2,22 min. ($UV_{254\ nm}$); masa calculada para la fórmula C17H18ClNO3 319,1, LCMS observada m/z 264,0 (M-(t-butilo)).

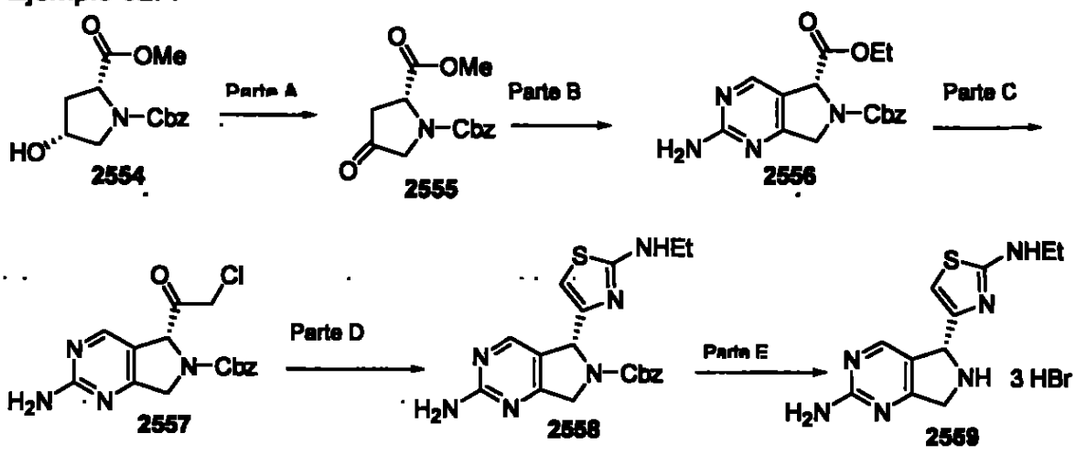
Parte E:

Se preparó pirazol **2552** usando procedimientos descriptos en el Ejemplo 62G Parte A. HPLC-MS t_R = 1,97 min. ($UV_{254\ nm}$); masa calculada para la fórmula C17H20ClN3O2 333,1, LCMS observada m/z 234 (M-BOC+H).

Parte F:

Se preparó amina **2553** usando un procedimiento similar a aquel descripto en el Ejemplo 51I, Parte D. HPLC-MS t_R = 0,89 min. ($UV_{254\ nm}$); masa calculada para la fórmula C12H12ClN3 233,1, LCMS observada m/z 234,1 (M+H).

Ejemplo 62F:



Parte A:

El Compuesto **2554** (3,7 g, 13,4 mmol) se disolvió en cloruro de metileno (35 ml) y se agregó periodinano Dess-Martin (8,55 g, 20,18 mmol) y se agitó a temperatura ambiente hasta el día siguiente. La reacción se desactivó con bicarbonato de sodio saturado y se agitó durante 1 hora. La mezcla de reacción se filtró a través de Celite. La capa acuosa se extrajo con cloruro de metileno. Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 50% de acetato de etilo/hexanos) dio **2555** (1,75 g). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,40-7,30 (m, 5 H), 5,25-5,20 (m, 2H), 4,90-4,80 (m, 1H), 4,00-3,80 (m, 2H), 3,80-3,60 (m, 3H), 3,00 (m, 1H), 2,60 (m, 1H).

Parte B:

El Compuesto **2556** se preparó de acuerdo con el procedimiento en *Bioorg. Med. Chem.* **2002**, *10, 5*, 1197-1206, ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,25 (s, 1H), 7,4-7,3 (m, 5 H), 5,3-5,15 (m, 3H), 4,7-4,55 (m, 2H), 4,3-4,2 (m, 2H), 1,3 (t, 3H).

Parte C:

El Compuesto **2557** se preparó a partir de compuesto **2556** de acuerdo con el procedimiento descripto en el Ejemplo 10B Parte B. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,00 (m, 1H), 7,60-7,40 (m, 5H), 5,30-5,20 (m, 2H), 5,10 (m, 2H), 4,80-4,60 (m, 1H).

Parte D:

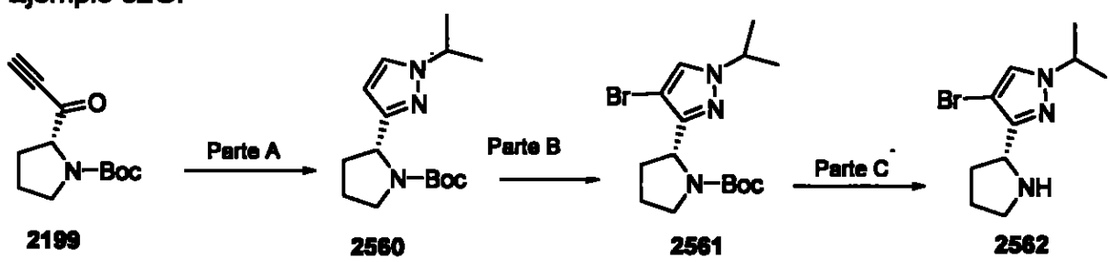
El Compuesto **2558** se preparó según se describe en el Ejemplo 51B Parte C del compuesto **2557**, ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,00 (s, 1H), 7,40-7,20 (m, 5H), 6,20 (s, 1H), 5,30-5,00 (m, 3H), 4,70 (m, 2H), 3,25 (m, 2H), 1,30 (m, 3H).

Parte E:

El Compuesto **2558** (80 mg, 0,202 mmol) se disolvió en 30% de HBr en ácido acético (3 ml) y se agitó durante 2 horas. El solvente se eliminó y el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se liofilizó para

dar **2559** como un sólido rojo (100 mg). HPLC-MS t_R = 0,414 min. ($UV_{254\ nm}$); masa calculada para la fórmula C11H14N6S 262,1, LCMS observada m/z 263,1 (M+H).

Ejemplo 62G:



2199 **2560** **2561** **2562**

Parte A:

Se disolvieron el Compuesto **2199** (1,11 g, 3,7 mmol), clorhidrato de isopropil hidracina (616 mg, 5,55 mmol), y carbonato de sodio (980 mg, 9,25 mmol) en etanol (12 ml) y se agitó a 80 °C durante 5 horas. La mezcla de reacción se enfrió hasta temperatura ambiente y se diluyó con acetato de etilo y agua. La capa acuosa se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua, salmuera, se secaron sobre sulfato de sodio y se concentraron. La purificación mediante cromatografía en columna (SiO_2, 33% de acetato de etilo/hexanos) dio **2560** (750 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,35 (d, 1 H), 6,00 (d, 1H), 5,10-4,90 (m, 1H), 4,50 (m, 1H), 3,60-3,40 (m, 2H), 2,30-2,10 (m, 1H), 2,10-1,80 (m, 3H), 1,50 (m, 9H), 1,30 (s, 6H).

Parte B:

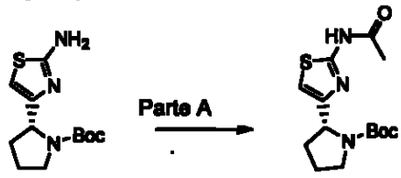
El Compuesto **2560** (541 mg, 1,93 mmol) se disolvió en cloroformo (10 ml) y se agregó N-bromosuccinimida (412 mg, 2,31 mmol) y se agitó a temperatura ambiente hasta el día siguiente. La reacción se diluyó con cloruro de metileno y agua. La capa orgánica se lavó con NaOH 1 N, salmuera, se secó sobre sulfato de sodio, y se concentró. La purificación mediante cromatografía en columna (SiO_2, 15% de acetato de etilo/hexanos) dio **2561** (350 mg). ^{1}H RMN (400 MHz,

$CDCl_3$) δ 7,35 (s, 1 H), 5,00-4,80 (m, 1H), 4,40 (m, 1H), 3,60-3,40 (m, 2H), 2,30-2,20 (m, 1H), 2,10-2,00 (m, 1H), 2,00-1,80 (m, 2H), 1,40 (m, 9H), 1,20 (s, 6H).

Parte C:

El Compuesto **2561** (86 mg, 0,238 mmol) se disolvió en HCl 4M en dioxano (2,0 ml) y se agitó durante 1 hora. El solvente se eliminó para dar **2562** como un sólido blanco (82 mg). ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,60 (bs, 1H), 8,80 (bs, 1H), 8,18 (s, 1 H), 4,60 (m, 1H), 4,50 (m, 1H), 3,25 (m, 2H), 2,35 (m, 1H), 2,10-1,90 (m, 3H), 1,40 (d, 6H).

Ejemplo 62H:

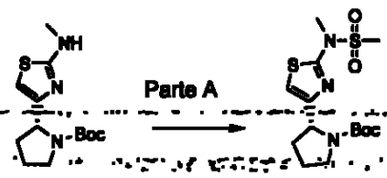


471 **2563**

Parte A:

A **471** (81 mg, 0,30 mmol) y DIEA (0,156 ml, 0,90 mmol) en diclorometano (5 ml) se agregó lentamente cloruro de acetilo (0,052 ml, 0,72 mmol) a 0 °C. La mezcla de reacción se dejó en agitación a temperatura ambiente durante 2 hr y se concentró. El residuo se disolvió luego en EtOAc y H_2O, se lavó con ácido cítrico 1N, $NaHCO_3$, salmuera, se secó sobre Na_2SO_4, y se concentró. El sólido pegajoso resultante se disolvió en metanol (5 ml) y se agitó con K_2CO_3 sólido (100 mg) durante 2 hr. Después de remover el solvente, el residuo se disolvió en EtOAc y H_2O, se lavó con H_2O, salmuera, se secó (Na_2SO_4) y se concentró para dar **2563** (82 mg, 87 %) como un sólido aceitoso. HPLC-MS t_R = 1,60 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{14}H_{21}N_3O_4S$ 311,1, LCMS observada m/z 312,1 (M+H).

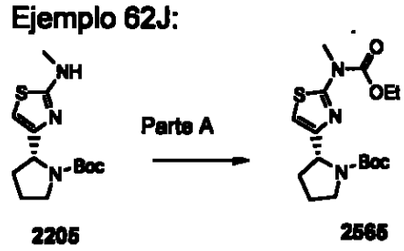
Ejemplo 62I:



Parte A:

Al compuesto **2205** (100 mg, 0,35 mmol) y DIEA (0,092 ml, 0,53 mmol) en diclorometano (5 ml) se agregó lentamente cloruro metilsulfónico (0,033 ml, 0,42 mmol) a 0 °C. La mezcla de reacción se dejó en agitación a temperatura ambiente durante 2 hr y se concentró. El residuo se disolvió en EtOAc, se lavó con agua, ácido cítrico 1N, $NaHCO_3$, y salmuera, se secó sobre Na_2SO_4 y se concentró para dar **2564** (120 mg, 94%) como un sólido aceitoso. HPLC-MS t_R = 1,96 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{14}H_{23}N_3O_4S_2$ 361,1, LCMS observada m/z 362,0 (M+H).

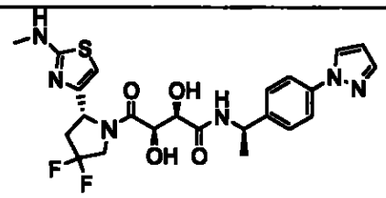
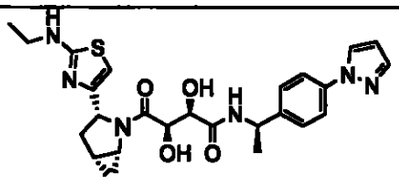
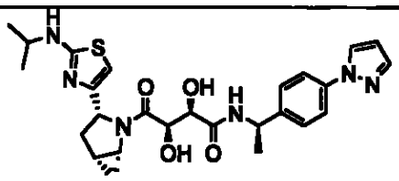
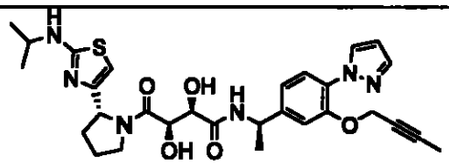
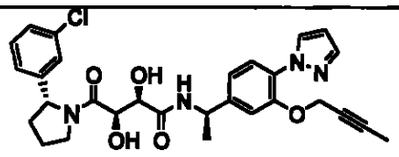
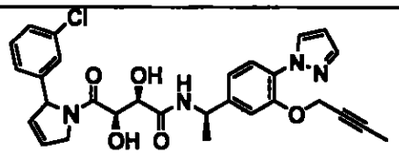
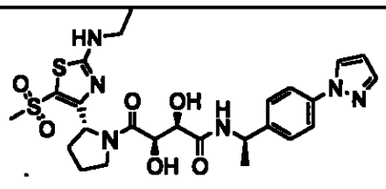
Ejemplo 62J:

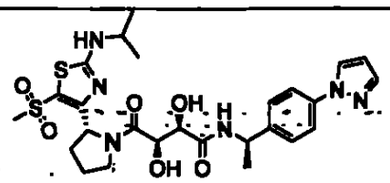
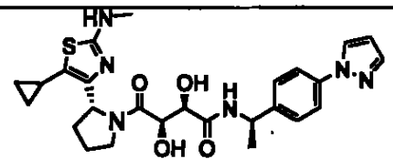
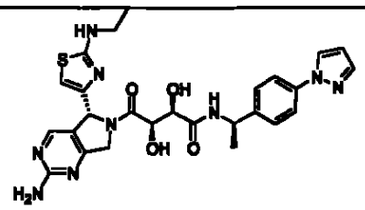
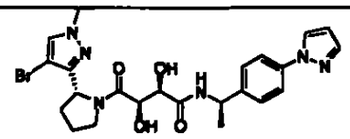
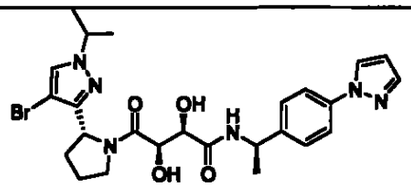
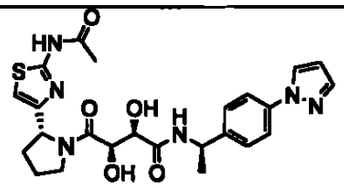
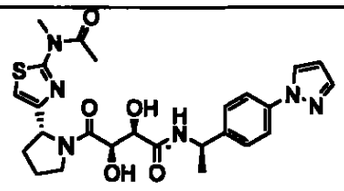
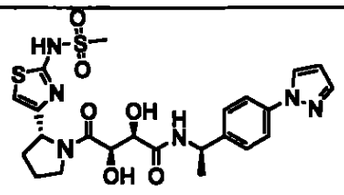


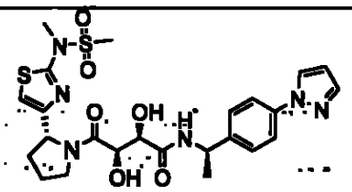
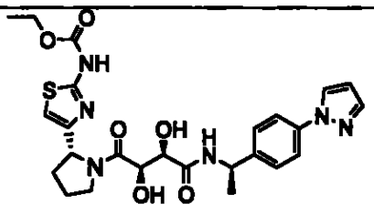
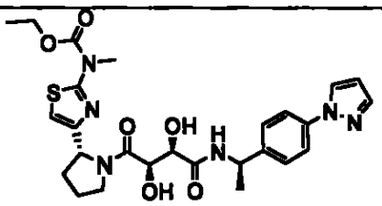
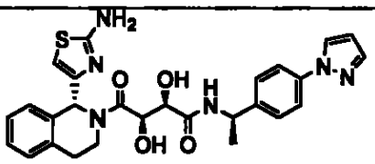
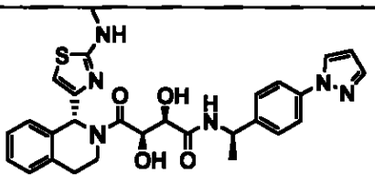
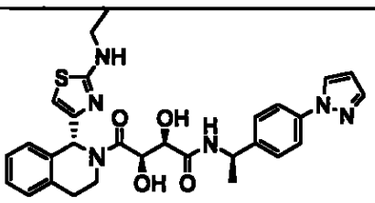
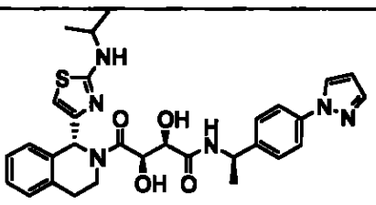
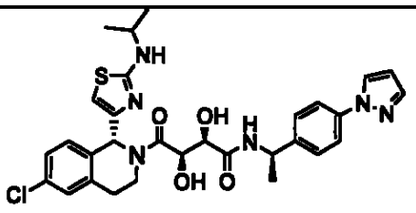
Parte A:

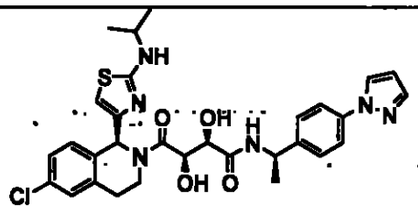
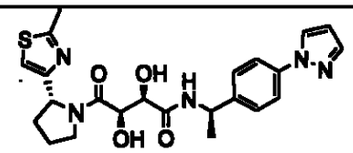
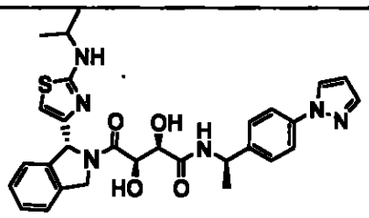
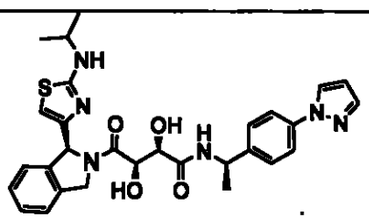
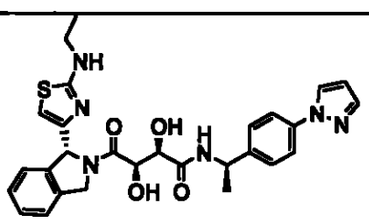
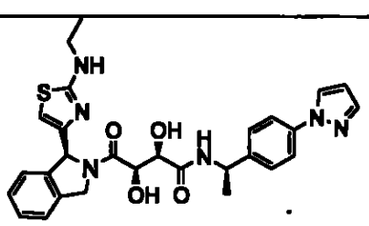
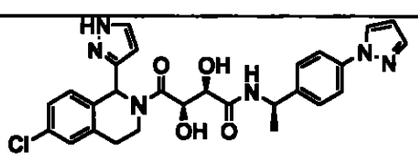
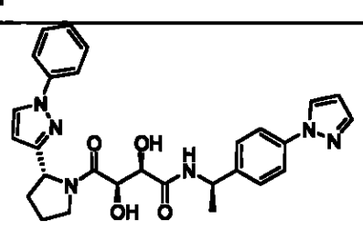
AL compuesto **2205** (80 mg, 0,28 mmol) y DIEA (0,098 ml, 0,56 mmol) en diclorometano (5 ml) se agregó lentamente cloroformiato de etilo (0,054 ml, 0,56 mmol) a 0°C. La mezcla de reacción se dejó en agitación a temperatura ambiente durante 2 hr y se concentró. El residuo se disolvió en EtOAc, se lavó con agua, 1N ácido cítrico, $NaHCO_3$ y salmuera, se secó sobre Na_2SO_4 y se concentró para dar **2565**(88 mg, 88%) como un sólido aceitoso. HPLC-MS t_R = 2,23 min. ($UV_{254\ nm}$); masa calculada para la fórmula $C_{11}H_{25}N_3O_4S$ 355,2, LCMS observada m/z 356,2 (M+H).

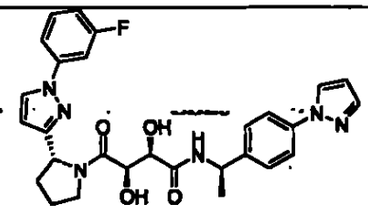
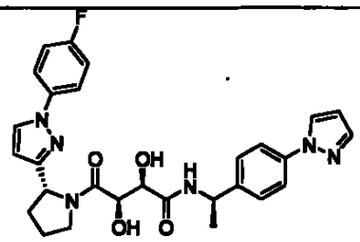
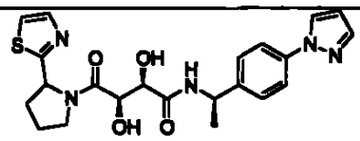
Los siguientes compuestos se prepararon usando los procedimientos descriptos anteriormente.

Compuesto #	Estructura	Masa exacta	MS m/z (M+H)
2567		520,17	521,0
2568		510,2	511,1
2569		524,2	525,3
2570		580,2	581,2
2571		550,2	551,0
2572		548,2	549,2
2573		576,2	577,3

2574		590,2	591,3
2575		524,2	525,2
2576		563,2	564,2
2577		530,1	531,1
2578		558,2	559,2
2579		512,2	513,2
2580		526,2	527,2
2581		548,2	549,2

2582		562,2	563,2
2583		542,2	543,2
2584		556,2	557,2
2585		532,2	533,2
2586		546,2	547,2
2587		560,2	561,1
2588		574,2	575,2
2589		608,2	609,2

2590		608,2	609,2
2591		469,2	470,2
2592		560,2	561,1
2593		560,2	561,1
2594		546,2	547,2
2595		546,2	547,2
2596		534,2	535,2
2597		514,2	515,2

2598		532,2	533,2
2599		532,2	533,2
2600		455,2	456,2

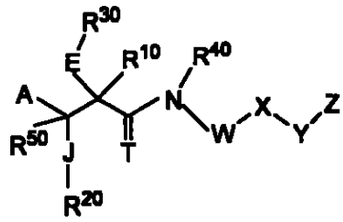
Aquellas personas con experiencia en la técnica apreciarán que se pueden llevar a cabo cambios en las realizaciones descriptas anteriormente sin apartarse del concepto inventivo amplio de las mismas. Se entiende, por lo tanto, que la presente invención no está limitada a las realizaciones en particular que se revelan, sino que se pretende abarcar las modificaciones que se encuentren dentro del espíritu y alcance de la invención, según se define en las reivindicaciones que se adjuntan.

1697 606

Reivindicaciones

Habiendo así especialmente descripto y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo:

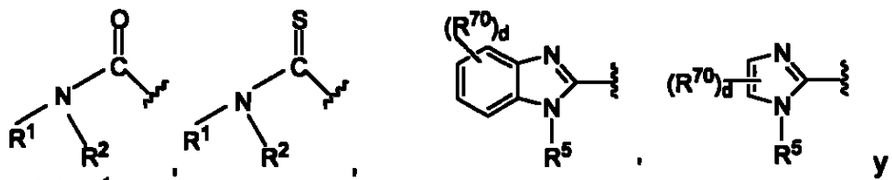
1. Un compuesto de fórmula (I):



fórmula (I)

o una sal o solvato farmacéuticamente aceptable del mismo, donde:

A se selecciona del grupo que consiste en:



$-CO_2R^1$;

d es 0 a 4;

J se selecciona del grupo que consiste en: O, S, y NR^5;

E se selecciona del grupo que consiste en: O, S, y NR^5;

T es O o S;

R^1 y R^2 son iguales o diferentes, seleccionándose cada uno independientemente del grupo que consiste en H, alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroaralquilo, y heteroarilo; o de manera alternativa R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 4-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico fusionado opcionalmente

con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde cada uno de dichos alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroaralquilo, heteroarilo y anillo heterocíclico de 4-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70} indicados más adelante;

R^{10} se selecciona del grupo que consiste en H, alquilo, y fluoroalquilo;

R^{20} se selecciona del grupo que consiste en H, alquilo, y fluoroalquilo;

R^{30} es H o alquilo, o de manera alternativa R^{30} y R^{40} tomados juntos con el N al cual R^{40} se muestra unido en la Fórmula I, se unen para formar un anillo heterocíclico de 4-7 miembros, donde dicho anillo heterocíclico es no sustituido o sustituido de manera independiente opcionalmente por uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70} indicados más adelante;

R^{40} es H o alquilo;

R^{50} es H o alquilo;

W es $-(CR^{13}{}_2)_n-$, donde n es 0 a 5 o un enlace covalente, o de manera alternativa dos grupos R^{13} se pueden fusionar para formar un cicloalquilo de 3-8 miembros, donde dicho cicloalquilo de 3-8 miembros puede ser no sustituido u sustituido opcionalmente de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^6 siguiente;

X está ausente o presente, y si se encuentra presente X se selecciona del grupo que consiste en un enlace covalente, alquilo, alquenilo, alquinilo, cicloalquilo, heterociclilo, arilo, y heteroarilo, donde dicho alquilo, alquenilo, alquinilo, cicloalquilo, heterociclilo, arilo, y heteroarilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que

pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70} siguientes;

Y está ausente o presente, y si se encuentra presente Y se selecciona del grupo que consiste en un enlace covalente, $-[C(R^6)_2]_n-$ donde n es 1 a 2, -O-, -S-, $-NR^1-$, $-SO_v-$ donde v es 1 a 2, $-SO_n(CR^6_2)_p-$ donde n es 1 o 2 y p es 1 a 4, $-O(CR^6_2)_q-$ o $-(CR^6_2)_qO-$ donde q es 1 a 4, $-N(R^7)S(O)_n-$ o $-S(O)_nN(R^7)-$ donde n es 1 o 2, y $-N(R^7)C(O)-$ o $-C(O)N(R^7)-$;

Z se selecciona del grupo que consiste en H, alquilo, alquenilo, alquinilo, cicloalquilo, heterociclilo, arilo, y heteroarilo, estando dichos cicloalquilo, heterociclilo, arilo y heteroarilo fusionados opcionalmente con arilo, heterociclilo, heteroarilo o cicloalquilo; donde cada uno de dichos alquilo, alquenilo, alquinilo, cicloalquilo, heterociclilo, arilo, y heteroarilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70} indicados más adelante;

R^5 se selecciona del grupo que consiste en hidrógeno, alquilo, y alquilarilo;

cada R^6 es igual o diferente y se selecciona independientemente del grupo que consiste en hidrógeno, halógeno, $-SR^{15}$, $-S(O)_qR^{15}$ donde q es 1 a 2, alquilo, cicloalquilo, heterociclilo, alcoxilo, hidroxi, nitro, ciano, amino, alquenilo, alquinilo, arilalquilo, aminocarbonilo, alquilcarbonilo, y alcoxicarbonilo;

cada R^7 es igual o diferente y se selecciona independientemente del grupo que consiste en hidrógeno, alquilo, arilo, cicloalquilo, heteroarilo, heterociclilo, alquenilo, alquinilo, arilalquilo, alquilcarbonilo, y alcoxicarbonilo, donde cada uno del arilo, heteroarilo y heterociclilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70} indicados más adelante;

R^{13} es igual o diferente y se selecciona independientemente del grupo que consiste en hidrógeno, halógeno, -OH, -OR^{14}, alquilo, cicloalquilo, heterociclilo, alquenilo, alquinilo, alquilarilo, alquilamino, y alquilcarbonilo;

R^{14} es alquilo;

cada R^{70} es un sustituyente para H donde se indicó y es igual o diferente y se selecciona independientemente del grupo que consiste en alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, halo, -CN, -CF_3, -OCF_3, -OR^{15}, -$C(O)R^{15}$, -$C(O)OR^{15}$, -$C(O)N(R^{15})(R^{16})$, -SR^{15}, -$S(O)_qN(R^{15})(R^{16})$ donde q es 1 a 2, -$C(=NOR^{15})R^{16}$, -$N(R^{15})(R^{16})$, -alquil-$N(R^{15})(R^{16})$, -$N(R^{15})C(O)R^{16}$, -CH_2-$N(R^{15})C(O)R^{16}$, -$N(R^{15})S(O)R^{16}$, -$N(R^{15})S(O)_2R^{16}$, -CH_2-$N(R^{15})S(O)_2R^{16}$, -$N(R^{17})S(O)_2N(R^{16})(R^{15})$, -$N(R^{17})S(O)N(R^{16})(R^{15})$, -$N(R^{17})C(O)N(R^{16})(R^{15})$, -$CH_2$-$N(R^{17})C(O)N(R^{16})(R^{15})$, -$N(R^{15})C(O)OR^{16}$, -$CH_2$-$N(R^{15})C(O)OR^{16}$ y -$S(O)_qR^{15}$ donde q es 1 a 2; y donde cada uno del alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, alquenilo y alquinilo son no sustituidos o sustituidos de manera independiente por 1 a 5 grupos seleccionados de manera independiente del grupo que consiste en alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, halo, -CF_3, -CN, -OR^{15}, -$N(R^{15})(R^{16})$, -$C(O)OR^{15}$, -$C(O)N(R^{15})(R^{16})$, y -$N(R^{15})S(O)R^{16}$;

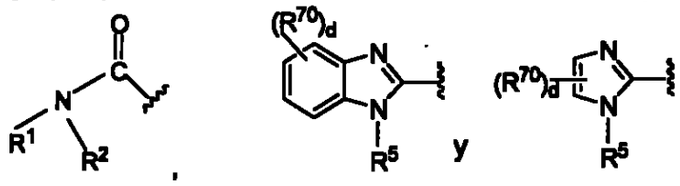
cada R^{15}, R^{16} y R^{17} se seleccionan de manera independiente del grupo que consiste en H, alquilo, cicloalquilo, heterociclilo, arilo, y heteroarilo, o de manera alternativa R^{15} y R^{16} tomados junto con el N al cual estos se muestran unidos, se unen para formar un anillo heterocíclico de 4-8 miembros, donde dicho cicloalquilo de 4-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de abajo restos R^{75};

1701 GP

cada R^{75} se selecciona independientemente del grupo que consiste en alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, alquenilo y alquinilo; y donde cada uno del alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, alquenilo y alquinilo son no sustituidos o sustituidos de manera independiente por 1 a 5 grupos seleccionados de manera independiente del grupo que consiste en alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, halo, $-CF_3$, -CN, $-OR^{19}$, $-N(R^{19})_2$, $-C(O)OR^{19}$, $-C(O)N(R^{19})_2$ y $-N(R^{19})S(O)R^{19}$; y

cada R^{19} se selecciona independientemente del grupo que consiste en H, alquilo, cicloalquilo, heterociclilo, arilo, y heteroarilo.

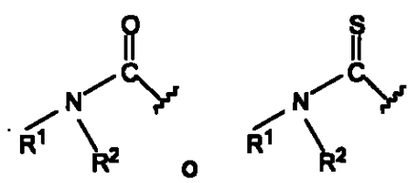
2. El compuesto de la reivindicación 1, donde A se selecciona del grupo que consiste en:



y

donde R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 4-8 miembros que posee 1-3 heteroátomos incluyendo dicho N, dicho anillo heterocíclico siendo sustituido opcionalmente por R^{70}, o fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 4-8 miembros puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70}.

3. El compuesto de la reivindicación 1, donde A es

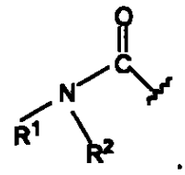


o

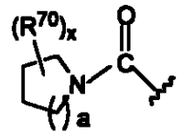
1702 CH

donde R^1 y R^2 son iguales o diferentes, seleccionándose cada uno independientemente del grupo que consiste en H, alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroaralquilo, y heteroarilo; donde dicho alquilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroaralalquilo y heteroarilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70}.

4. El compuesto de la reivindicación 3, donde A es



5. El compuesto de la reivindicación 2, donde A es

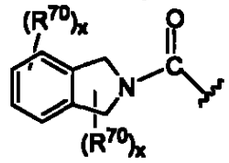


donde

a es de 0 a 4; y

x es de 0 a 4.

6. El compuesto de la reivindicación 2, donde A es

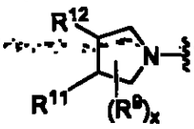


donde

cada x es independientemente de 0 a 4.

1703

7. El compuesto de la reivindicación 2, donde se forma un anillo a partir de $-NR^1R^2$ y dicho anillo es



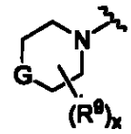
donde

cada R^9 es un sustituyente para H donde se indicó y puede ser igual o diferente, seleccionándose cada uno independientemente del grupo que consiste en -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alquilo, arilo, heteroarilo, alquenilo, alquinilo, cicloalquilo y heterociclilo, donde dicho alquilo, arilo, heteroarilo, alquenilo, alquinilo, cicloalquilo y heterociclilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70};

R^{11} y R^{12} tomados junto con el carbono al cual cada R^{11} y R^{12} se muestran unidos son heteroarilo fusionado o cicloalquilo fusionado, donde cada heteroarilo fusionado y cicloalquilo fusionado puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70}; y

x es de 0 a 4, y cuando x es mayor que 1, cada resto R^9 puede ser igual o diferente, seleccionándose cada resto independientemente del grupo de restos R^9.

8. El compuesto de la reivindicación 2, donde se forma un anillo a partir de $-NR^1R^2$ y dicho anillo es



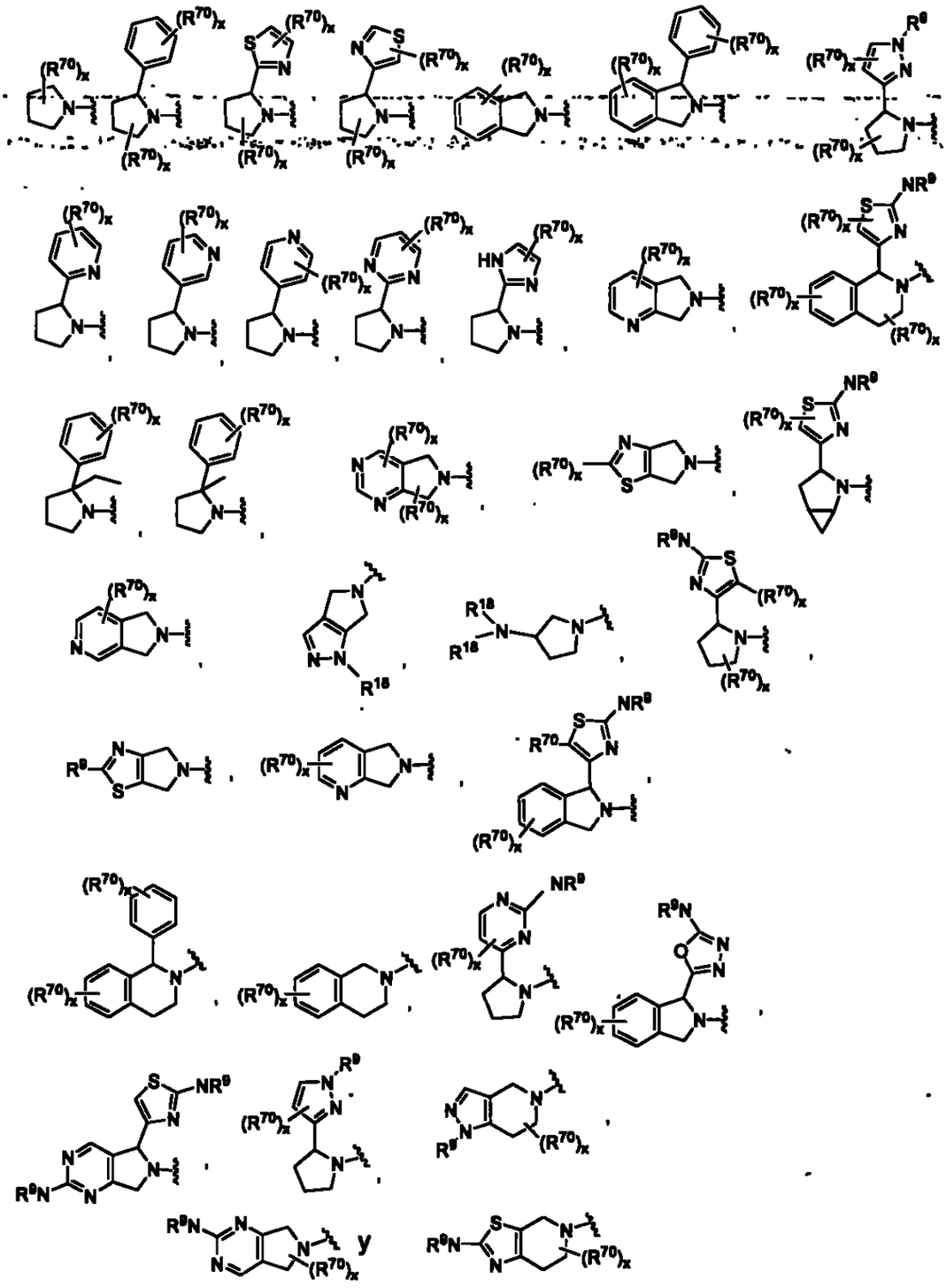
1704 599

donde cada R^9 es un sustituyente para H donde se indicó y puede ser igual o diferente, seleccionándose cada uno independientemente del grupo que consiste en -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alquilo, arilo, heteroarilo, alquenilo, alquinilo, cicloalquilo y heterociclilo, donde dicho alquilo, arilo, heteroarilo, alquenilo, alquinilo, cicloalquilo y heterociclilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70};

x es de 0 a 4, y cuando x es mayor que 1, cada resto R^9 puede ser igual o diferente, seleccionándose cada resto independientemente del grupo de restos R^9; y

G se selecciona del grupo que consiste en CH_2, NR^7, O, S, o SO_2.

9. El compuesto de la reivindicación 2, donde se forma un anillo a partir de $-NR^1R^2$ y dicho anillo se selecciona del grupo que consiste en



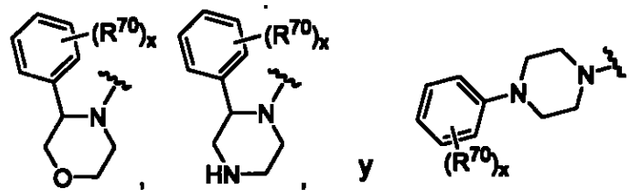
donde

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x es de 0 a 4, y cuando x es mayor que 1, cada resto R^{70} puede ser igual o diferente, seleccionándose cada resto independientemente del grupo de restos R^{70}; y

cada R^{18} es igual o diferente y es independientemente H o alquilo.

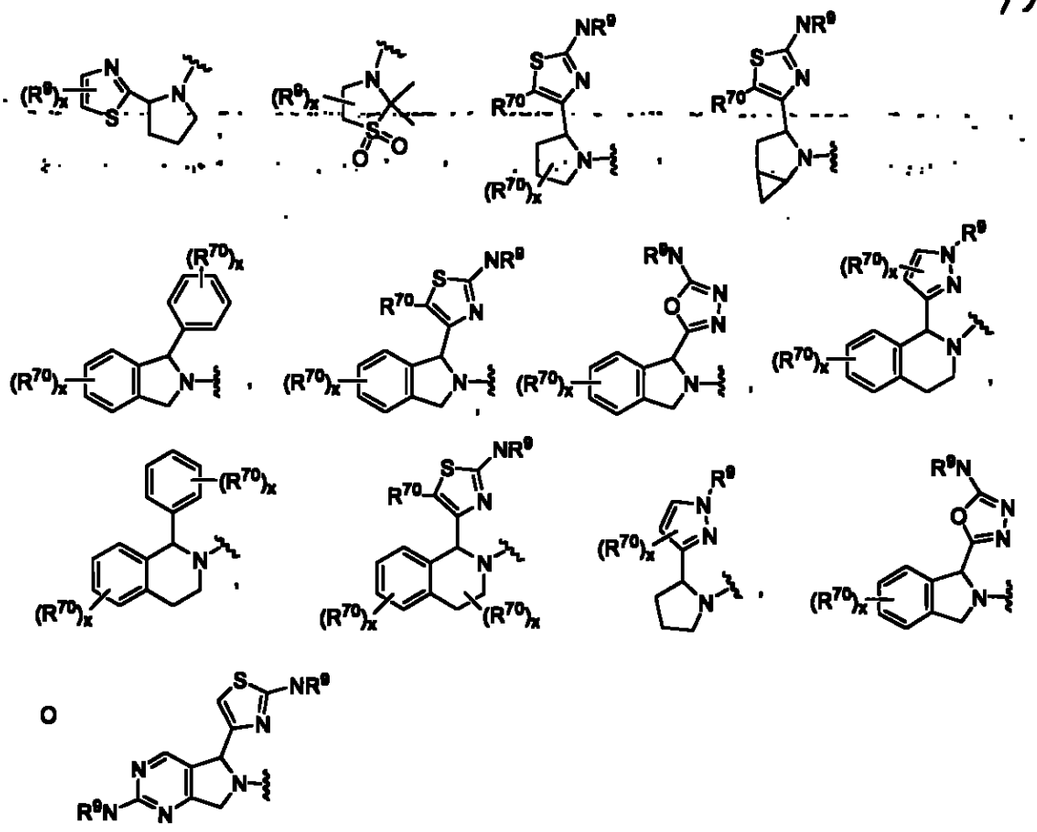
10. El compuesto de la reivindicación 2, donde se forma un anillo a partir de $-NR^1R^2$ y dicho anillo se selecciona del grupo que consiste en:



donde

x es de 0 a 4, y cuando x es mayor que 1, cada resto R^{70} puede ser igual o diferente, seleccionándose cada resto independientemente del grupo de restos R^{70}.

11. El compuesto de la reivindicación 2, donde se forma un anillo a partir de $-NR^1R^2$ y es



donde

cada R^9 es un sustituyente para H donde se indicó y puede ser igual o diferente, seleccionándose cada uno independientemente del grupo que consiste en -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alquilo, arilo, heteroarilo, alquenilo, alquinilo, cicloalquilo y heterociclilo, donde dicho alquilo, arilo, heteroarilo, alquenilo, alquinilo, cicloalquilo y heterociclilo puede ser no sustituido u opcionalmente sustituido de manera independiente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo de restos R^{70}; y

x es de 0 a 4, y cuando x es mayor que 1, cada resto R^9 puede ser igual o diferente, seleccionándose cada resto independientemente del grupo de restos R^9.

12. El compuesto de la reivindicación 2, donde J es O.

13. El compuesto de la reivindicación 2, donde E es O.

14. El compuesto de la reivindicación 2, donde R^{10} es H o alquilo.

15. El compuesto de la reivindicación 2, donde R^{20} es H.

16. El compuesto de la reivindicación 2, donde R^{30} es H.

17. El compuesto de la reivindicación 2, donde R^{40} es H.

18. El compuesto de la reivindicación 2, donde R^{50} es H.

19. El compuesto de la reivindicación 2, donde R^{13} es H o alquilo.

20. El compuesto de la reivindicación 19, donde R^{13} es H o $-CH_3$.

21. El compuesto de la reivindicación 2, donde R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 4-6 miembros que posee 1-3 heteroátomos incluyendo dicho N, estando dicho anillo heterocíclico sustituido opcionalmente con R^{70}, donde R^{70} es arilo.

22. El compuesto de la reivindicación 2, donde Y es un enlace covalente o $-[C(R^6)_2]_n-$ donde n es 1 a 2.

23. El compuesto de la reivindicación 2, donde Y se selecciona del grupo que consiste en un enlace covalente, $-CH_2-$, -C(H)(OH)-, -C(O)- y –O-.

24. El compuesto de la reivindicación 23, donde Y es un enlace covalente o $-CH_2-$.

25. El compuesto de la reivindicación 24, donde Y es un enlace covalente.

26. El compuesto de la reivindicación 2, donde W es $-(CR^{13}_2)_n-$, en el cual n es 1-5 y cada R^{13} es H o alquilo.

27. El compuesto de la reivindicación 2, donde W se selecciona del grupo que consiste en $-CH_2-$, $-C(H)(CH_3)-$, $-C(CH_3)_2-$ y $-CH_2CH_2-$.

28. El compuesto de la reivindicación 27, donde W es $-CH_2-$ o $-C(H)(CH_3)-$.

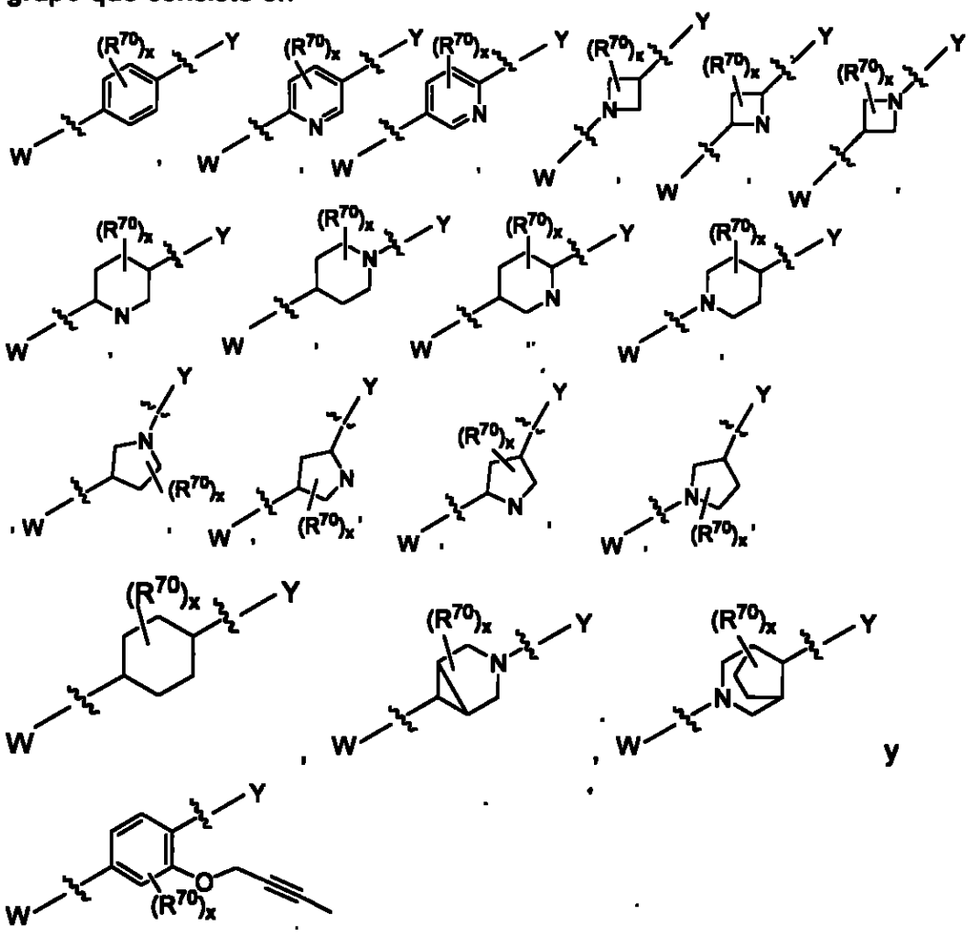
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29. El compuesto de la reivindicación 2, donde X se selecciona del grupo que consiste en alquilo, arilo, heterociclilo y heteroarilo.

30. El compuesto de la reivindicación 29, donde X se selecciona del grupo que consiste en fenilo, azetidinilo, pirrolidinilo, piperidinilo, piridinilo, tienilo, tiazolilo, oxazolilo, imidazolilo y pirazolilo.

31. El compuesto de la reivindicación 30, donde X se selecciona del grupo que consiste en fenilo, piperidinilo y piridinilo.

32. El compuesto de la reivindicación 29, donde X se selecciona del grupo que consiste en

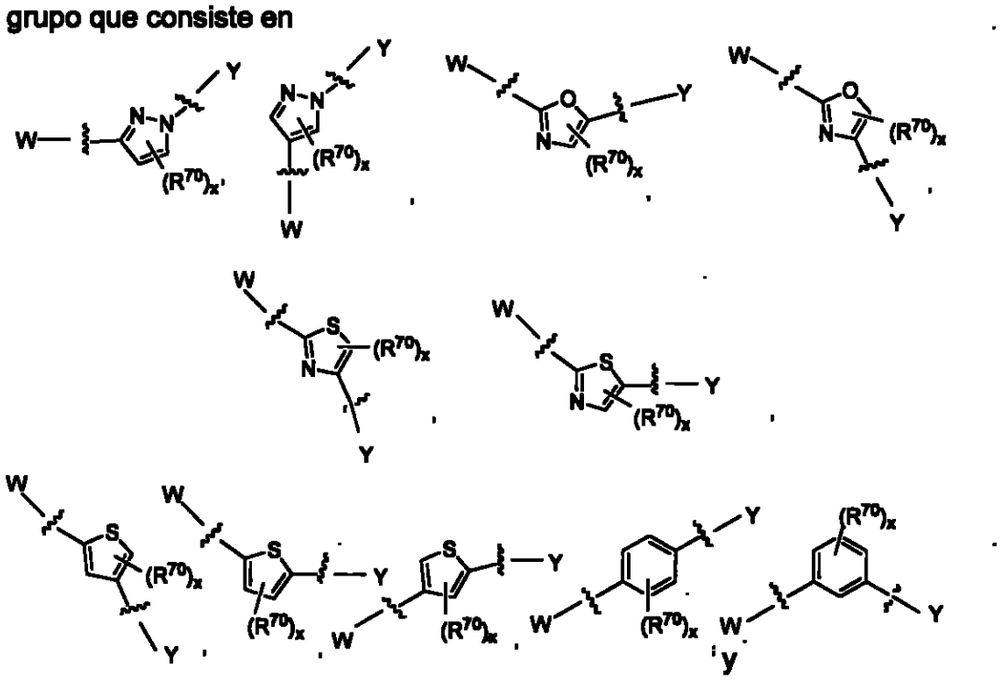


y

donde

x es de 0 a 4, y donde x es mayor que 1, cada resto R^{70} puede ser igual o diferente, seleccionándose cada resto de manera independiente del grupo de restos R^{70}.

33. El compuesto de la reivindicación 29, donde X se selecciona del grupo que consiste en



donde

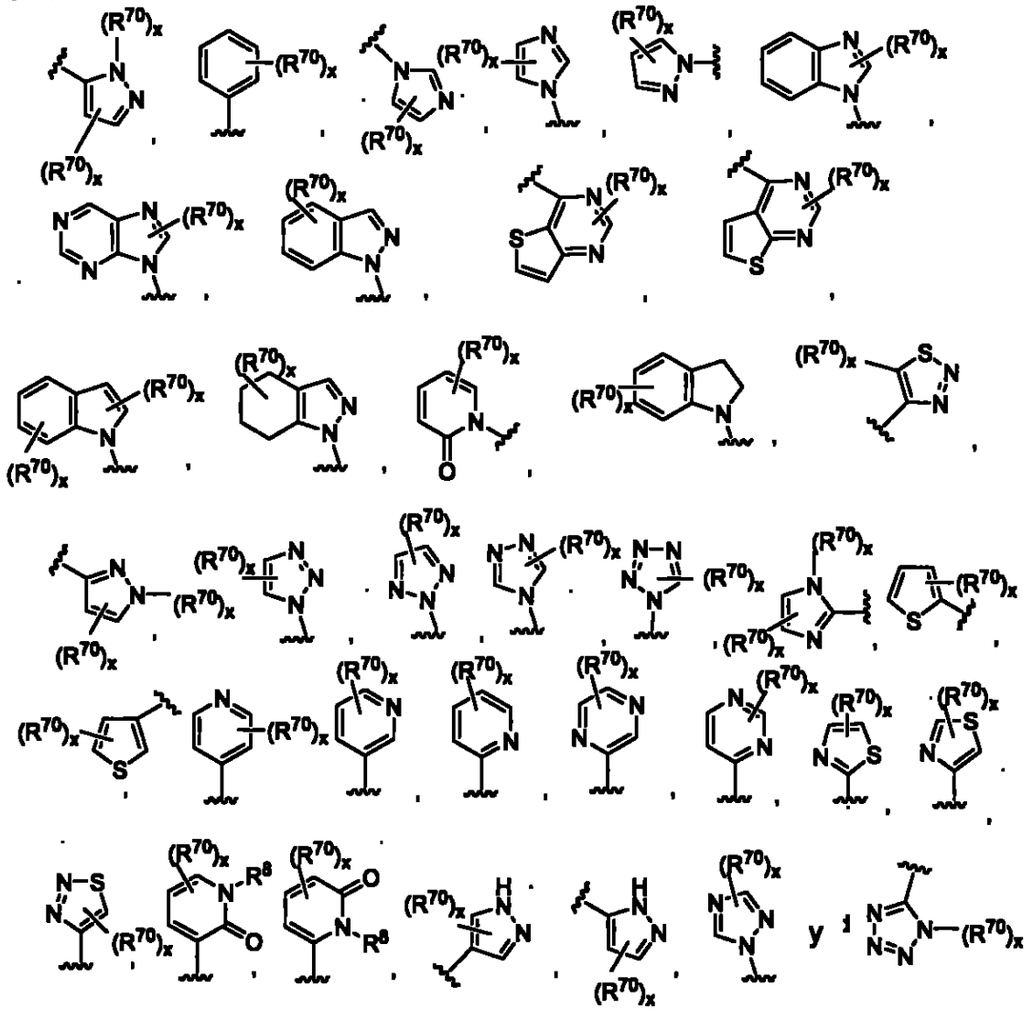
x es de 0 a 4, y cuando x es mayor que 1, cada resto R^{70} puede ser igual o diferente, cada resto siendo seleccionado de manera independiente del grupo de restos R^{70}.

34. El compuesto de la reivindicación 2, donde Z se selecciona del grupo que consiste en H, arilo y heteroarilo.

35. El compuesto de la reivindicación 34, donde Z se selecciona del grupo que consiste en H, fenilo, indolilo, benzoimidazolilo, pirazolilo, tienilo, piridinilo, tiazolilo, tiadiazolilo, imidazolilo, pirrolidinilo, pirazinilo, triazolilo, tetrazolilo y tetrazinilo, donde dicho fenilo, indolilo, benzoimidazolilo, pirazolilo, tienilo, piridinilo, tiazolilo, tiadiazolilo, imidazolilo, pirrolidinilo, pirazinilo, triazolilo,

tetrazolilo y tetrazinilo puede ser no sustituido o sustituido opcionalmente de manera independiente por uno o más restos que pueden ser iguales o diferentes, cada resto siendo seleccionado de manera independiente del grupo que consiste en restos R^{70}.

36. El compuesto de la reivindicación 35, donde Z se selecciona del grupo que consiste en



donde

x es de 0 a 4, y cuando x es mayor que 1, cada resto R^{70} puede ser igual o diferente, cada resto siendo seleccionado de manera independiente del grupo de restos R^{70}.

37. El compuesto de la reivindicación 35, donde Z es fenilo.

38. El compuesto de la reivindicación 37, donde dicho fenilo está sustituido con al menos un sustituyente seleccionado del grupo que consiste en ciano, alcoxi, halógeno, alquilo, haloalquilo, hidroxi, arilo, heteroarilo, ariloxi, amino y tetrazol.

39. El compuesto de la reivindicación 35, donde Z es tienilo.

40. El compuesto de la reivindicación 39, donde dicho tienilo está sustituido con al menos un sustituyente seleccionado del grupo que consiste en ciano, alcoxi, halógeno, alquilo, haloalquilo, hidroxi, arilo, heteroarilo, ariloxi, amino y tetrazol.

41. El compuesto de la reivindicación 35, donde Z es pirazolilo.

42. El compuesto de la reivindicación 41, donde dicho pirazolilo está sustituido con al menos un sustituyente seleccionado del grupo que consiste en ciano, alcoxi, halógeno, alquilo, haloalquilo, hidroxi, arilo, heteroarilo, ariloxi, amino y tetrazol.

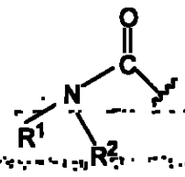
43. El compuesto de la reivindicación 35, donde Z es piridinilo.

44. El compuesto de la reivindicación 43, donde dicho piridinilo está sustituido con al menos un sustituyente seleccionado del grupo que consiste en ciano, alcoxi, halógeno, alquilo, haloalquilo, hidroxi, arilo, heteroarilo, ariloxi, amino y tetrazol.

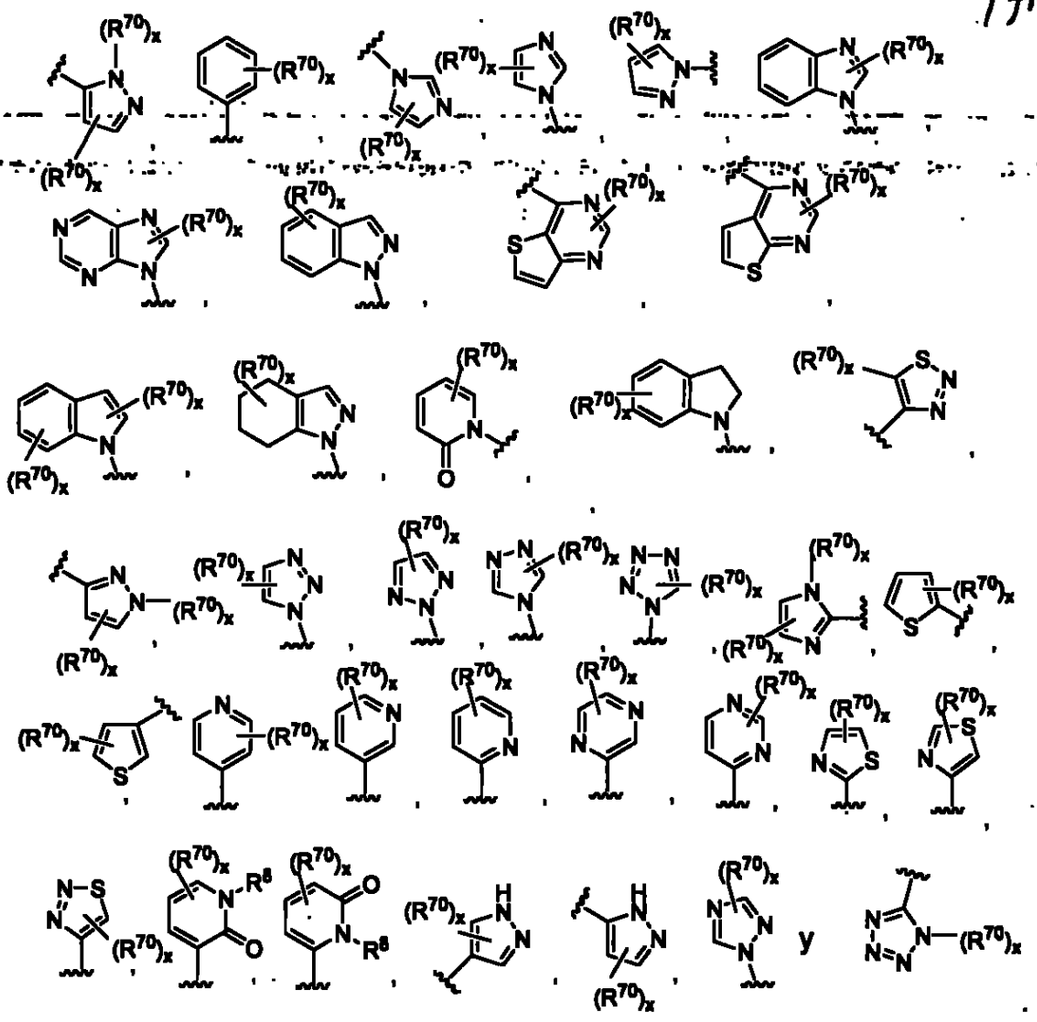
45. El compuesto de la reivindicación 35, donde Z es imidazolilo.

46. El compuesto de la reivindicación 45, donde dicho imidazolilo se sustituye con al menos un sustituyente seleccionado del grupo que consiste en ciano, alcoxi, halógeno, alquilo, haloalquilo, hidroxi, arilo, heteroarilo, ariloxi, amino y tetrazol.

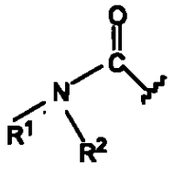
47. El compuesto de la reivindicación 2, donde A es



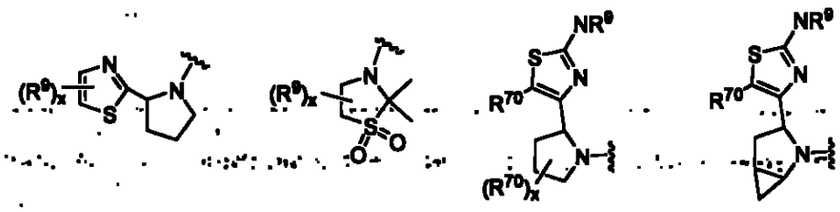
donde R^1 y R^2, tomados junto con el N al cual R^1 y R^2 se muestran unidos, representan un anillo heterocíclico de 4-8 miembros que posee 1-3 hetero-atomos incluyendo dicho N, dicho anillo heterocíclico siendo sustituido opcionalmente con uno o más R^{70}, fusionado opcionalmente con arilo, heteroarilo, cicloalquilo, o heterociclilo, donde dicho anillo heterocíclico de 4-8 miembros puede ser no sustituido o sustituido opcionalmente de manera independiente por uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto de manera independiente del grupo de restos R^{70}; E, J y T son iguales y son O; R^{10} es H o alquilo; R^{20}, R^{30}, R^{40}, y R^{50} son iguales y son H; W es $-(CR^{13}_2)_n-$, donde n es de 0 a 5; X se selecciona del grupo que consiste en arilo, heteroarilo y heterociclilo; Y se selecciona del grupo que consiste en un enlace covalente, $-[C(R^6)_2]_n-$ donde n es 1 a 2, -O-, -S-, y $-NR^1-$; y Z se selecciona del grupo que consiste en

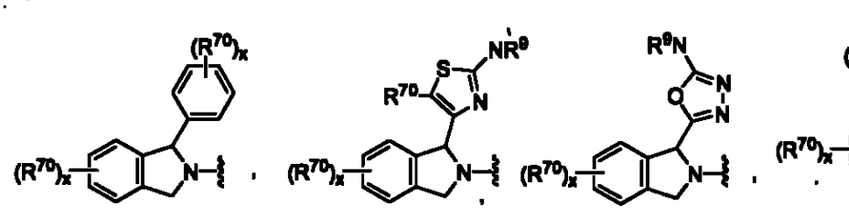


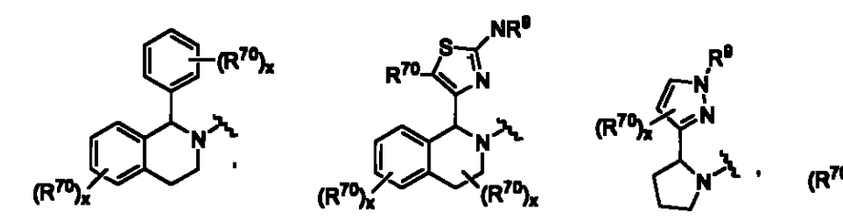
48. El compuesto de la reivindicación 47 donde el $-NR^1R^2$ de



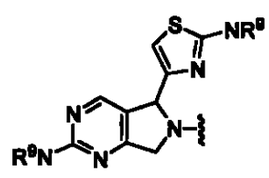
es







o



donde

cada R^9 es un sustituyente para H donde se indica y puede ser igual o diferente, seleccionándose cada uno independientemente del grupo que consiste en -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alquilo, arilo, heteroarilo, alquenilo, alquinilo, cicloalquilo y heterociclilo, donde dicho alquilo, arilo, heteroarilo, alquenilo, alquinilo, cicloalquilo y heterociclilo puede ser no sustituido o sustituido opcionalmente de manera independiente por uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto de manera independiente del grupo de restos R^{70}; y

x es de 0 a 4, y cuando x es mayor que 1, cada resto R^9 puede ser igual o diferente, seleccionándose cada resto de manera independiente del grupo de restos R^9.

49. El compuesto de la reivindicación 47, donde X se selecciona del grupo que consiste en fenilo, piperidinilo, piridinilo, tienilo, tiazolilo, oxazolilo y pirazolilo.

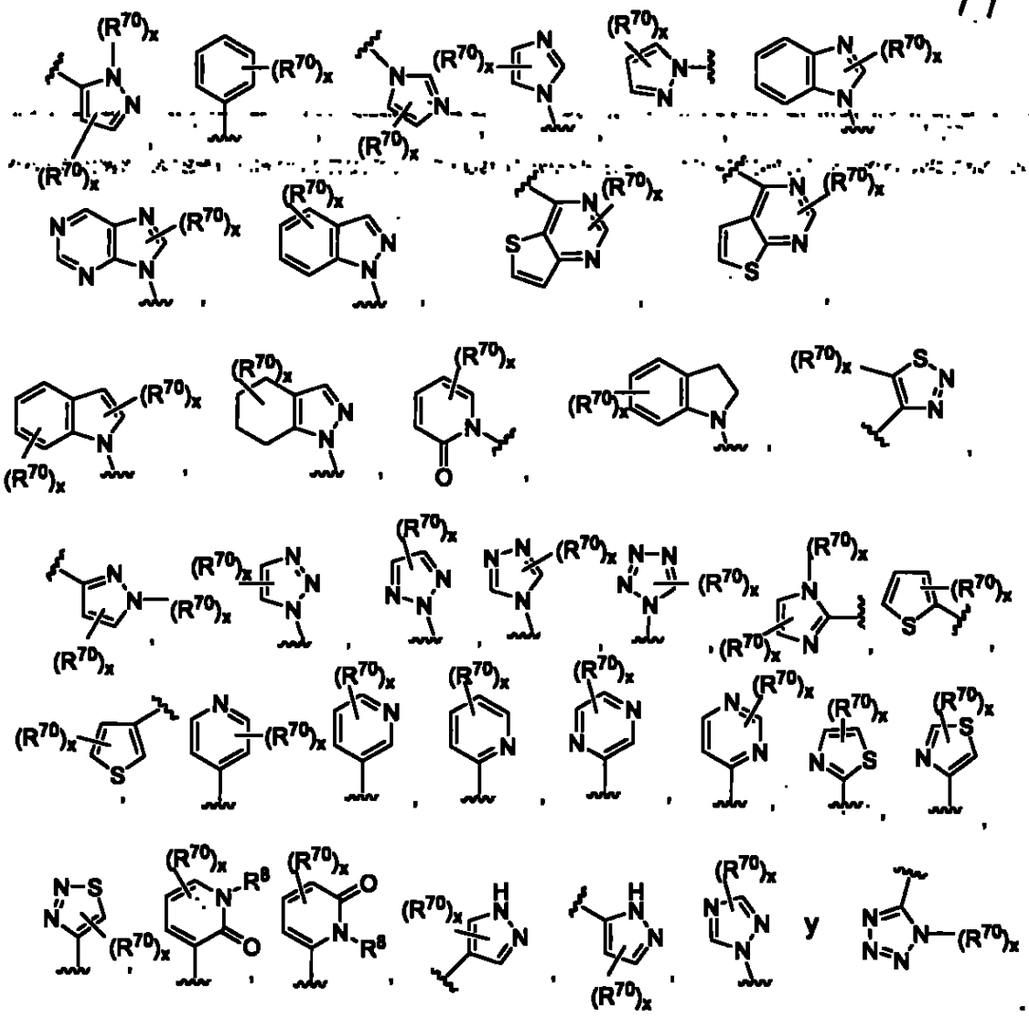
50. El compuesto de la reivindicación 48, donde X se selecciona del grupo que consiste en fenilo, piperidinilo, tienilo, y piridinilo e Y se selecciona del grupo que consiste en un enlace covalente, $-[C(R^6)_2]_n-$ donde n es 1 a 2 y -O-.

51. El compuesto de la reivindicación 48, donde X es piperidinilo, Y es un enlace covalente, y Z es arilo o heteroarilo que poseen dos sustituyentes que pueden ser iguales o diferentes, seleccionándose cada resto de manera independiente del grupo que consiste en ciano, alcoxi, halógeno, alquilo, haloalquilo, hidroxi, arilo, heteroarilo, ariloxi y amino.

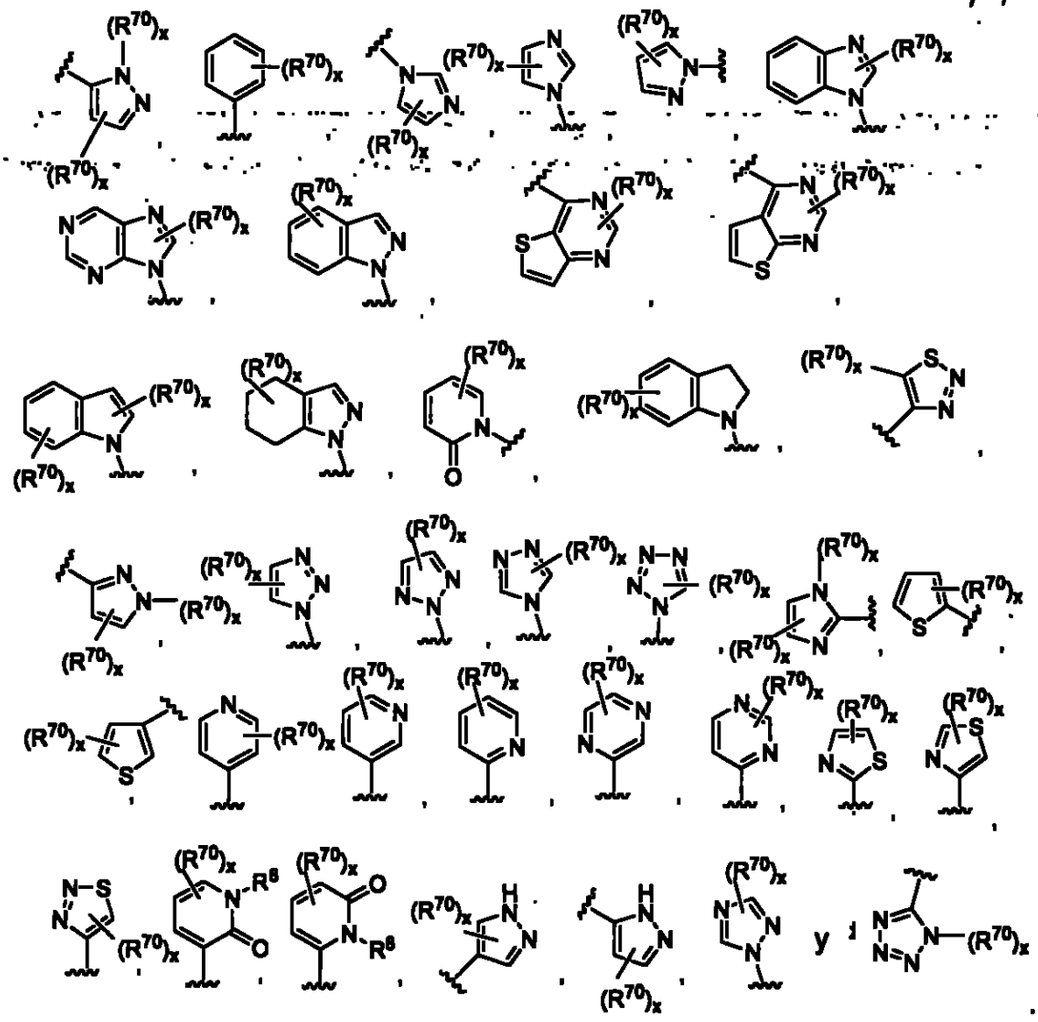
52. El compuesto de la reivindicación 47, donde W se selecciona del grupo que consiste en $-CH_2-$, $-C(H)CH_3-$, $-C(CH_3)_2-$ e Y es un enlace covalente.

53. El compuesto de la reivindicación 47, donde W es $-CH_2-$ o $-C(H)(CH_3)-$ e Y es $-CH_2-$.

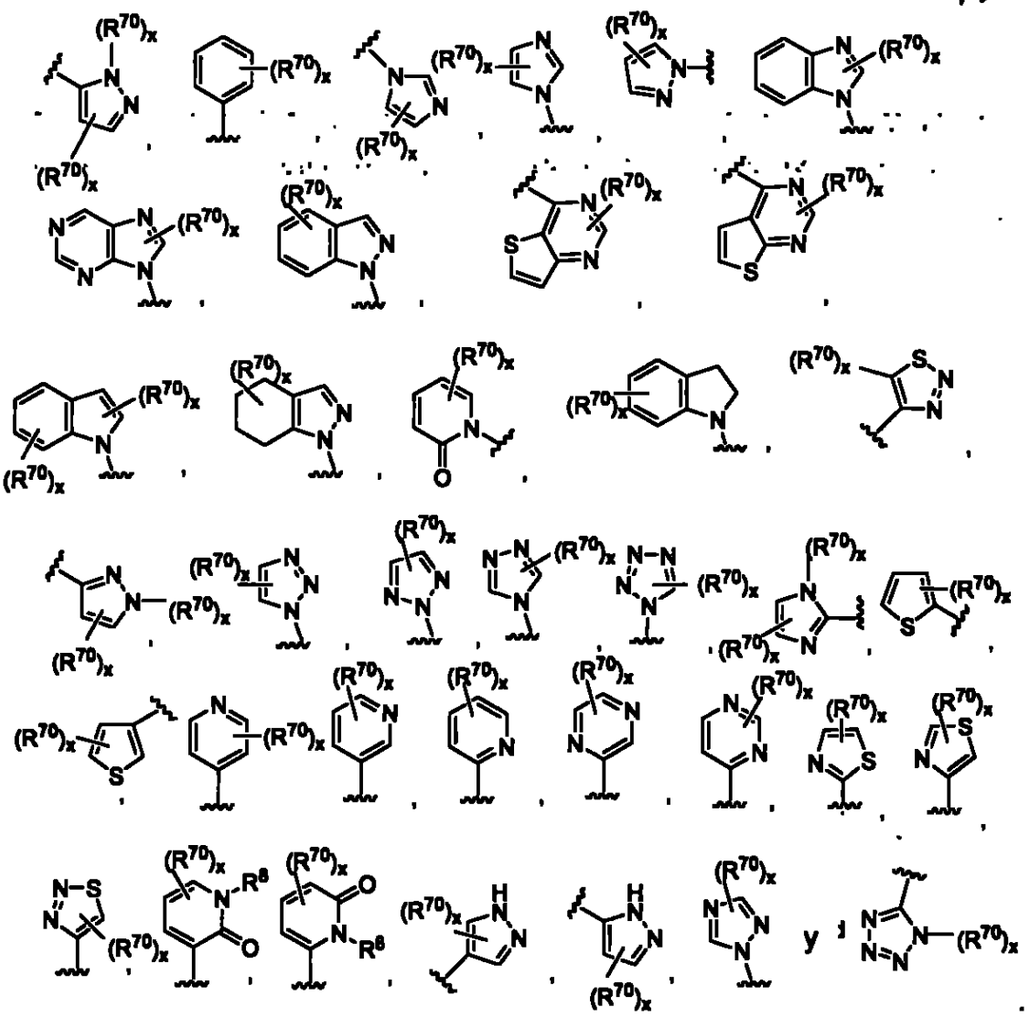
54. El compuesto de la reivindicación 47, donde X se selecciona del grupo que consiste en fenilo, piperidinilo, piridinilo, tienilo, tiazolilo, oxazolilo y pirazolilo; Y es $-[C(R^6)_2]_n-$ donde n es 1 a 2; y Z se selecciona del grupo que consiste en



55. El compuesto de la reivindicación 47, donde X se selecciona del grupo que consiste en fenilo, piperidinilo, piridinilo, tienilo, tiazolilo, oxazolilo y pirazolilo; Y se selecciona del grupo que consiste en O-, -S-, y -NR^1-; y Z se selecciona del grupo que consiste en

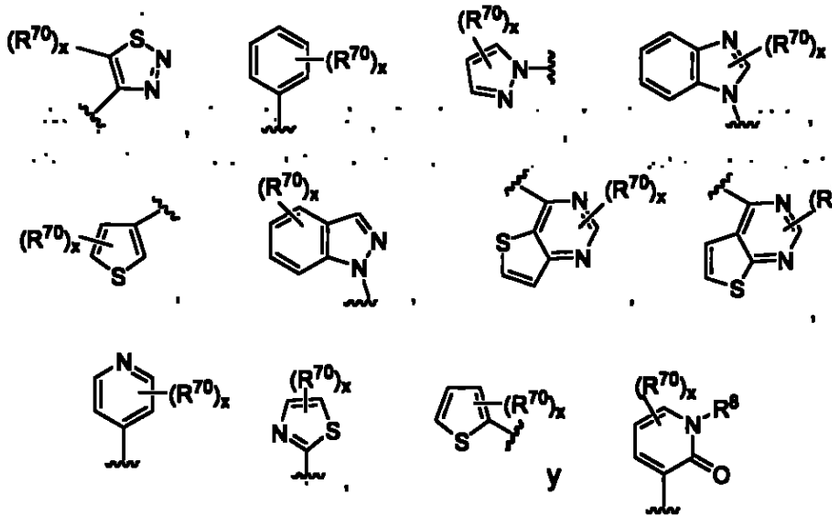


56. El compuesto de la reivindicación 47, donde W es -$(CR^{13}_2)_n$-, donde n es 1 o 2; X se selecciona del grupo que consiste en fenilo, piperidinilo, piridinilo, tienilo, tiazolilo, oxazolilo y pirazolilo; Y es un enlace covalente y Z se selecciona del grupo que consiste en

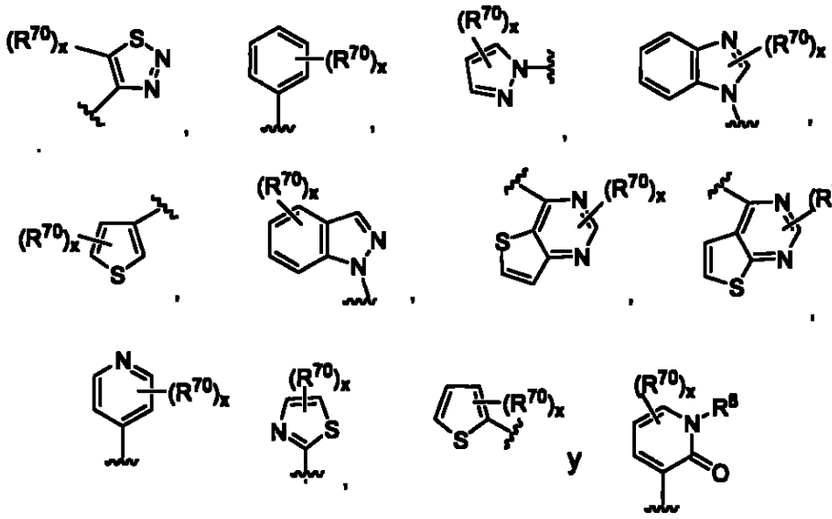


57. El compuesto de la reivindicación 53, donde Z se selecciona del grupo que consiste en

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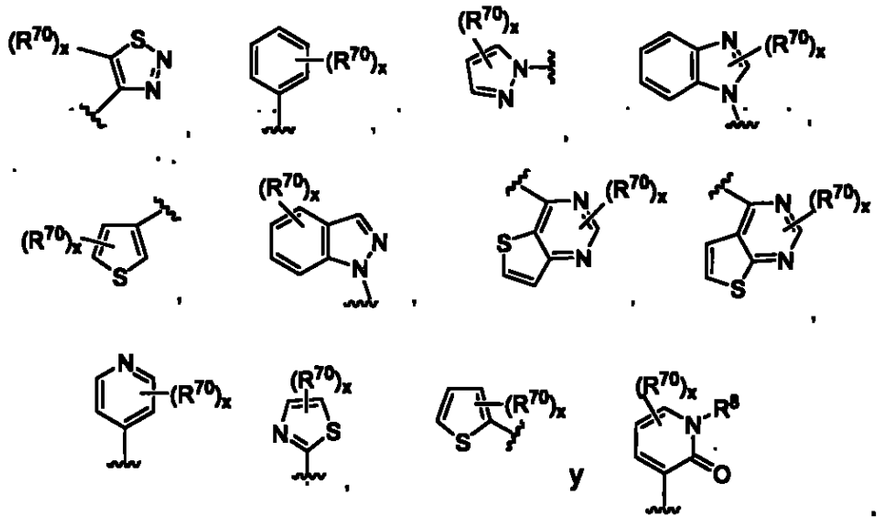


58. El compuesto de la reivindicación 54, donde Z se selecciona del grupo que consiste en

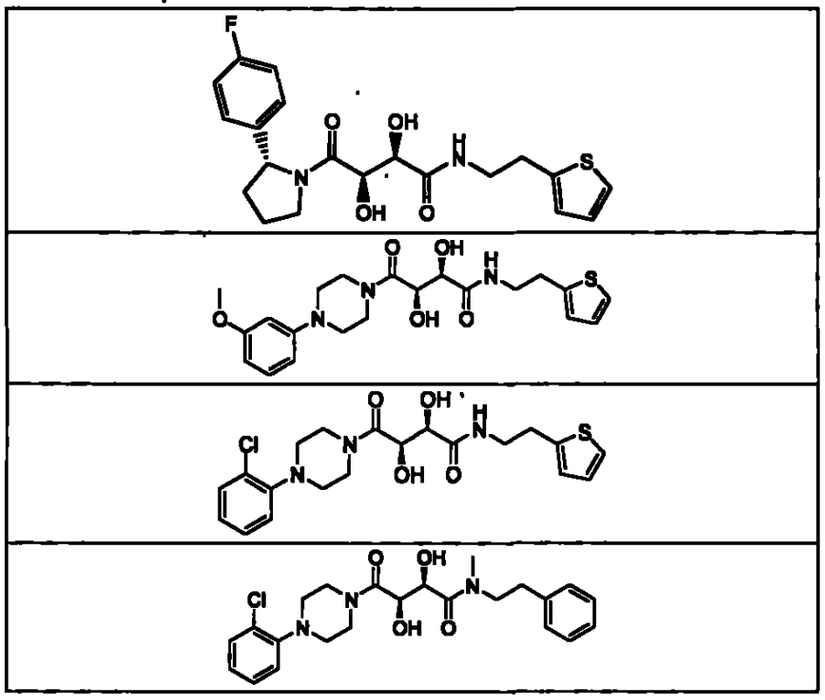


59. El compuesto de la reivindicación 55, donde Z se selecciona del grupo que consiste en

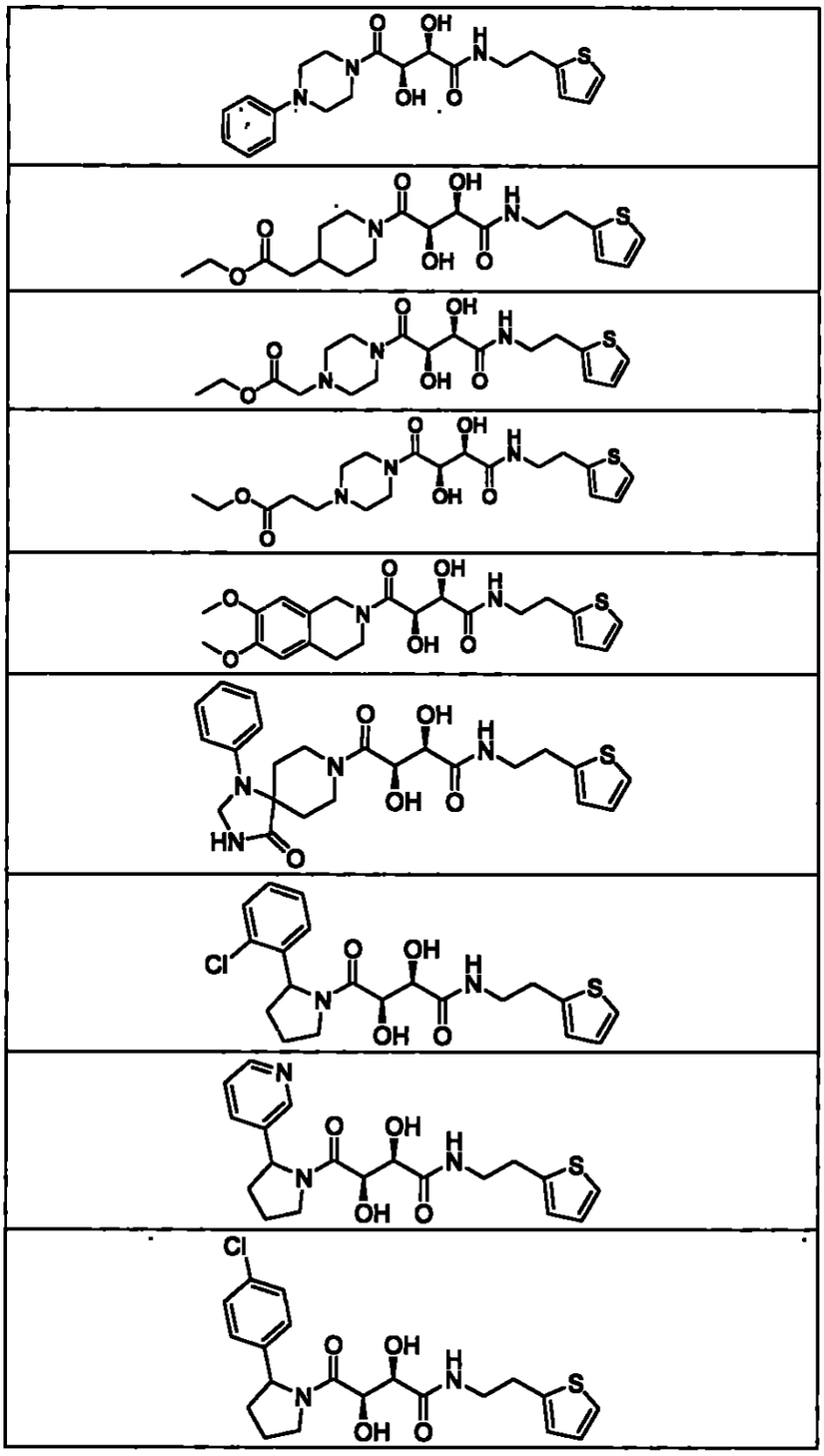
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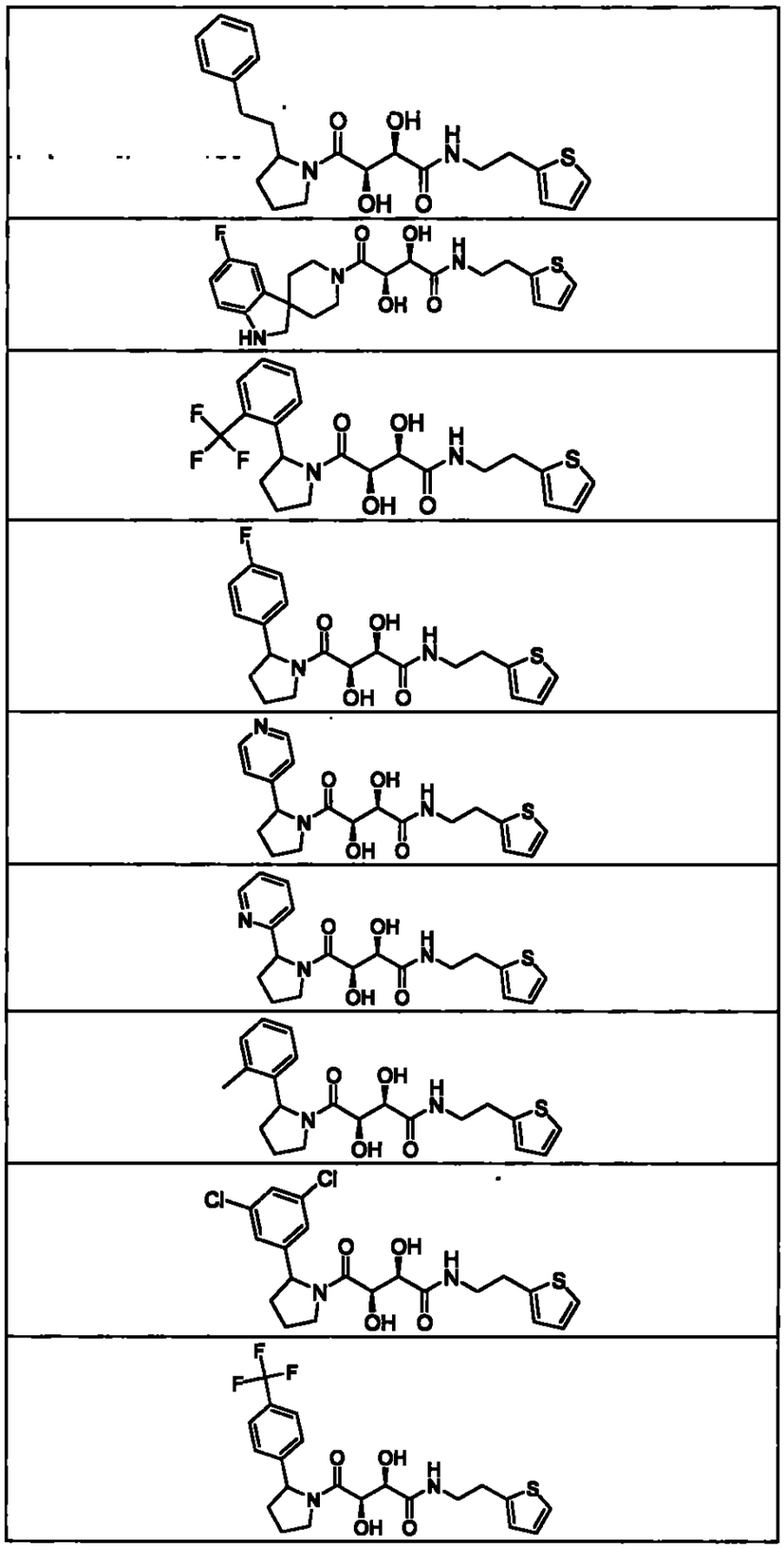
60. Un compuesto que muestra actividad inhibidora de TACE, TNF-α, MMP o cualquier combinación de las mismas, incluyendo enantiómeros, estereoisómeros y tautómeros de dicho compuesto y sales aceptables para uso farmacéutico o solvatos de dicho compuesto, seleccionándose dicho compuesto de los compuestos de las estructuras enumeradas a continuación:



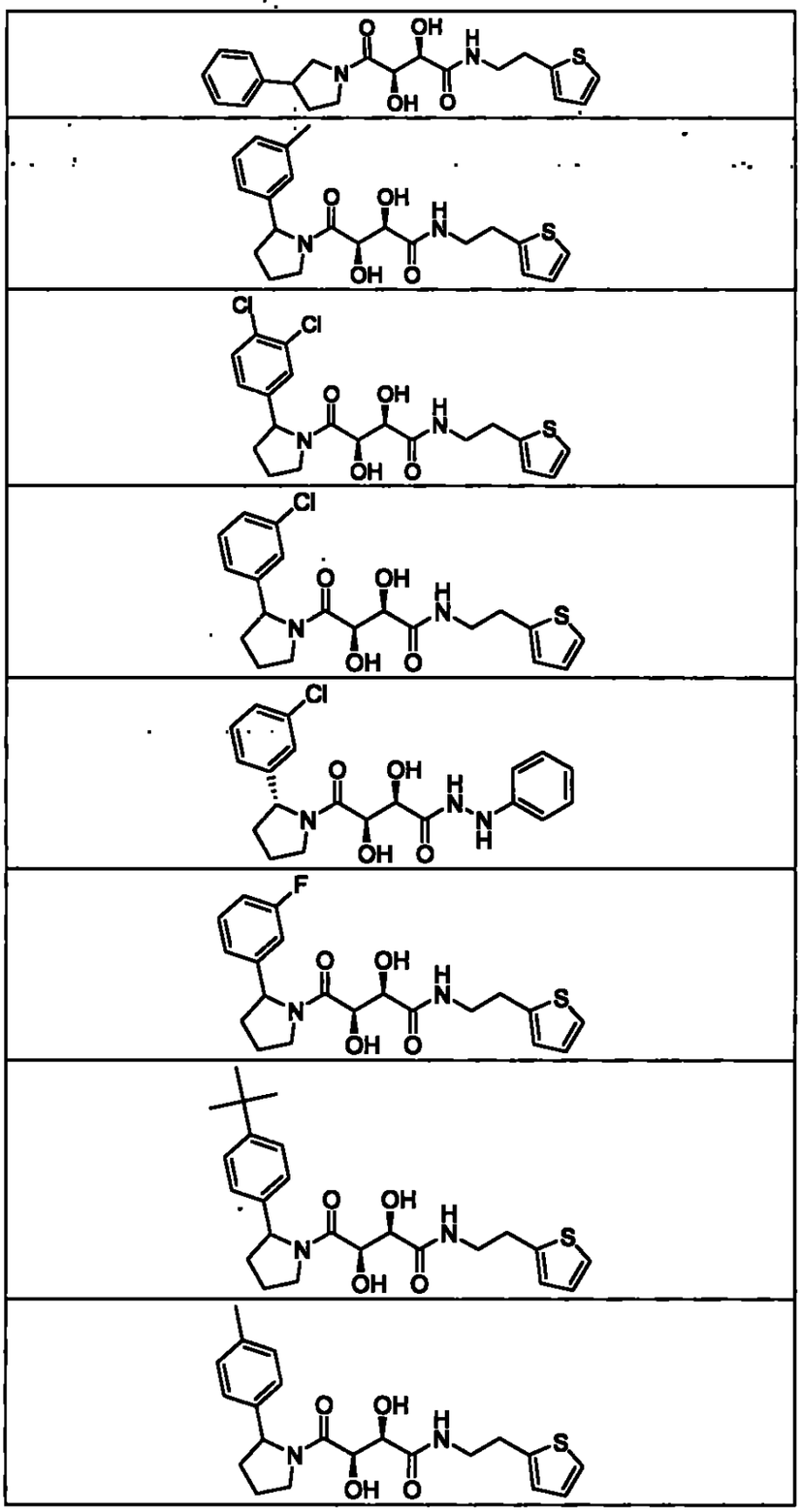
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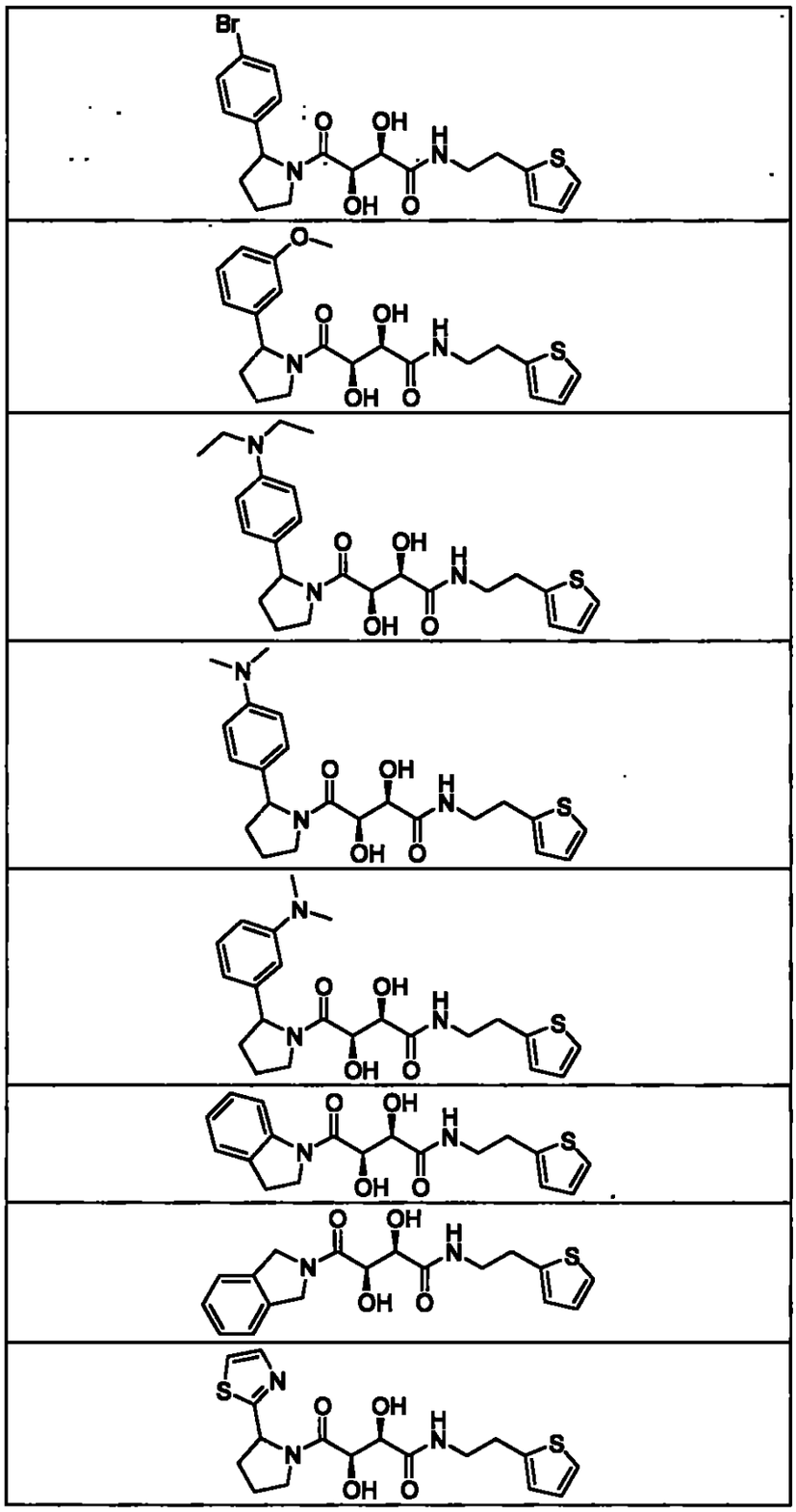


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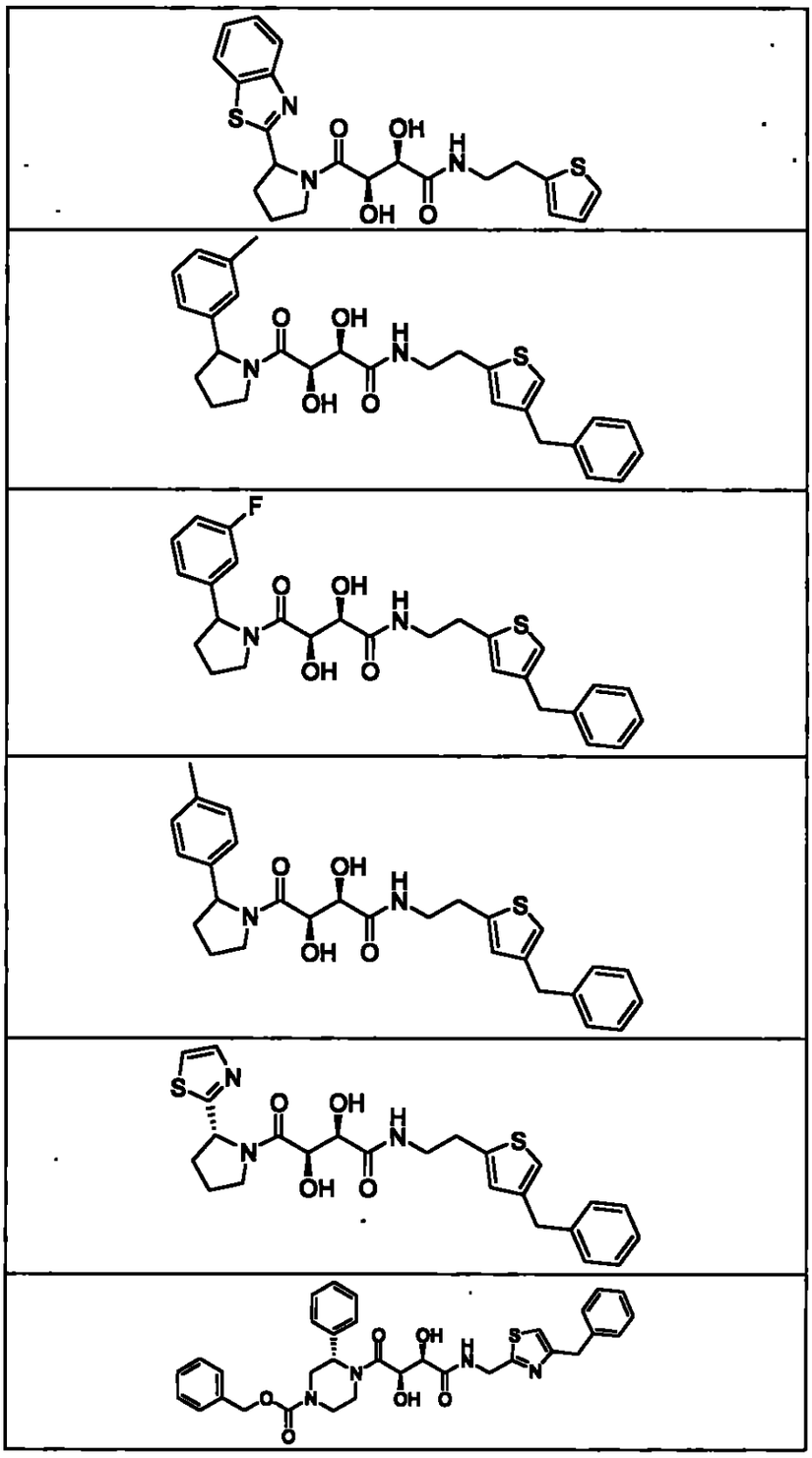


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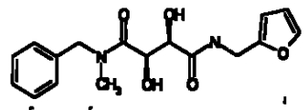
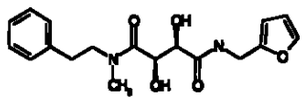
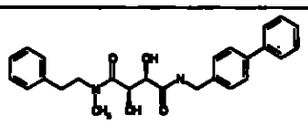
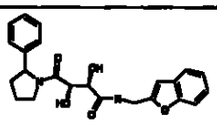
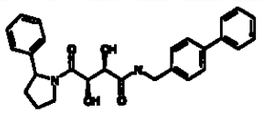
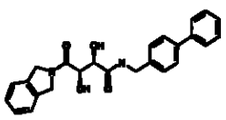
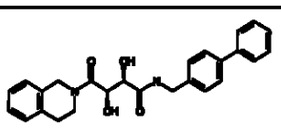
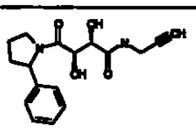
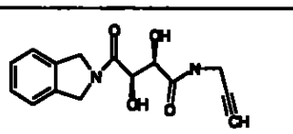


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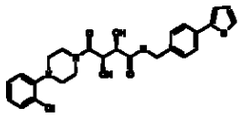


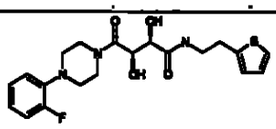
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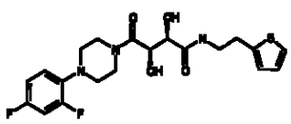
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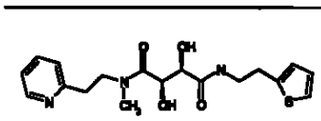










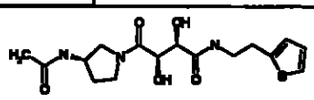
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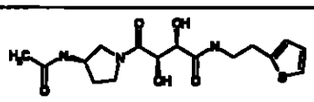


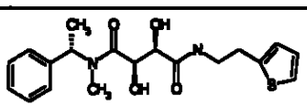


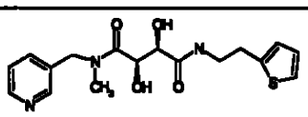


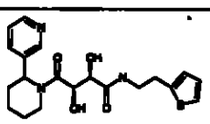


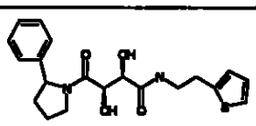




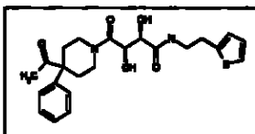
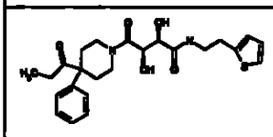
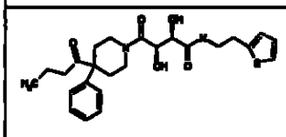
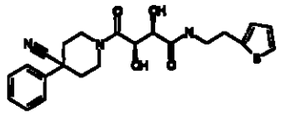
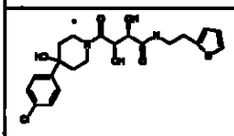
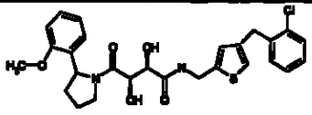
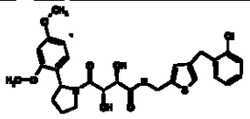
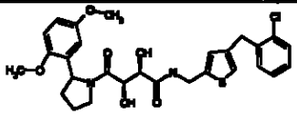
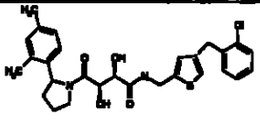




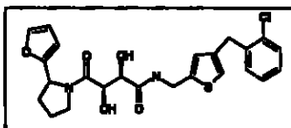
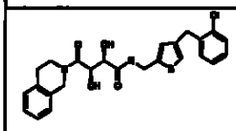
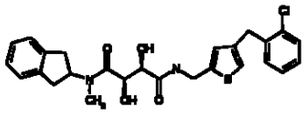
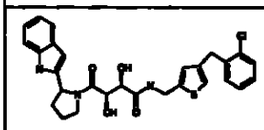
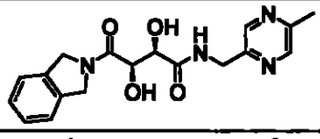
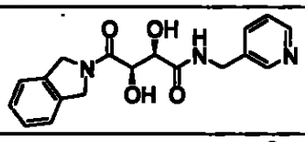
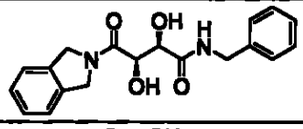
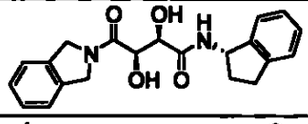
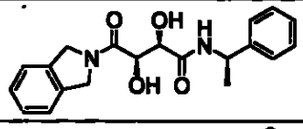
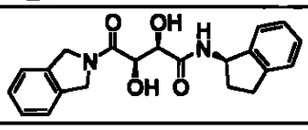


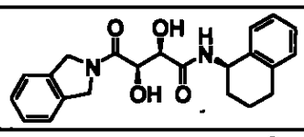
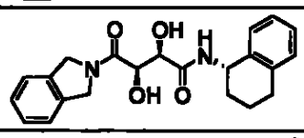
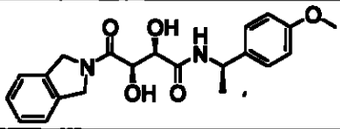
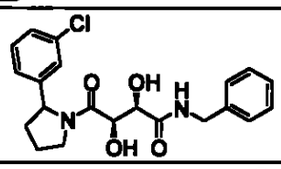
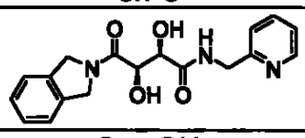
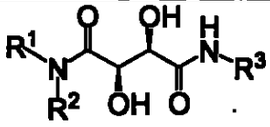
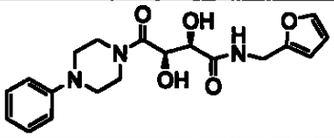
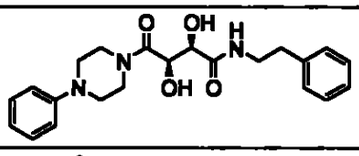
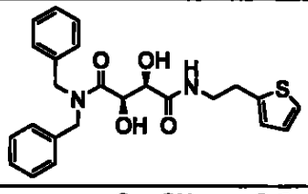
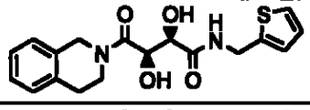
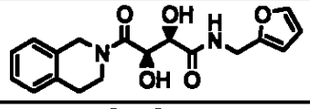
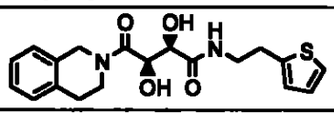


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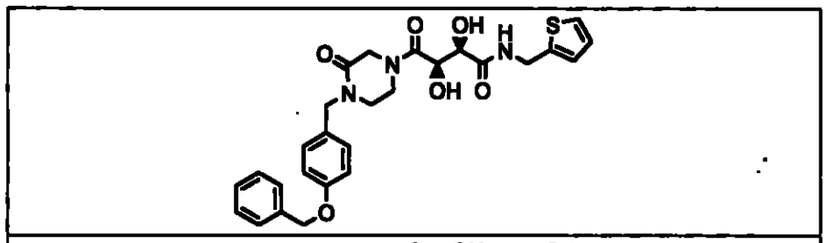










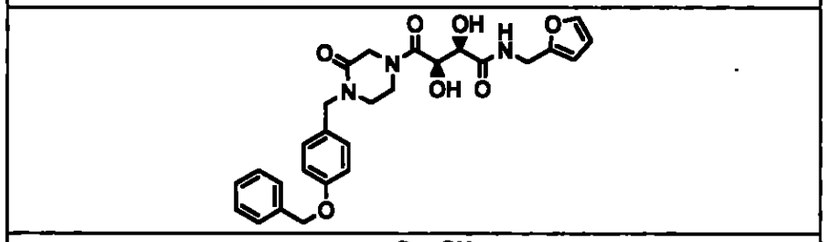
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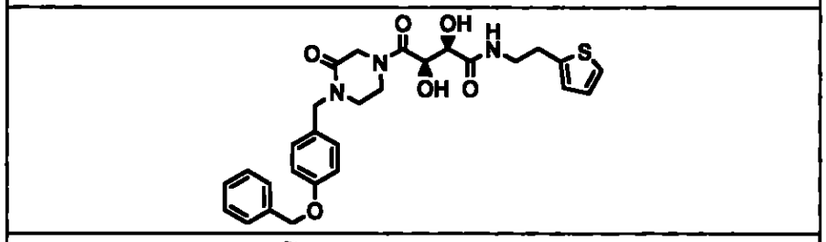











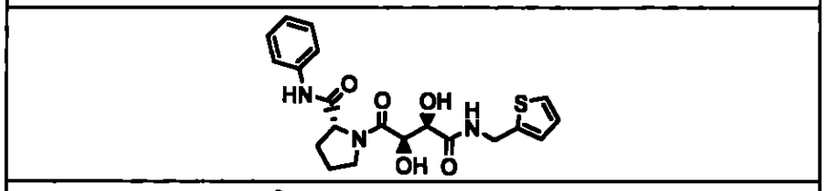





 (R1 = R2 = CH_2Ph, R3 = $CH_2CH_2(C_4H_4O)$)







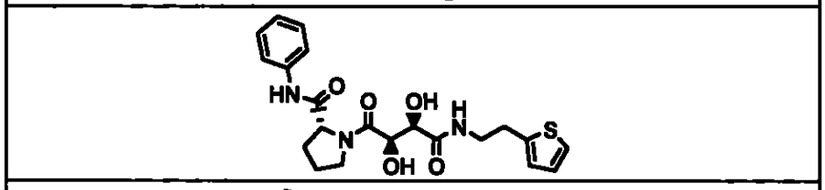
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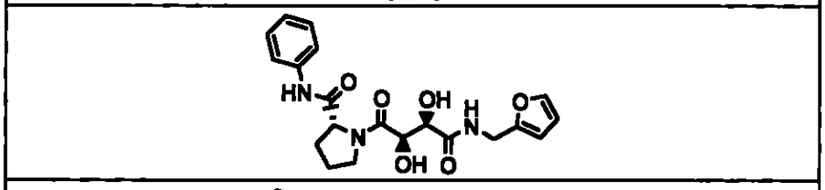


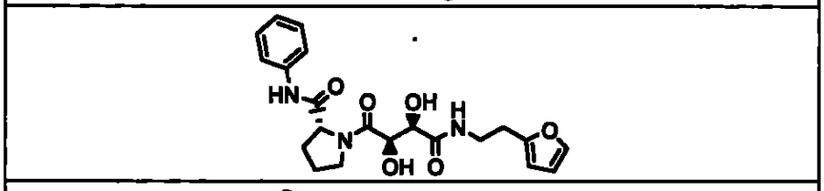


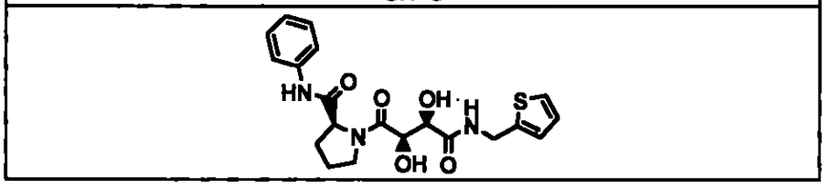




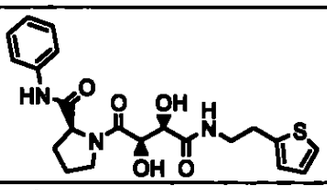
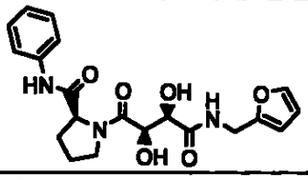
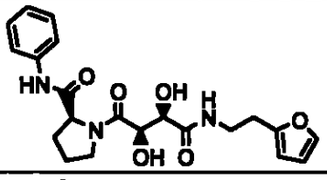
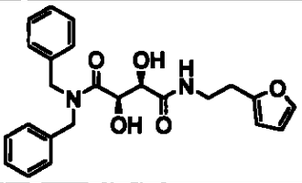
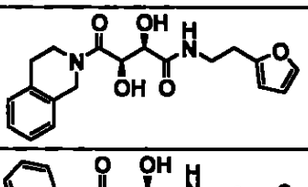
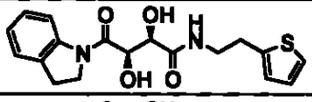
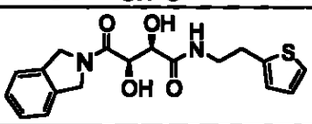
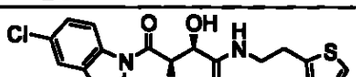
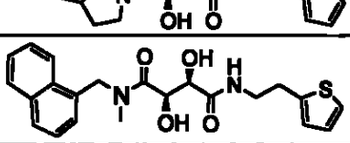
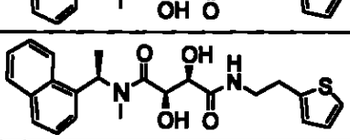
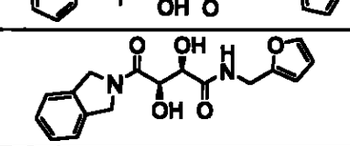
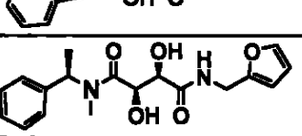
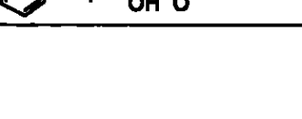




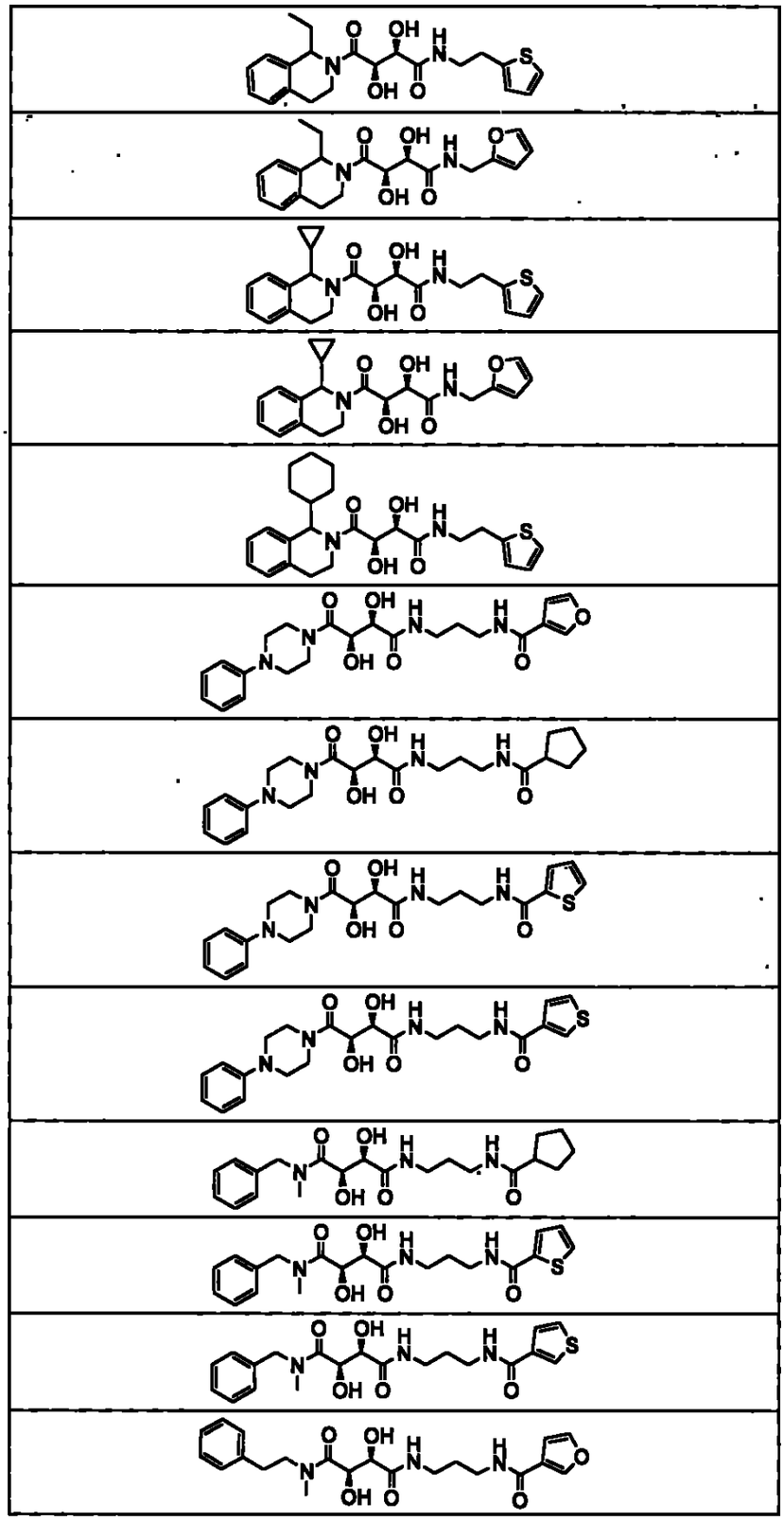




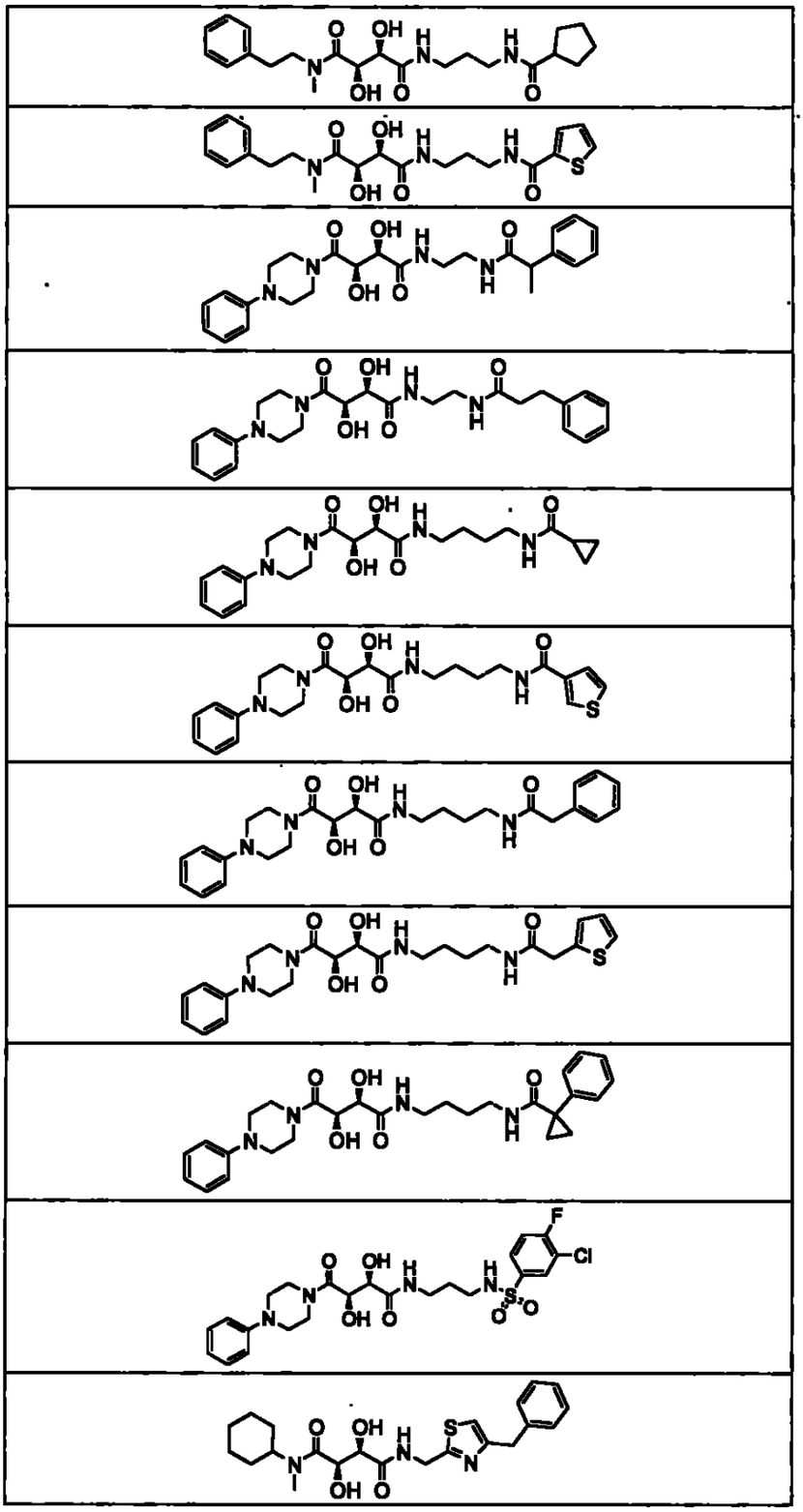
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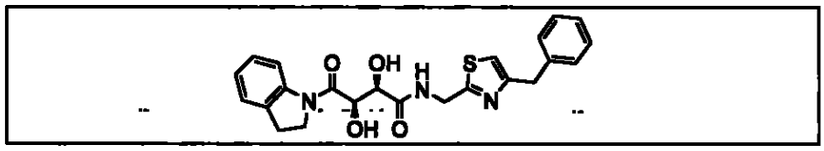
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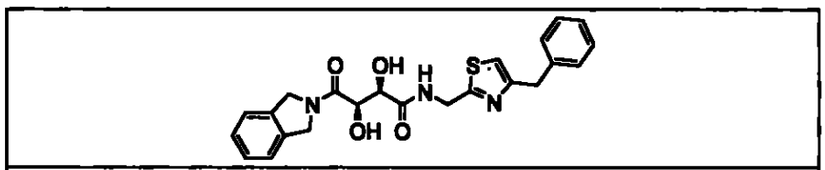


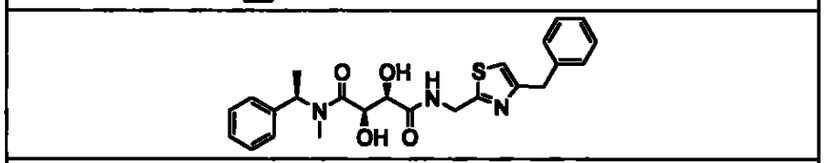
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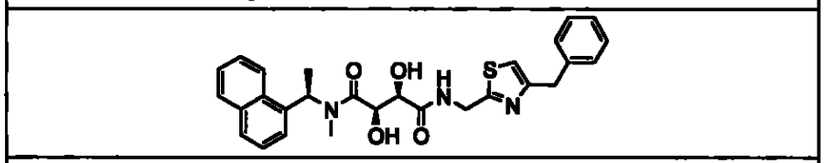


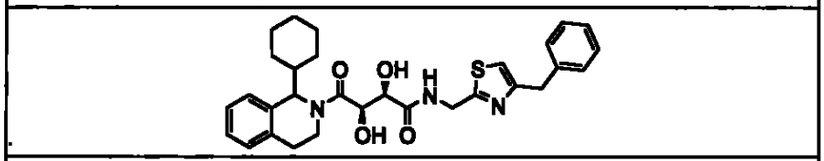
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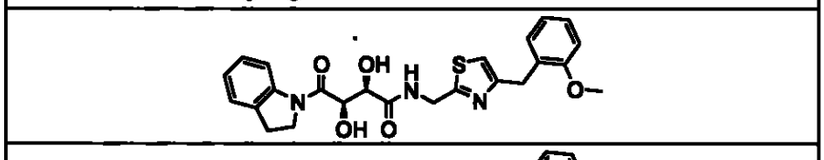


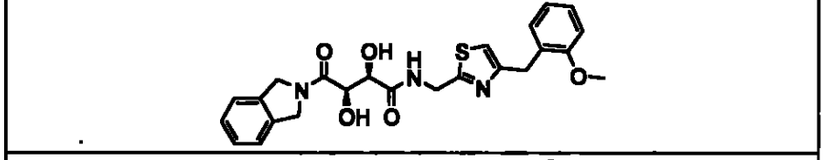


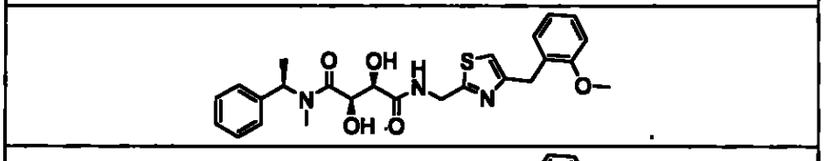


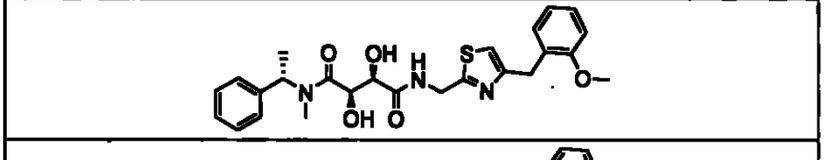


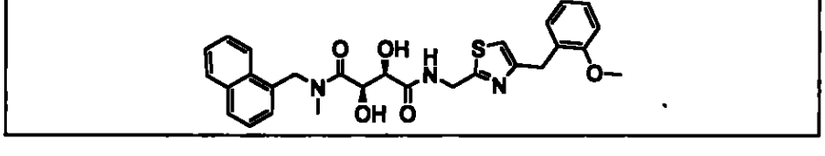




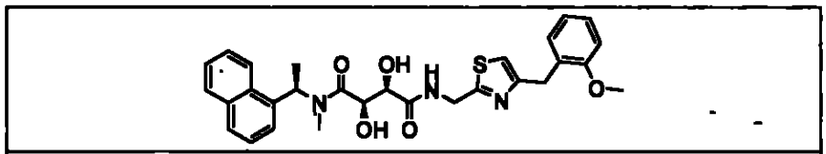


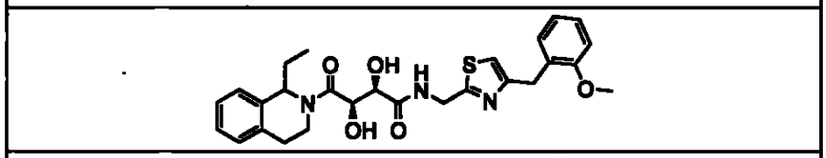


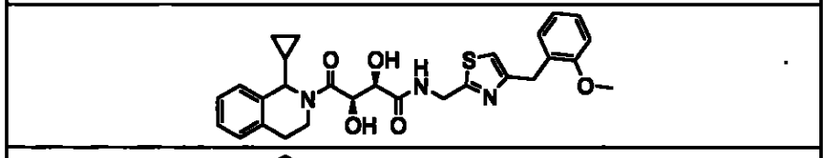


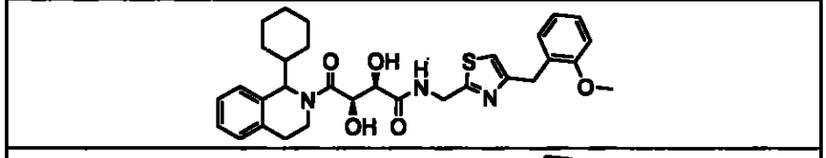


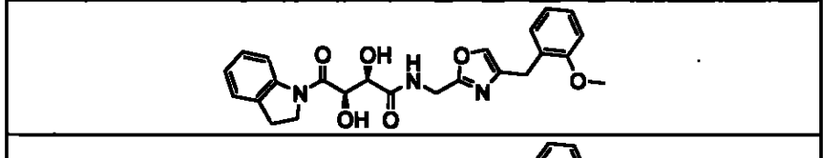
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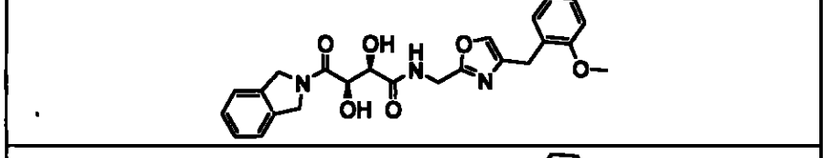


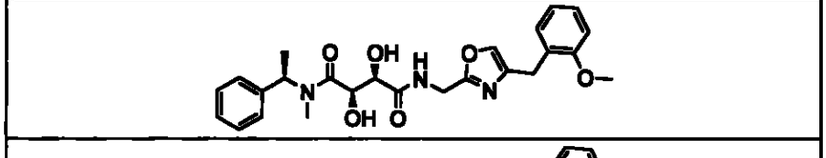


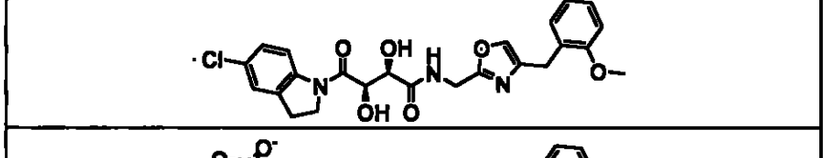


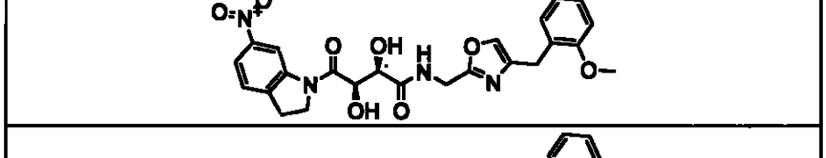


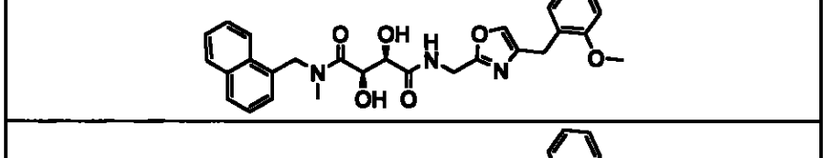




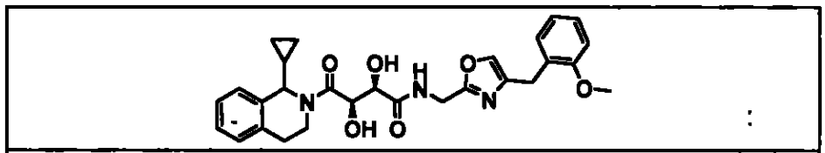


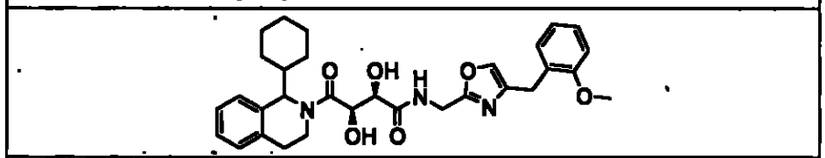


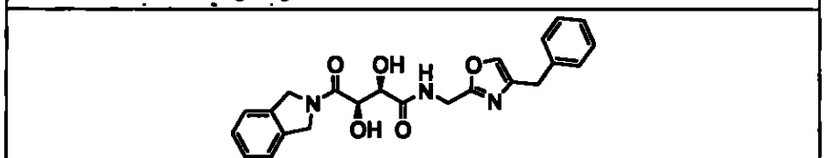


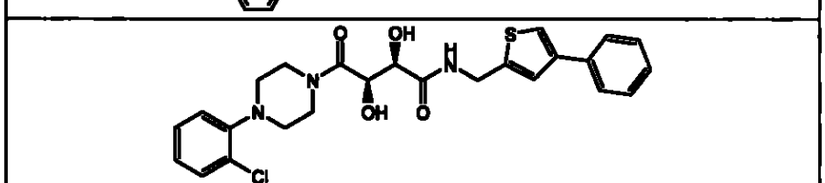


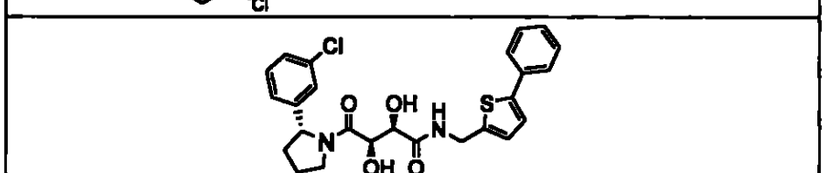
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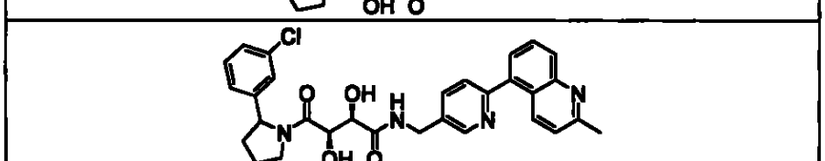


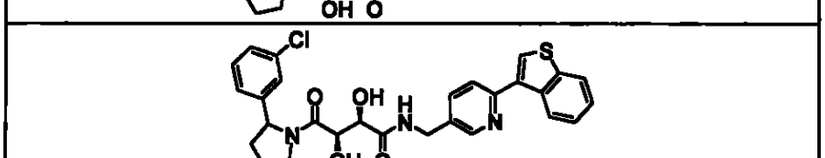


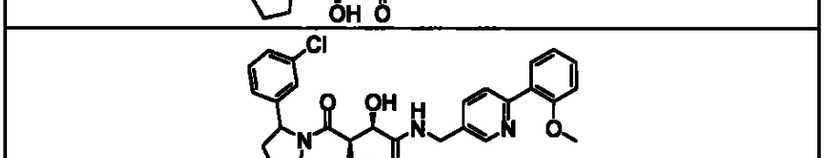


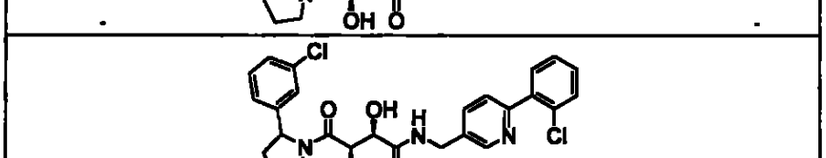


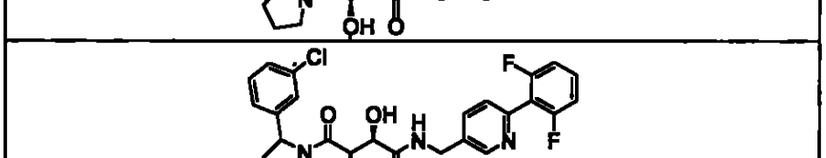


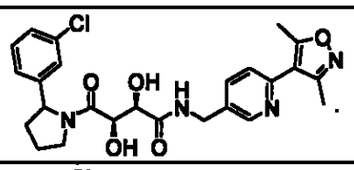
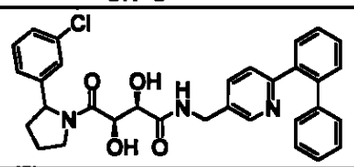
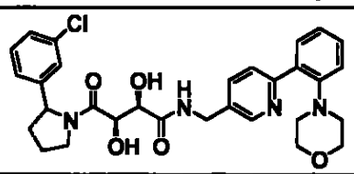
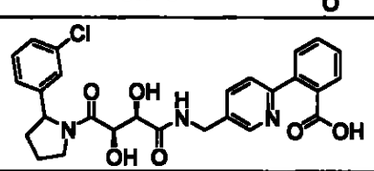
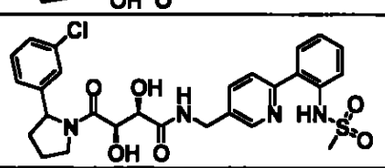
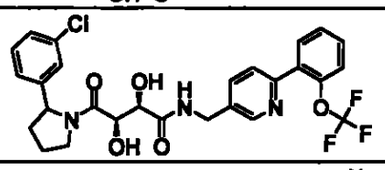
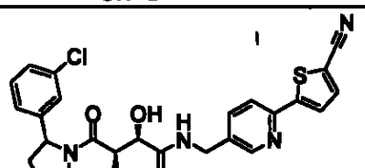
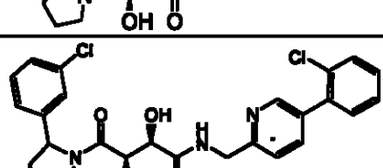
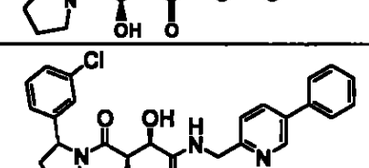
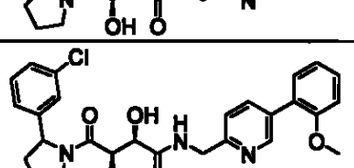




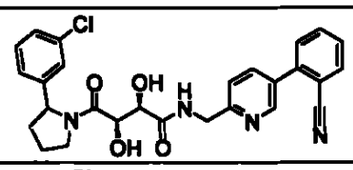
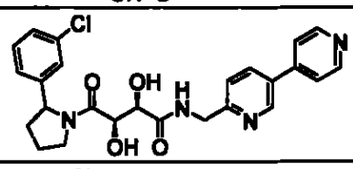
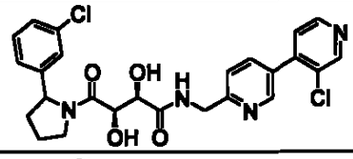
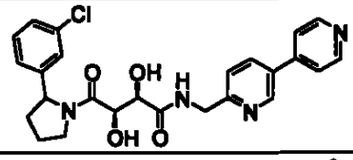
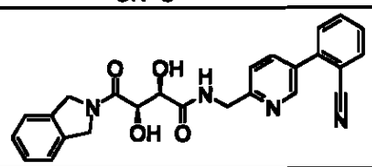
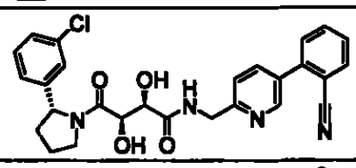
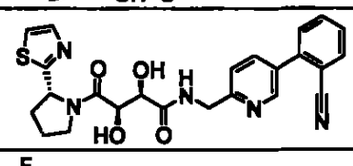
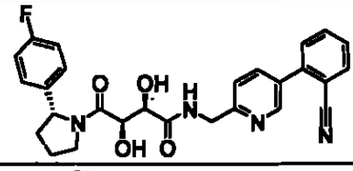
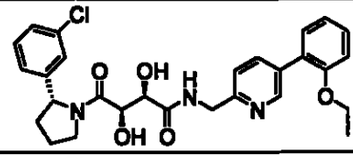
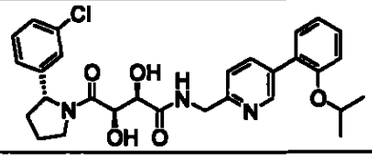




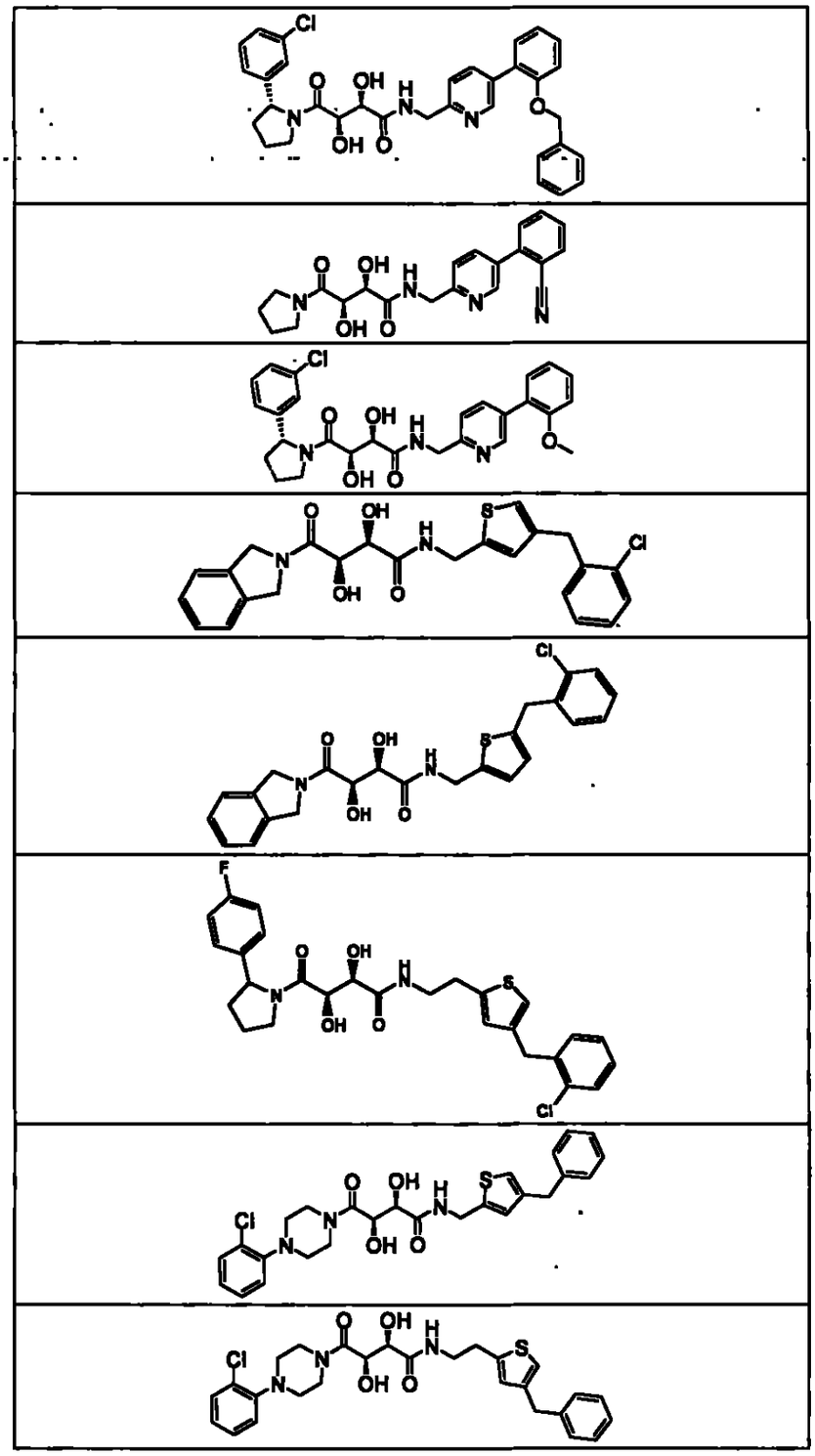


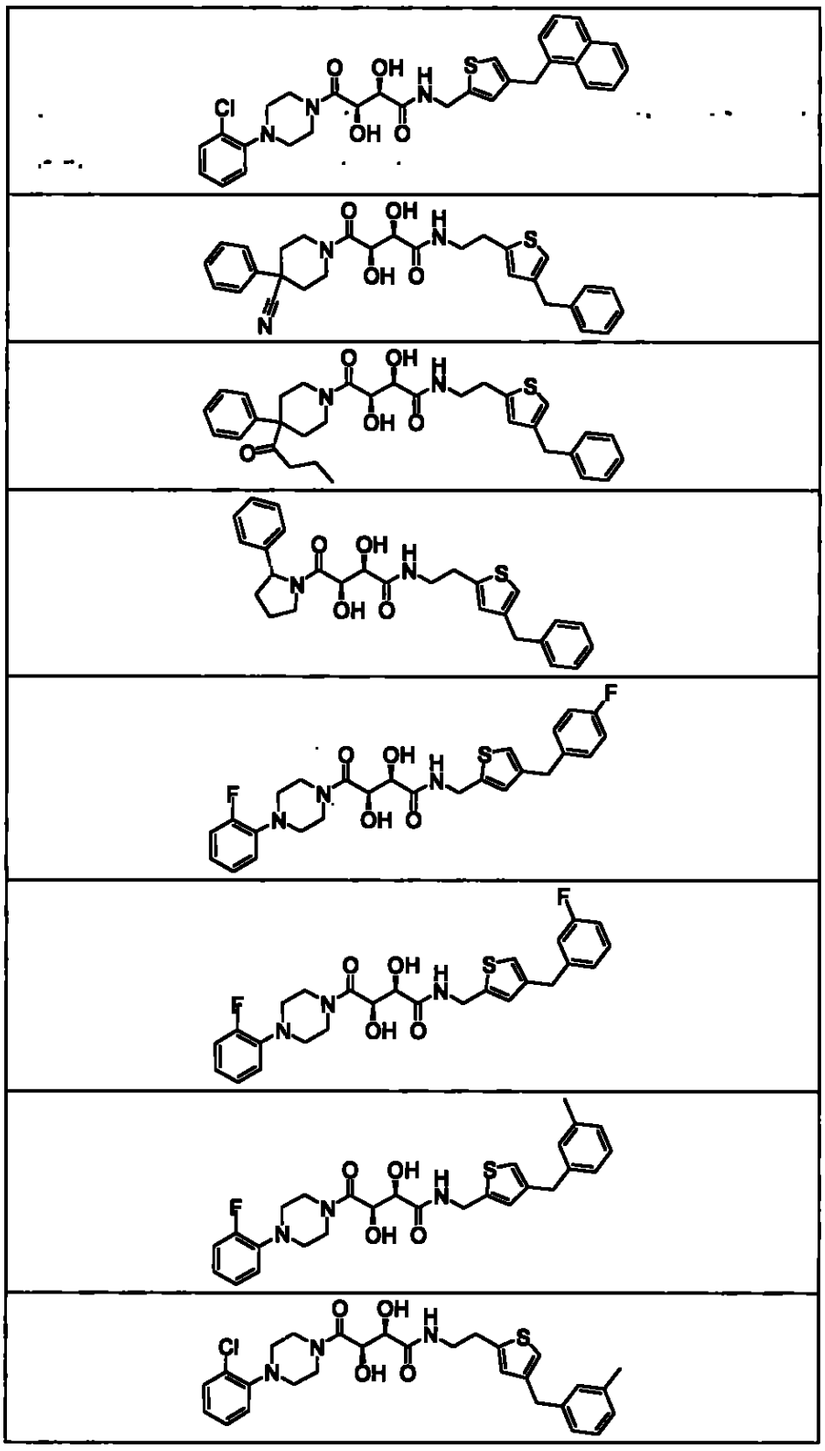
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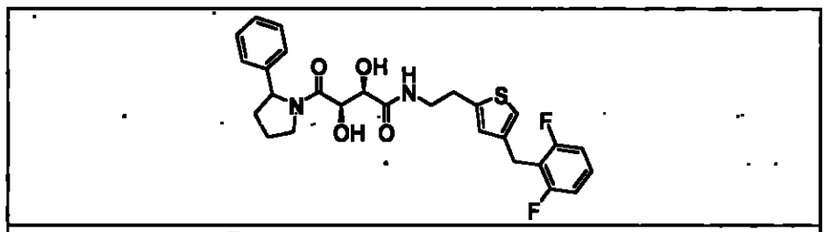
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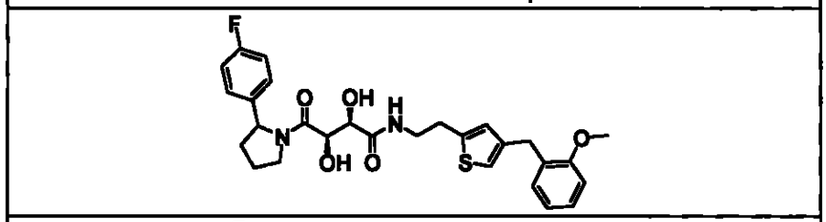


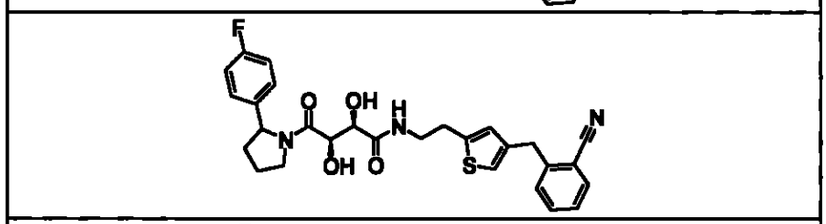
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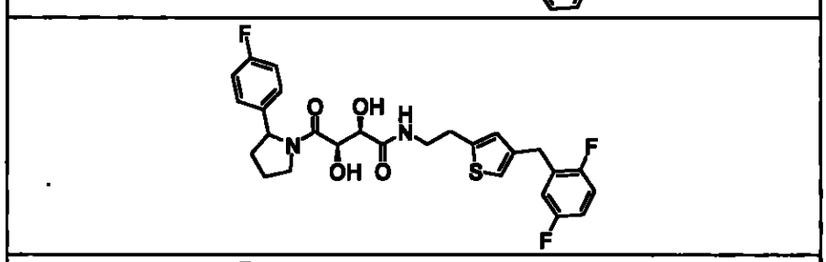


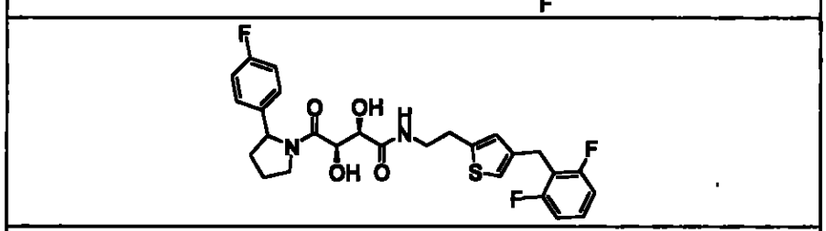
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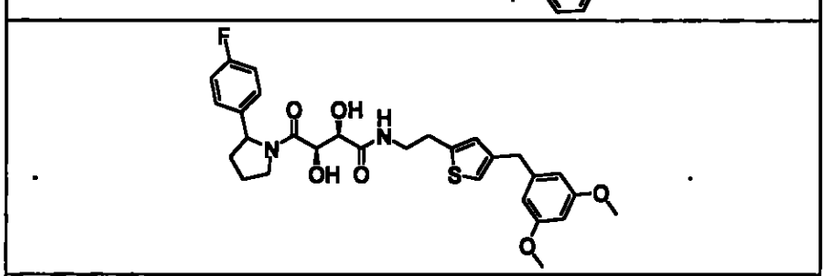


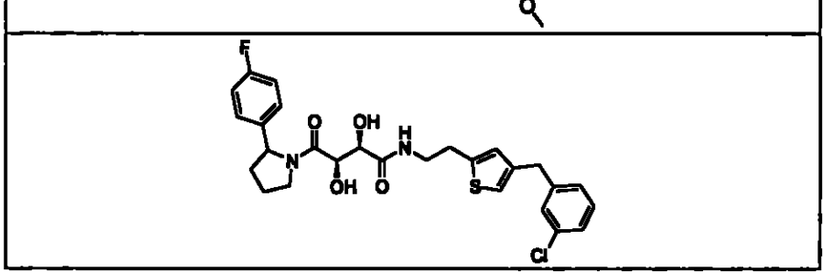




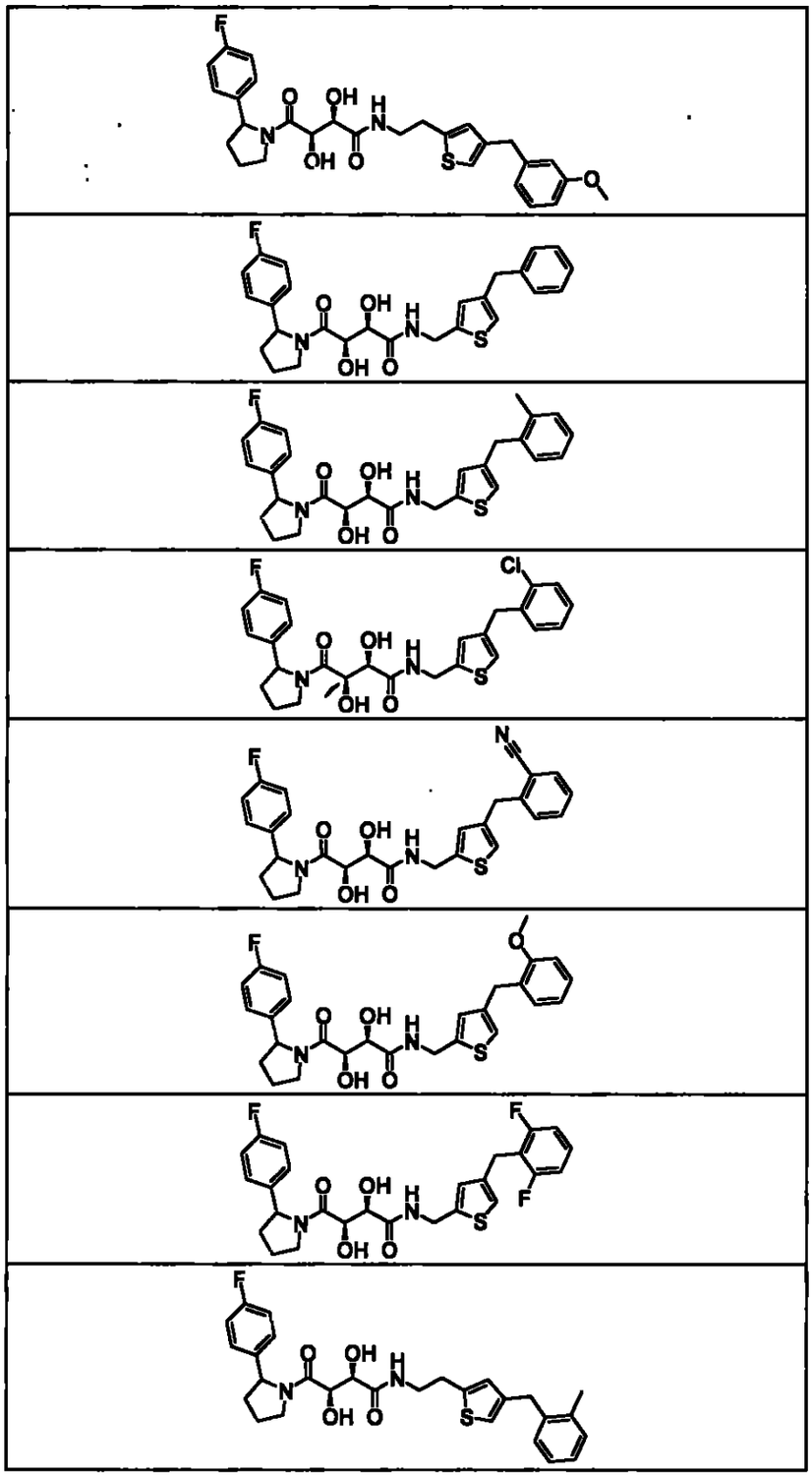


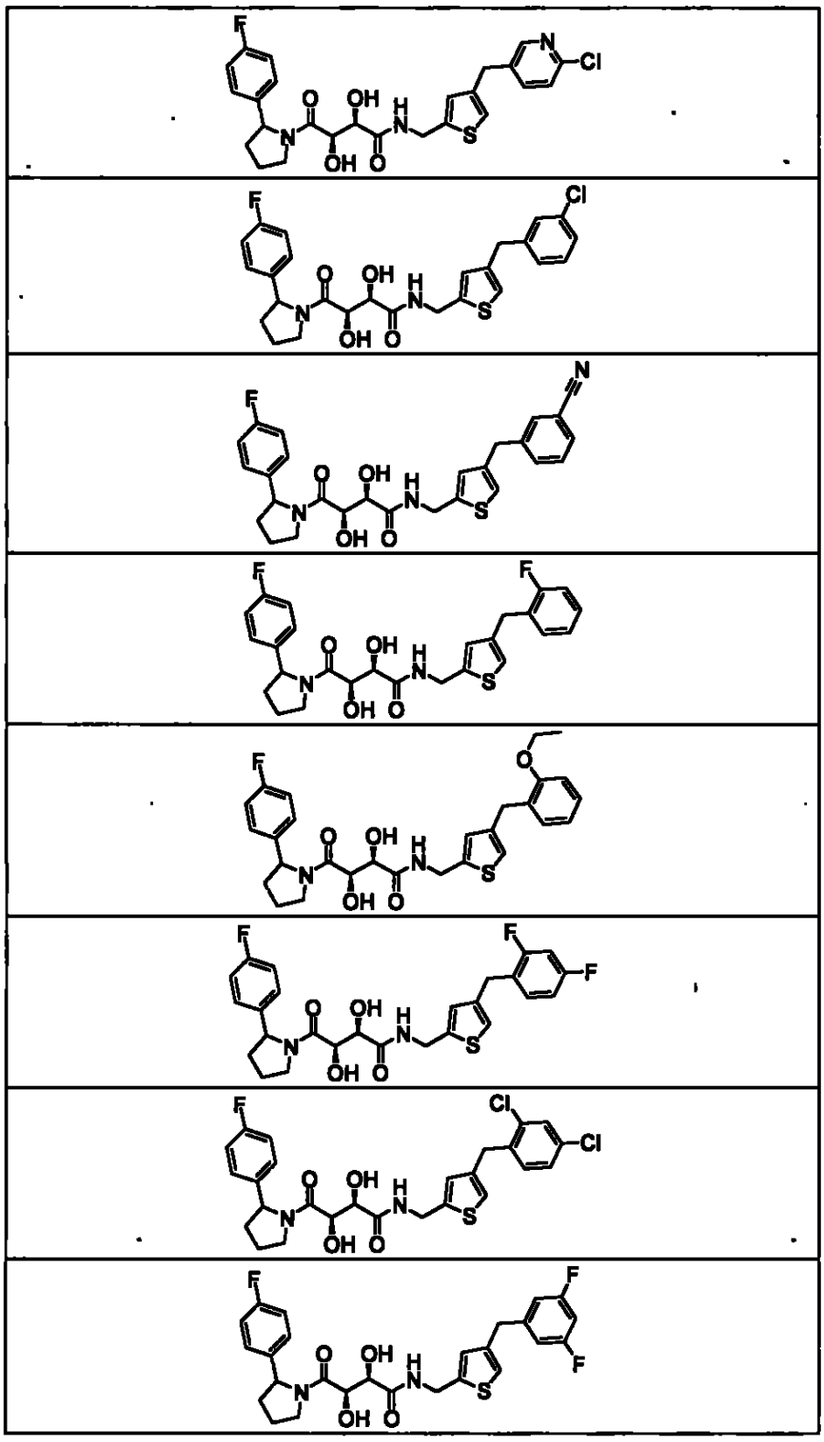




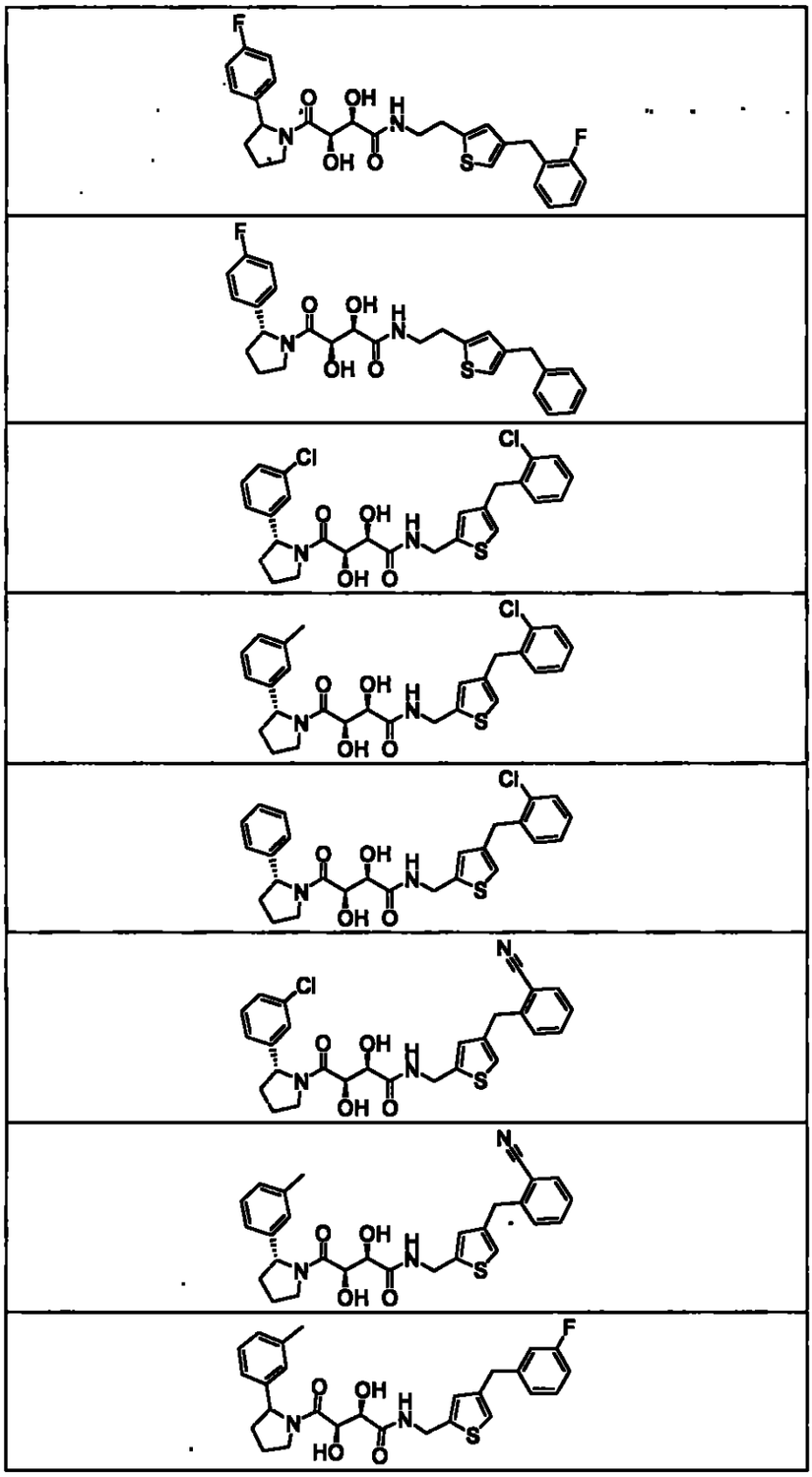


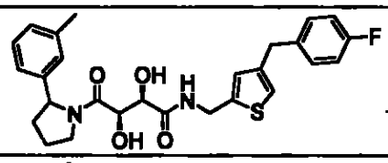
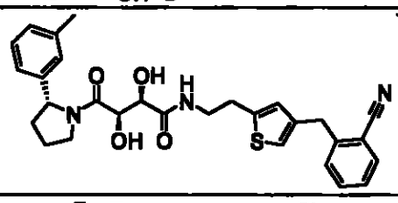
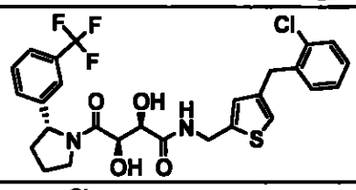
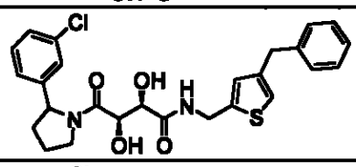
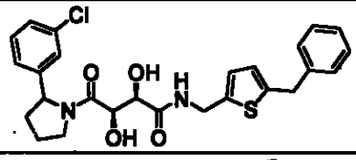
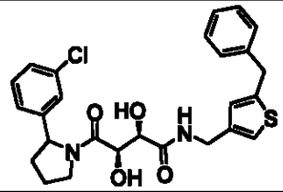
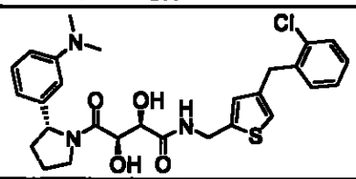
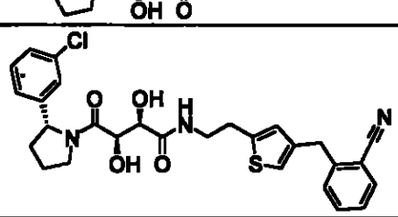
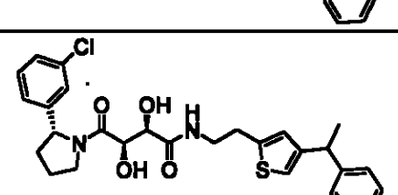
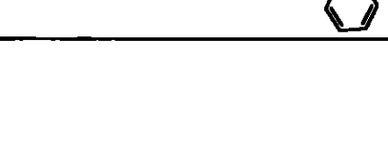
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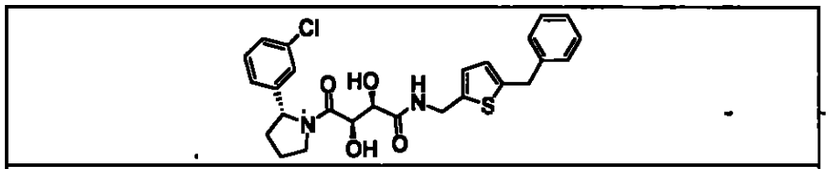


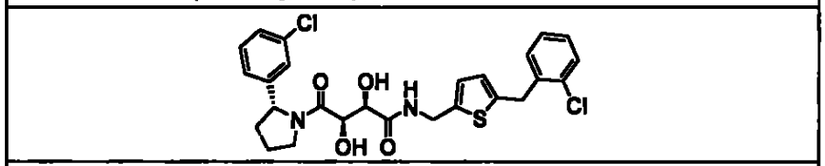
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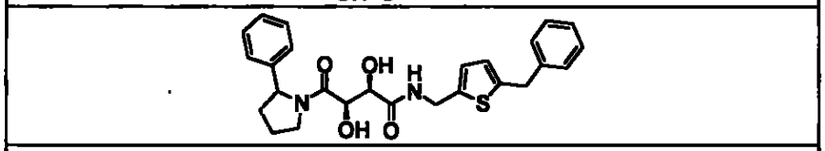


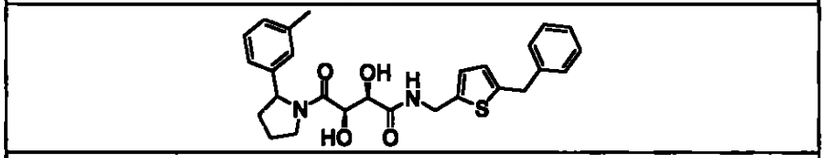











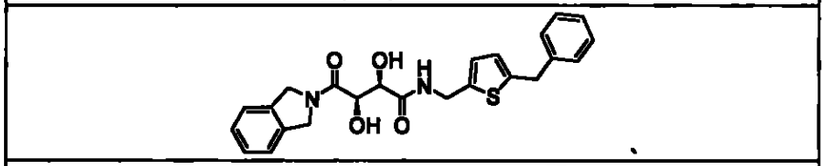
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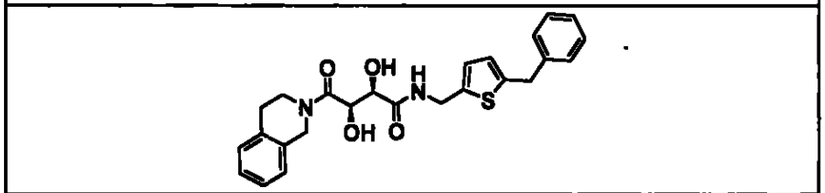


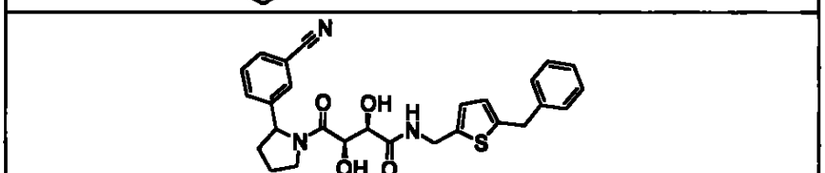


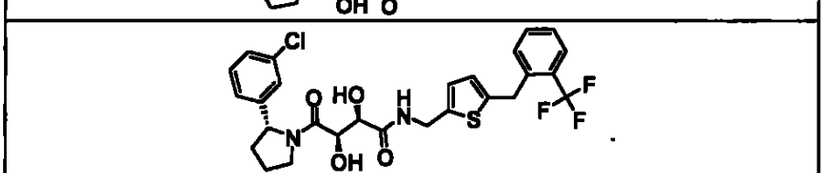


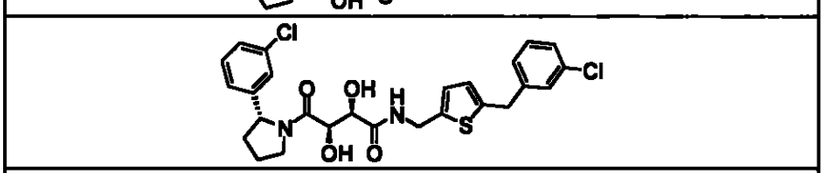


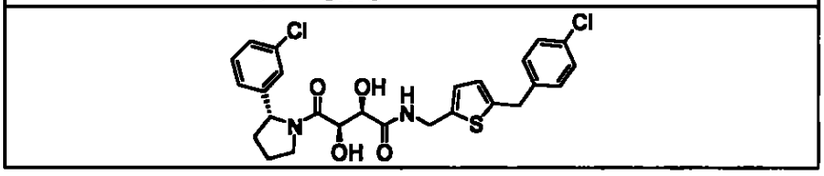




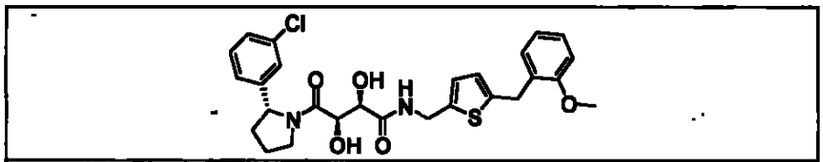


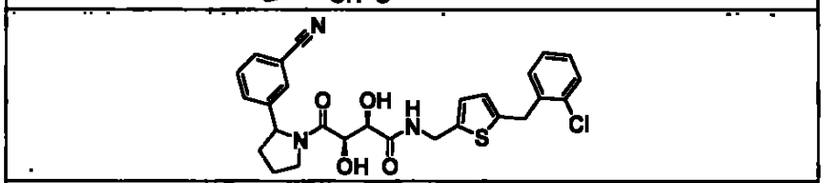


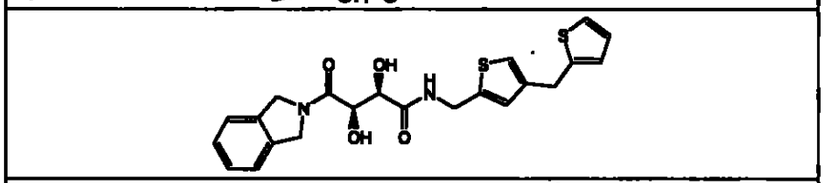


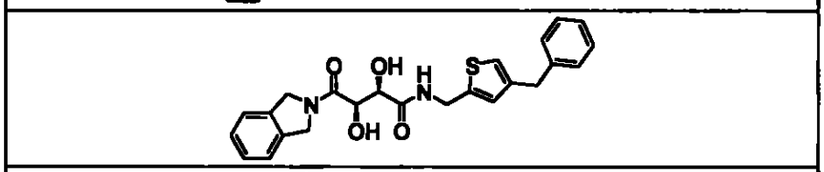


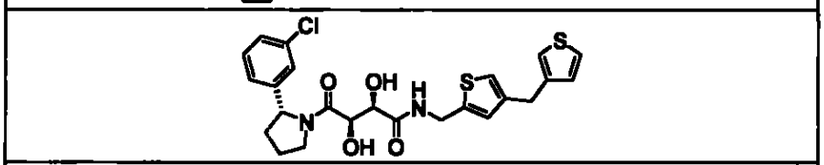
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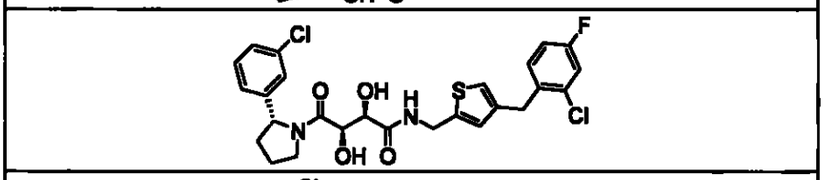


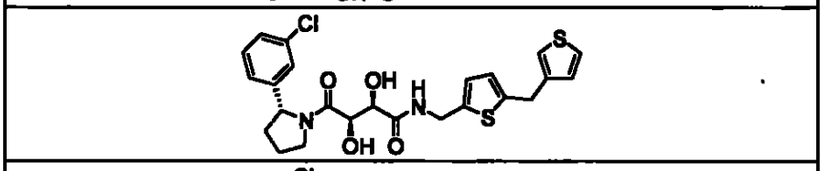


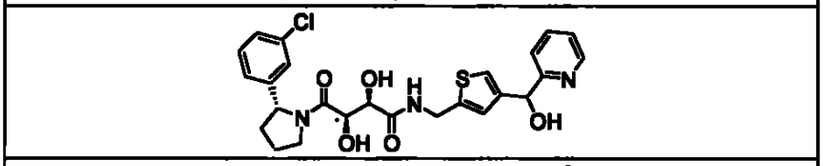


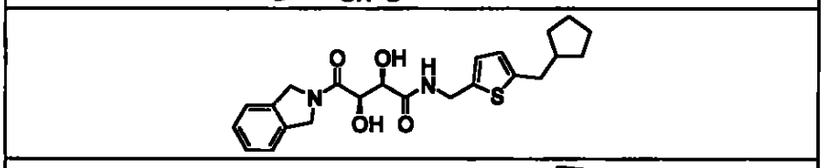


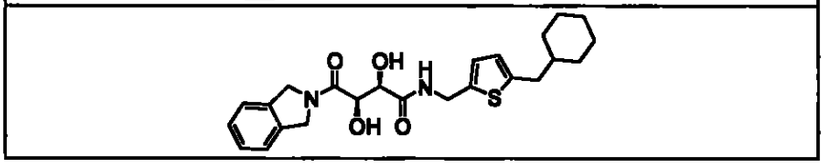




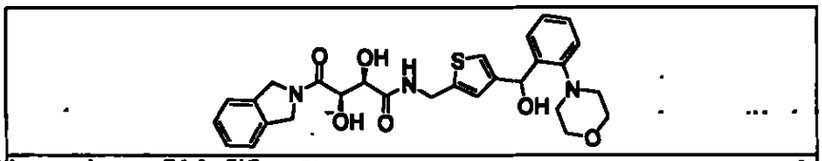


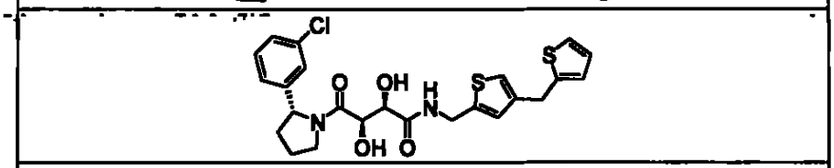


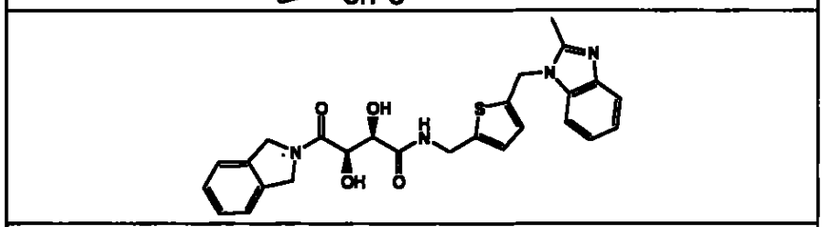


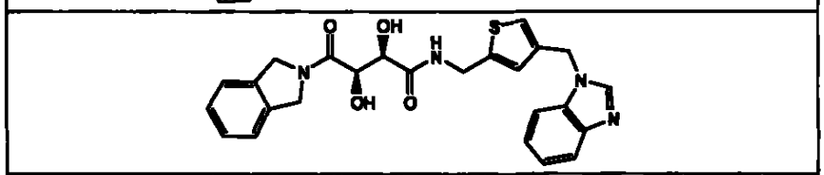


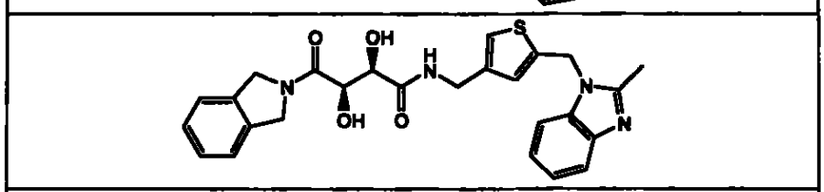
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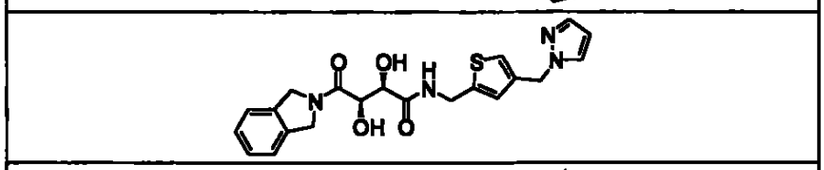


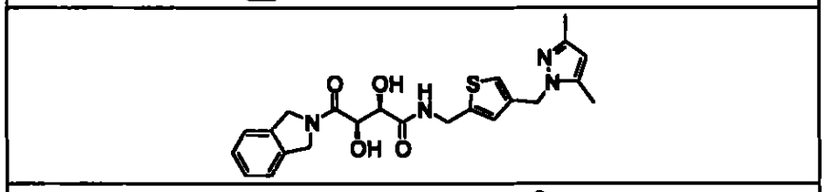


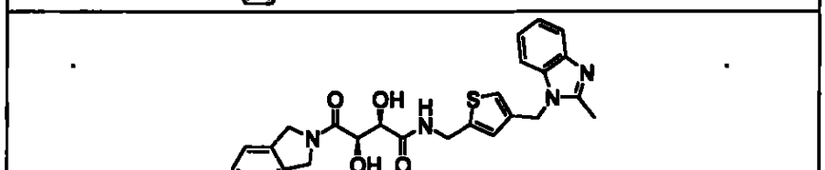


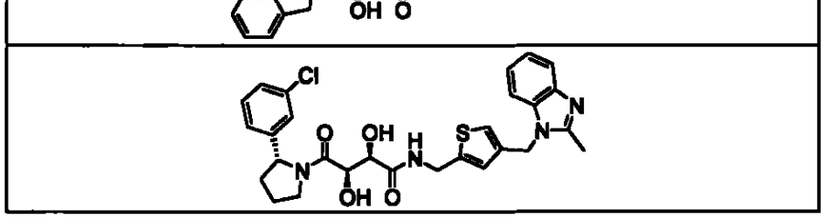




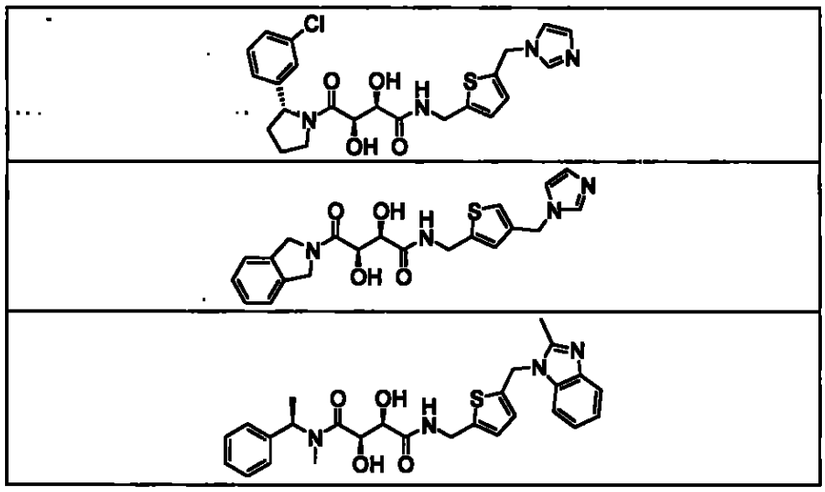


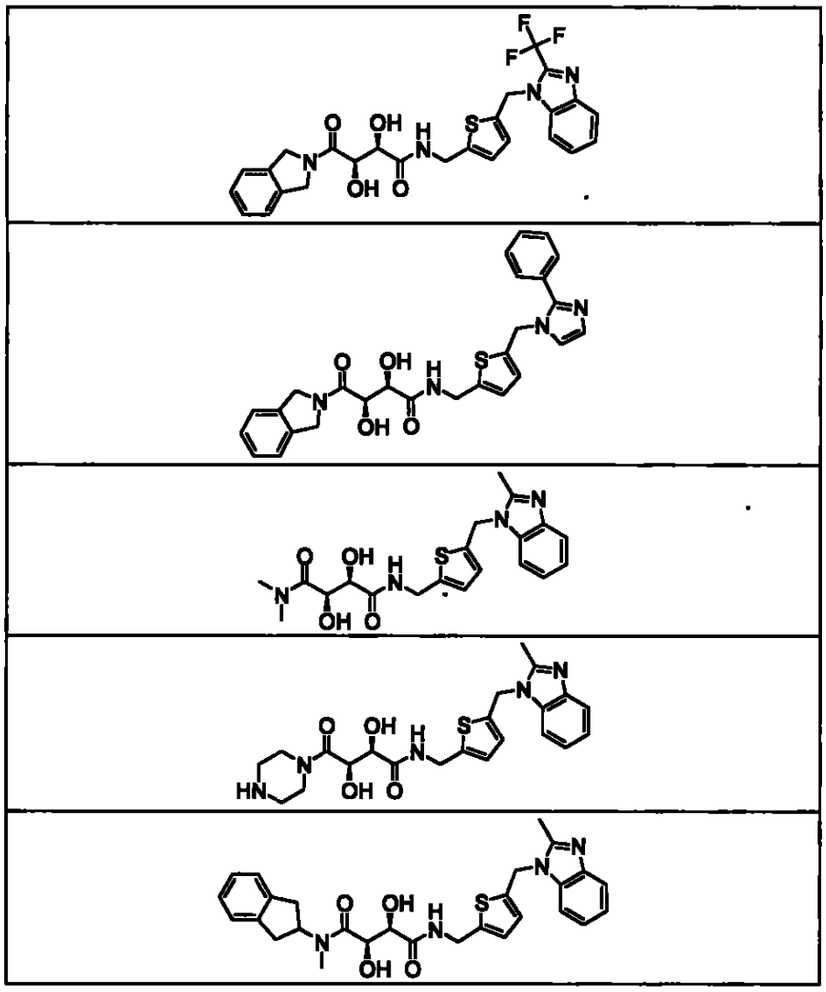




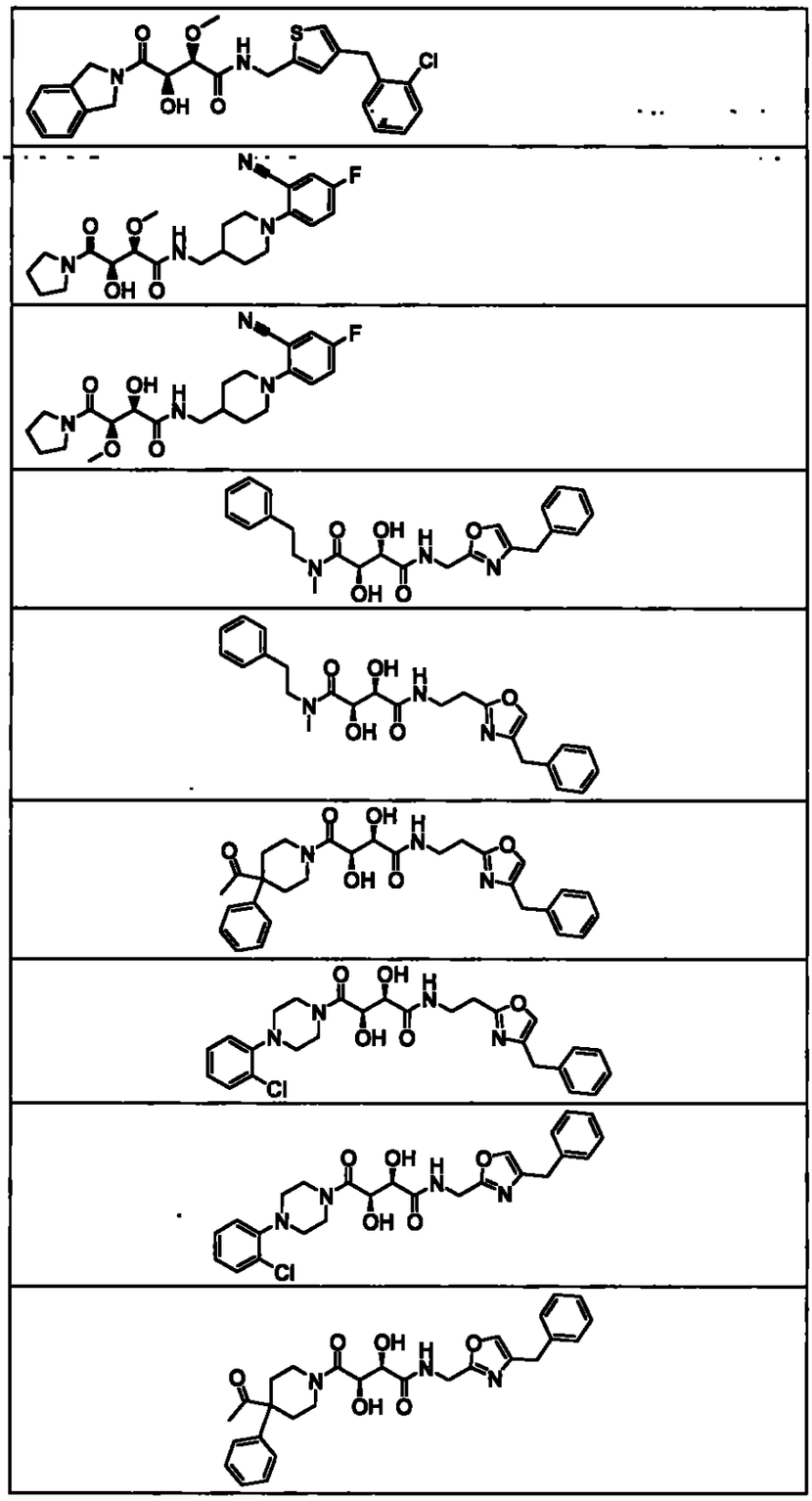


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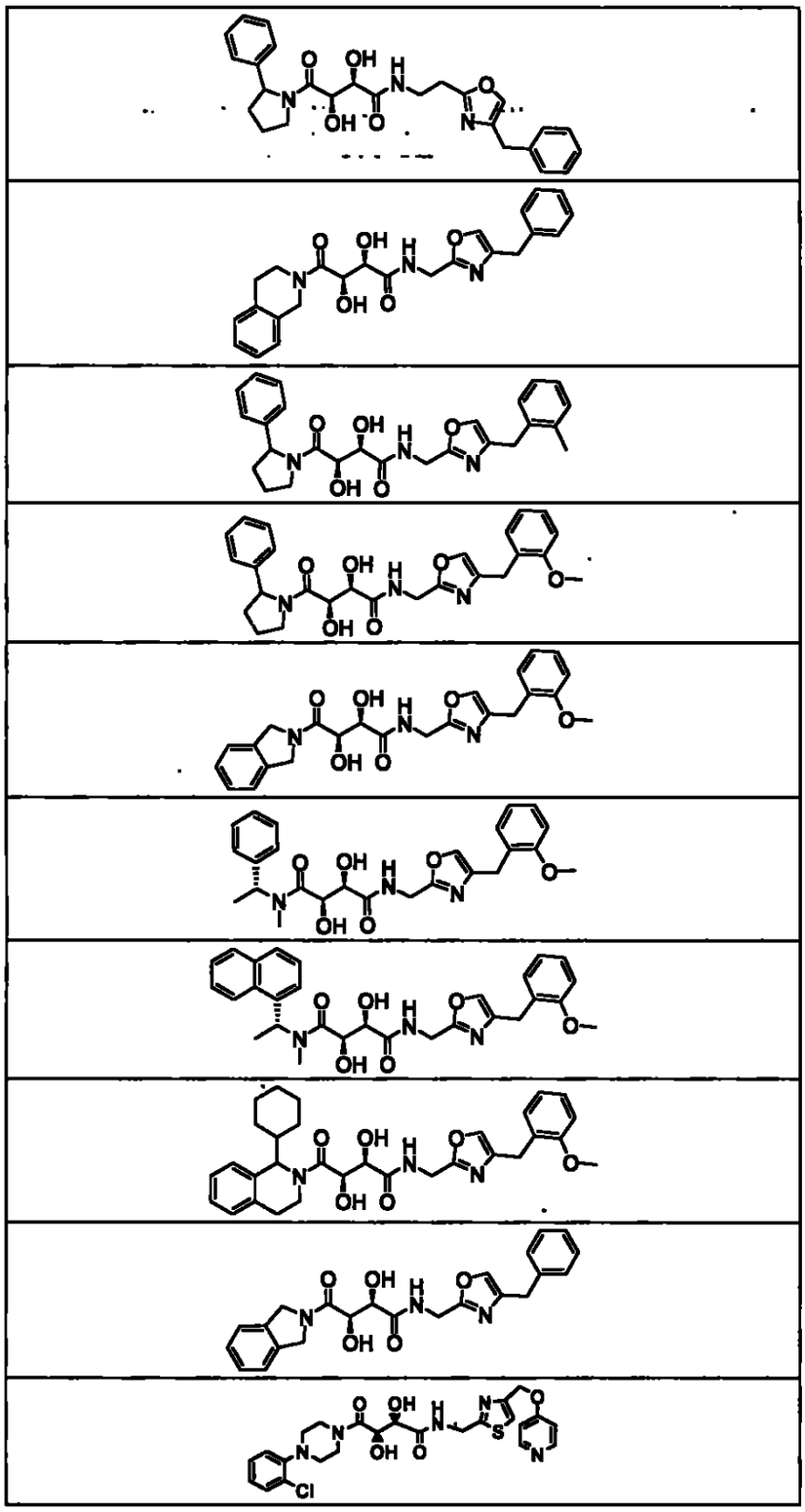


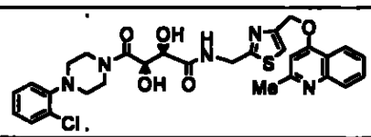
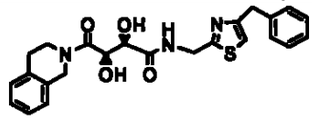
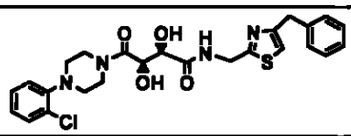
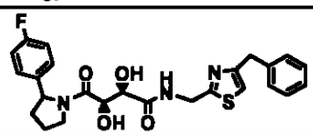
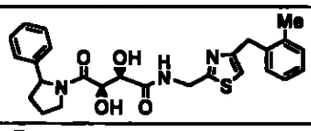
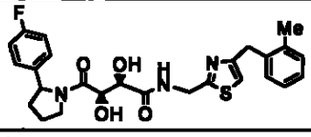
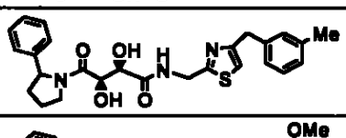
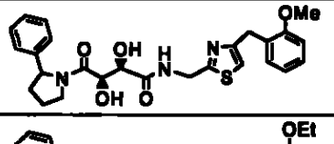
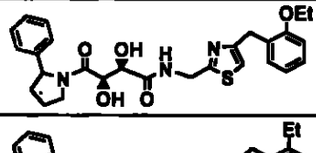
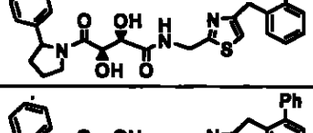
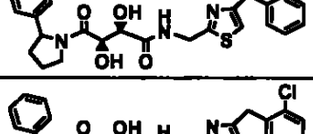
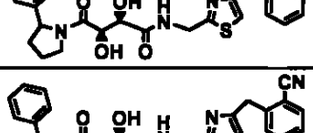
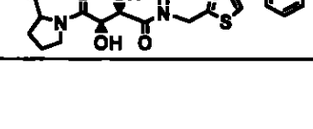


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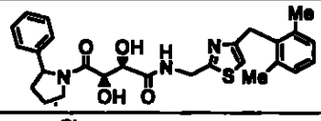
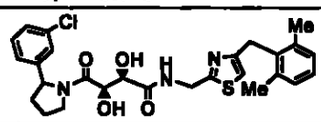
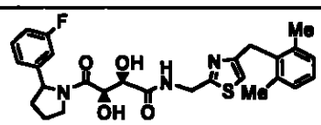
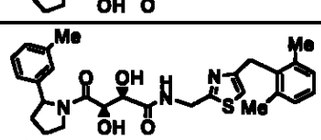
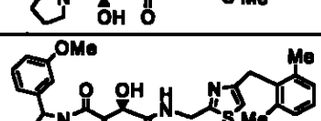
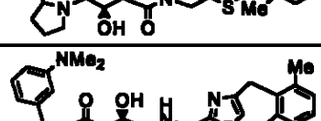
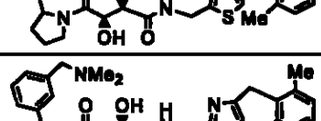
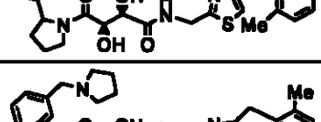
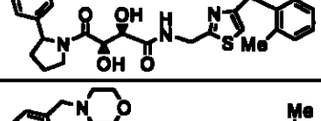
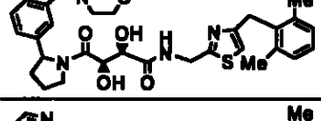
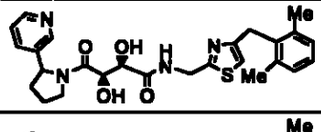
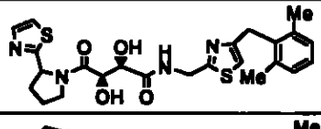
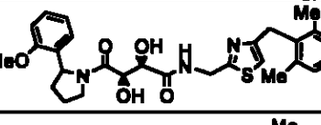
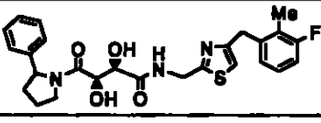


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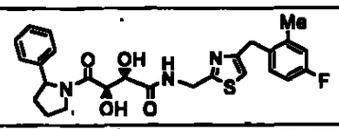
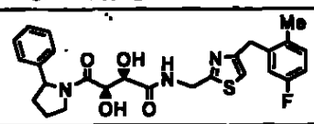
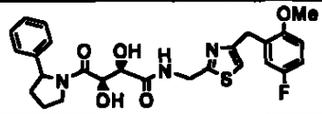
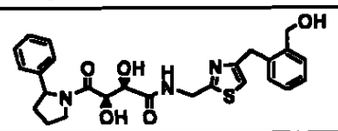
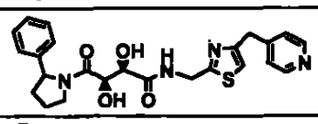
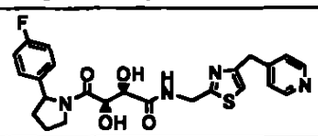
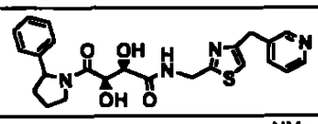
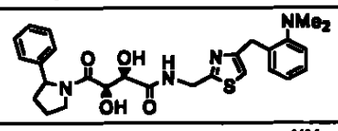
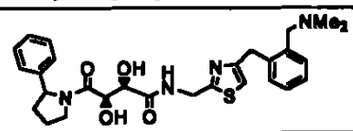
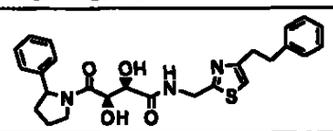
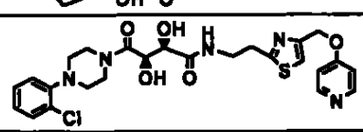
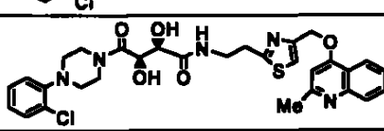
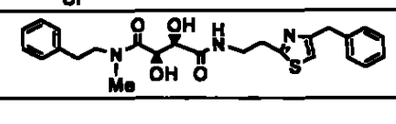


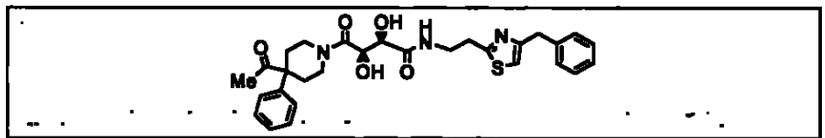














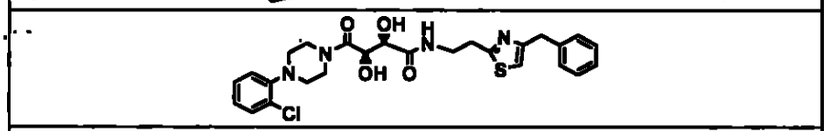
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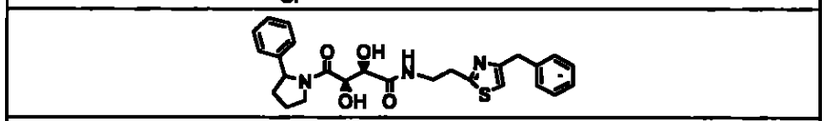















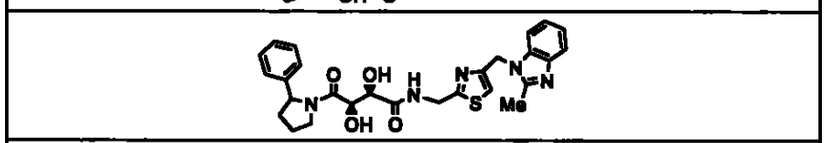
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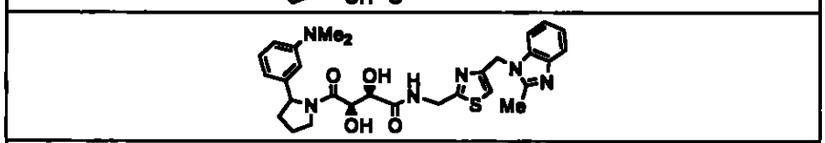














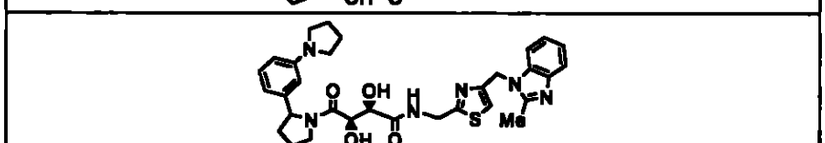


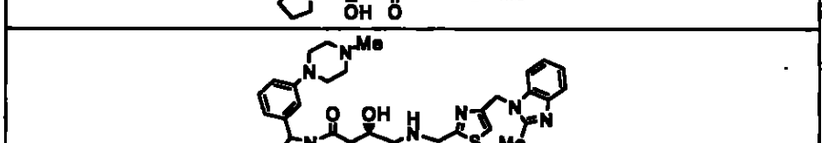


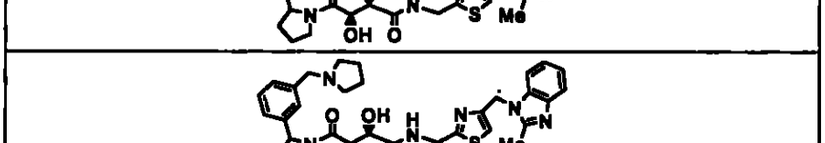


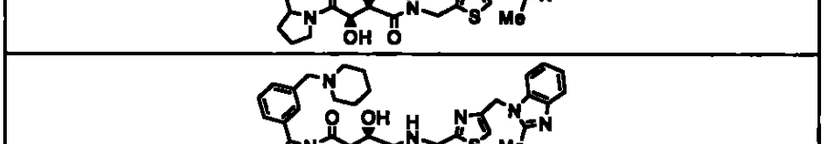


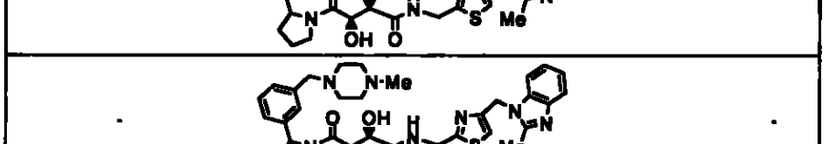


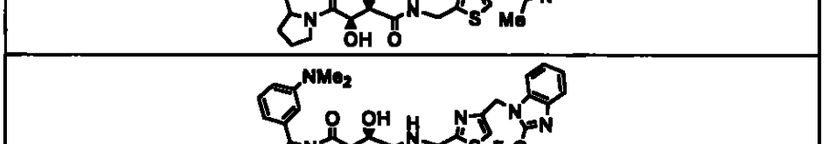


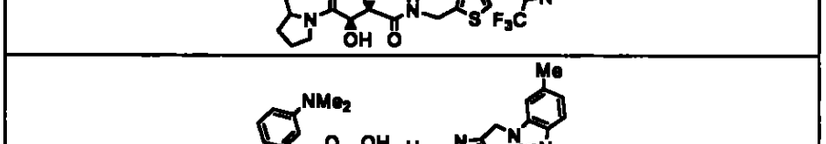


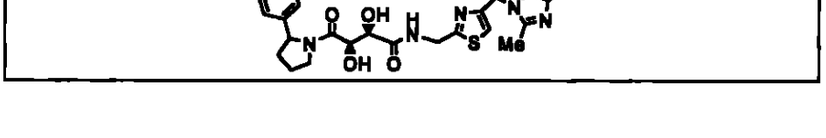




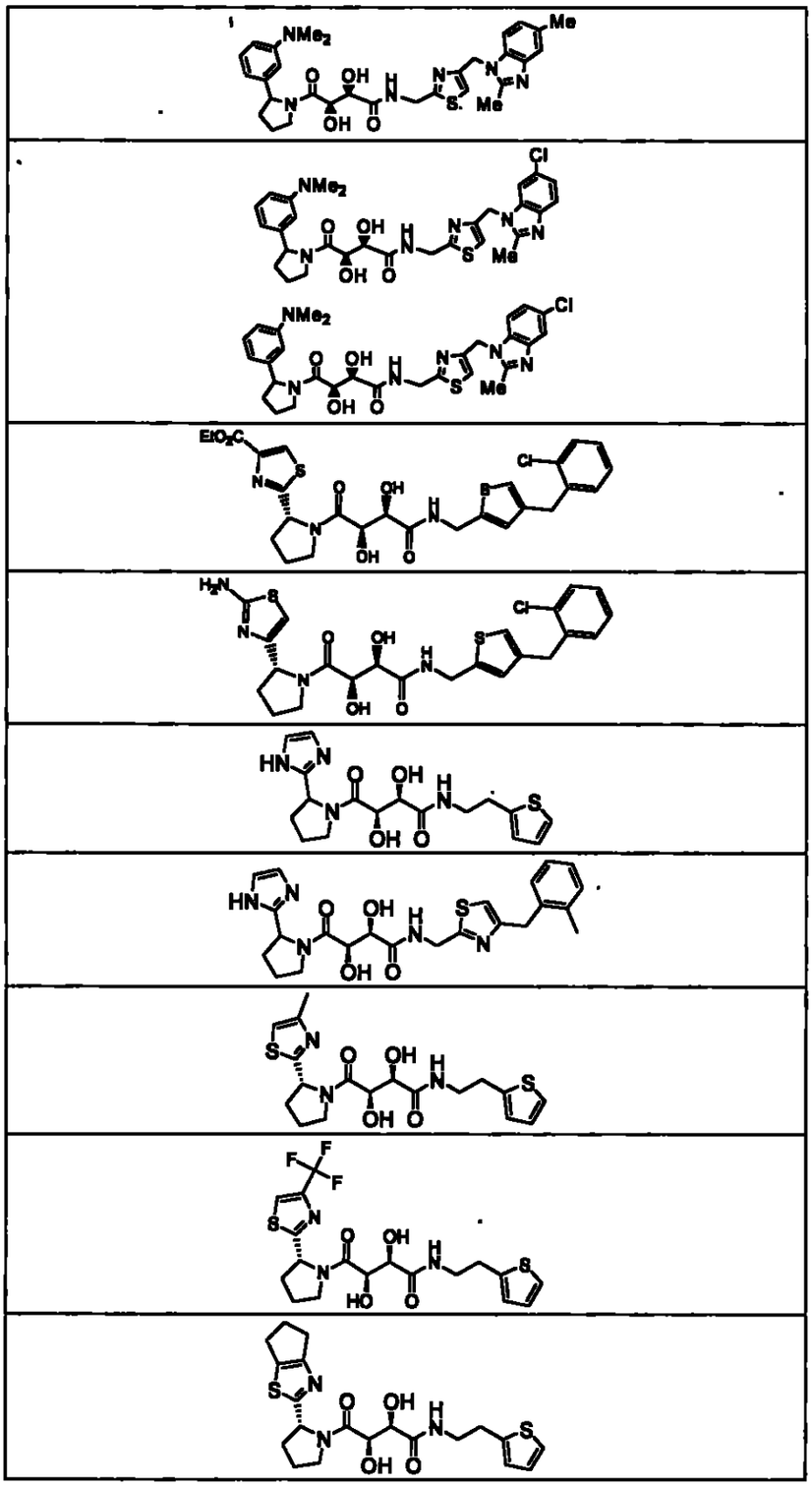




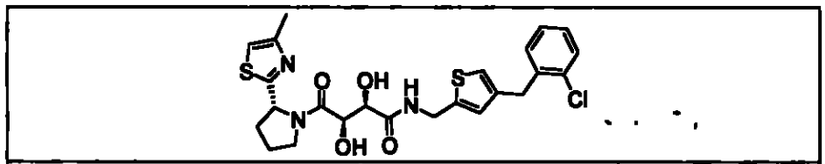


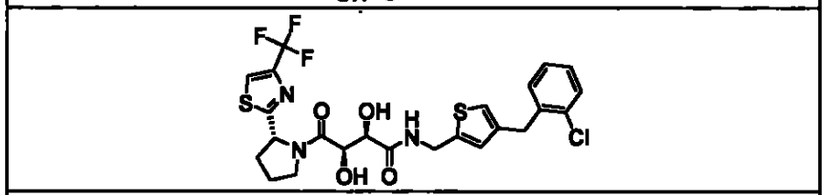


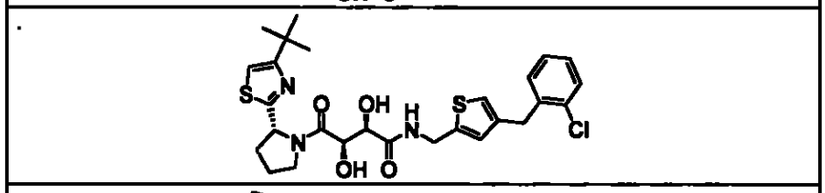
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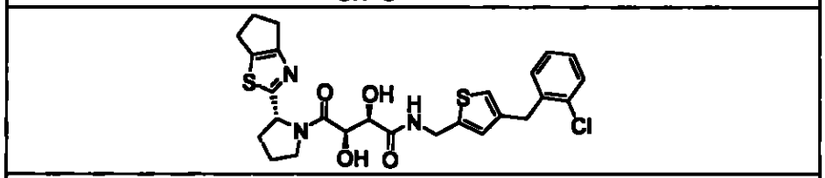


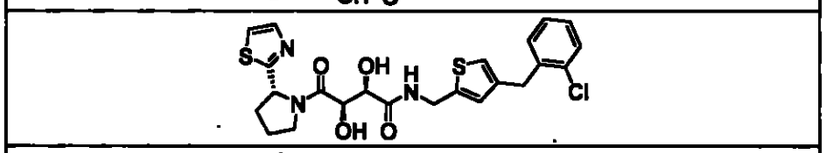
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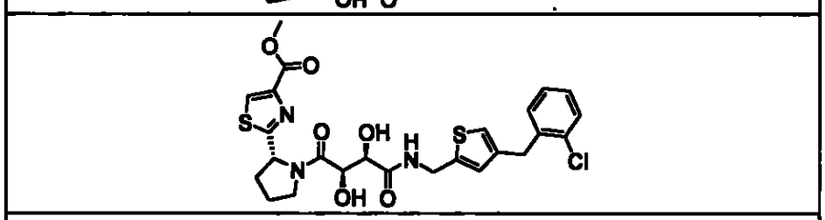


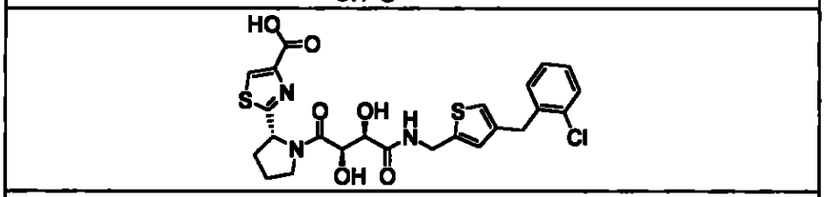


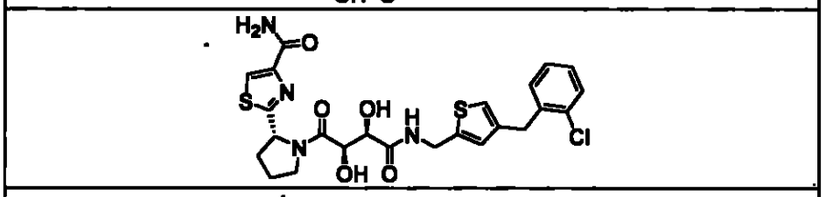


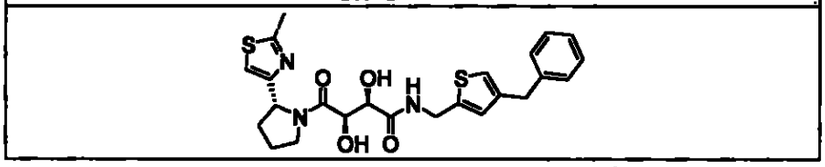




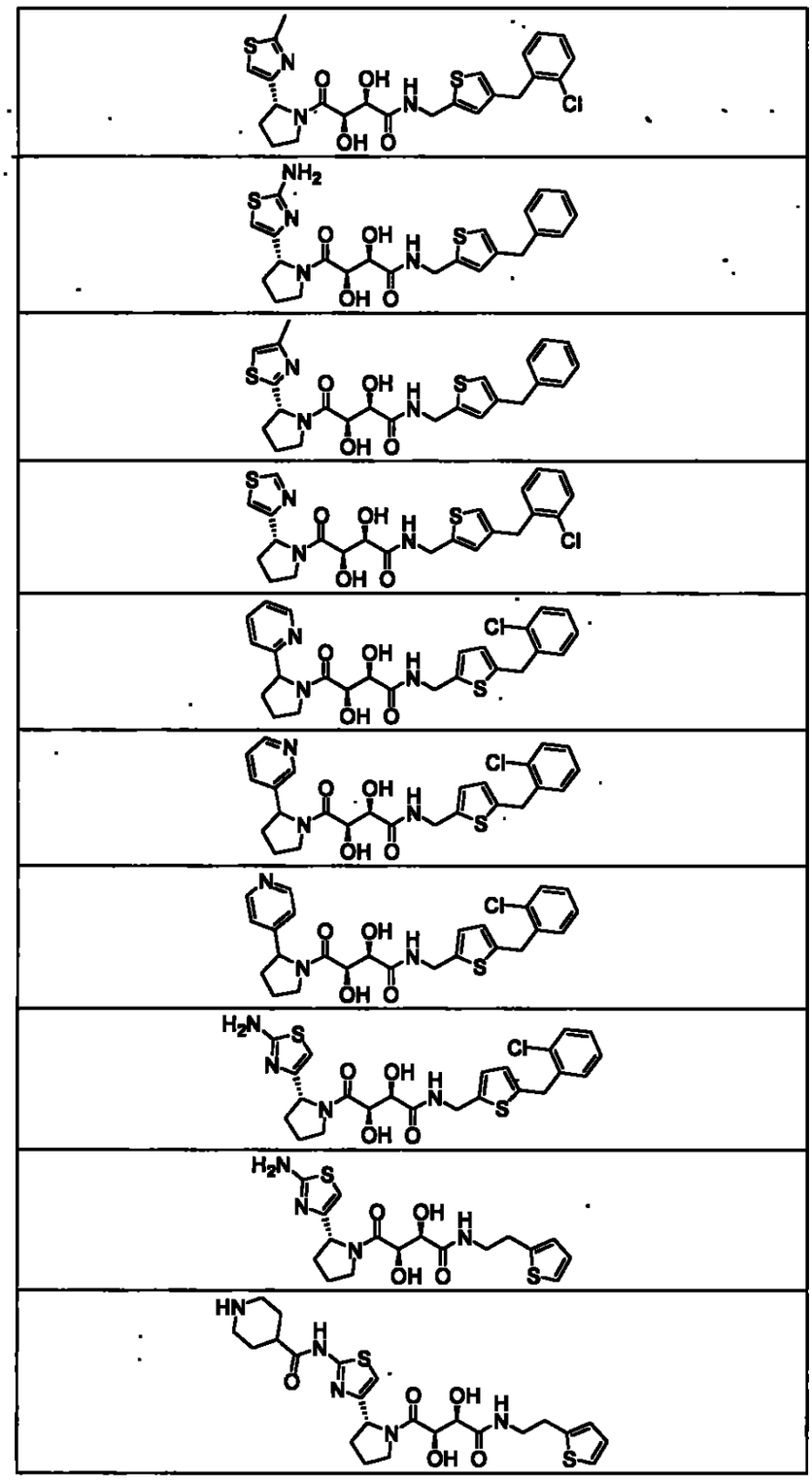




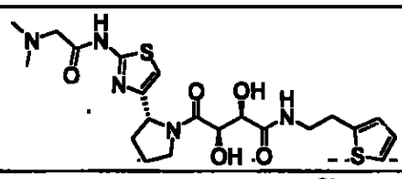
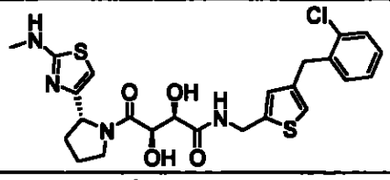
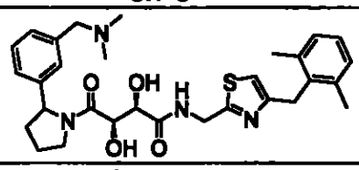
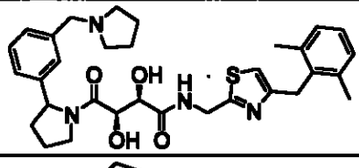
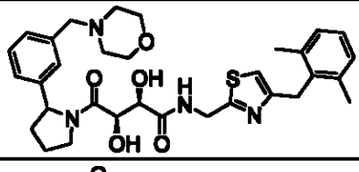
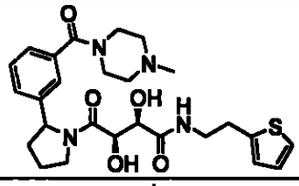
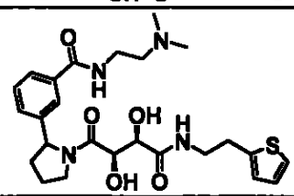
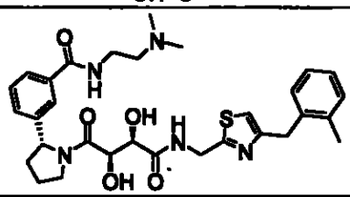
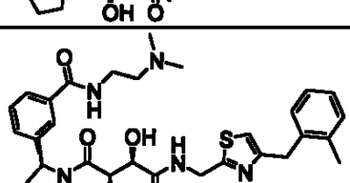




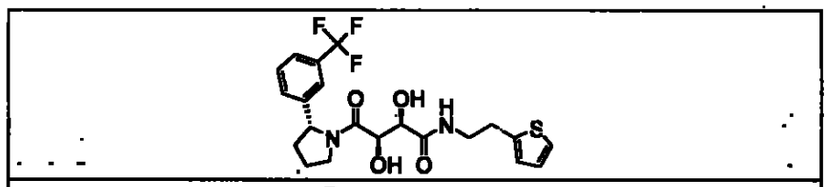
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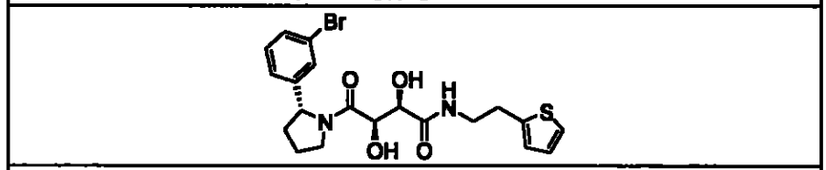


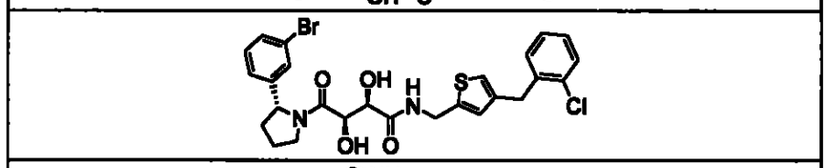
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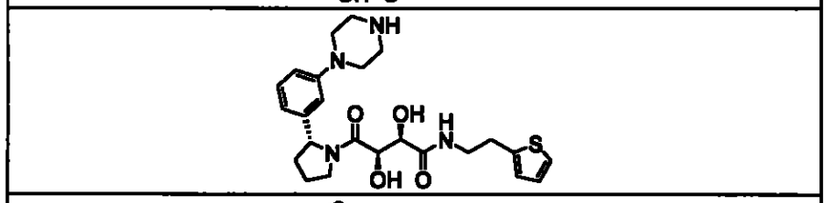










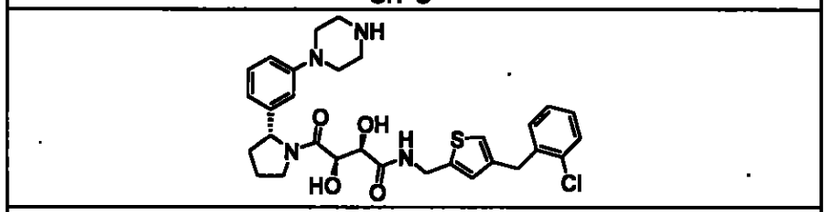
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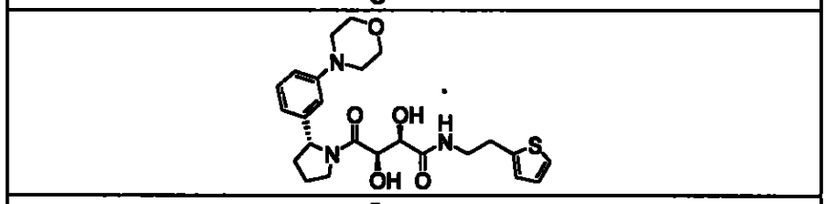


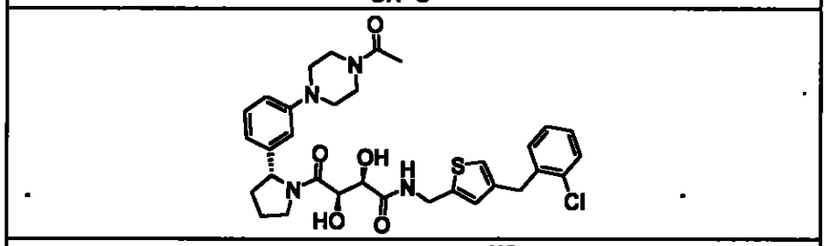


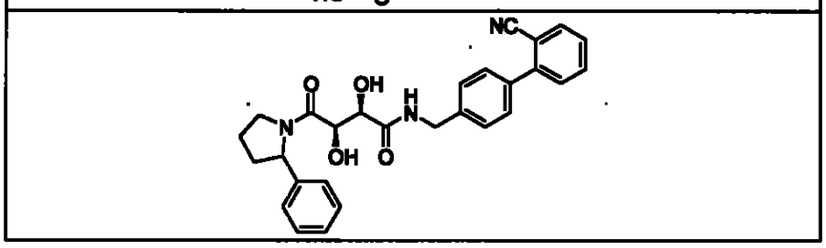




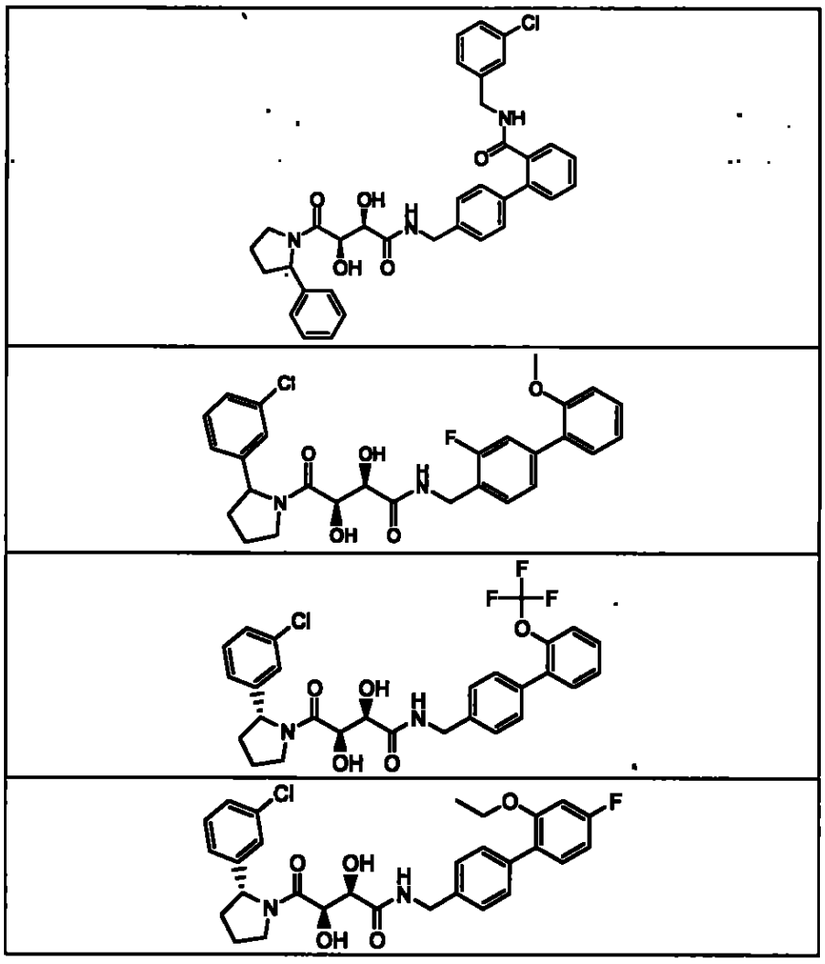


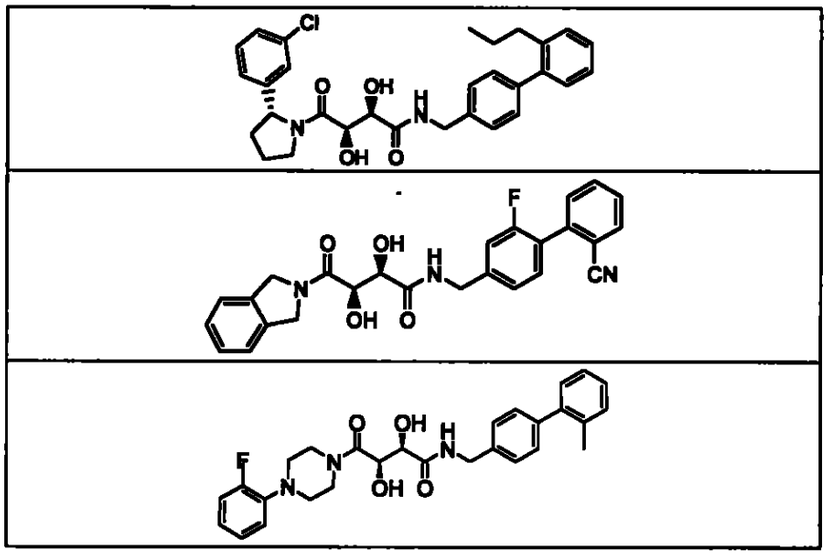




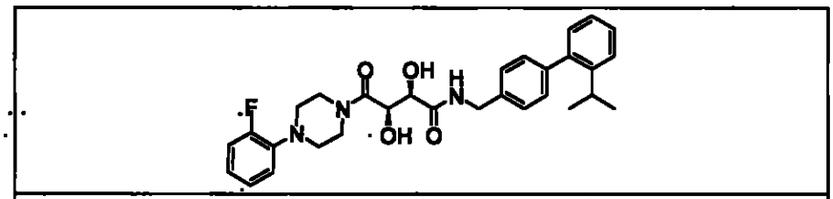


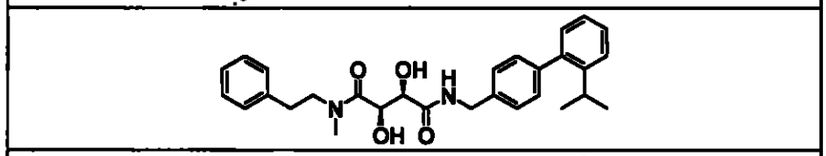
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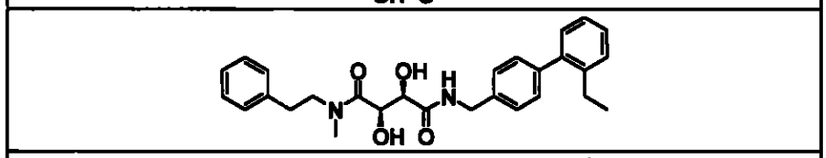

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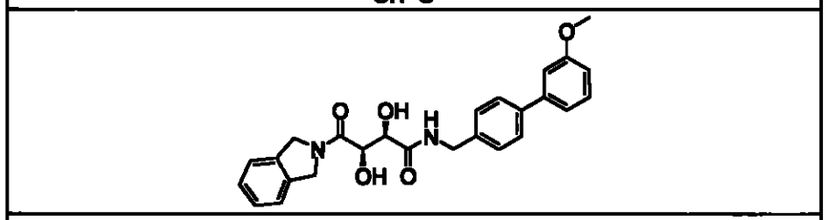

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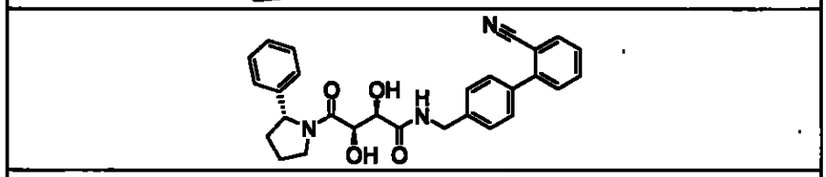
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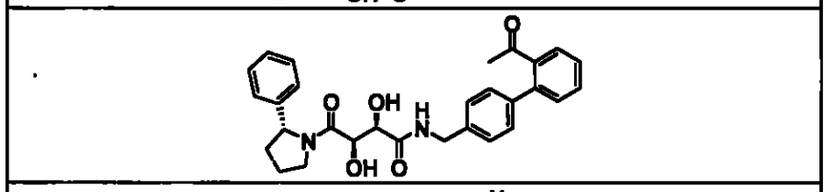


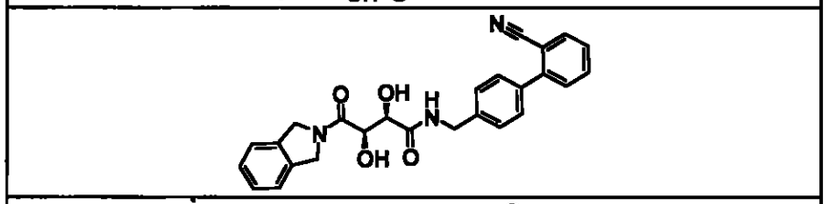


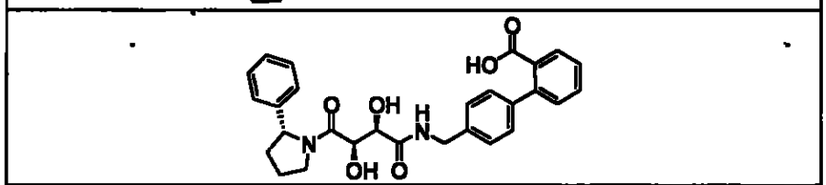


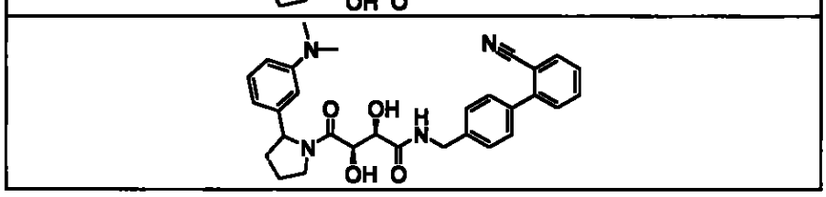


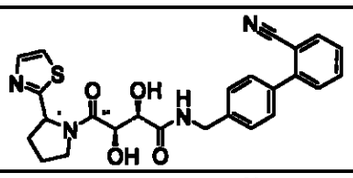
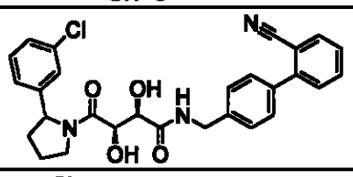
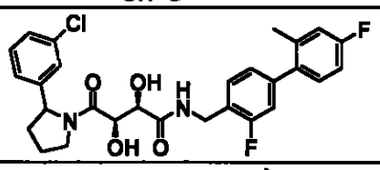
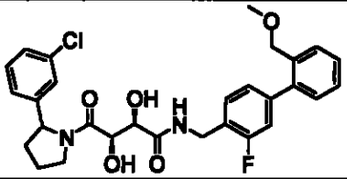
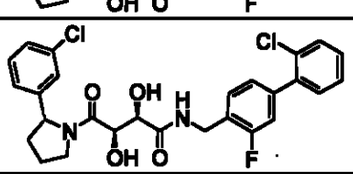
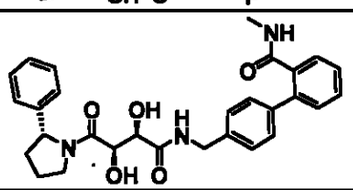
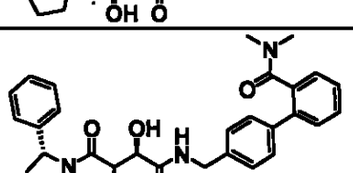
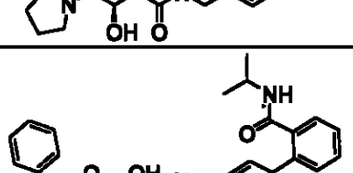
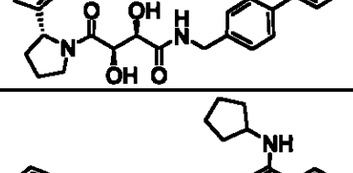




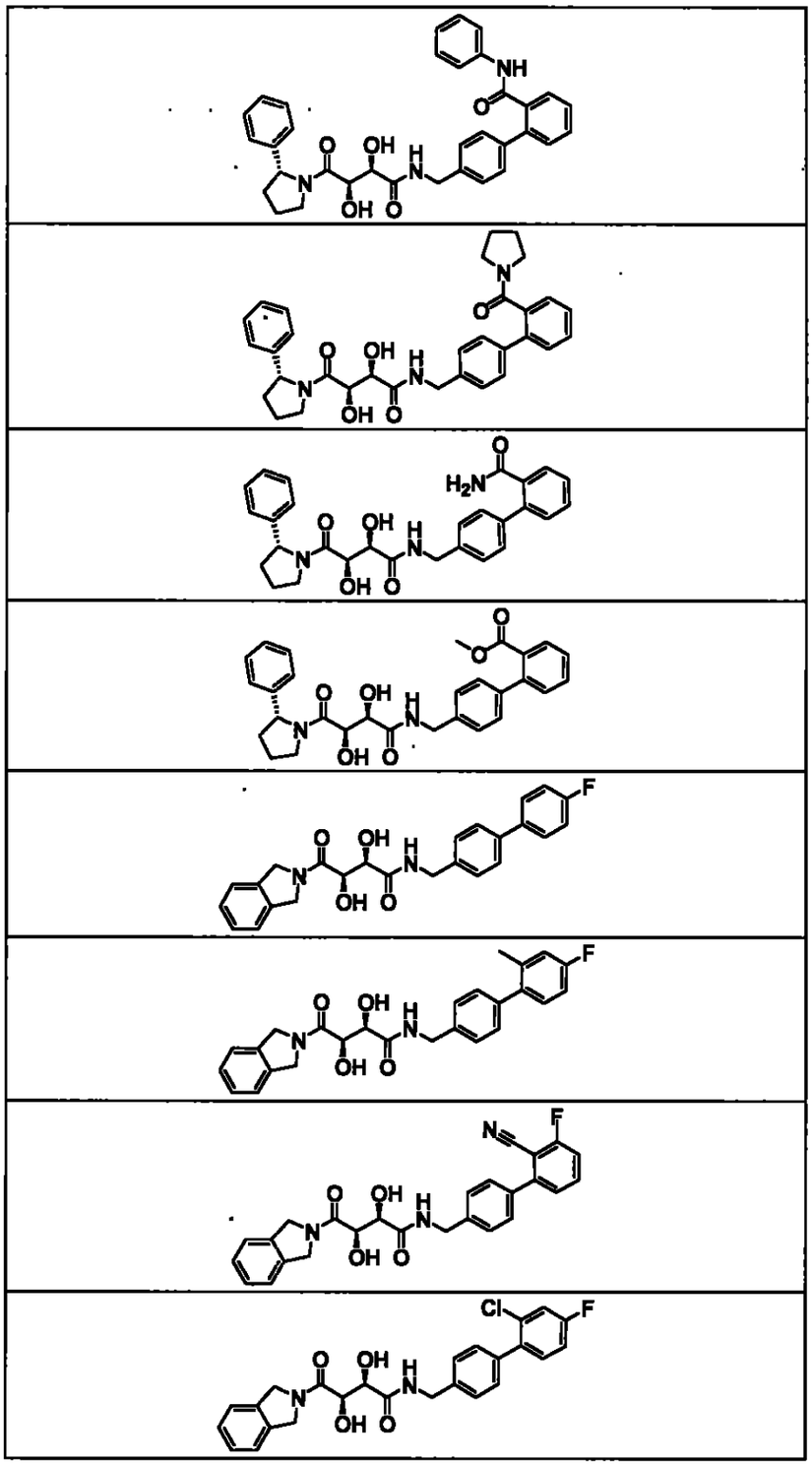




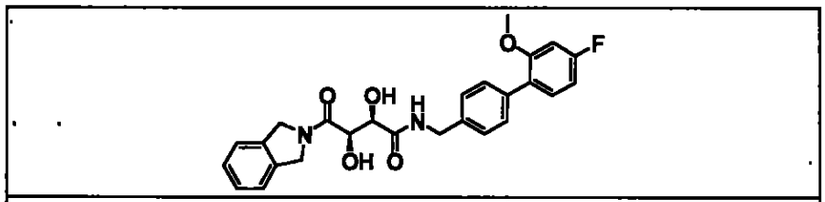


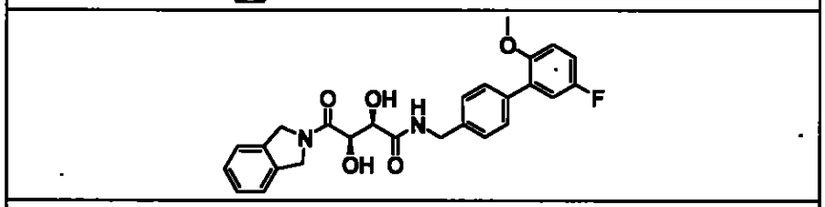










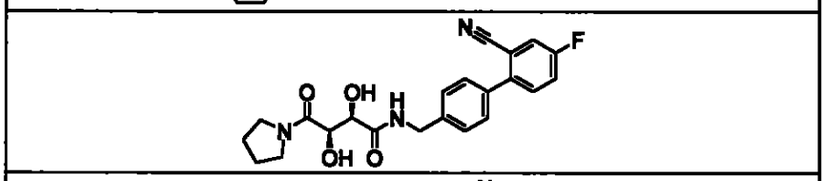
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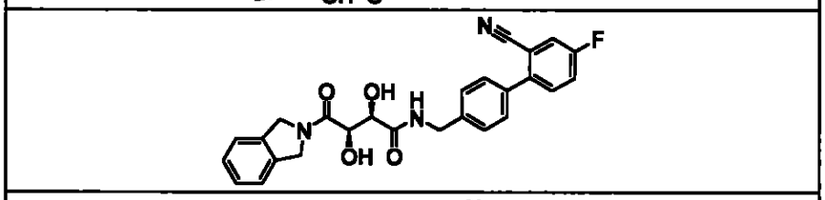


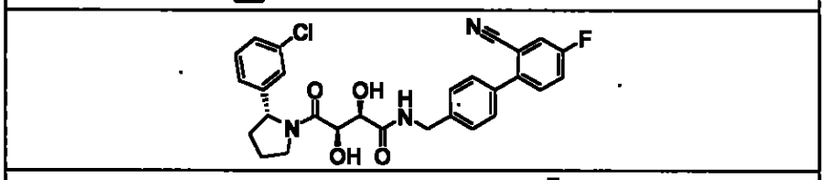
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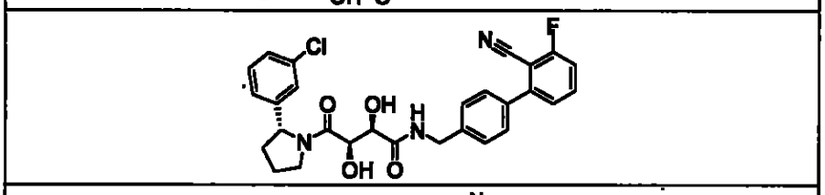


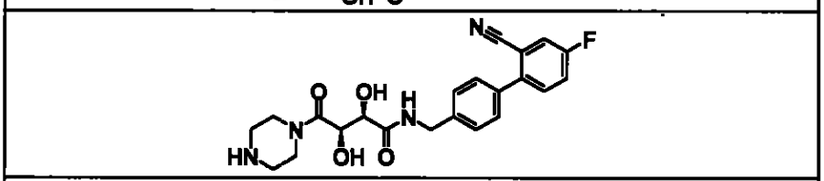


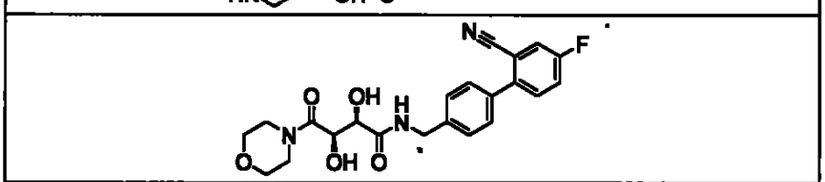


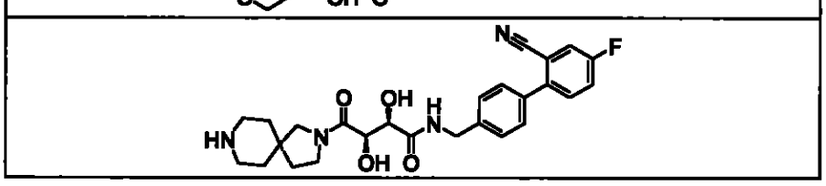




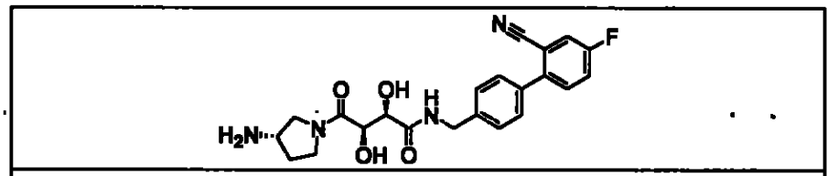


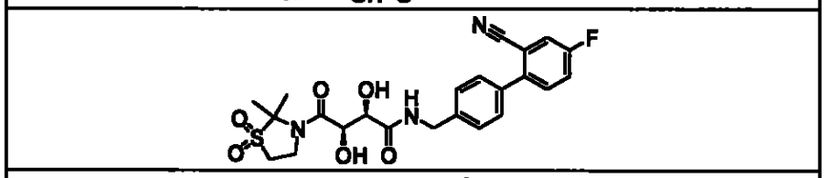


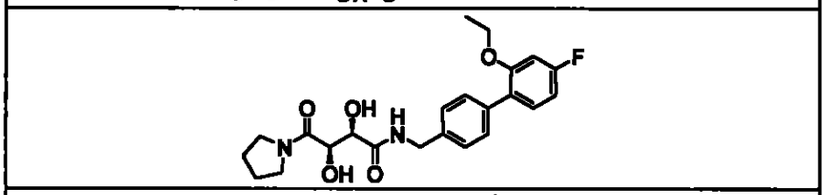


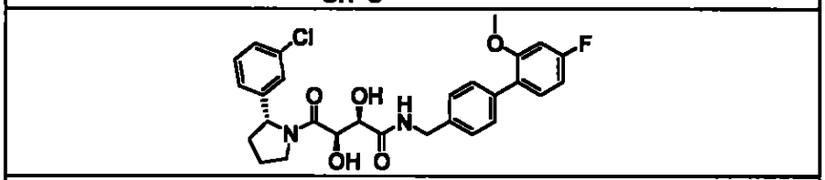


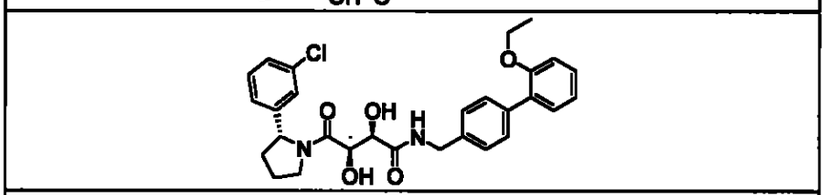
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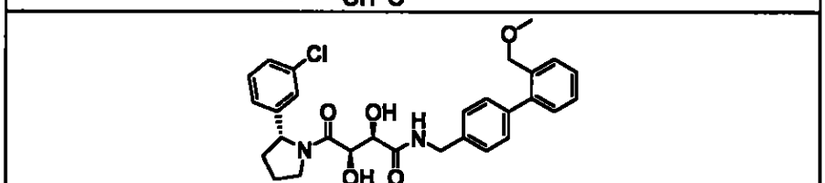


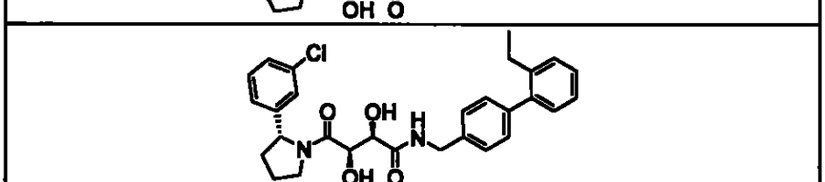


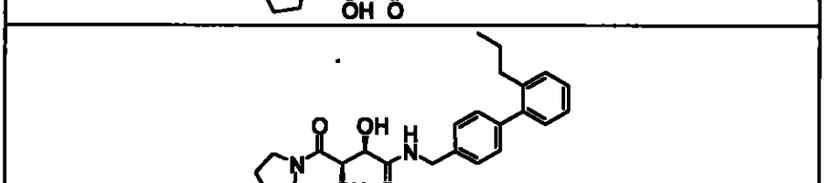


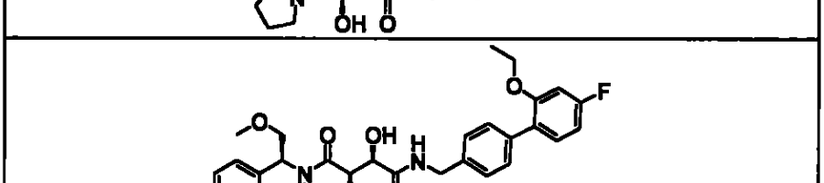


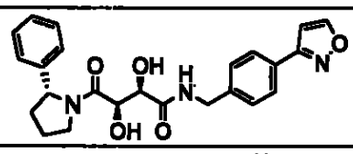
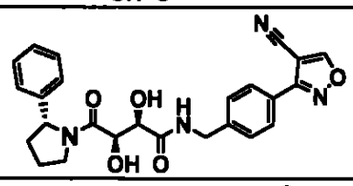
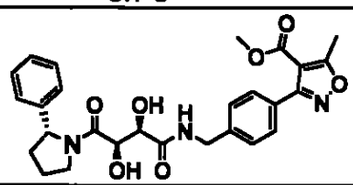
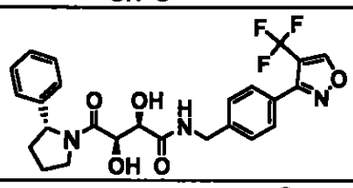
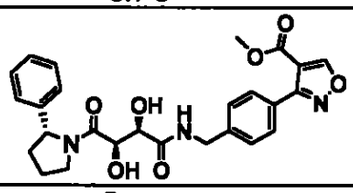
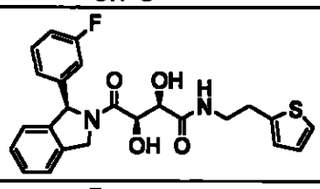
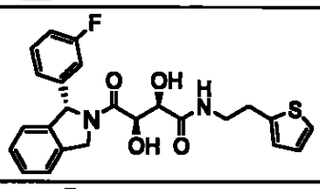
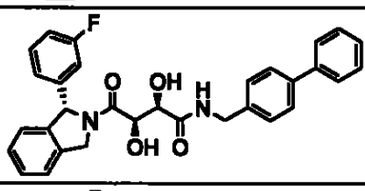
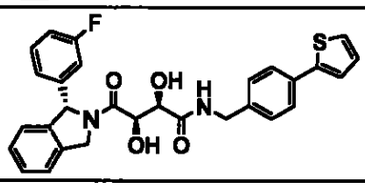


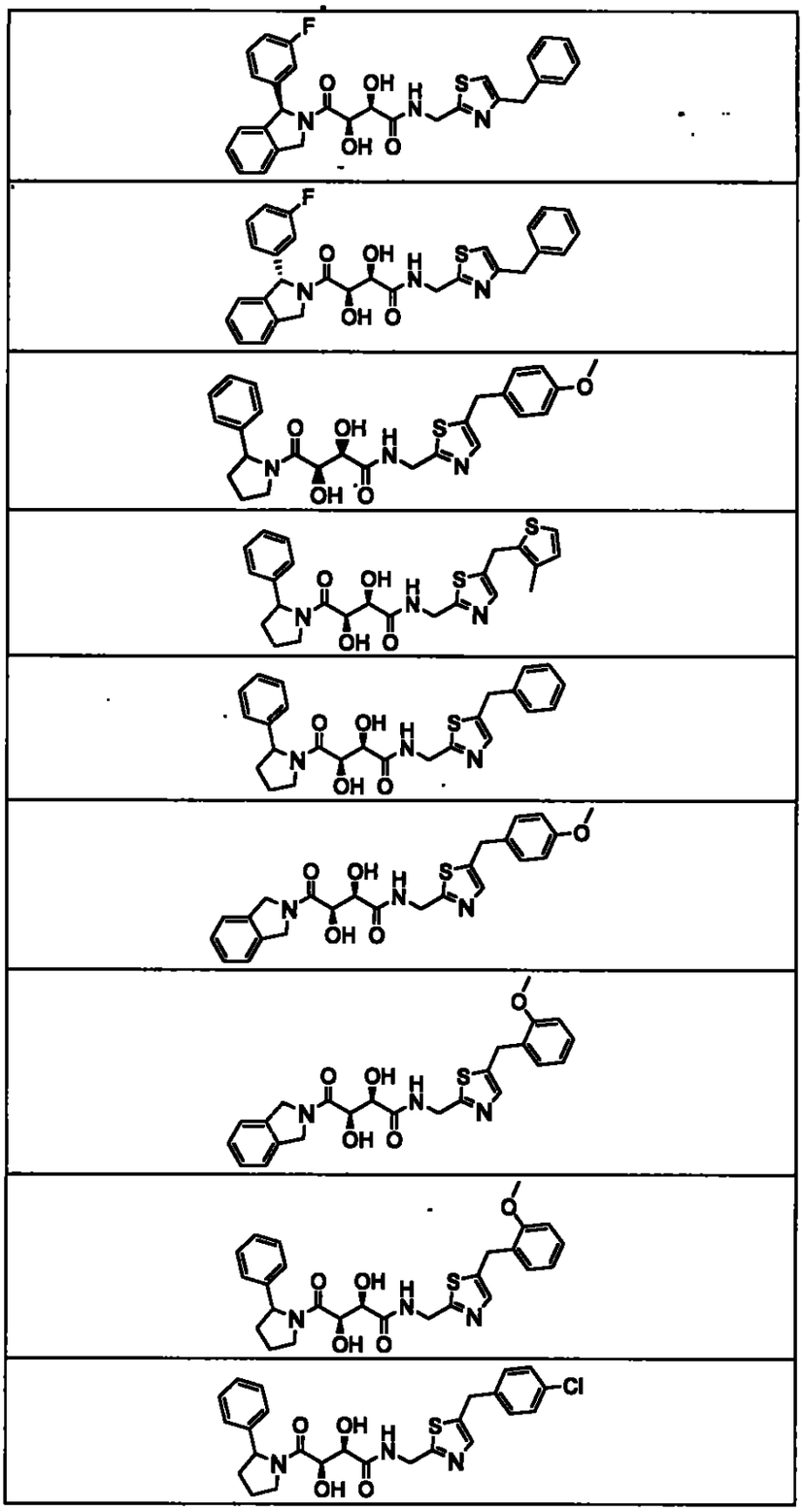




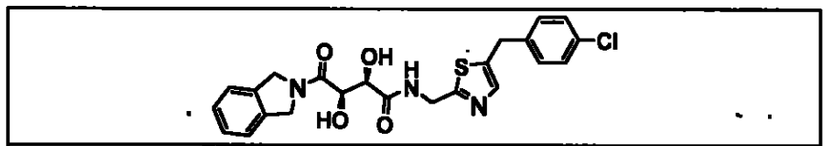
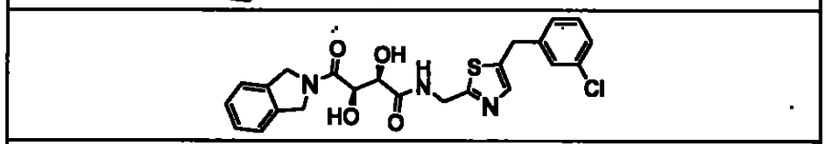
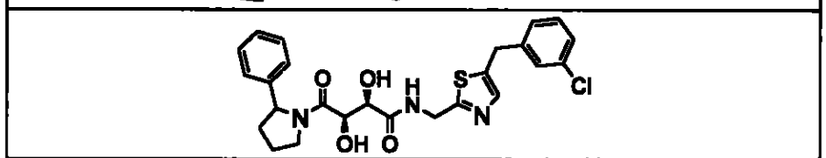
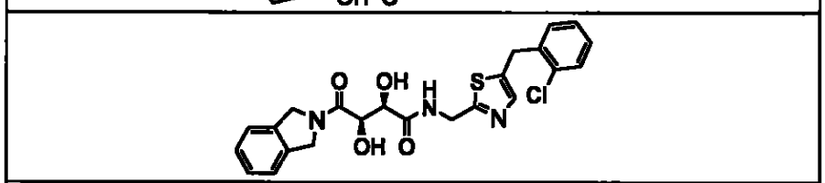
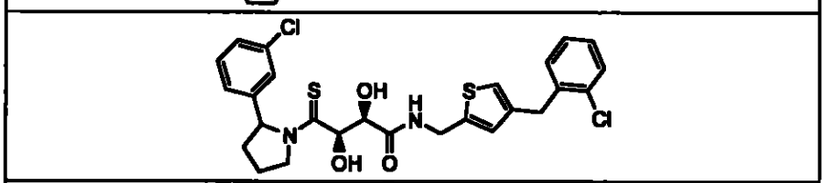
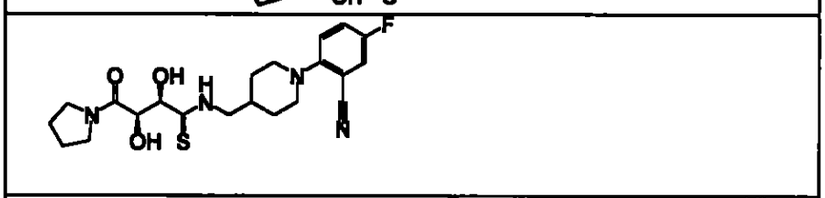
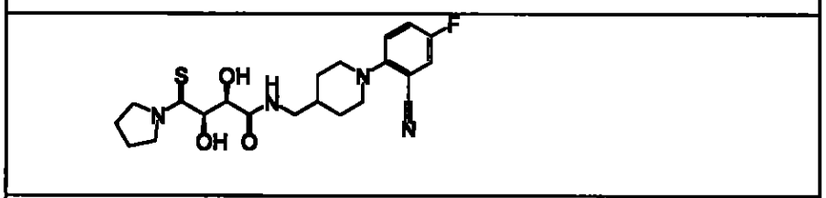
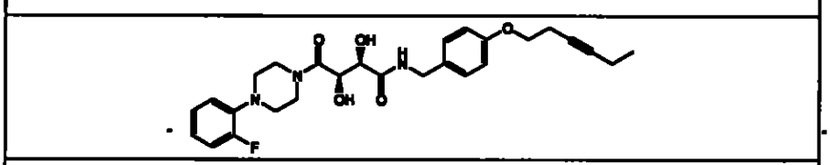
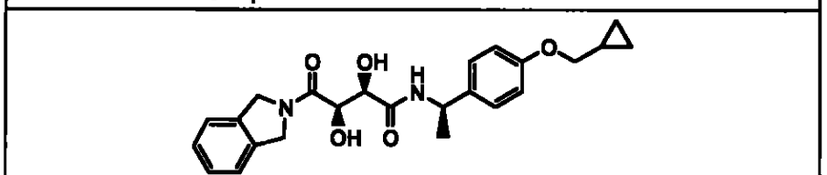
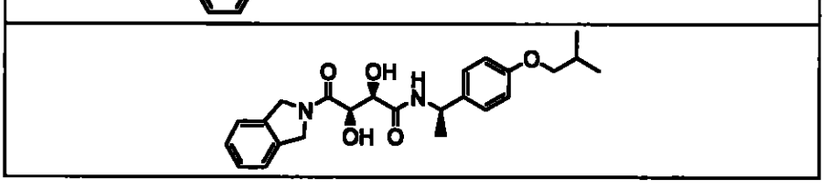


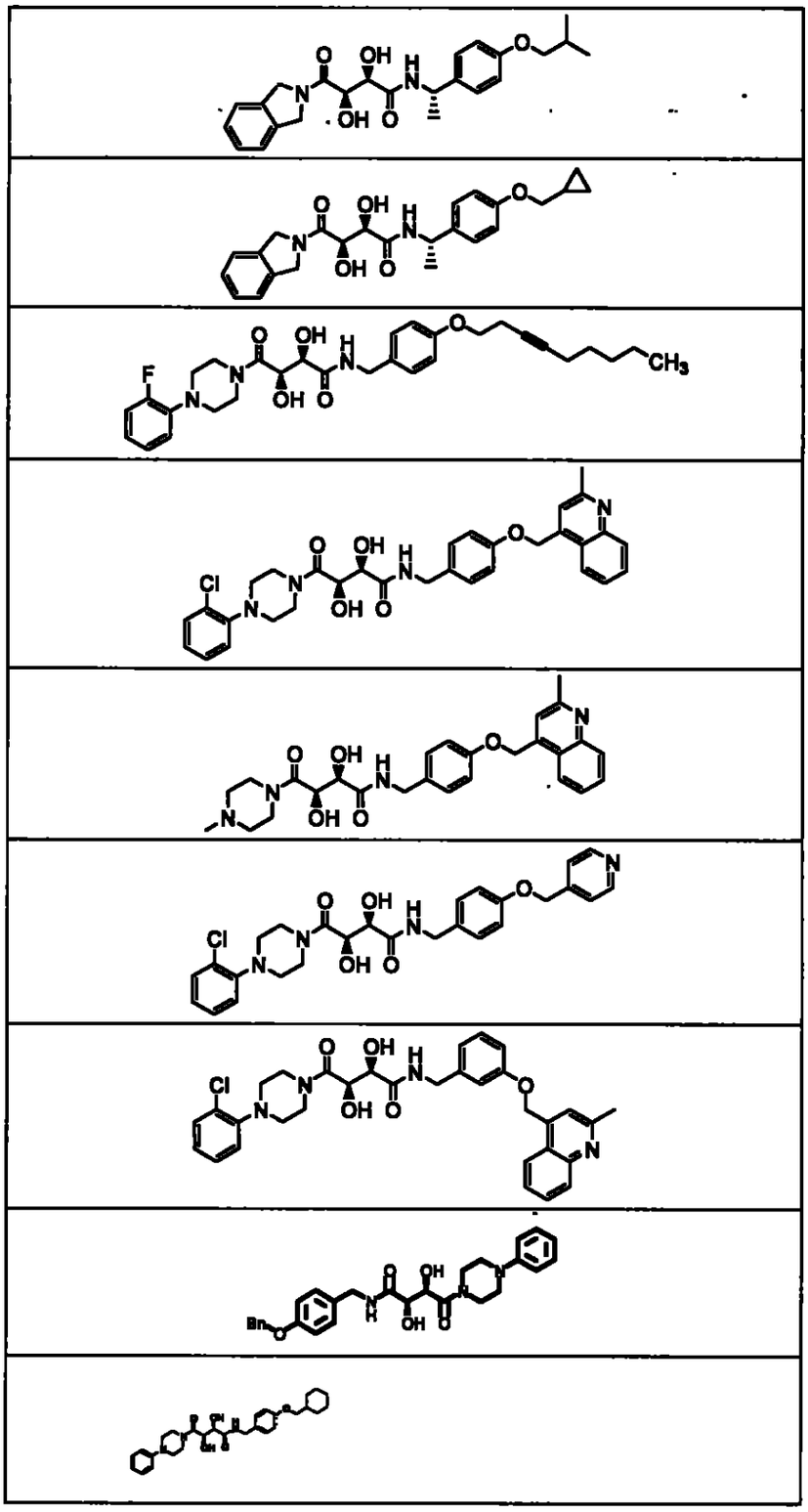


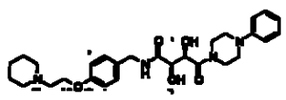
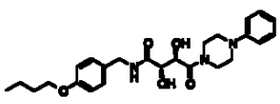
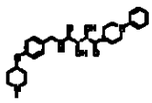
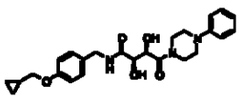
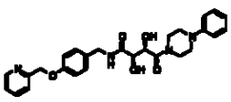
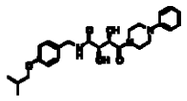
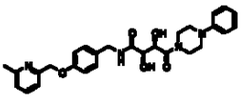
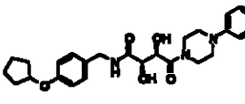
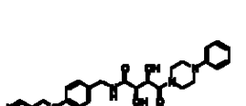
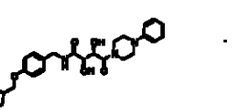


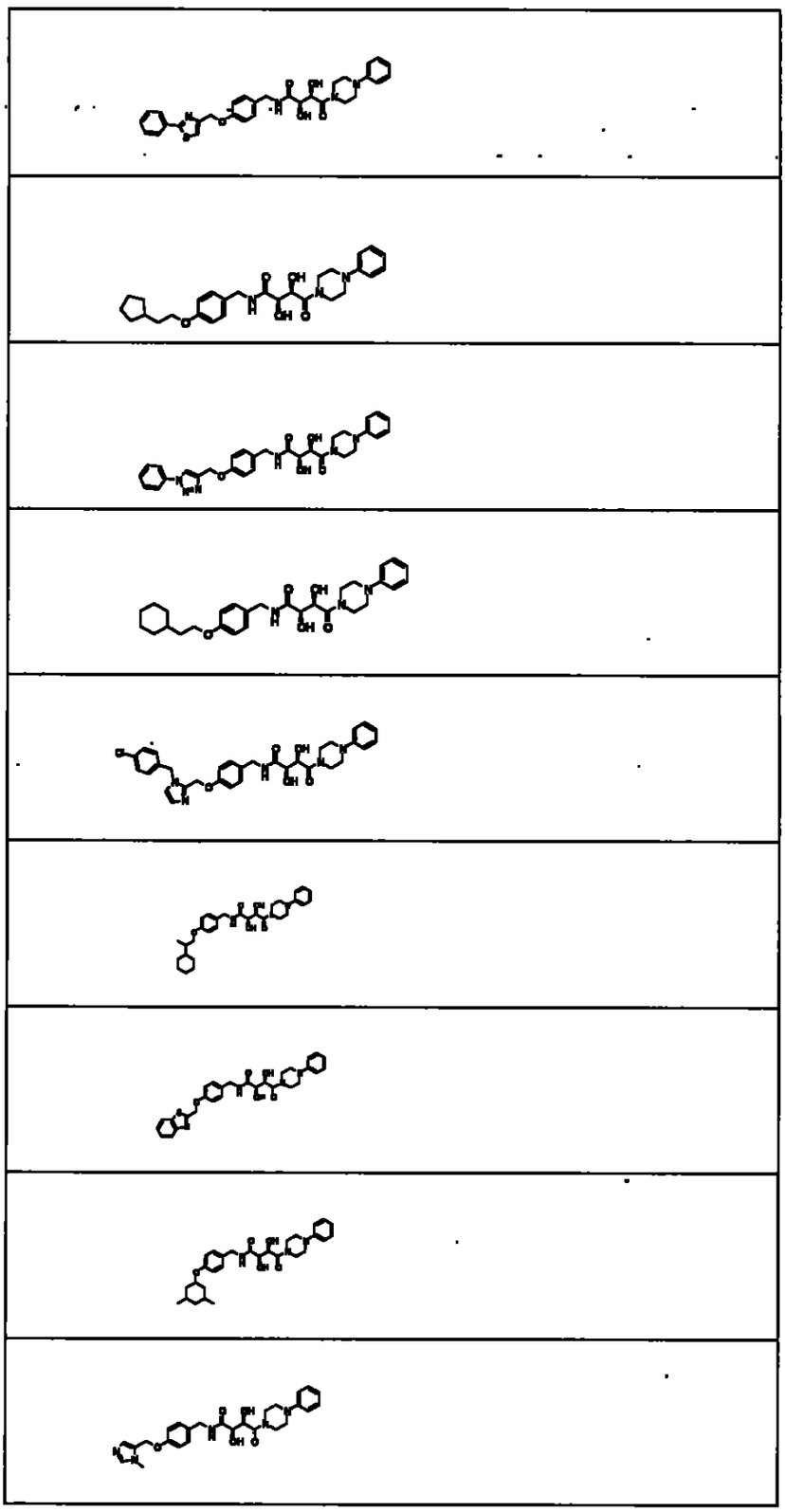
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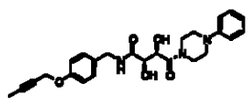
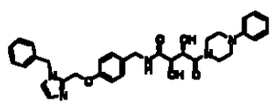
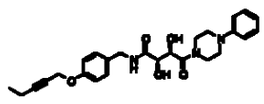
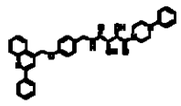
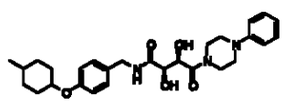
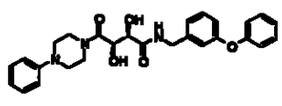
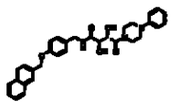
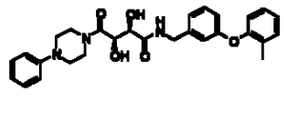
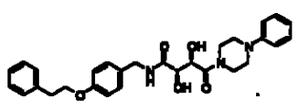


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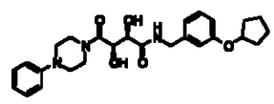
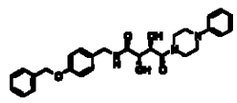
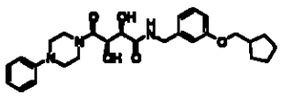
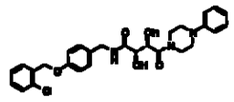
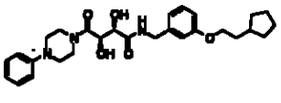
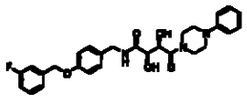
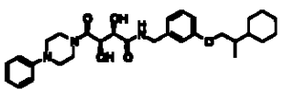
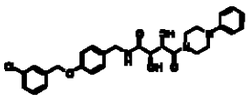
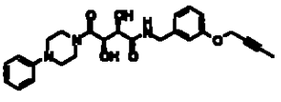











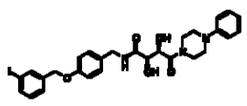
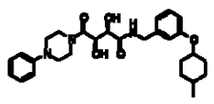
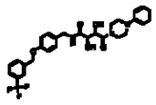
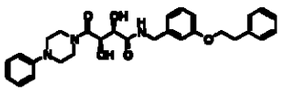
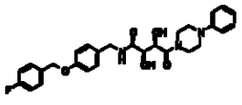
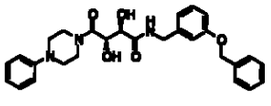
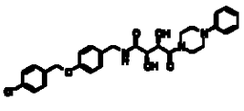
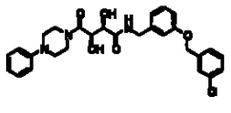
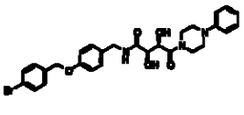


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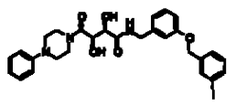
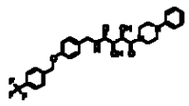
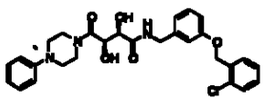
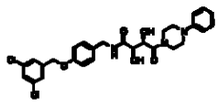
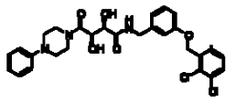
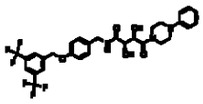
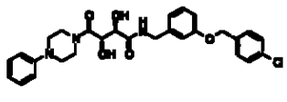
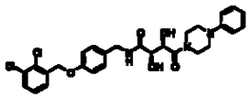
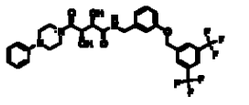










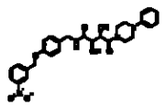
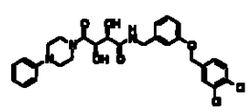
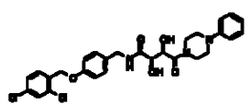
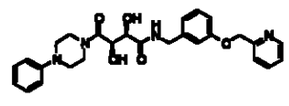
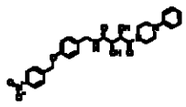
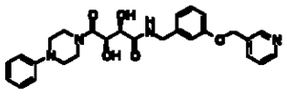
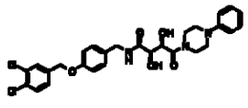
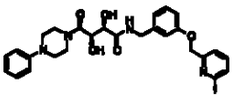
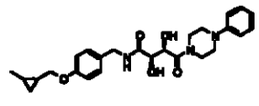
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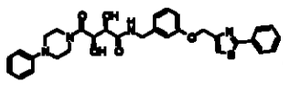
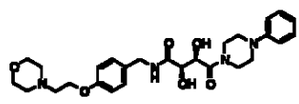
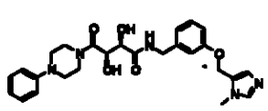
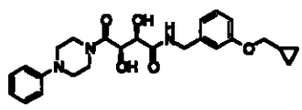
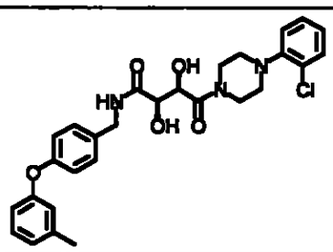
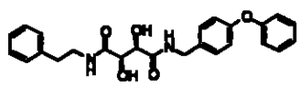
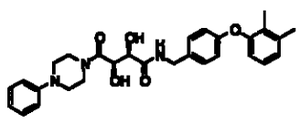
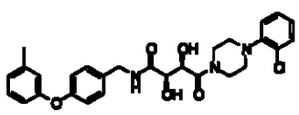










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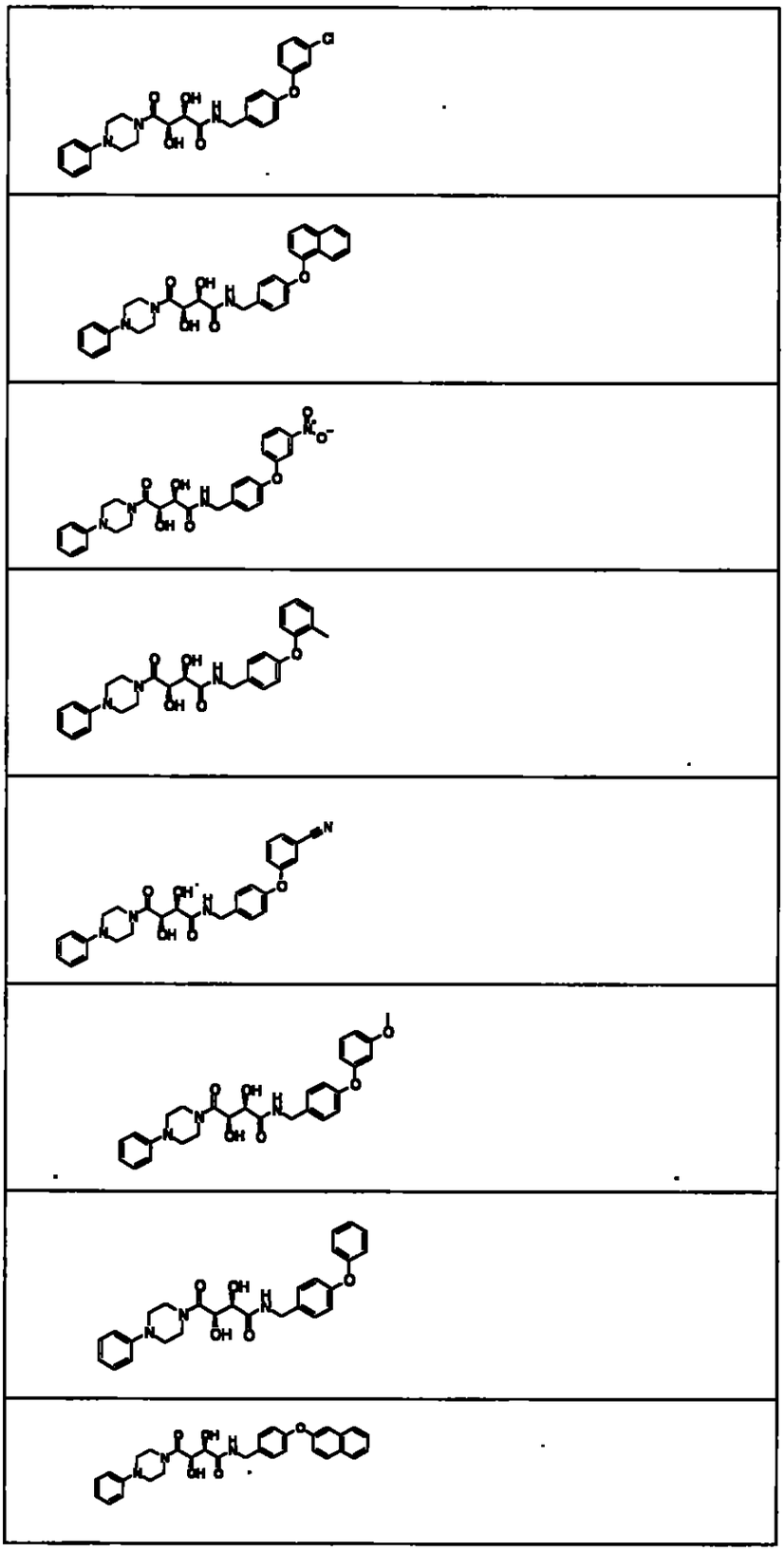










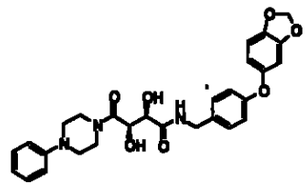
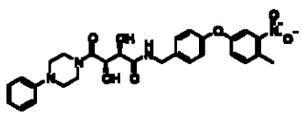
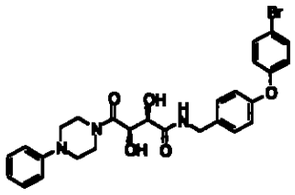
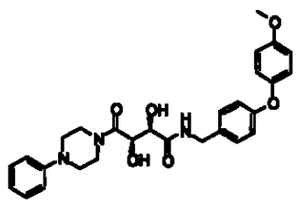
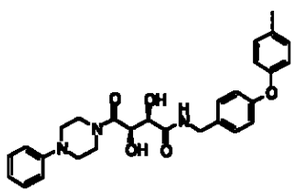
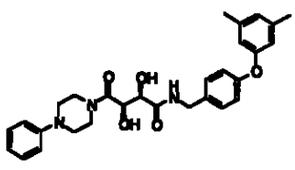
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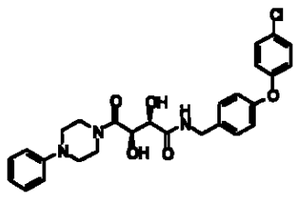
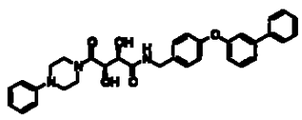
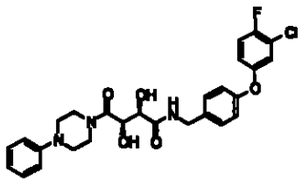
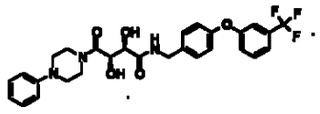
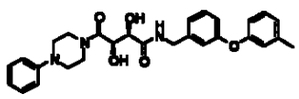
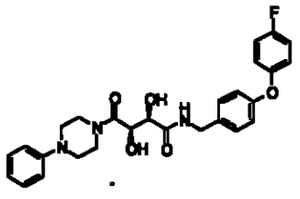
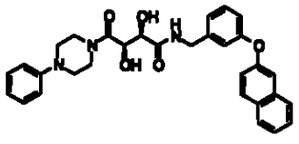









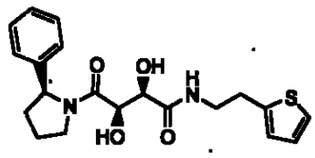
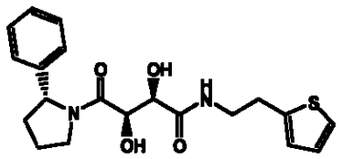
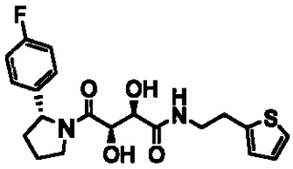
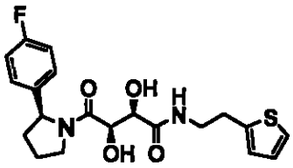
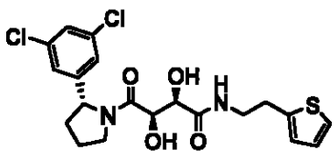
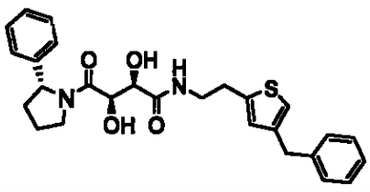
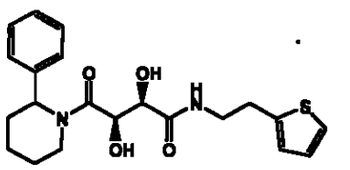
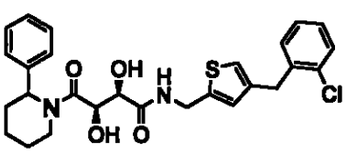
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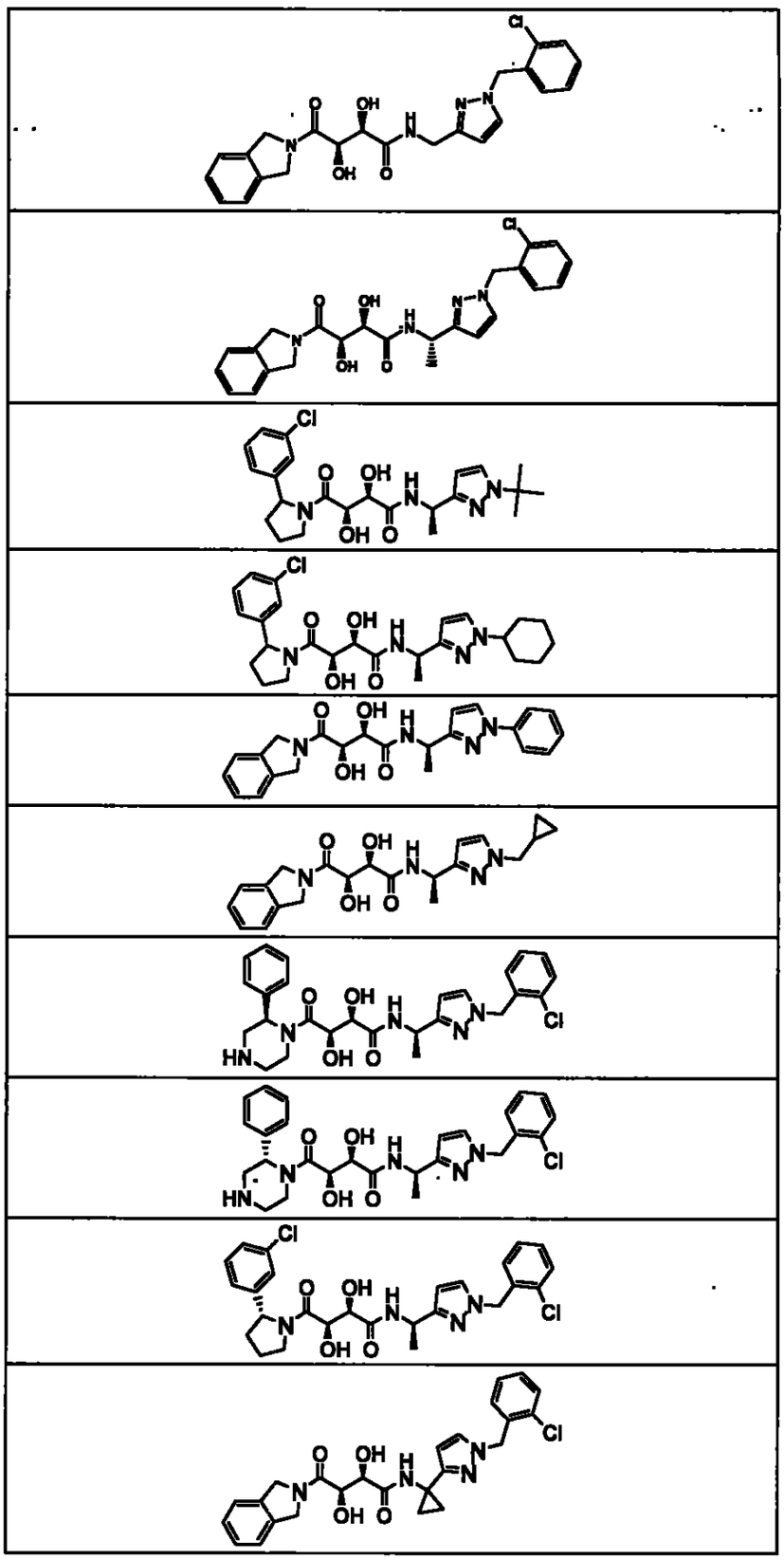


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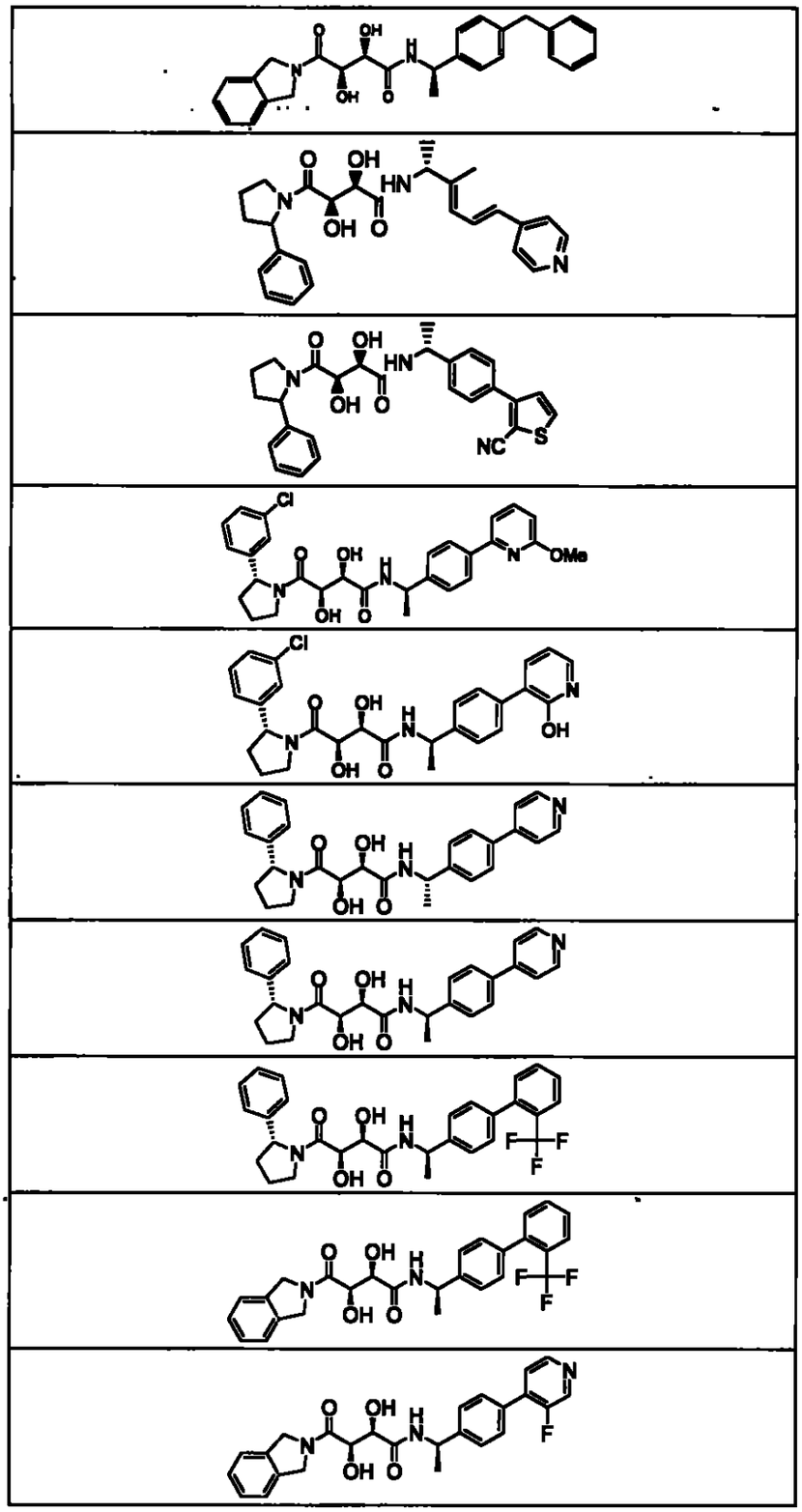







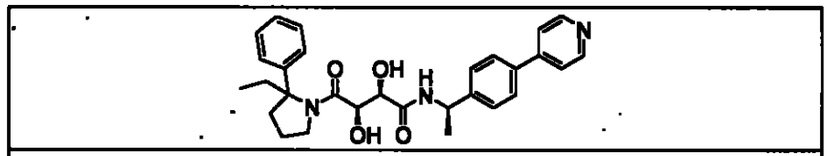








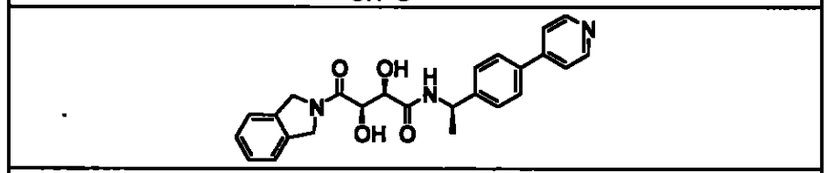









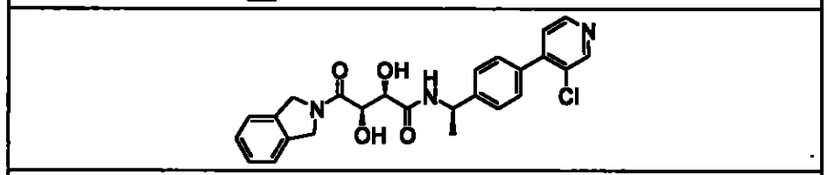


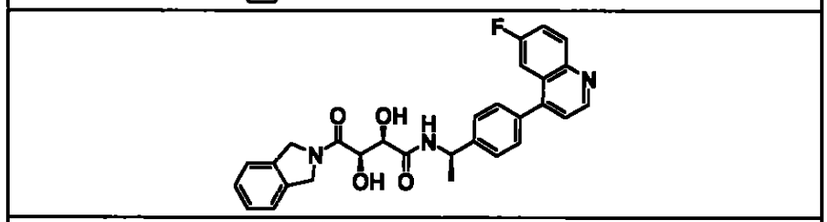
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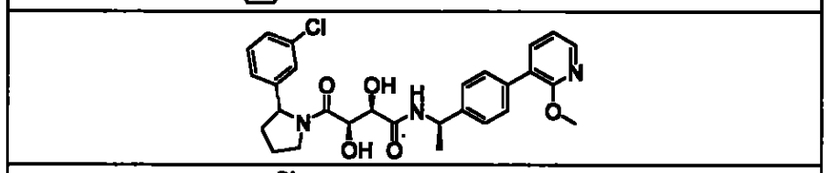


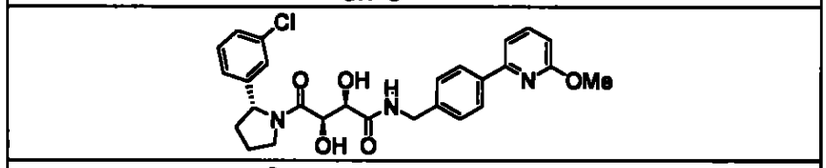


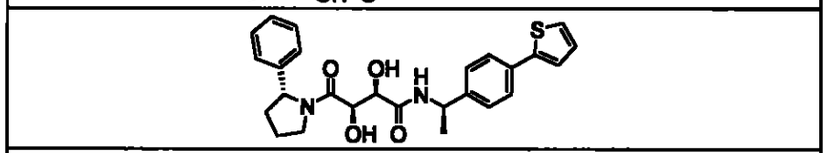


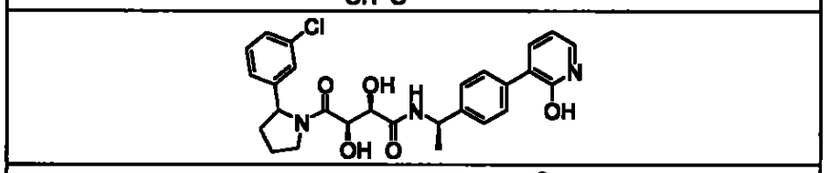


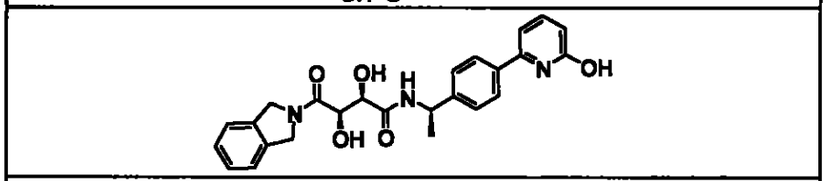


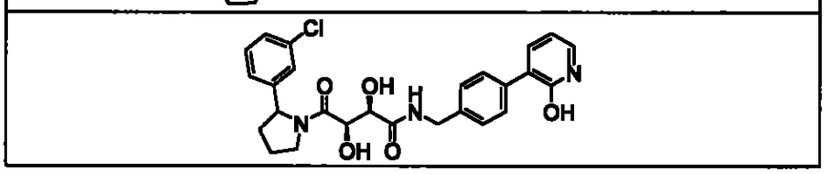


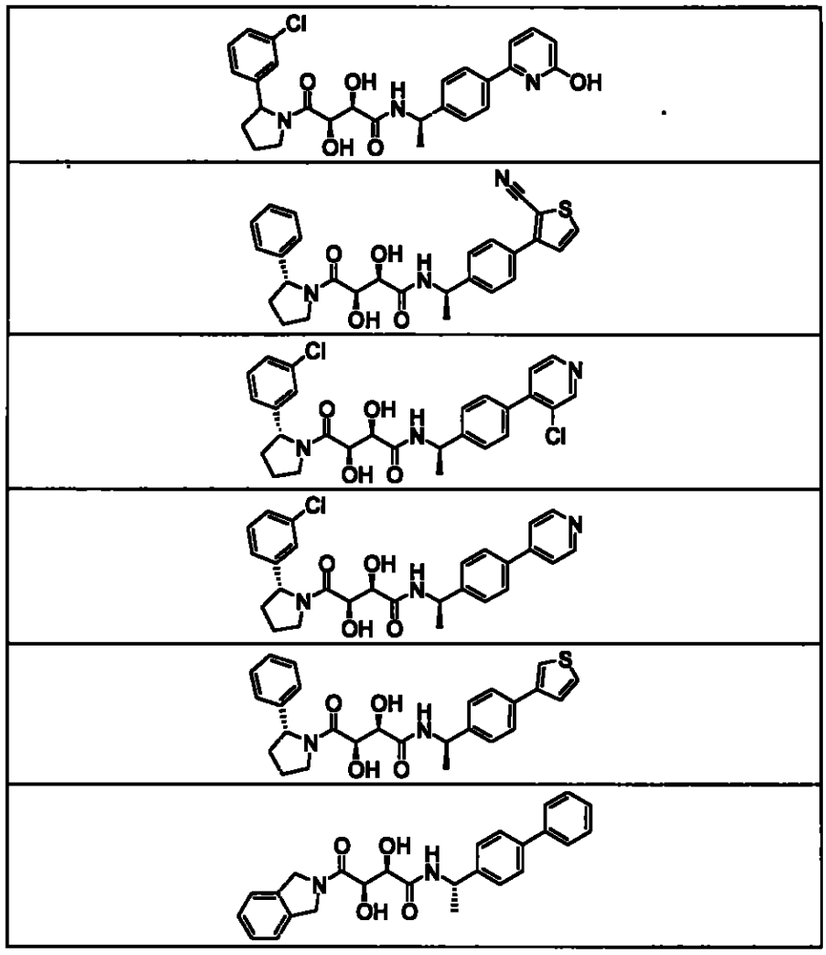


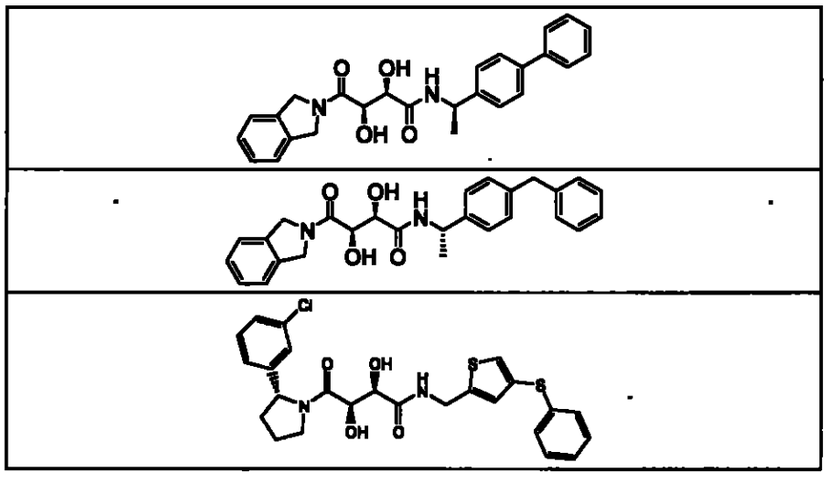


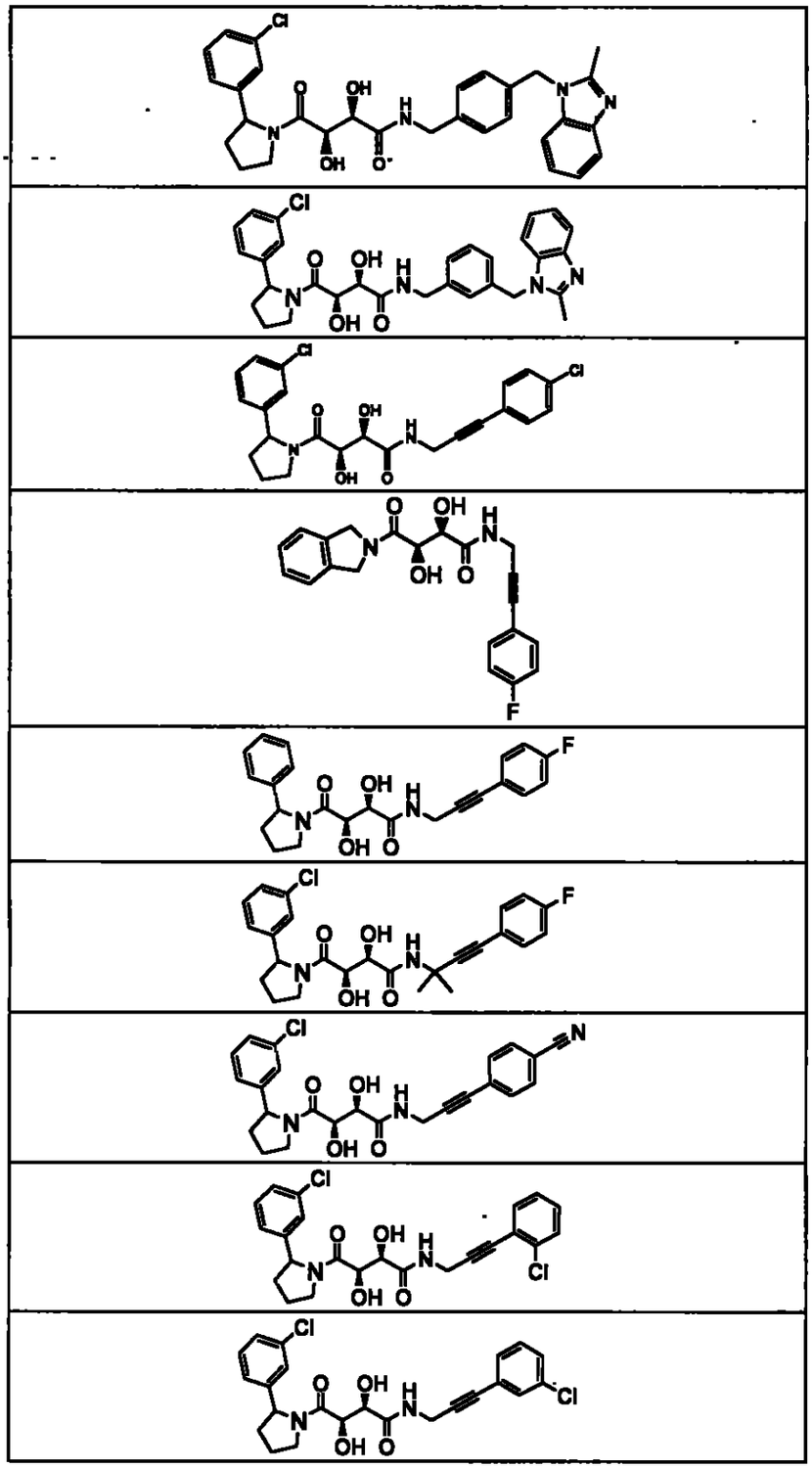




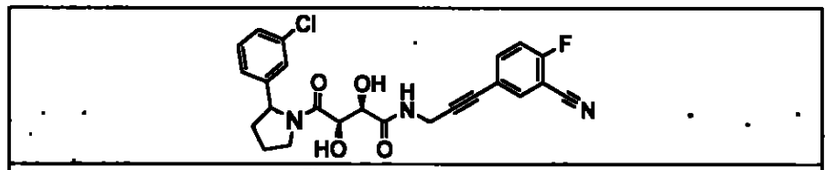


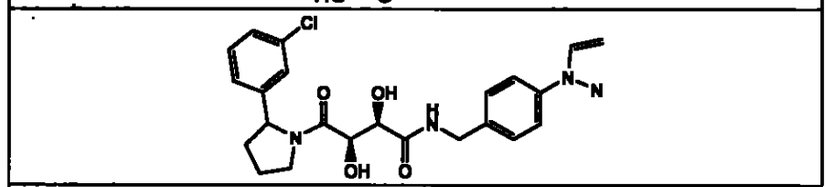


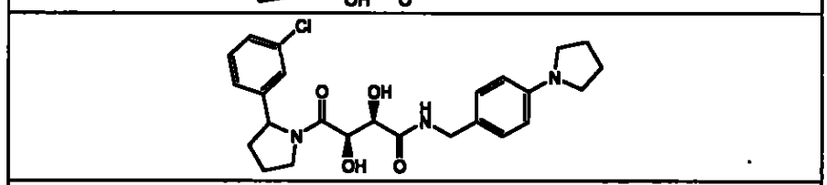


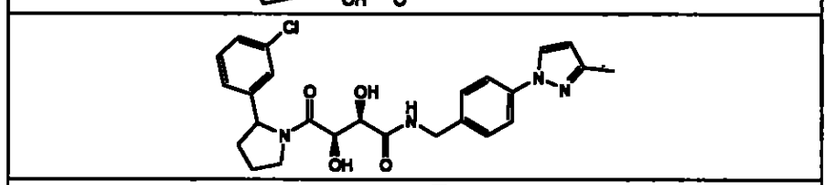


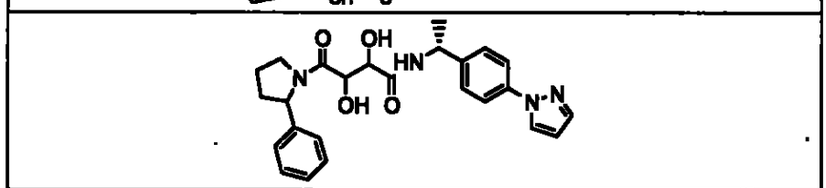
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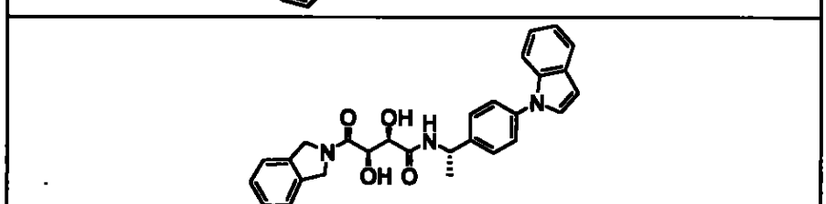


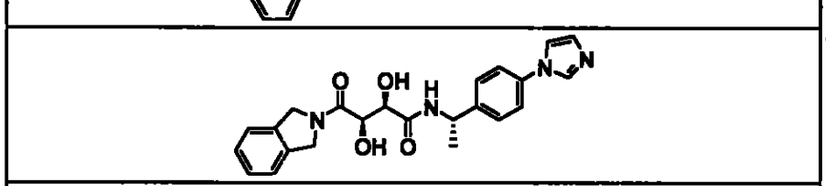


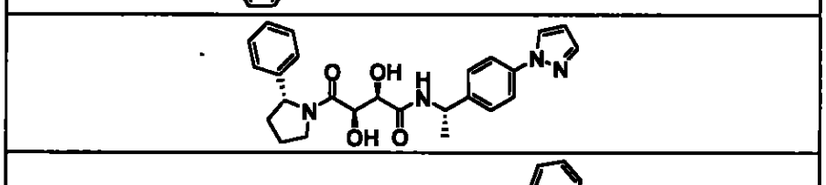


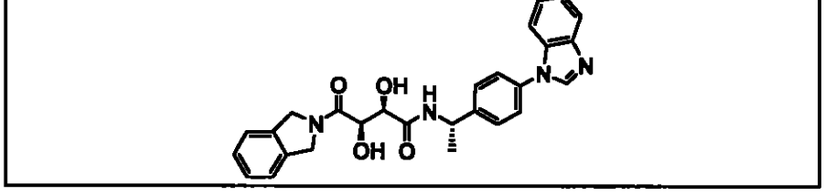


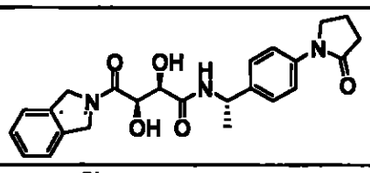
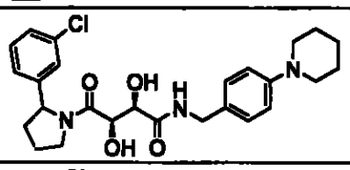
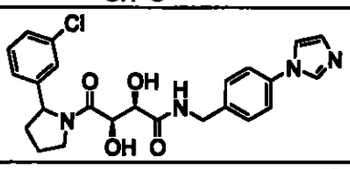
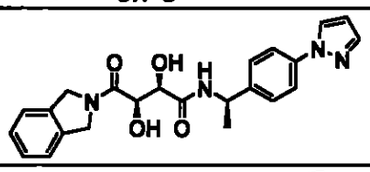
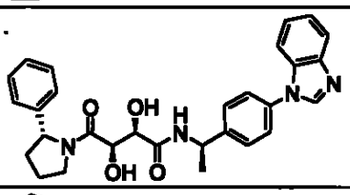
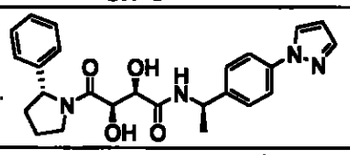
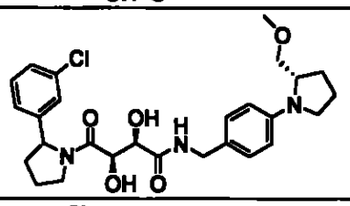
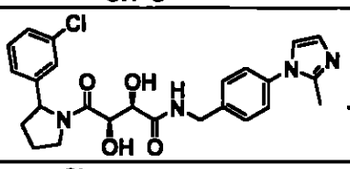
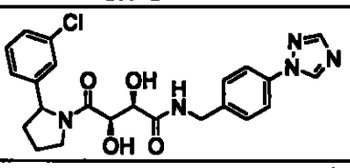
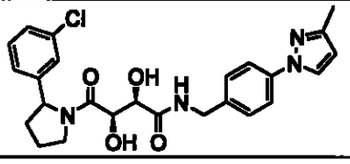


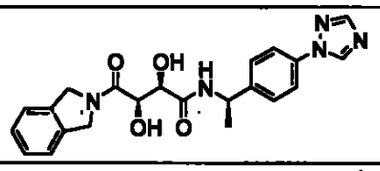
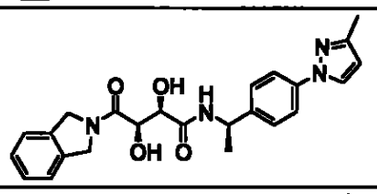
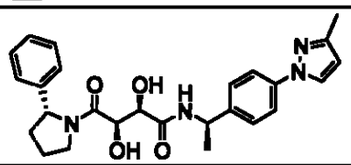
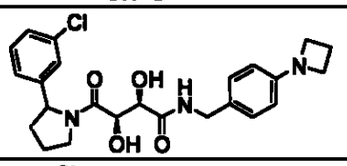
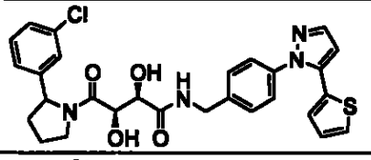
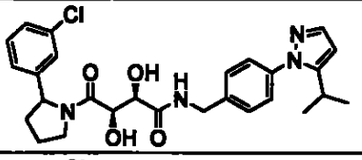
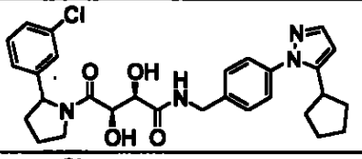
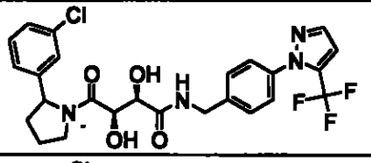
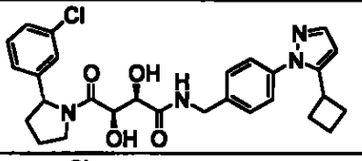
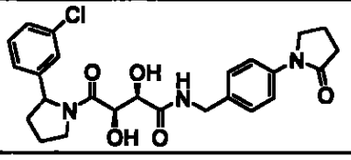


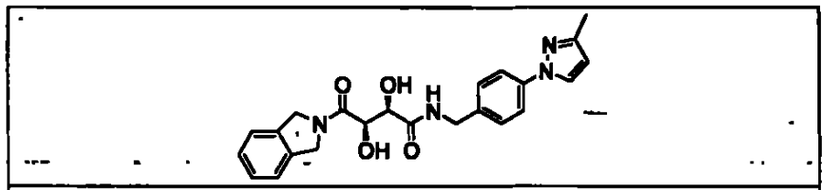


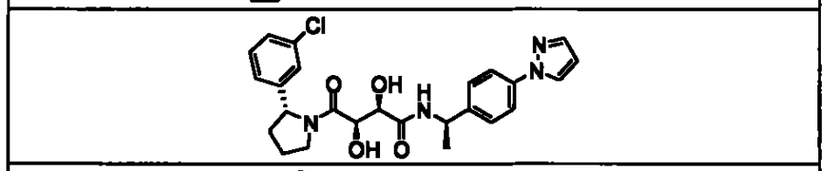


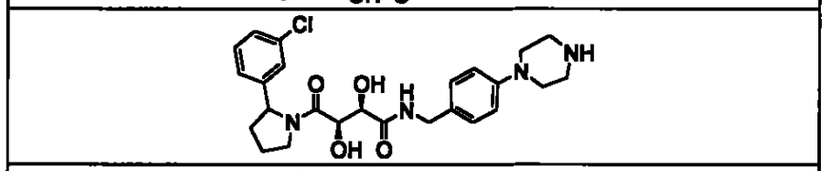


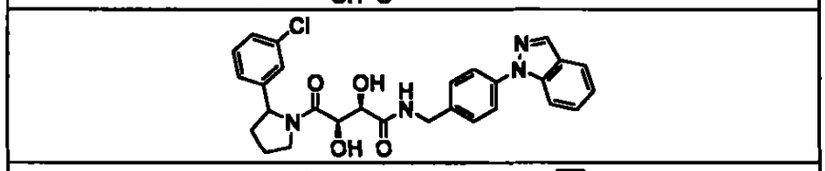











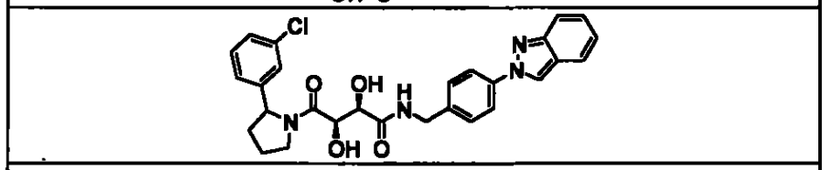











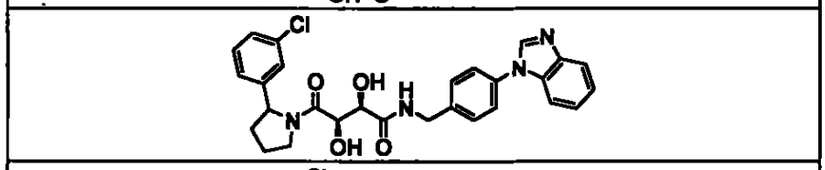


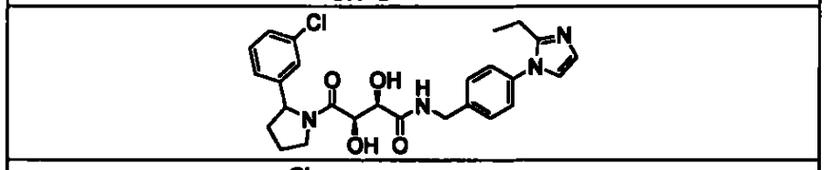


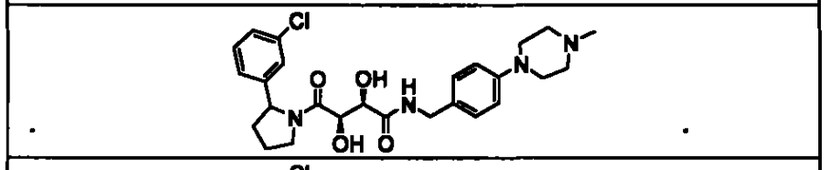


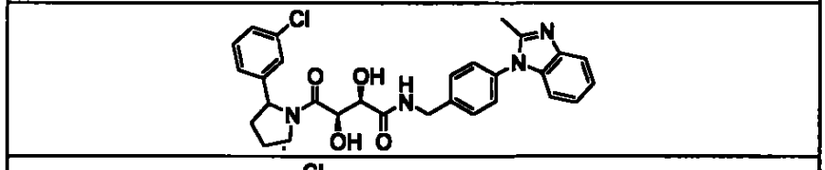


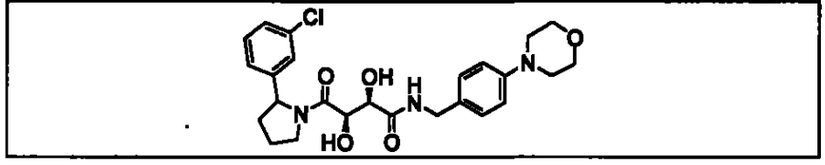


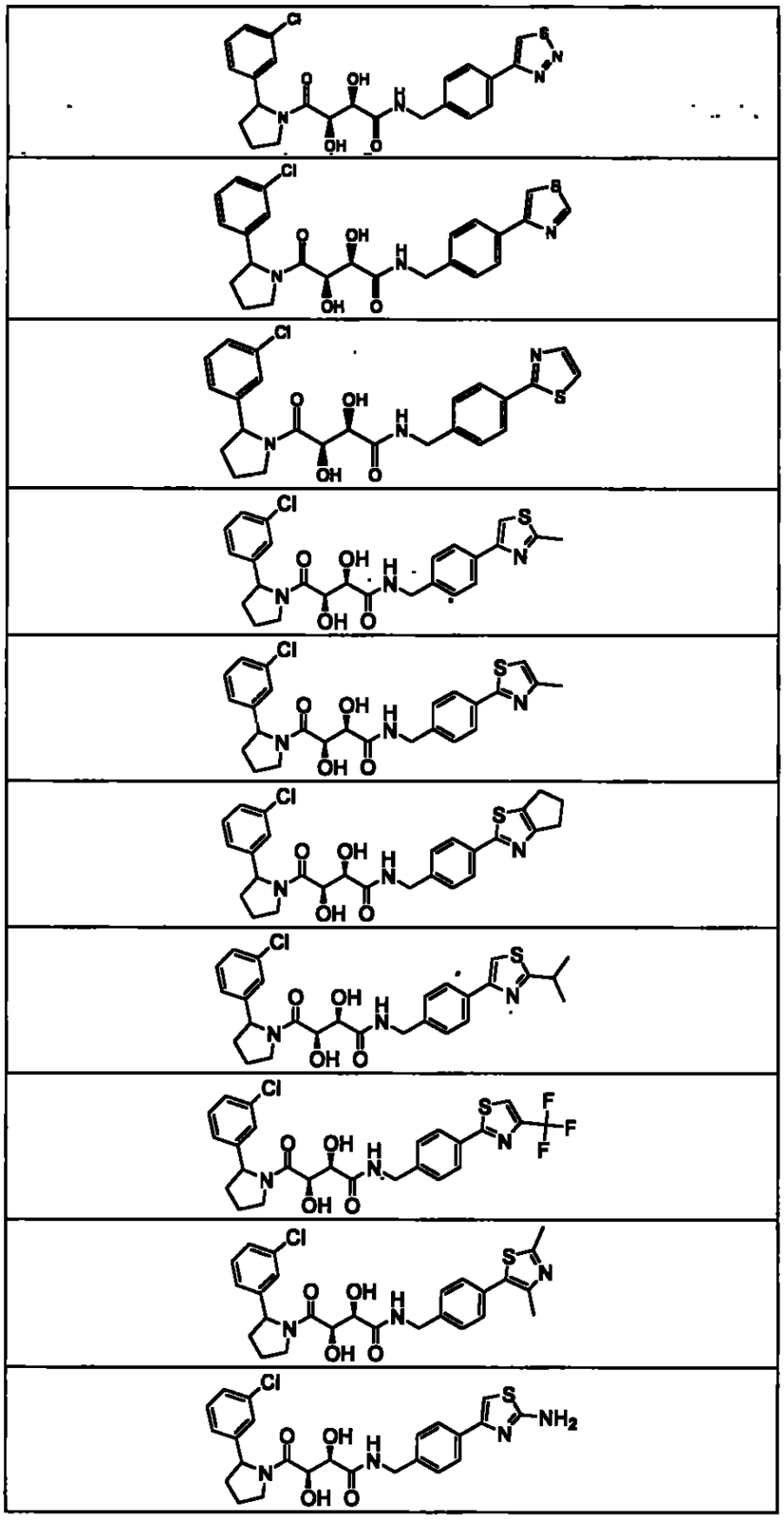


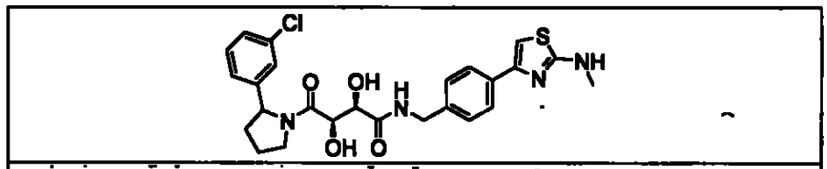


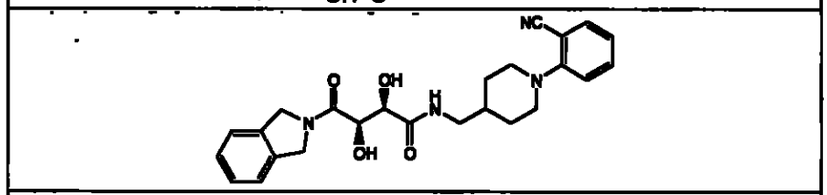


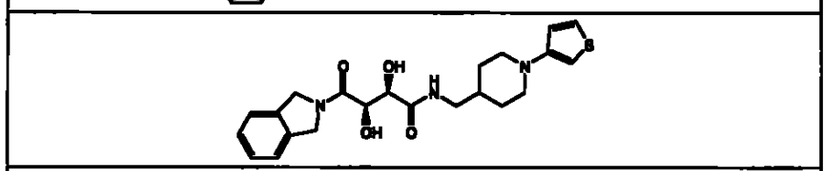


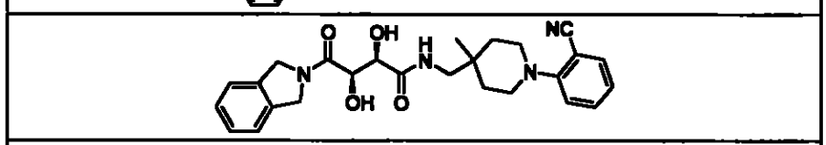


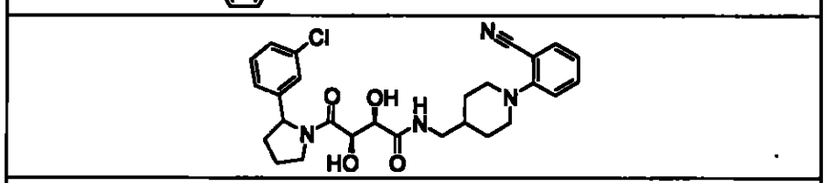


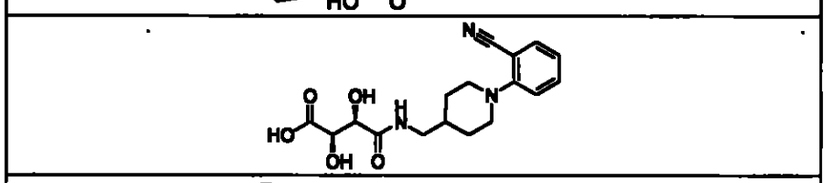


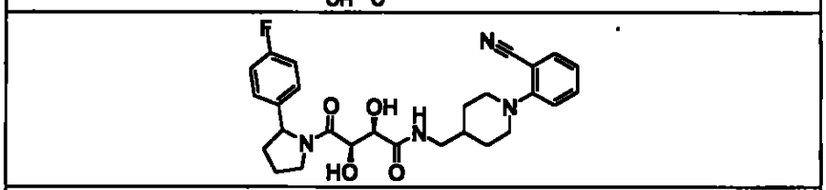


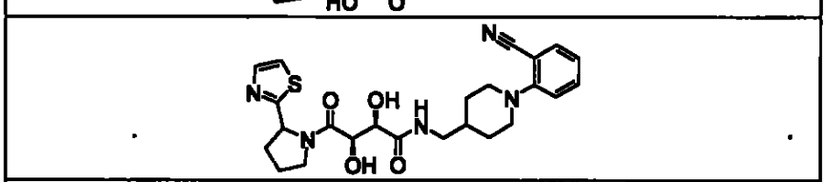


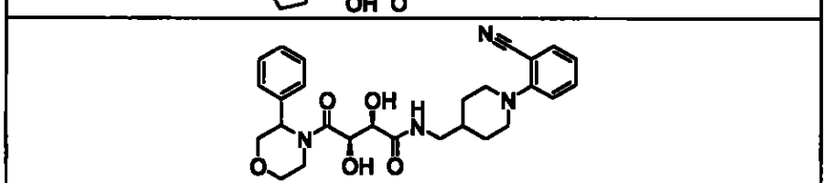


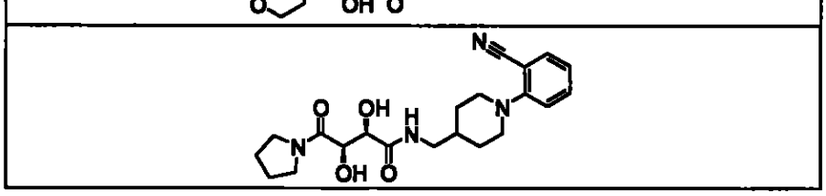


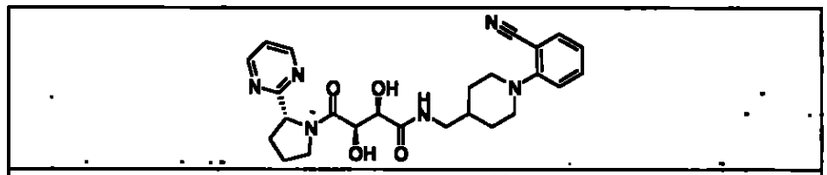


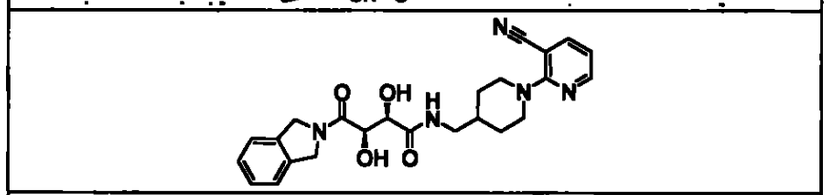


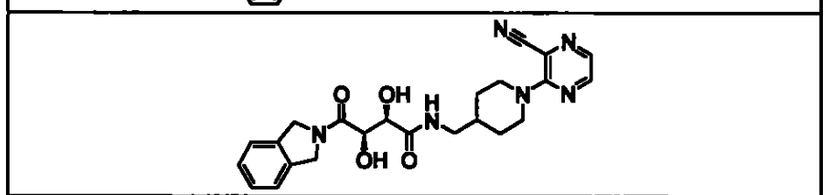


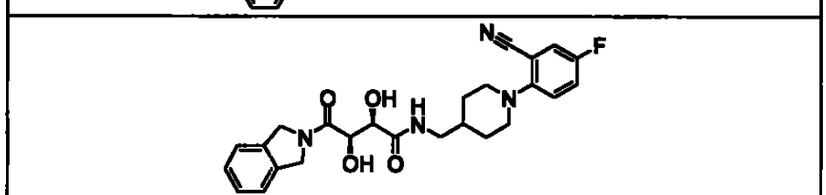


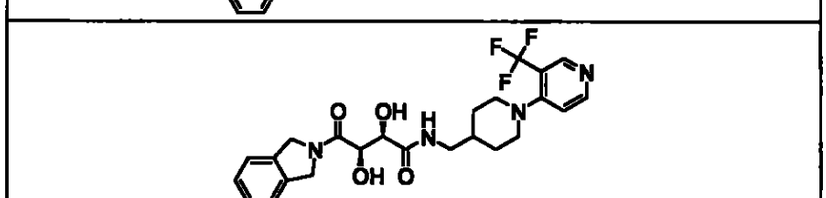


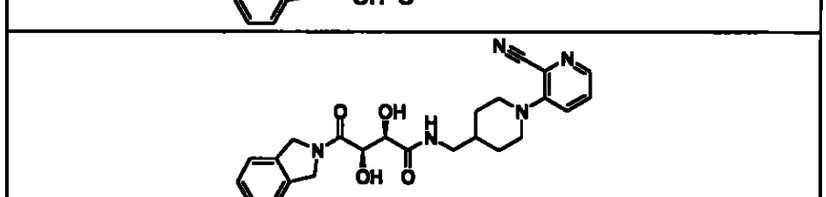


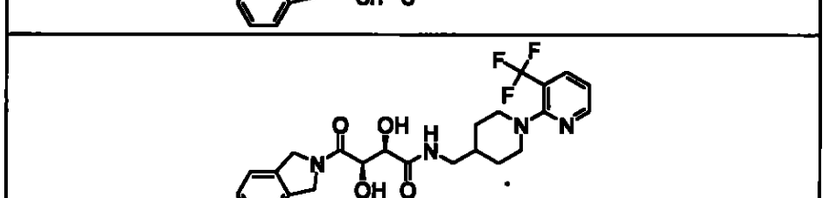


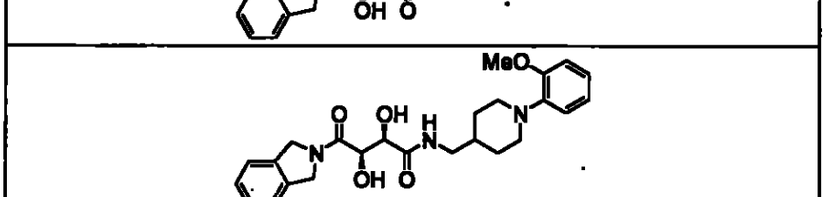


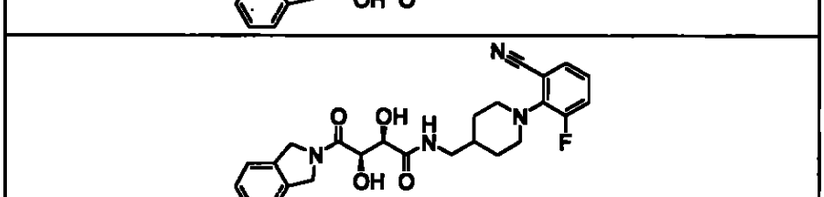


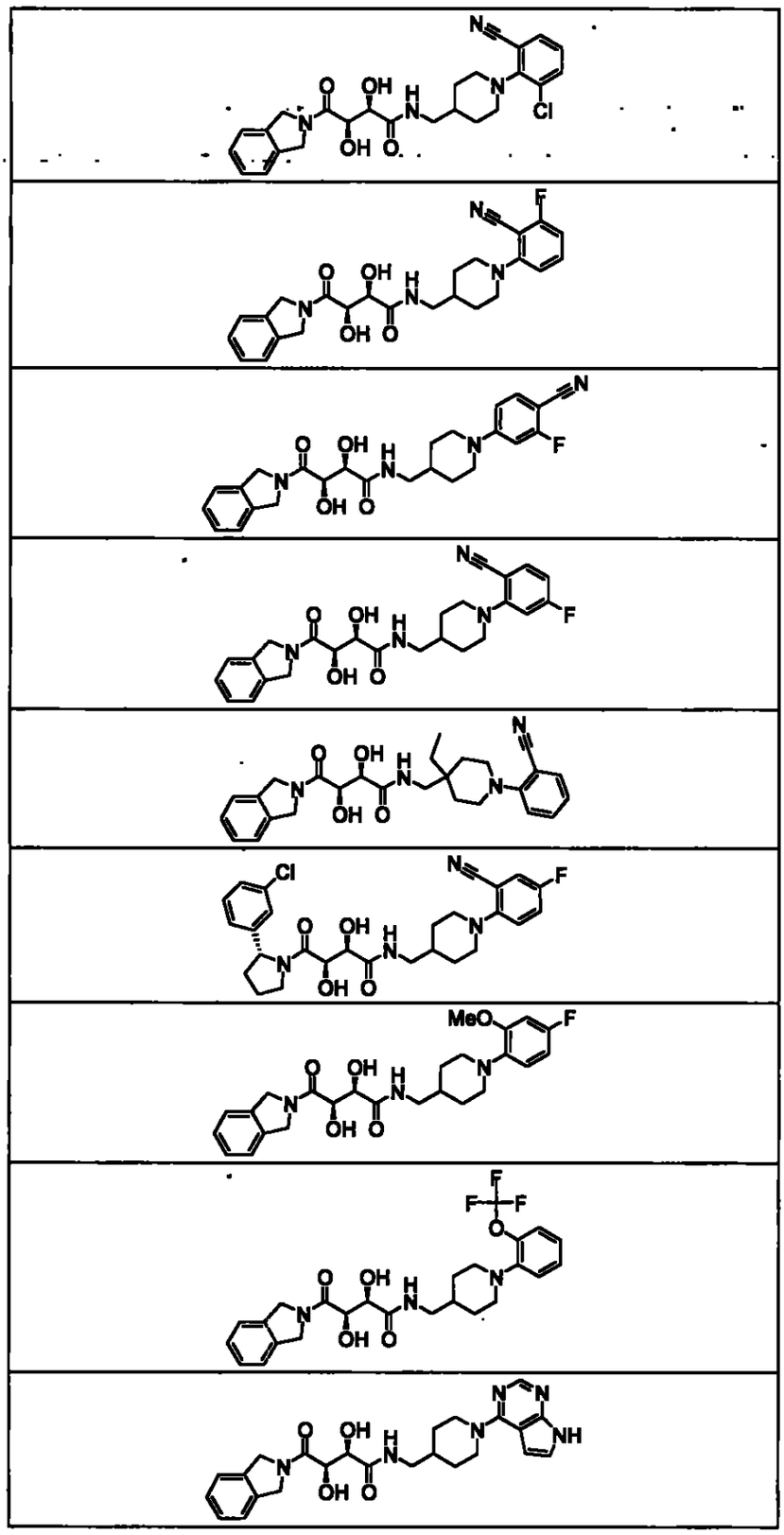


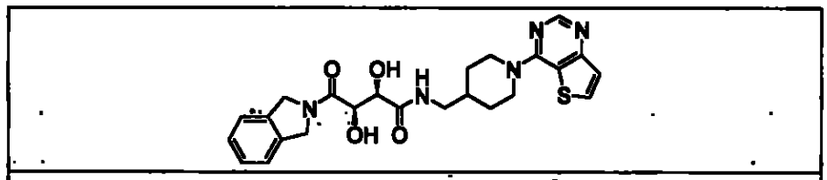


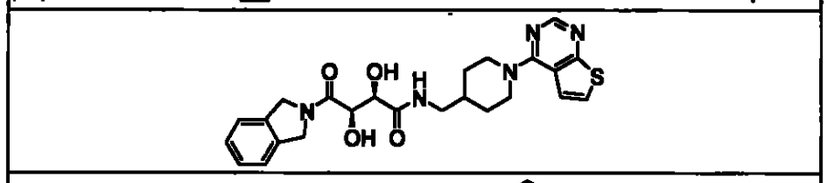


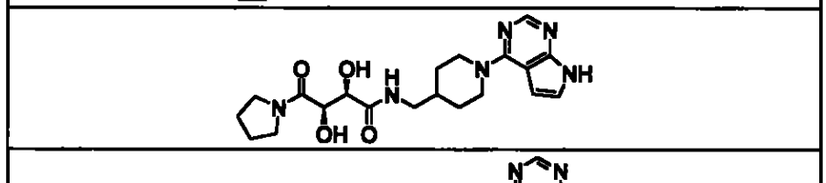


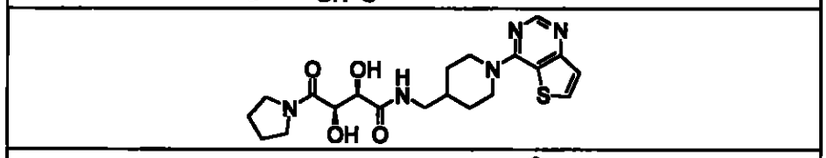


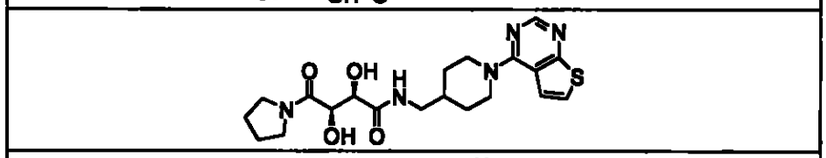


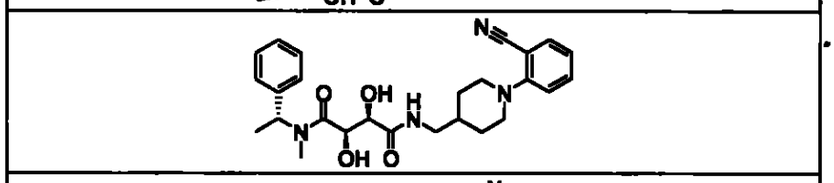


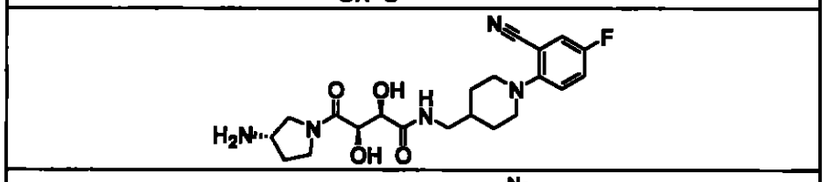


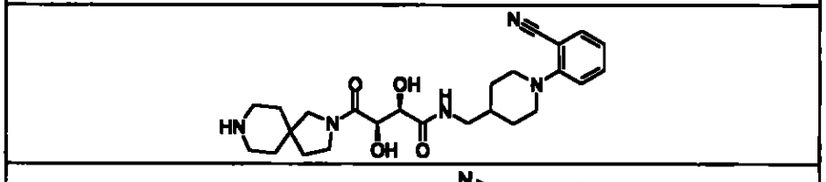


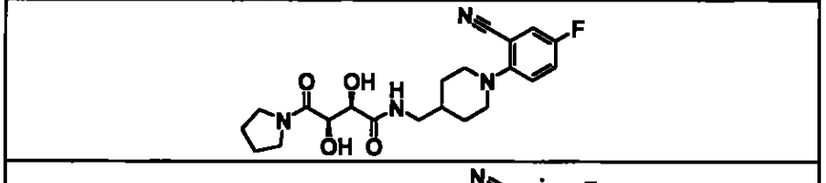


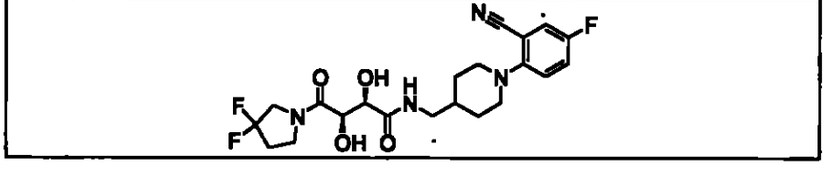


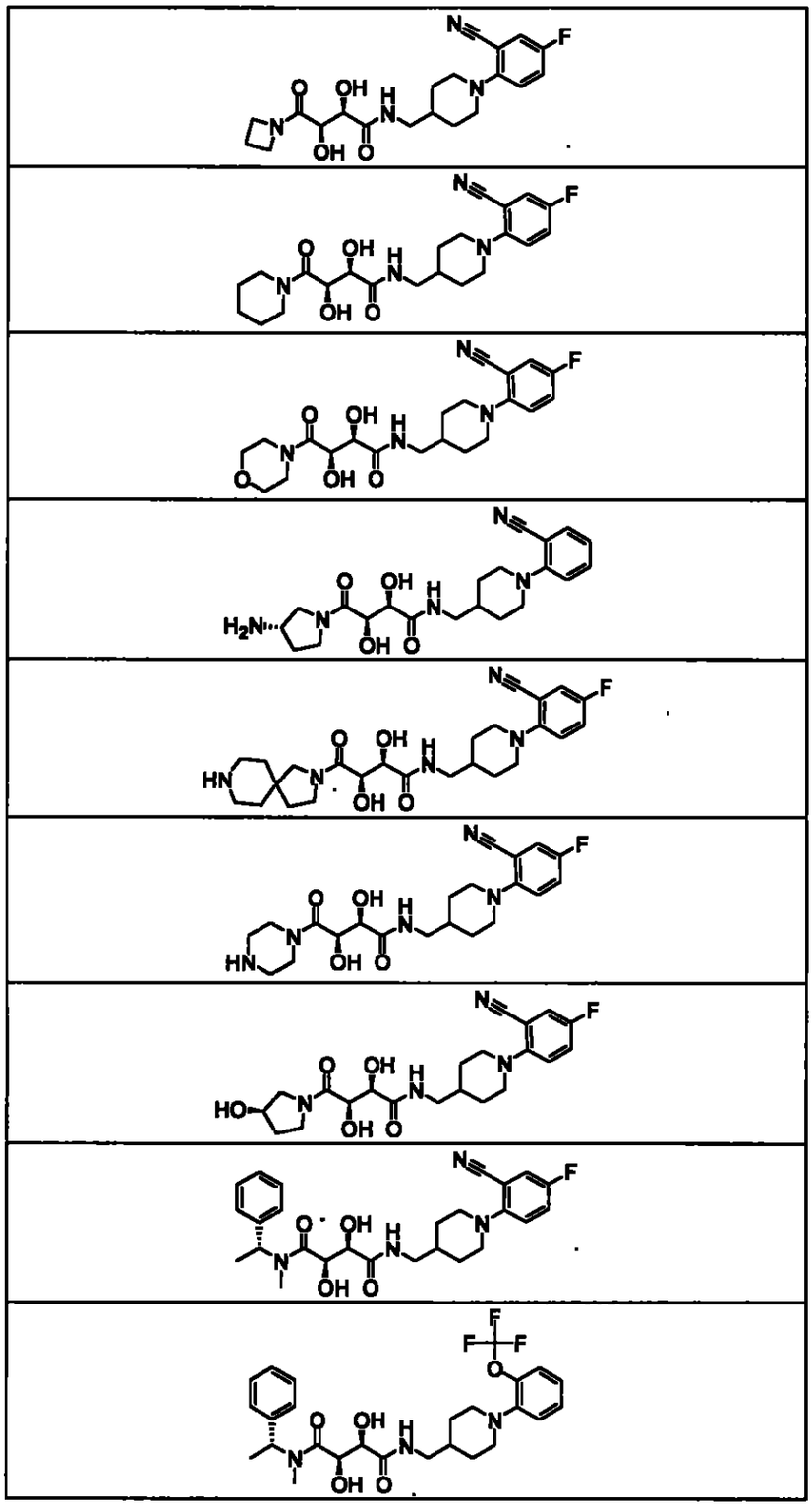




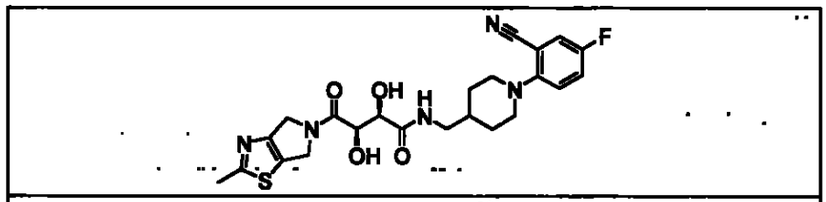


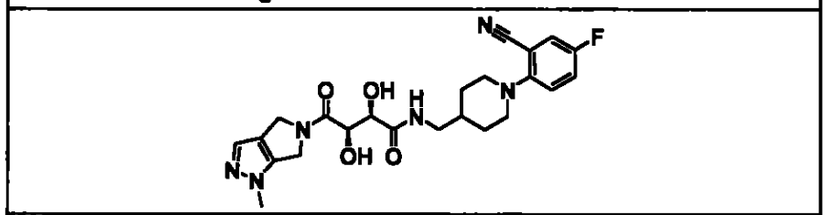


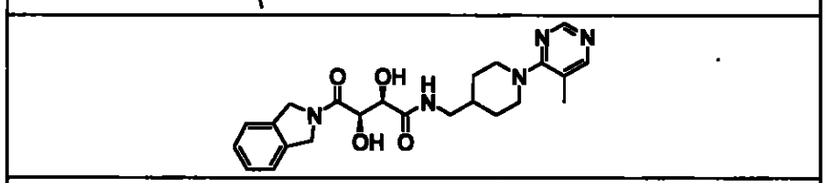


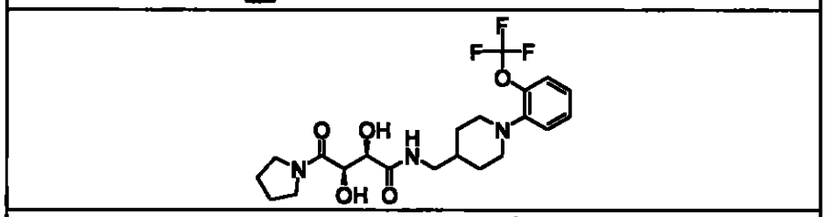


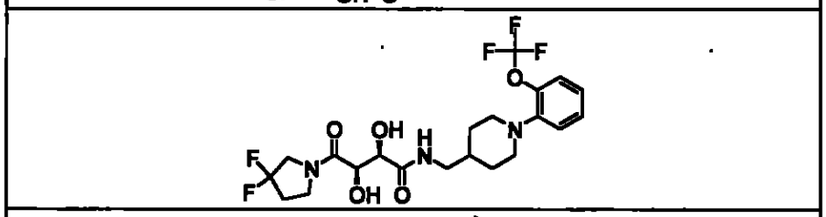
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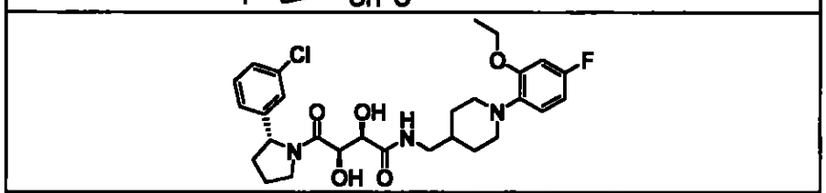


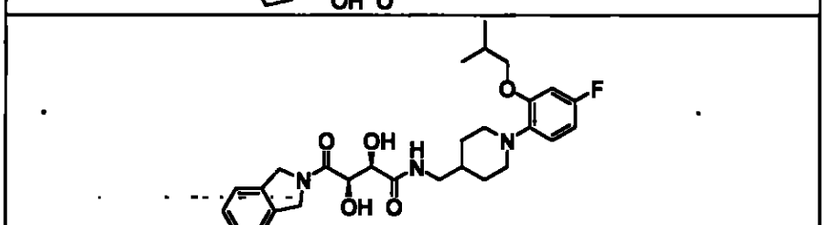


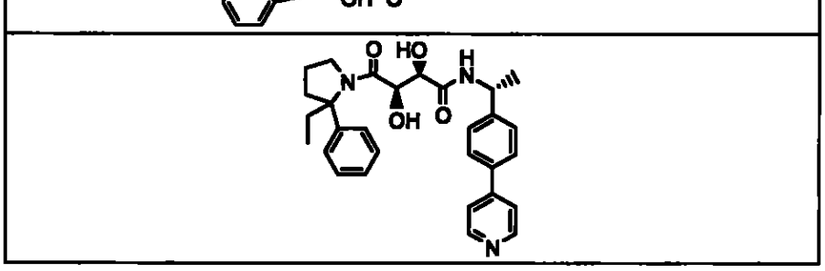




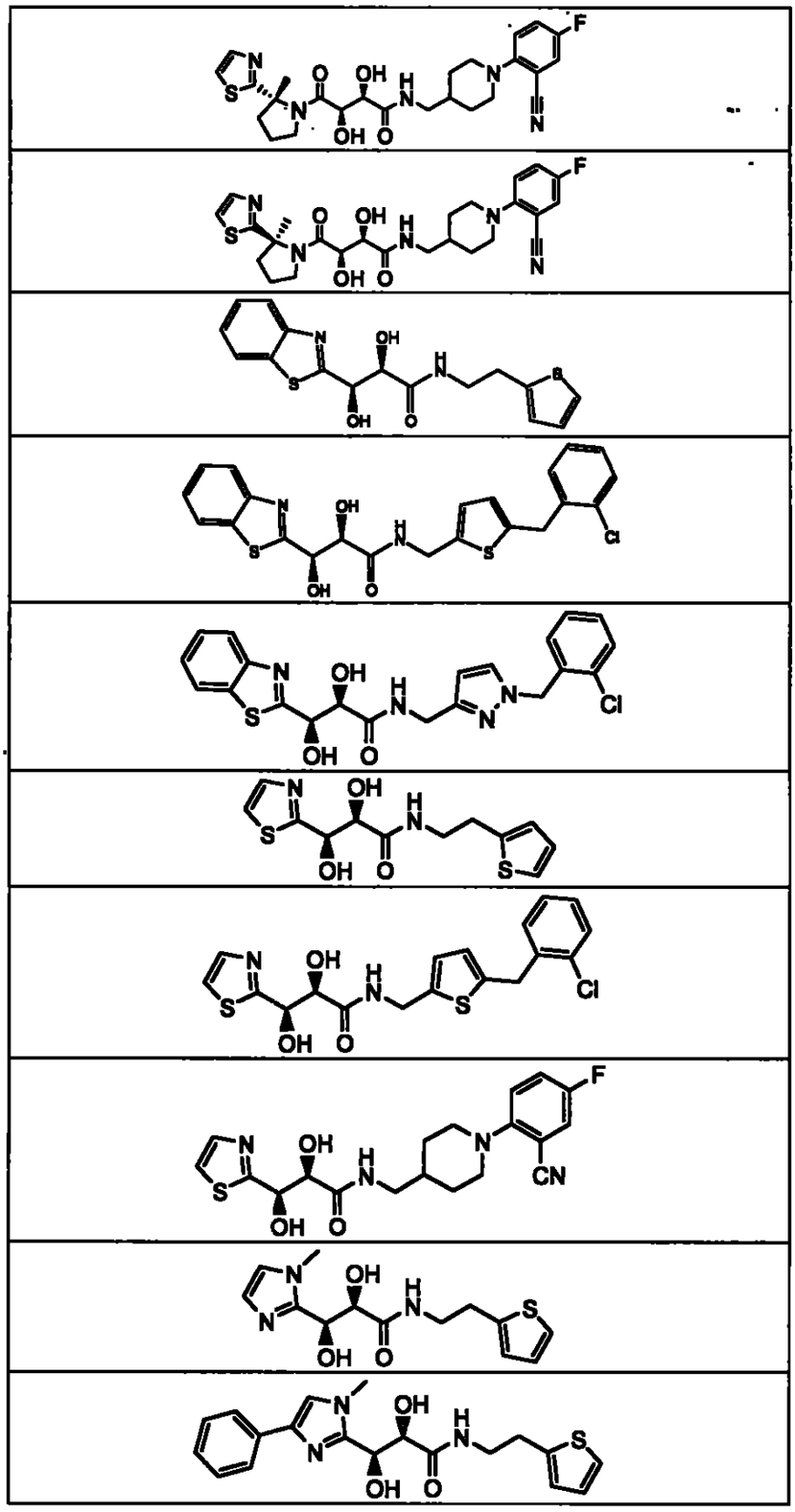




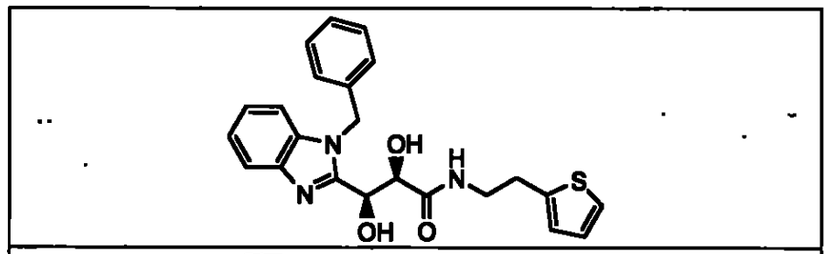


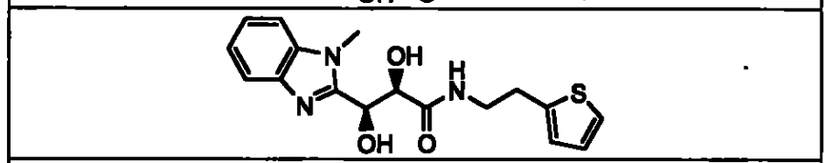


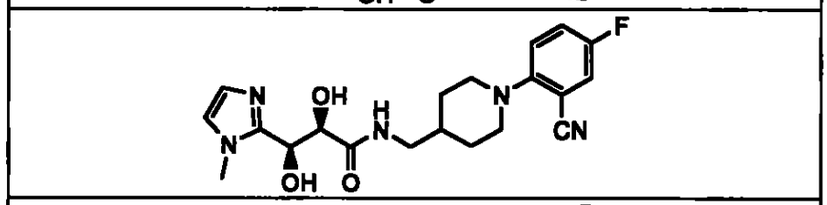
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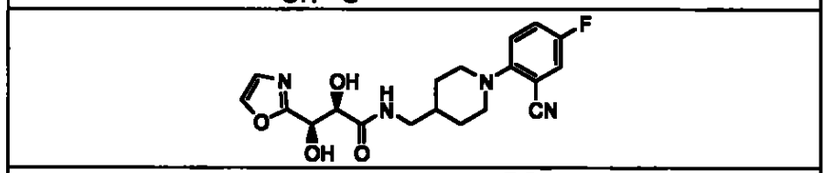


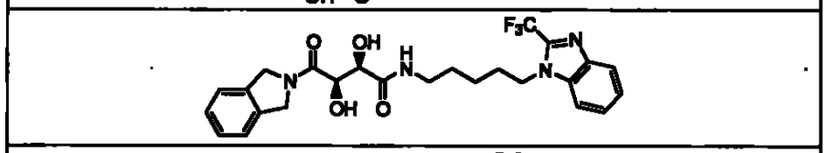
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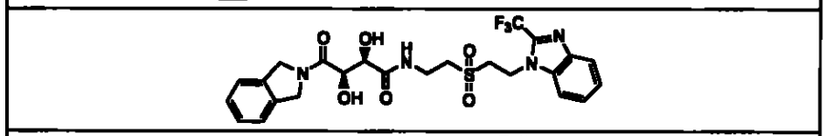


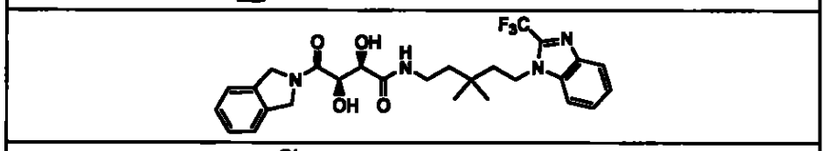


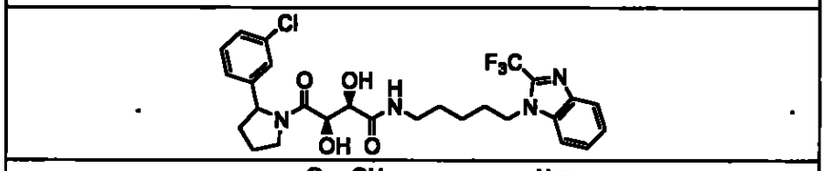


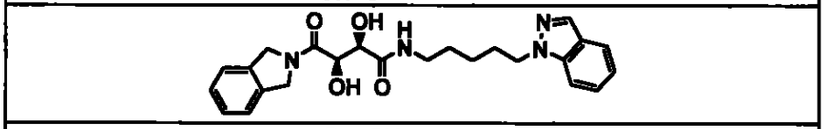


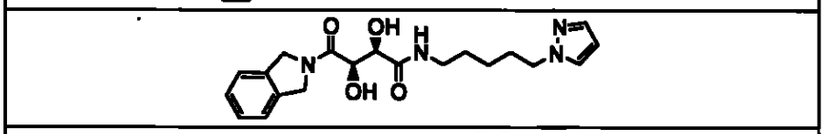


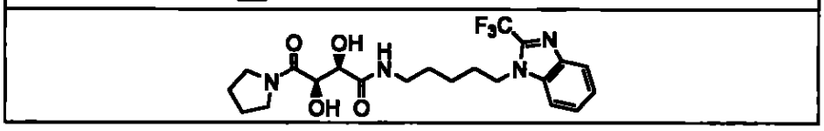




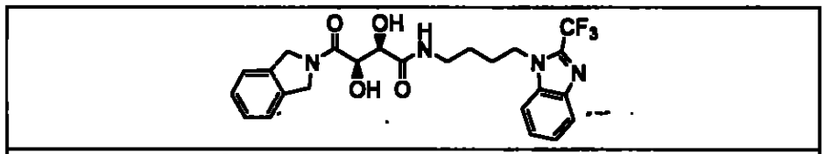


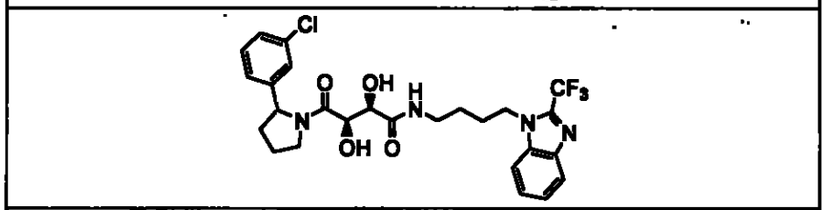


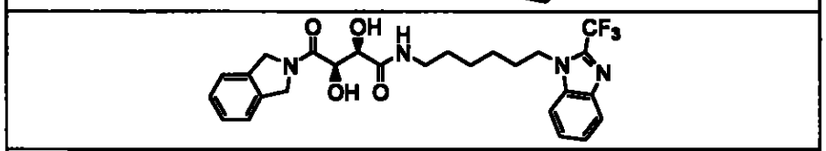


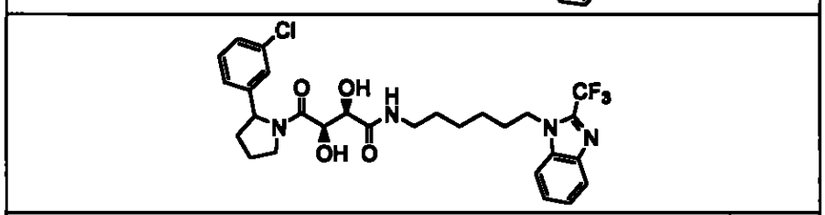


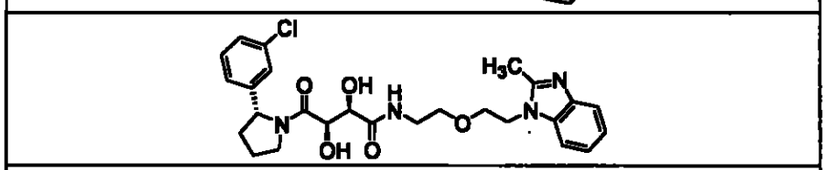
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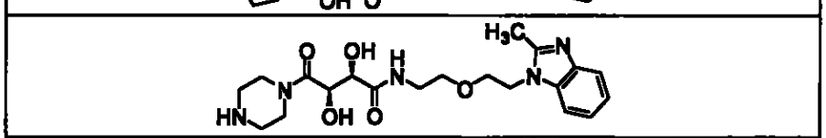


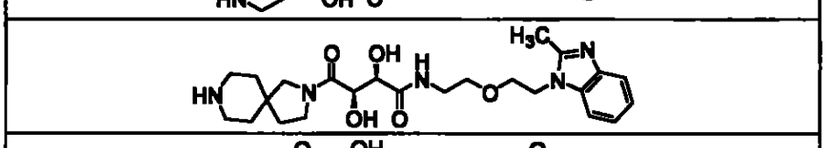


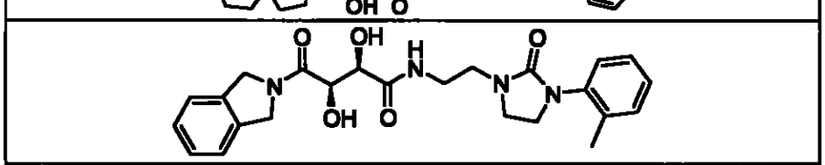


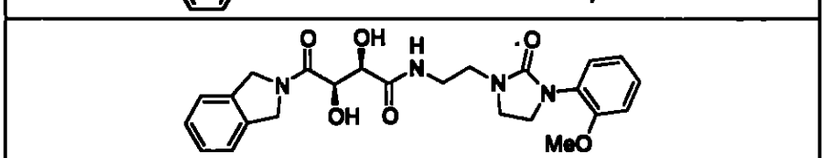


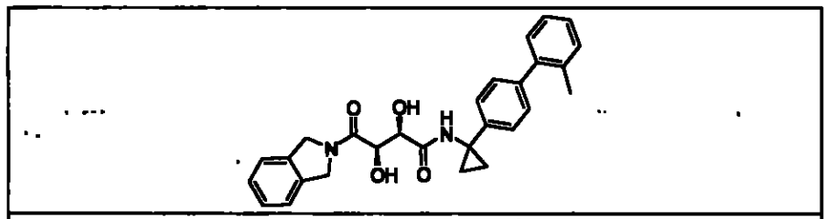


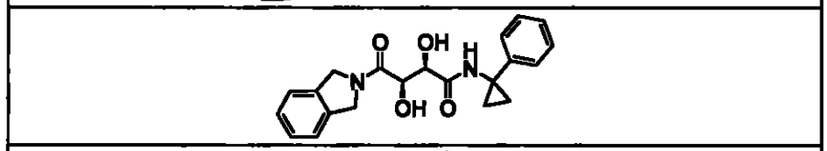


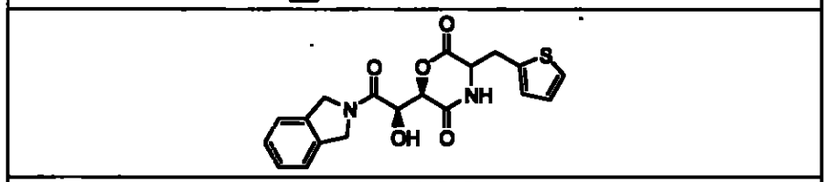


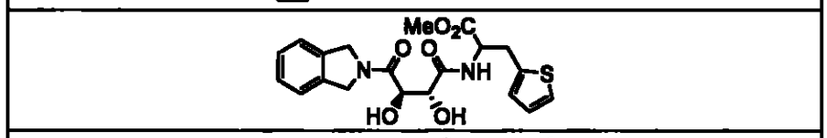


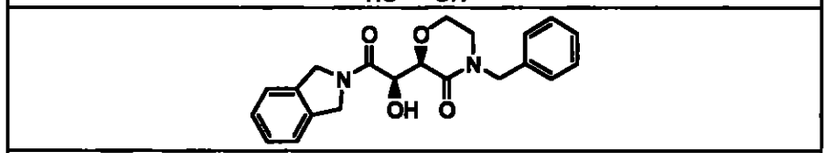


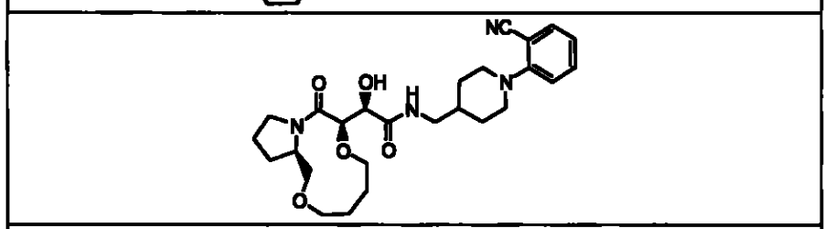


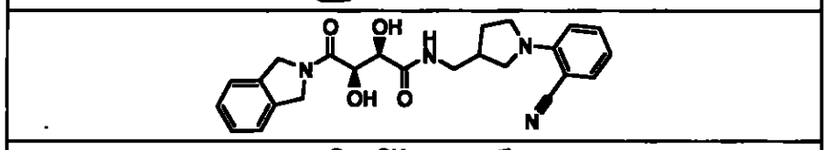


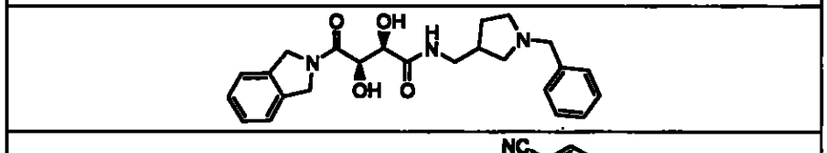


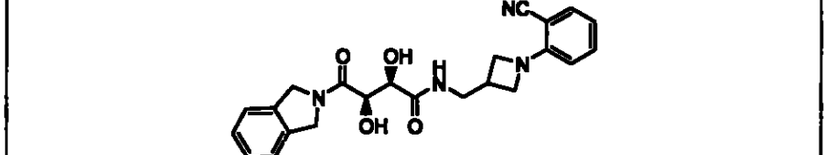


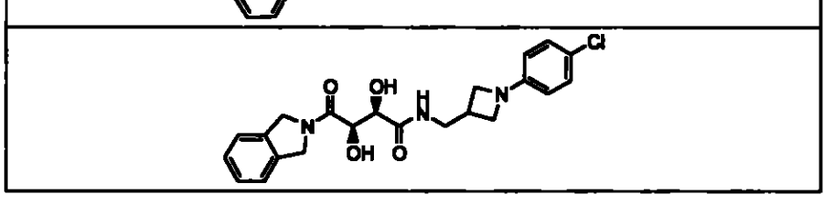


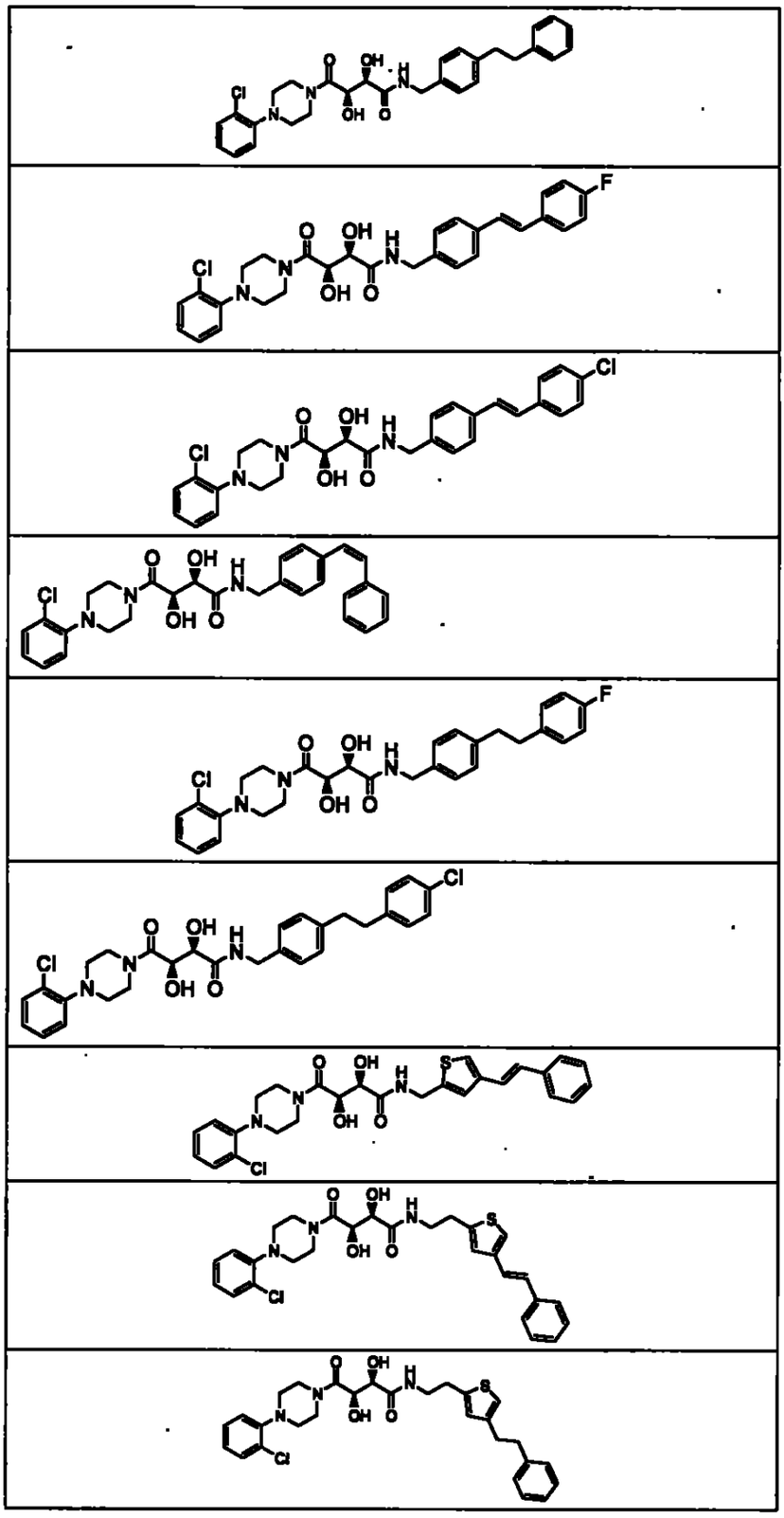


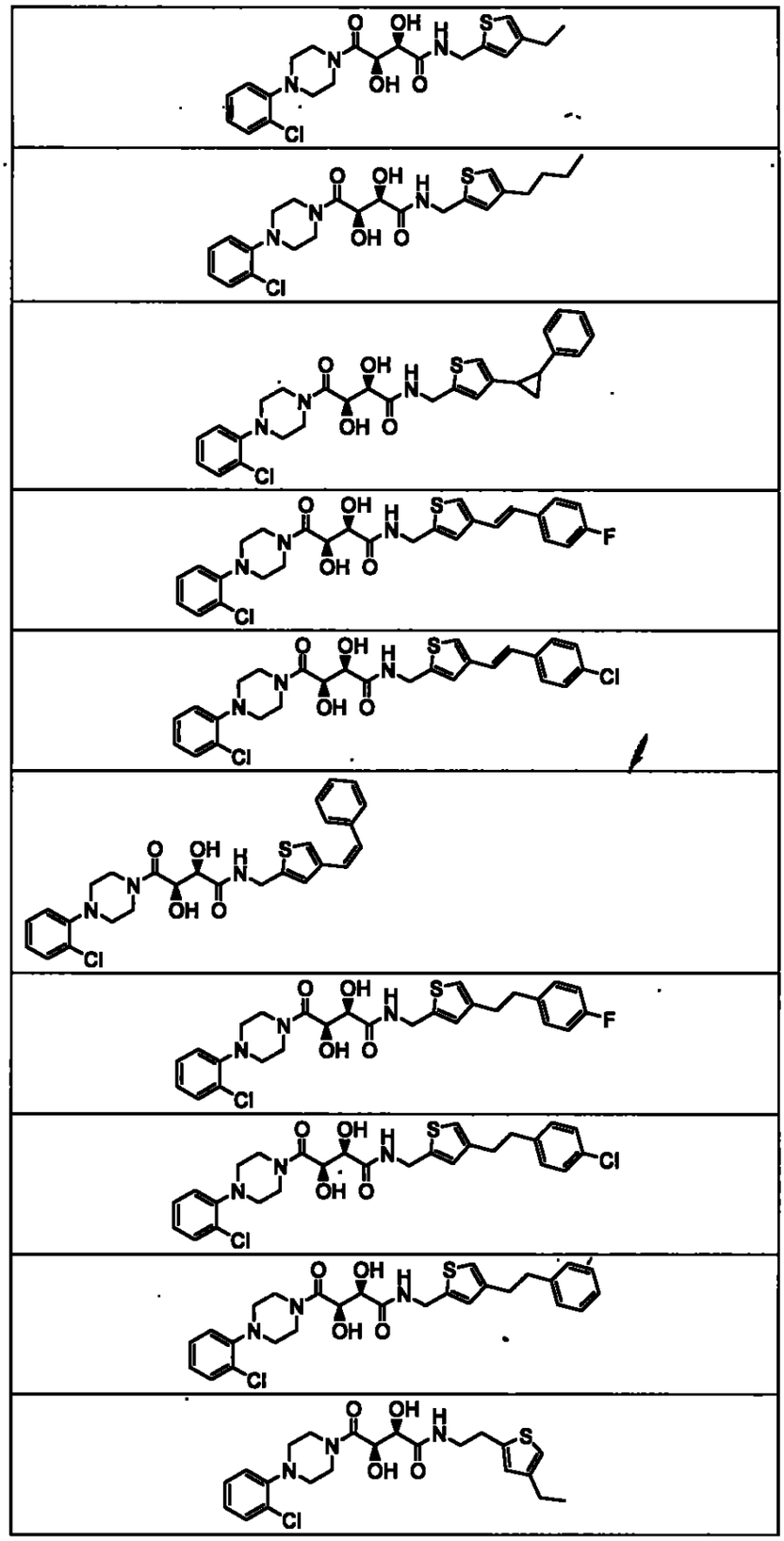


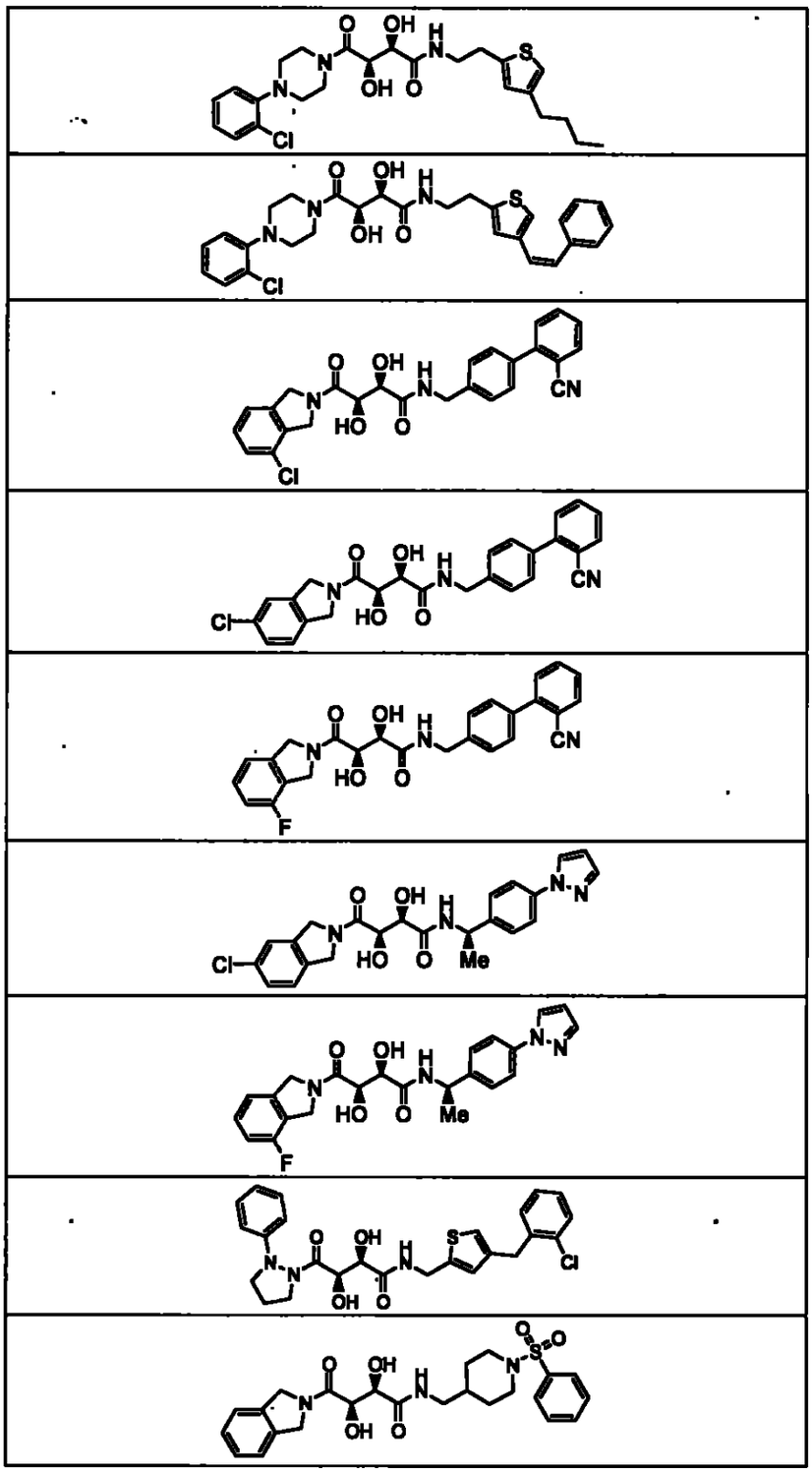


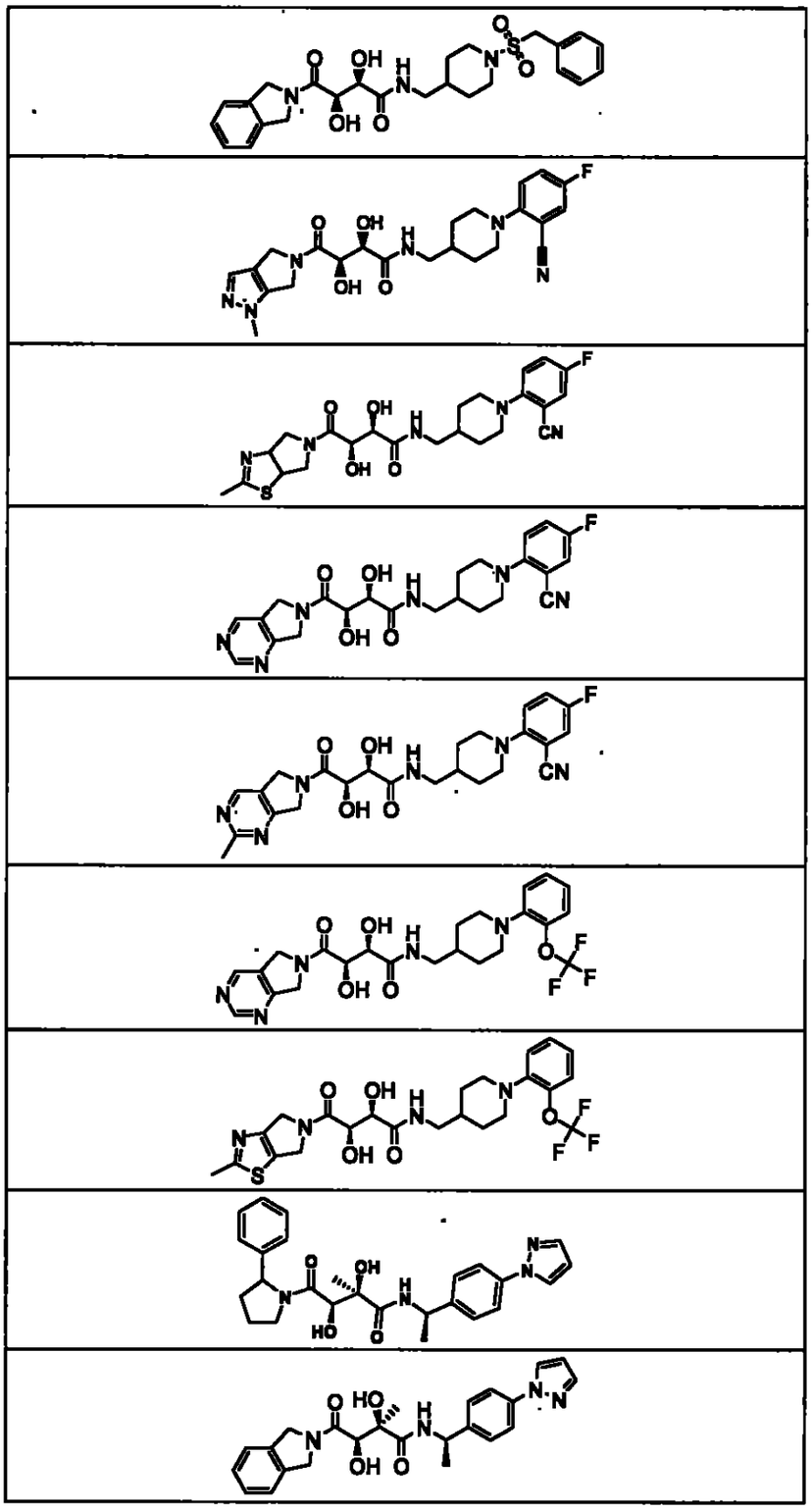


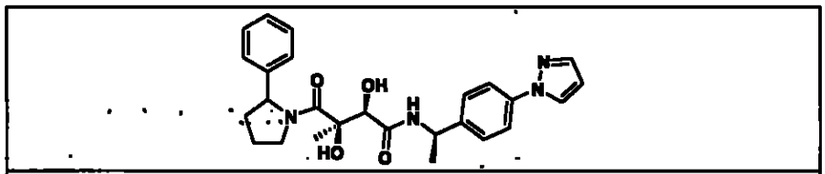


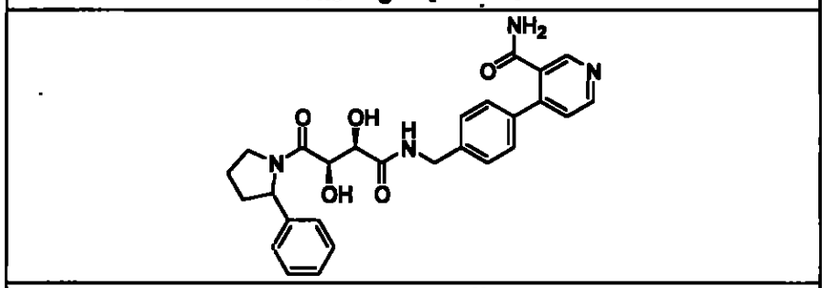


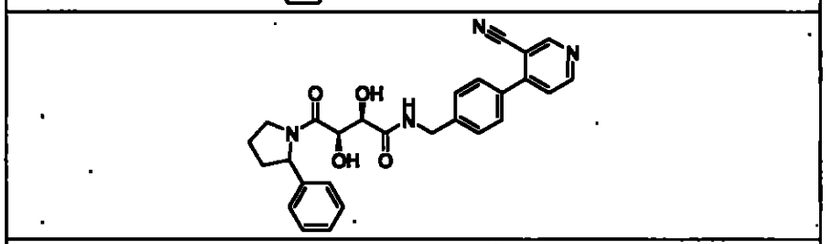


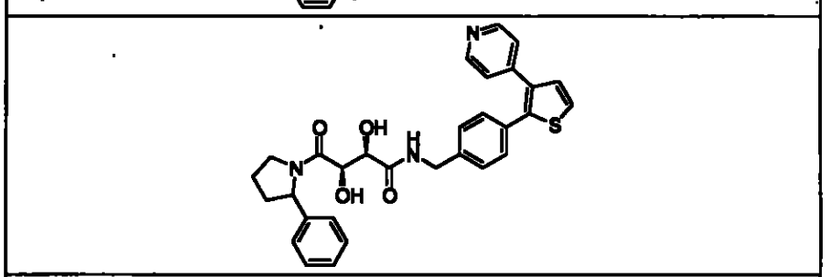


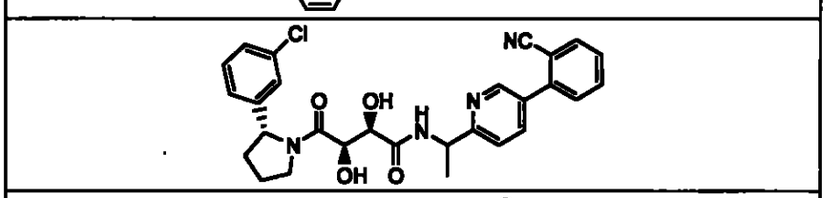


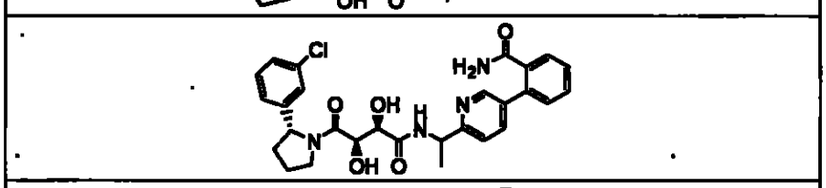


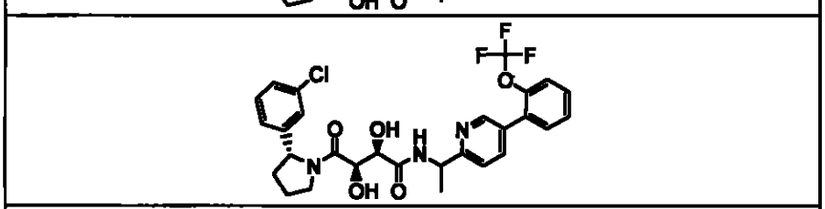


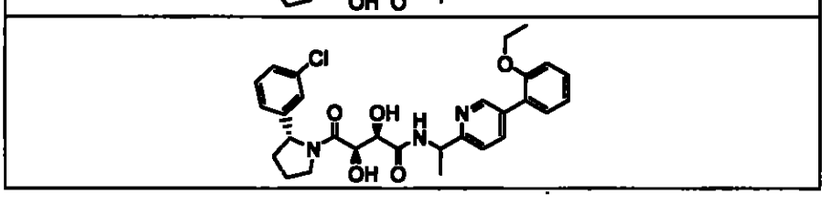


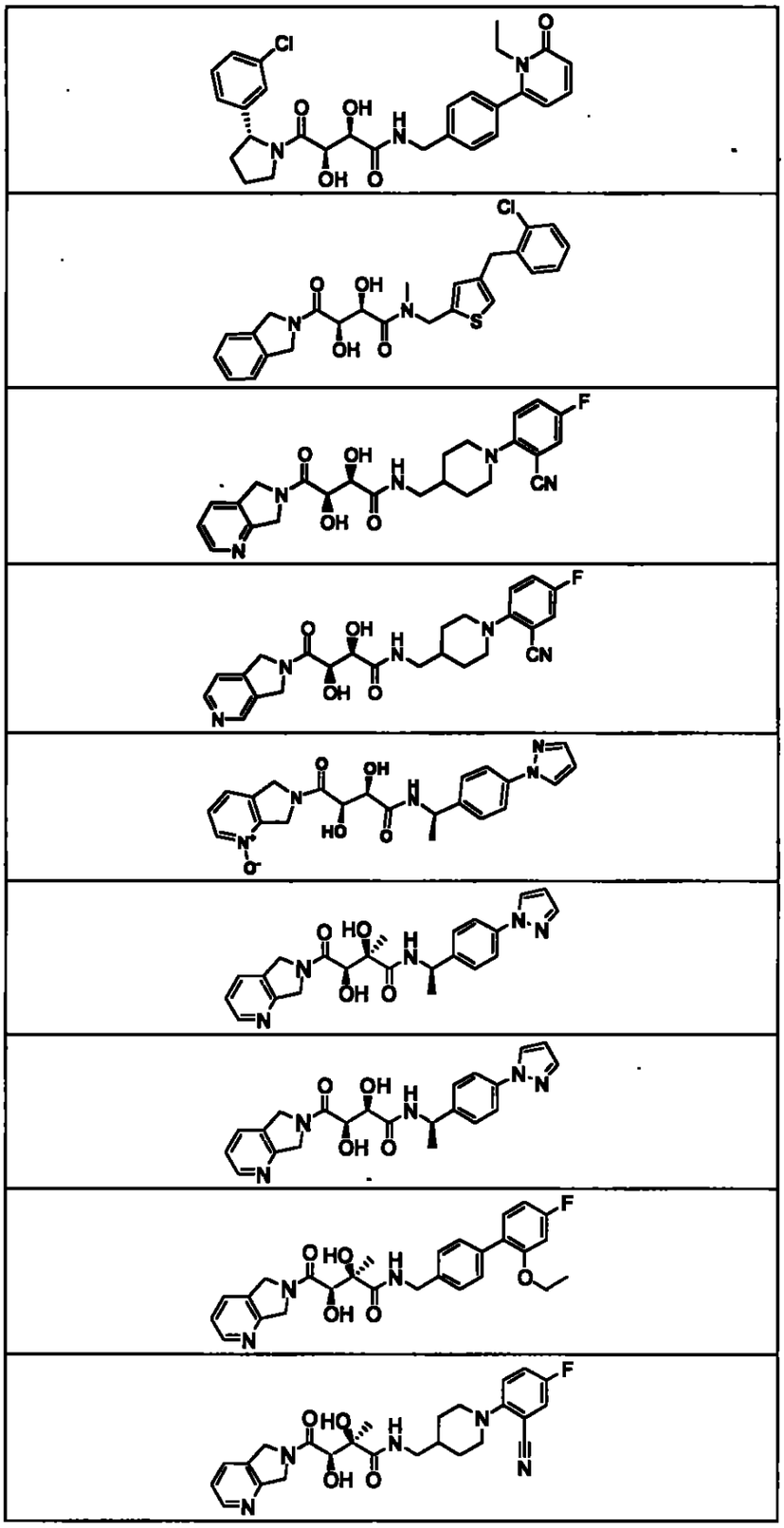


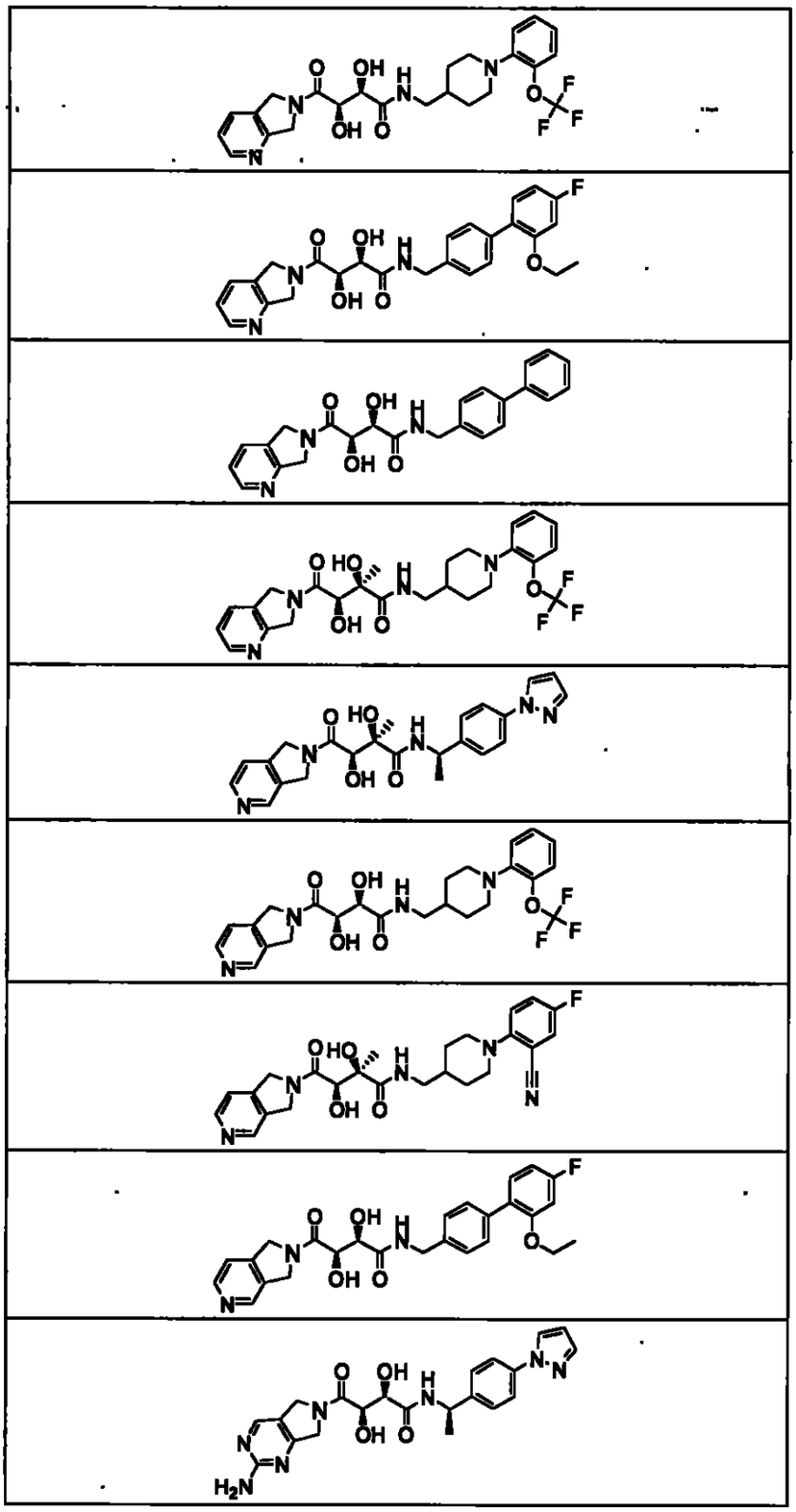


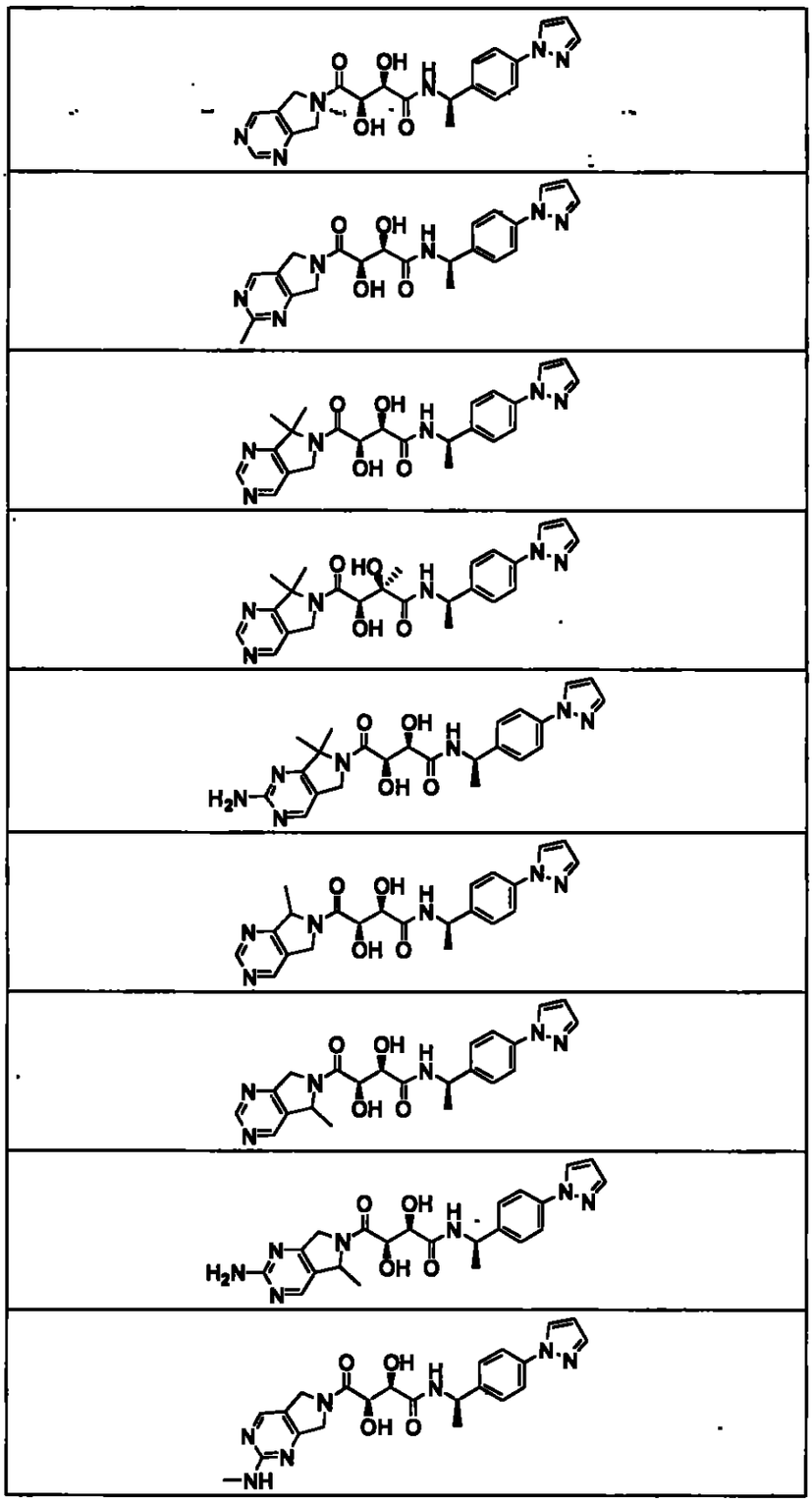




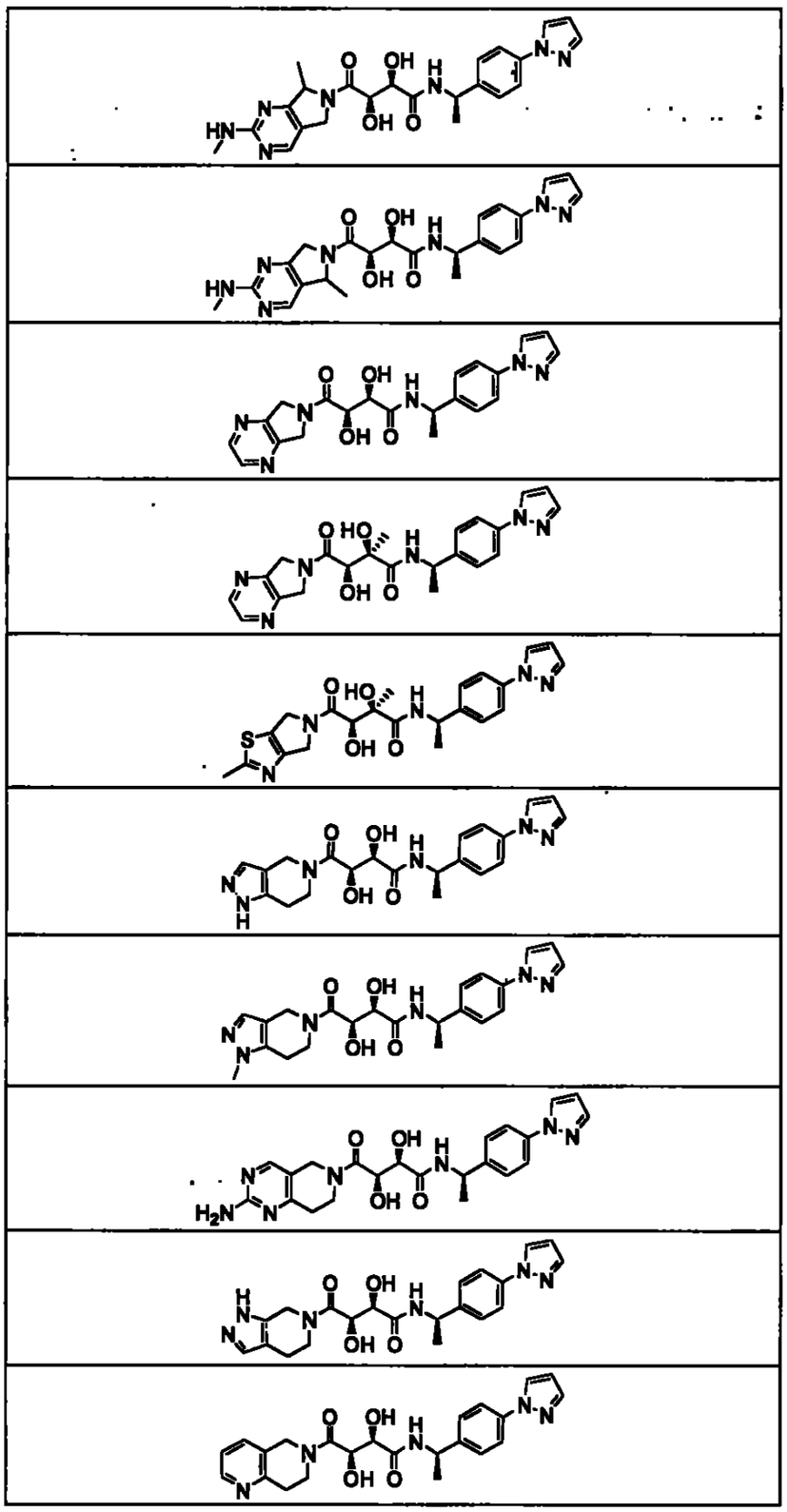


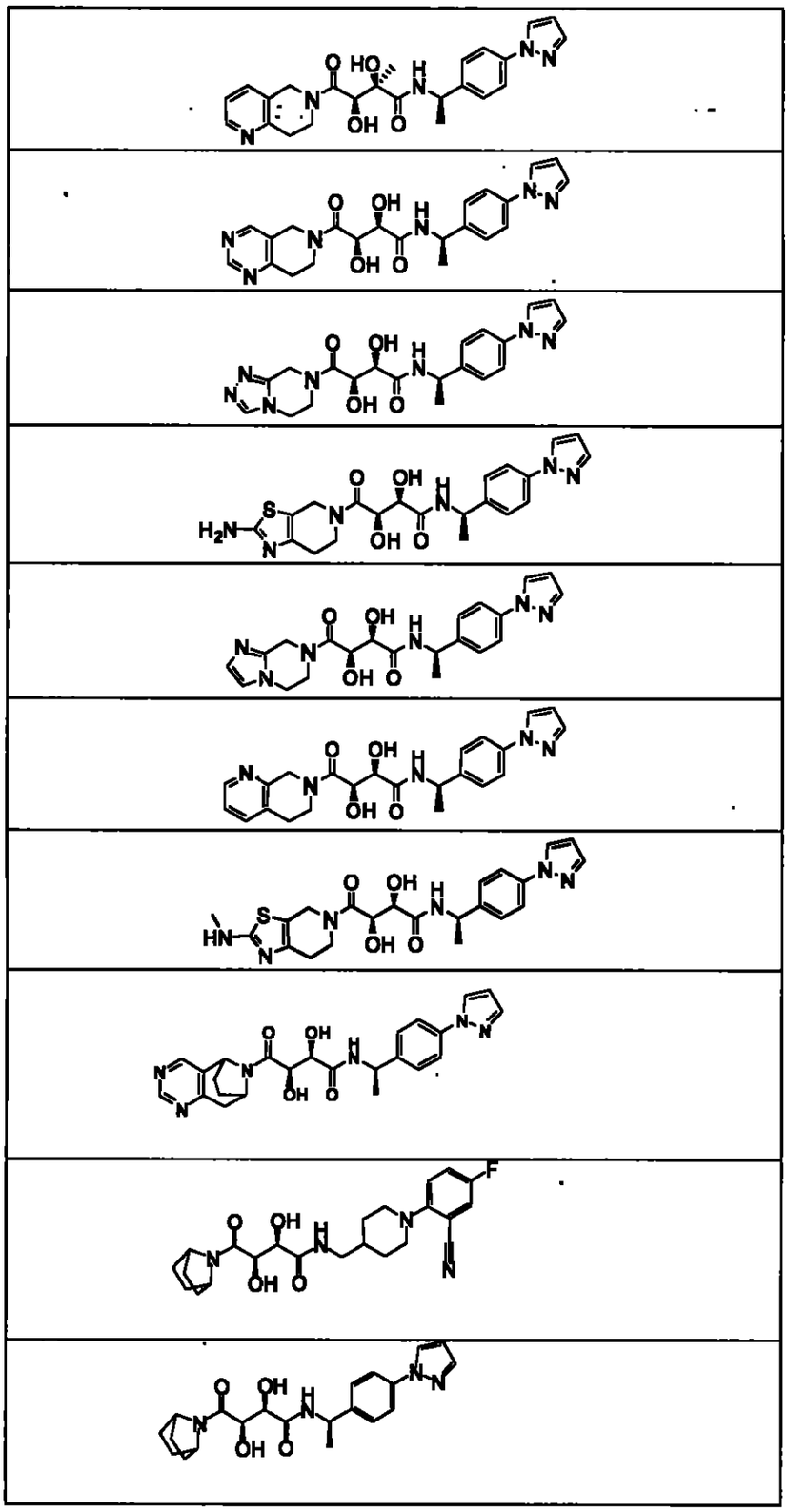




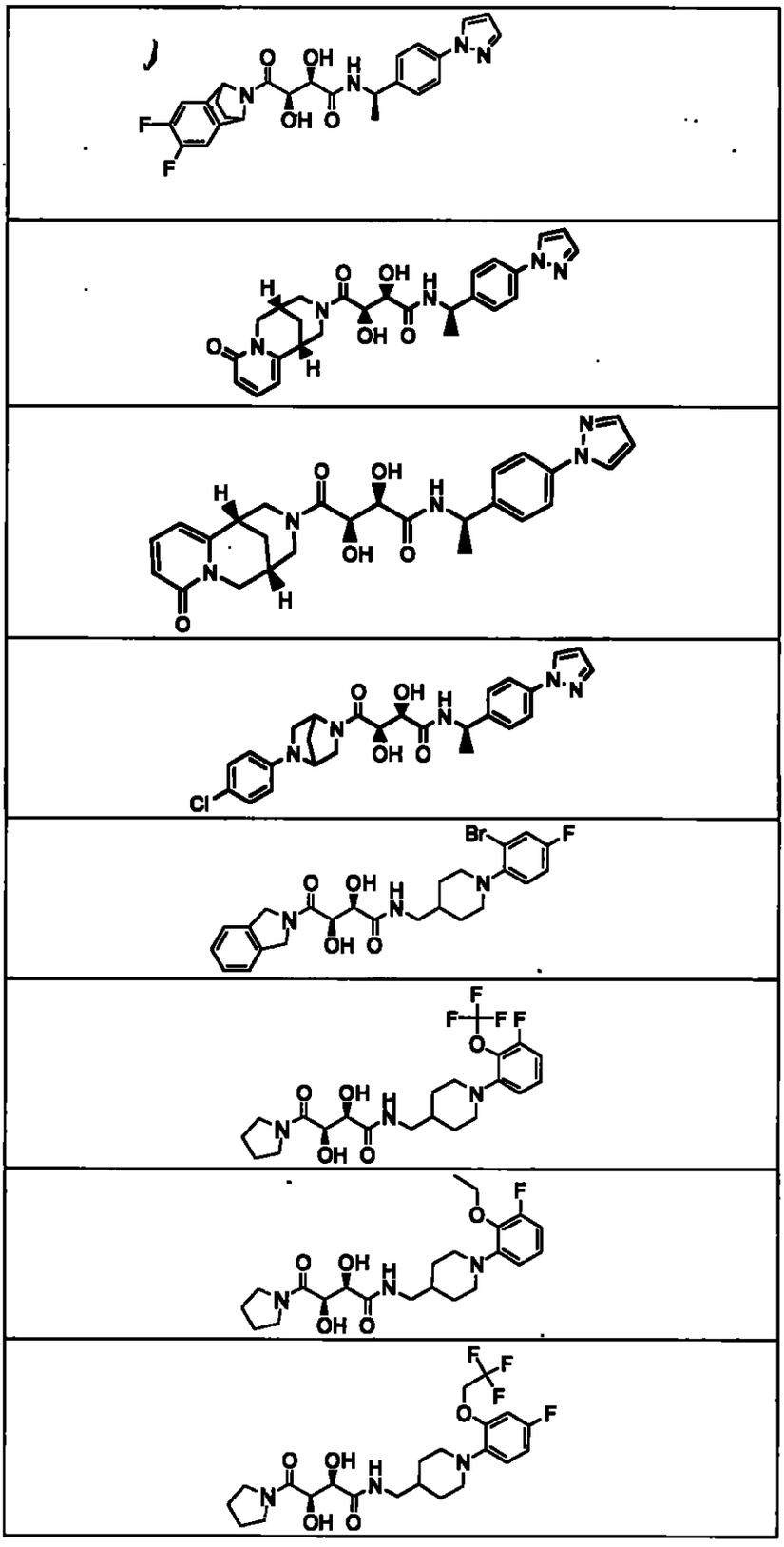


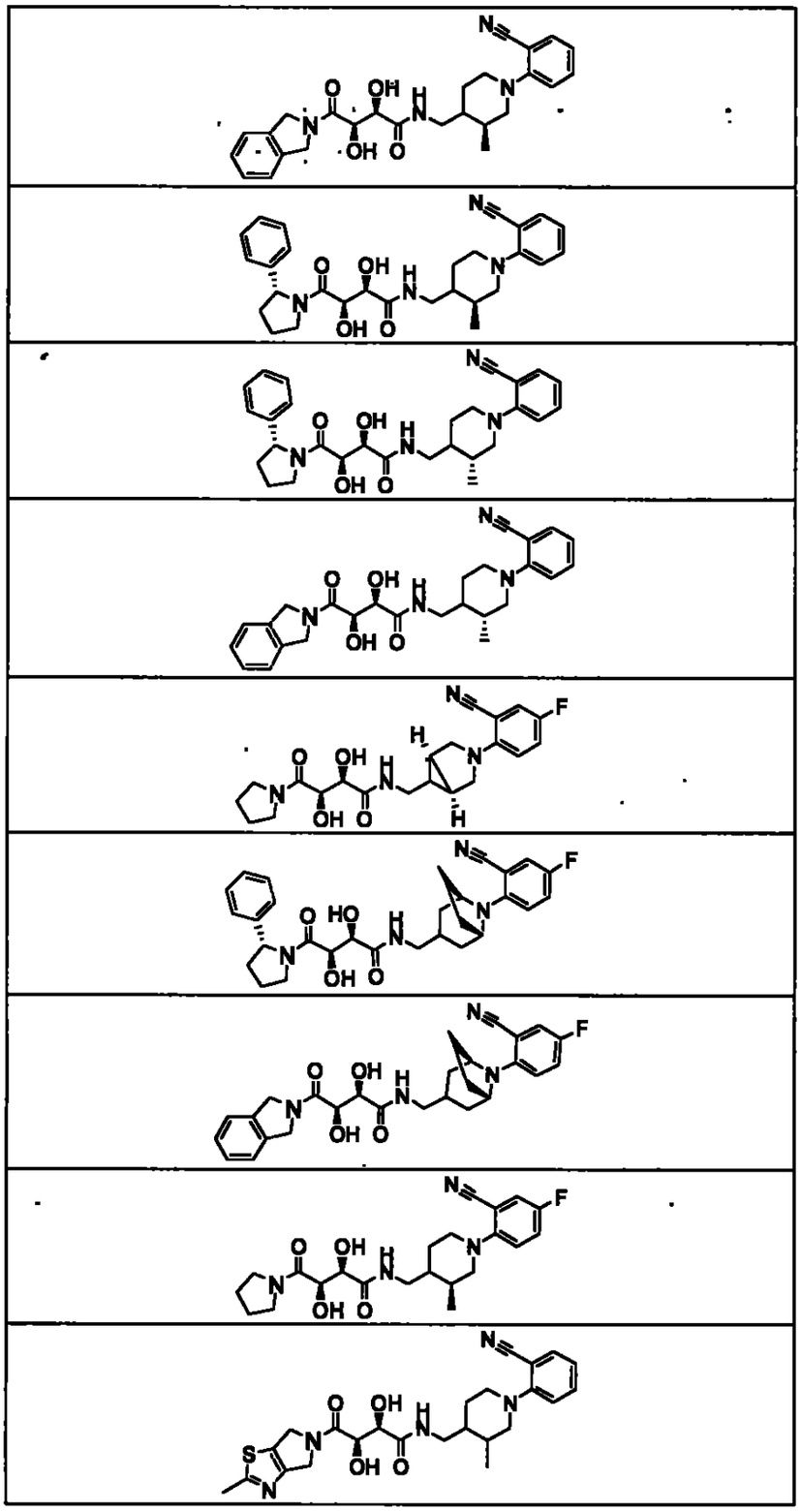
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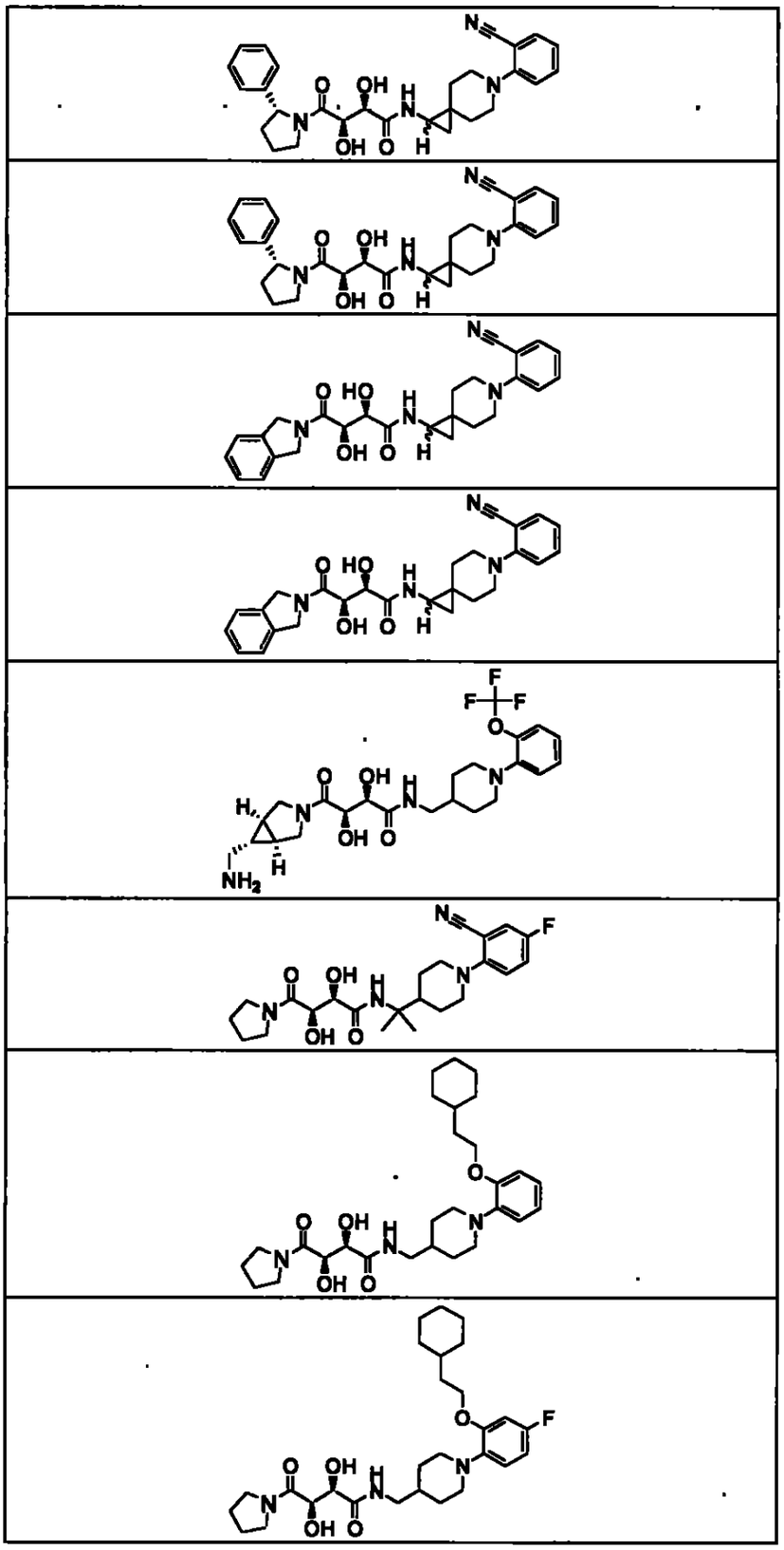


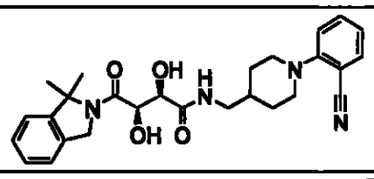
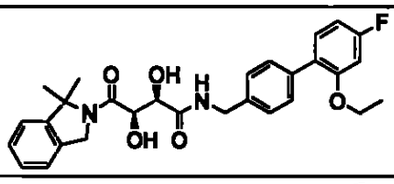
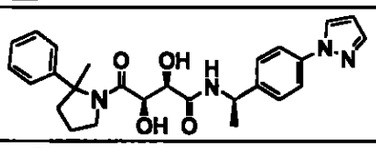
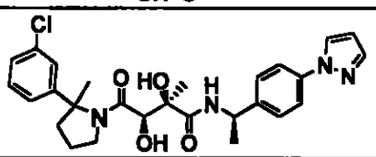
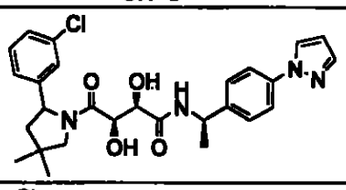
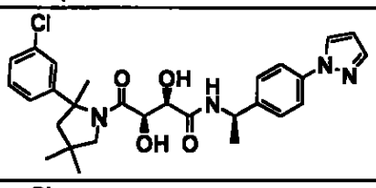
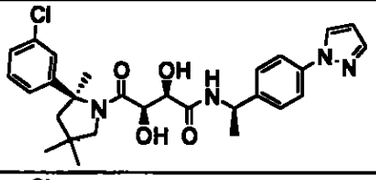
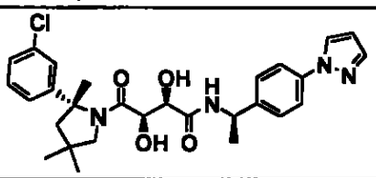
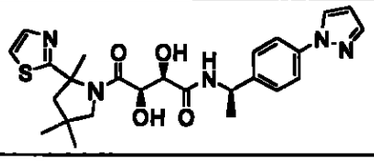
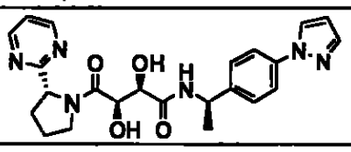


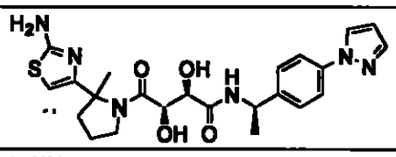
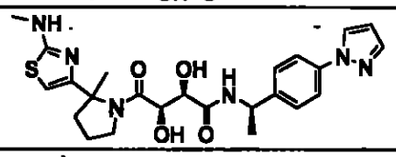
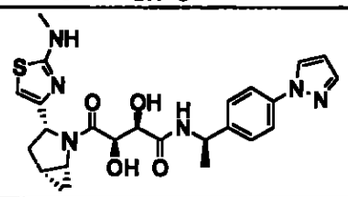
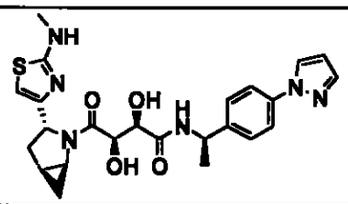
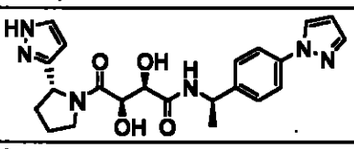
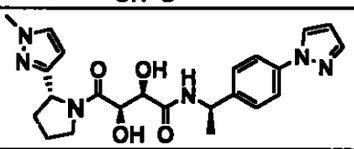
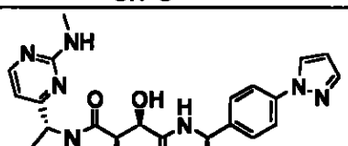
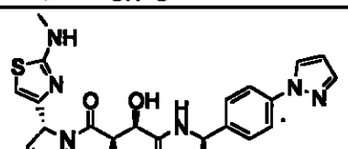
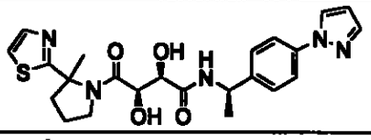
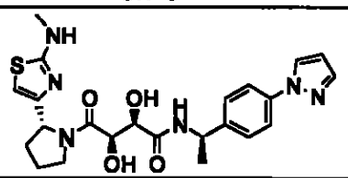
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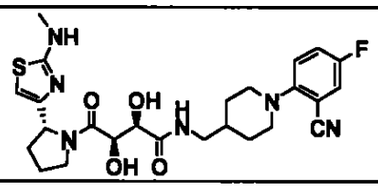
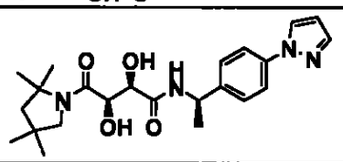
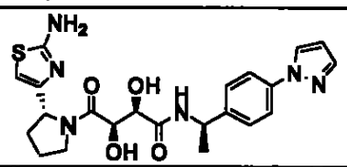
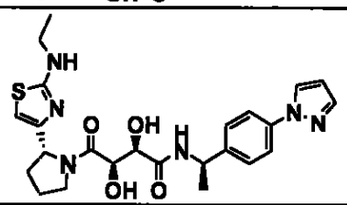
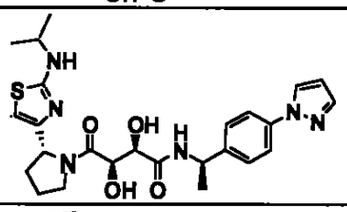
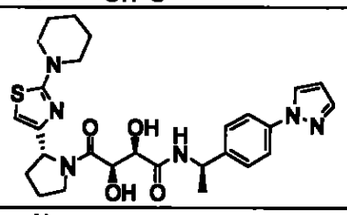
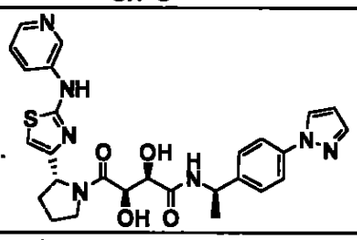
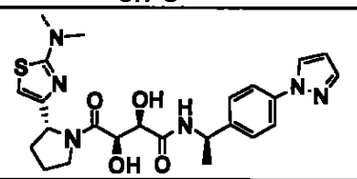




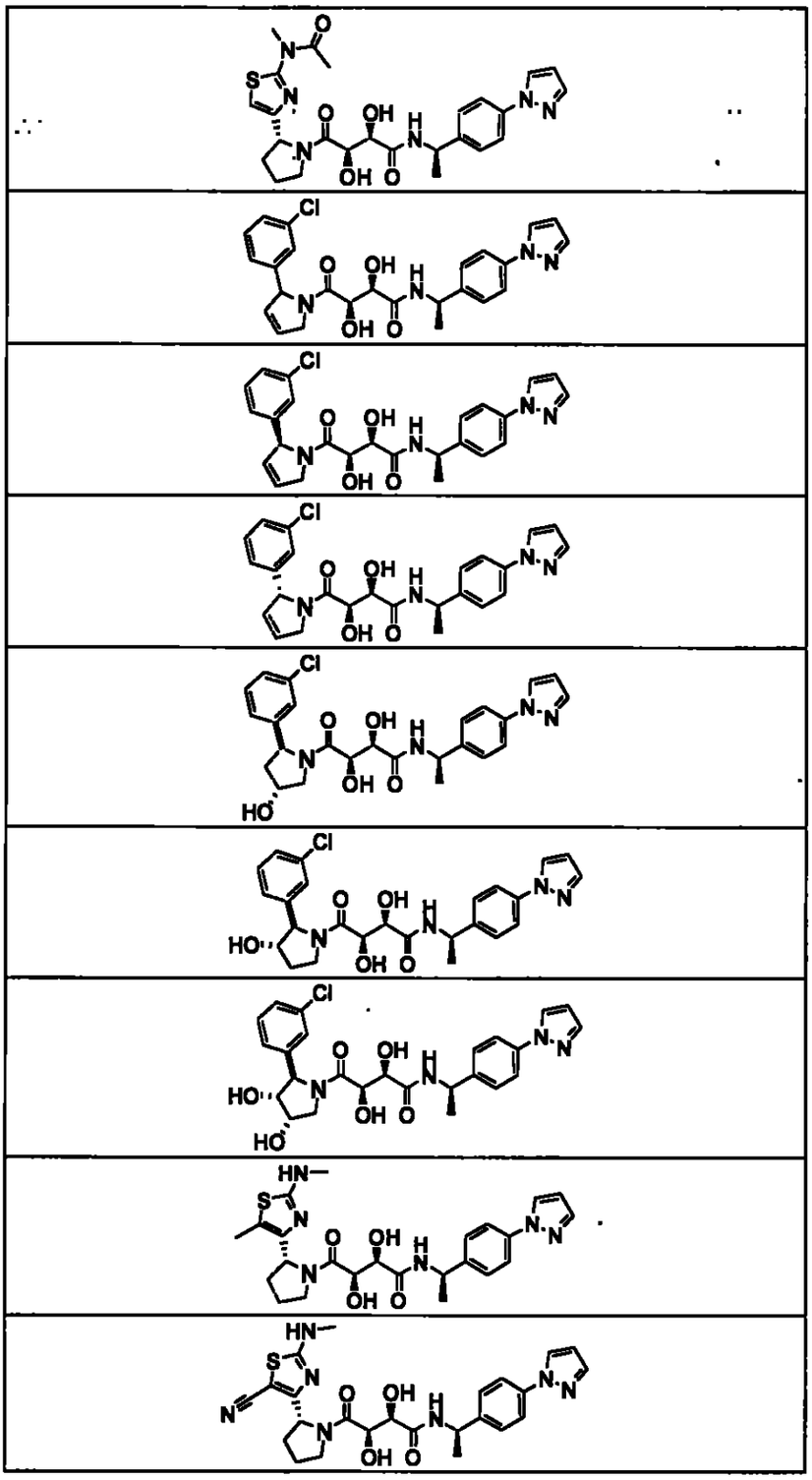


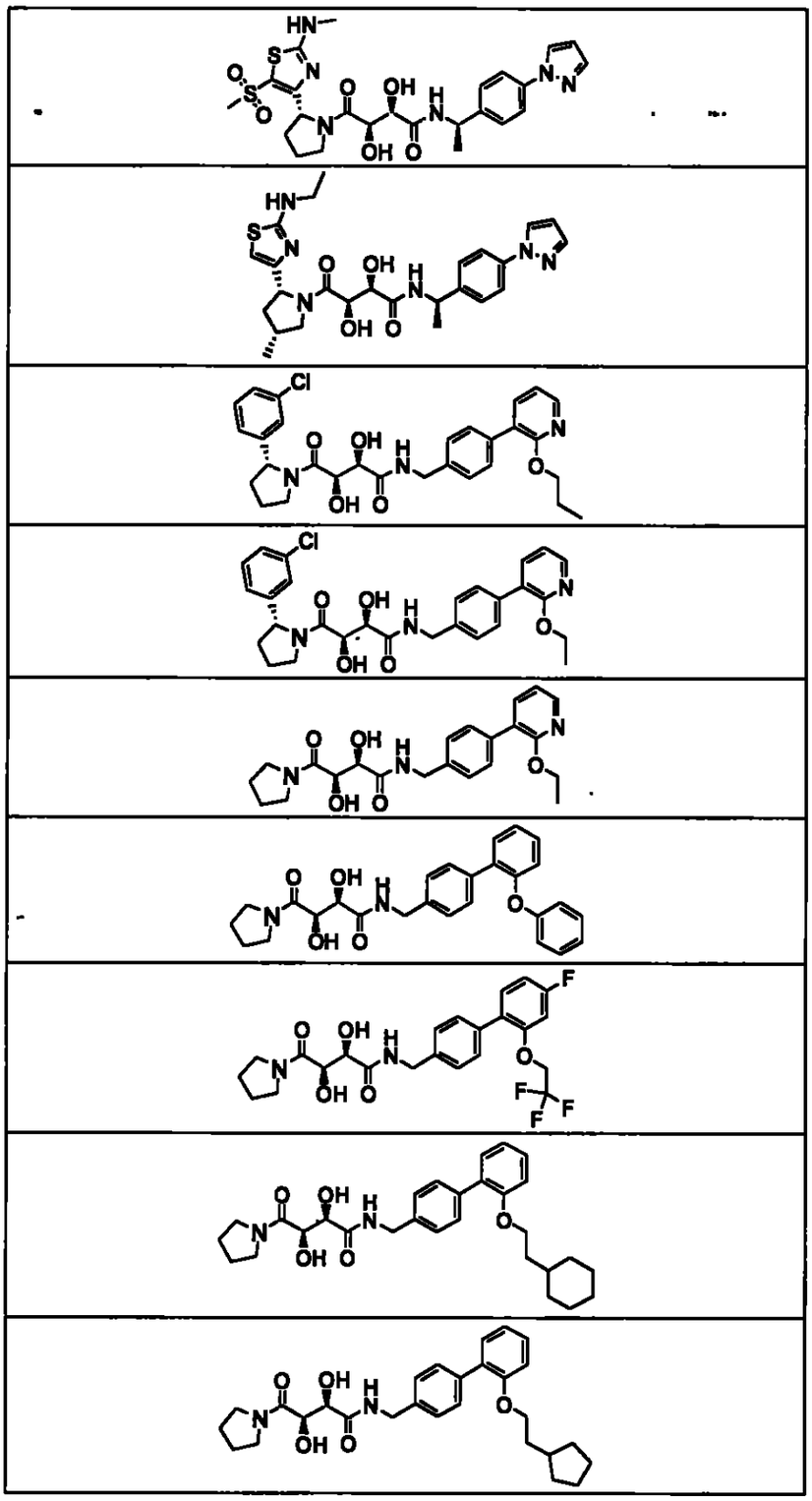











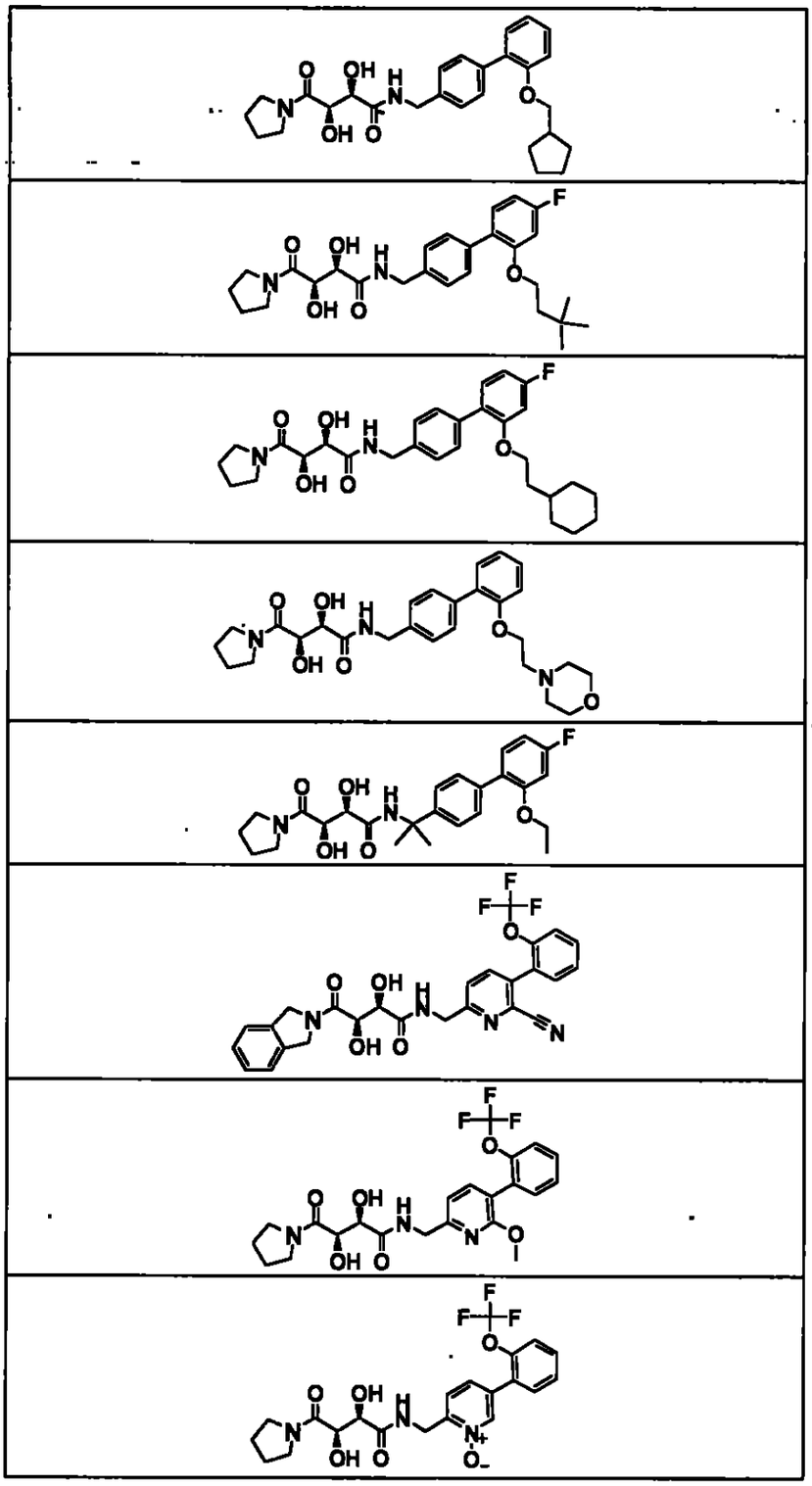
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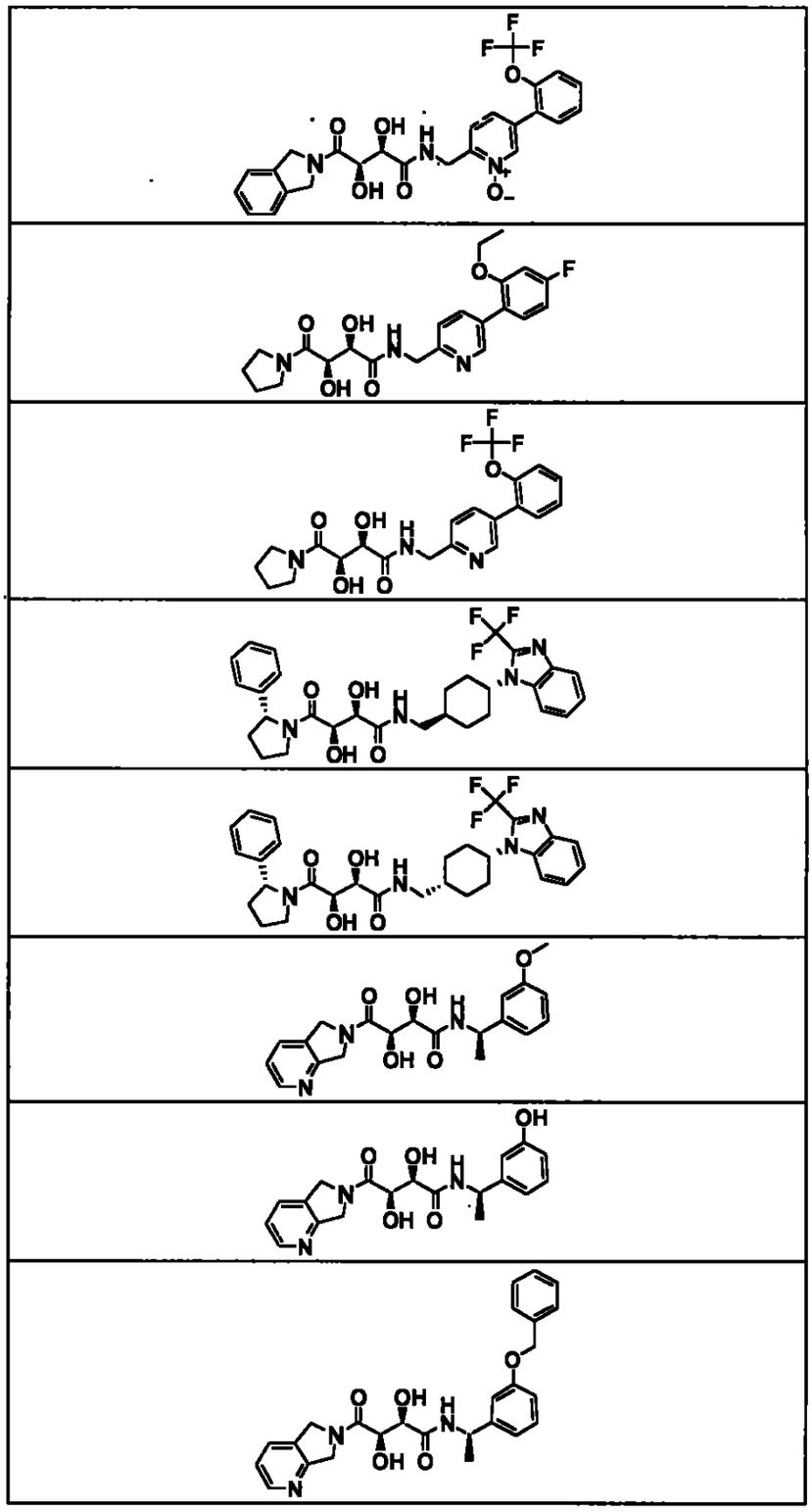
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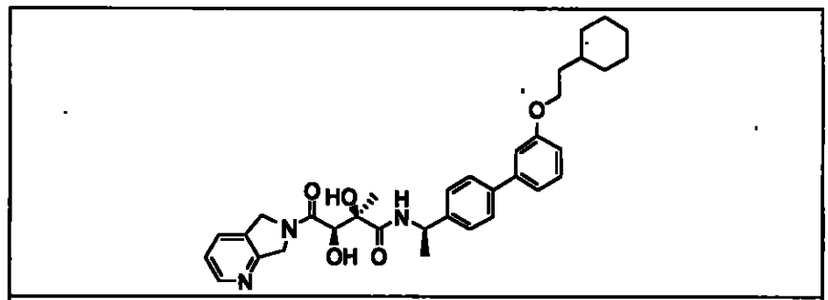
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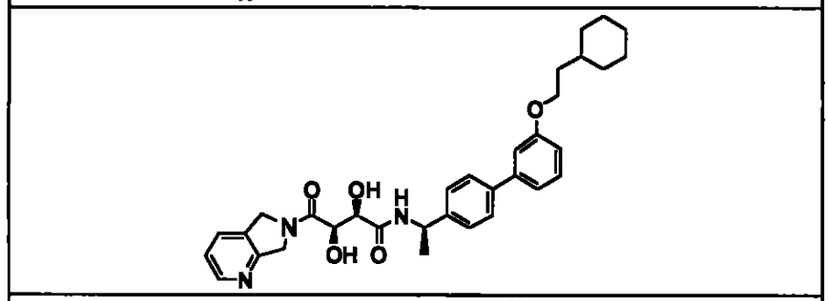


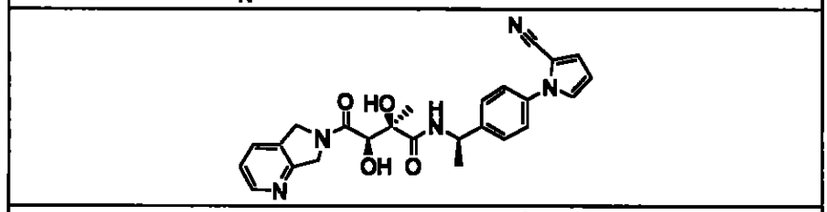
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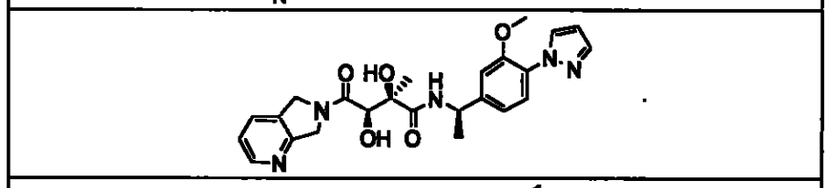


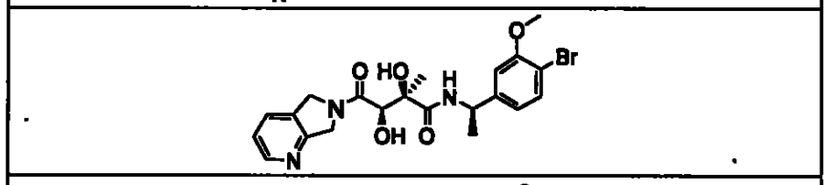
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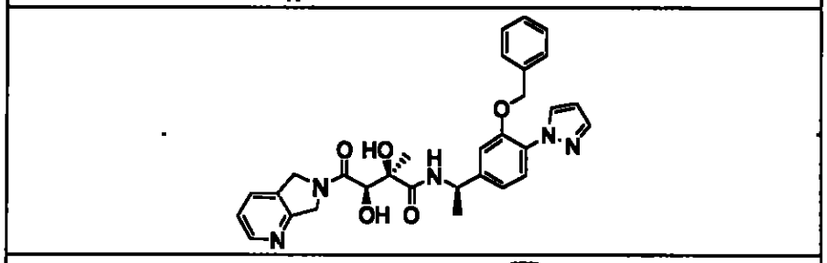


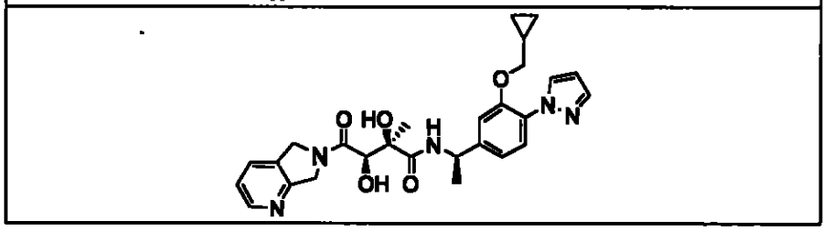


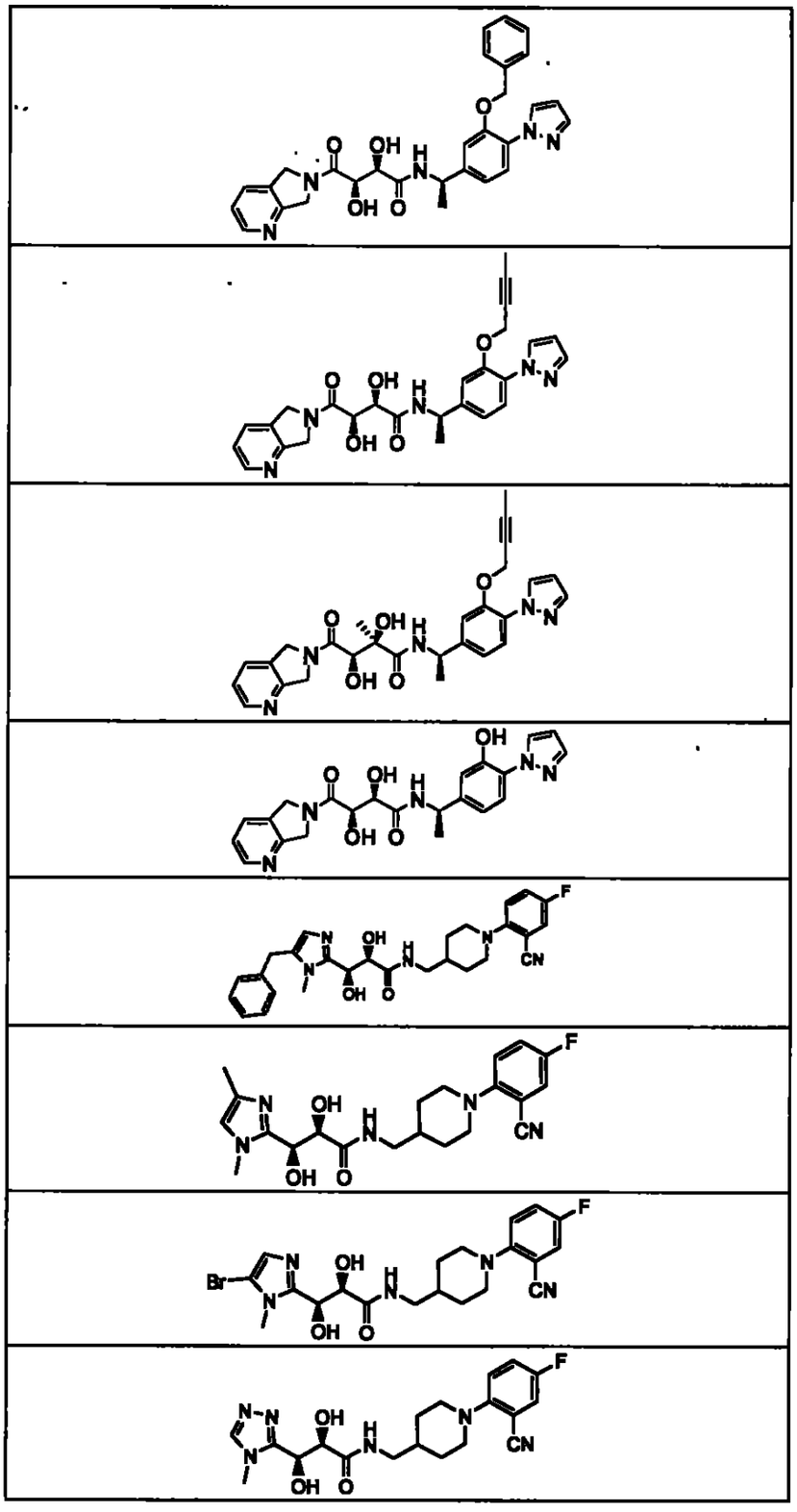


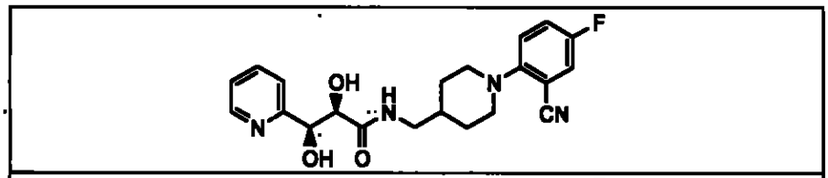


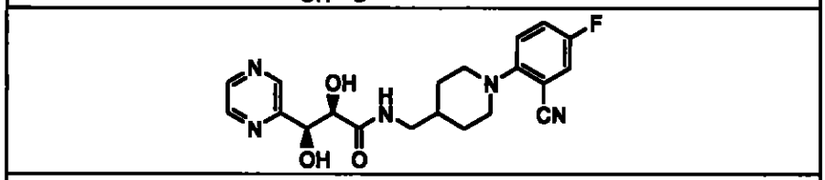


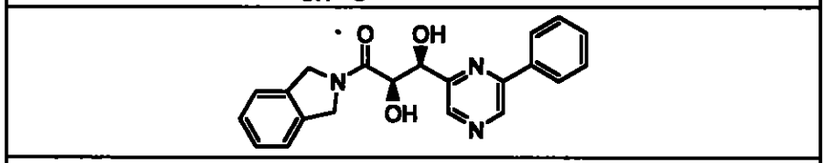


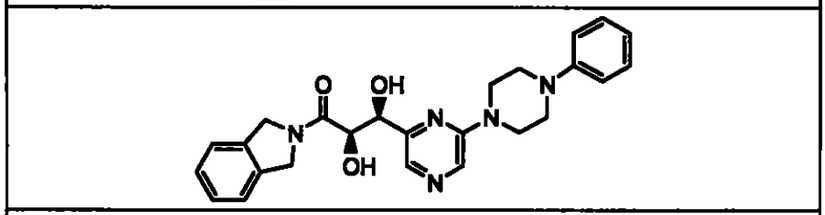


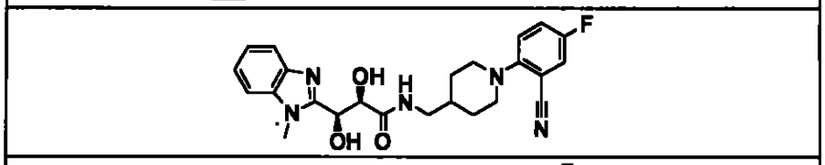


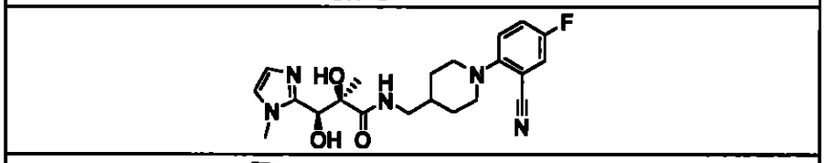


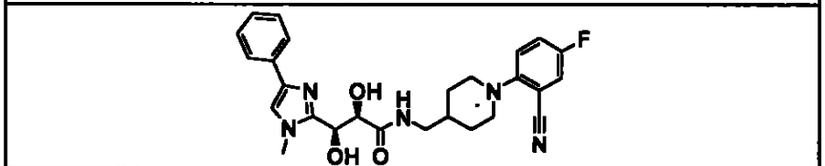


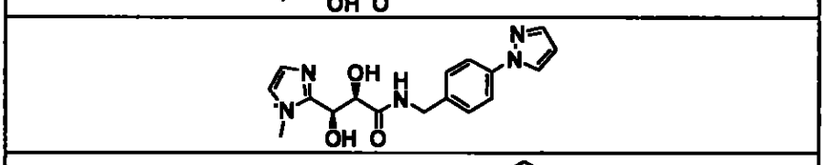


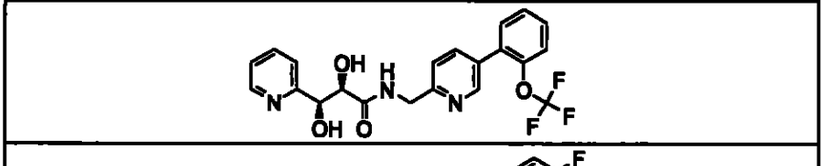


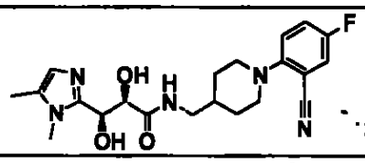
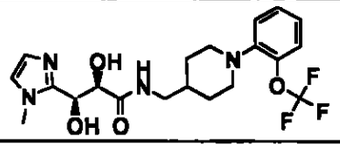
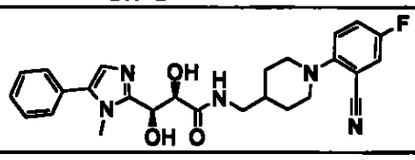
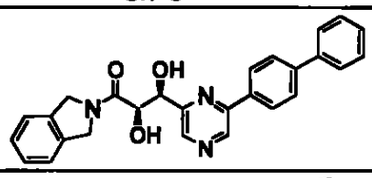
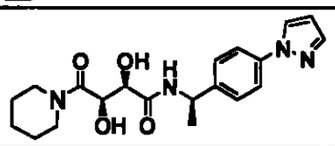
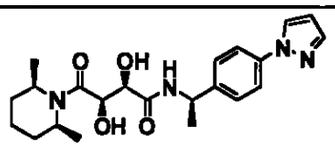
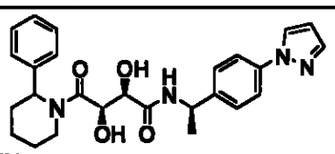
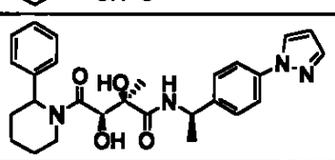
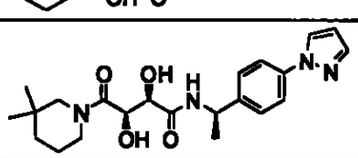
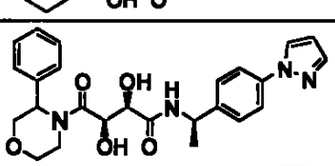
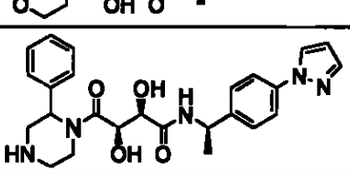




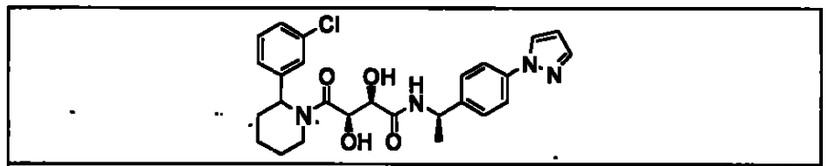


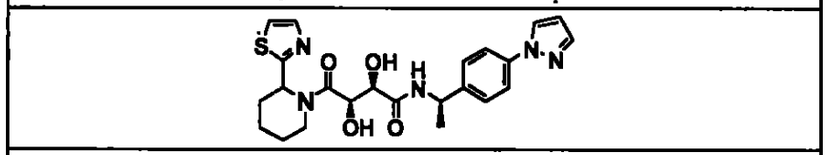


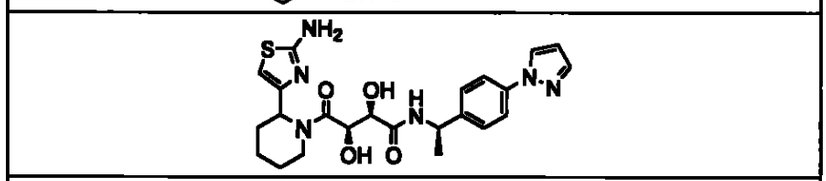


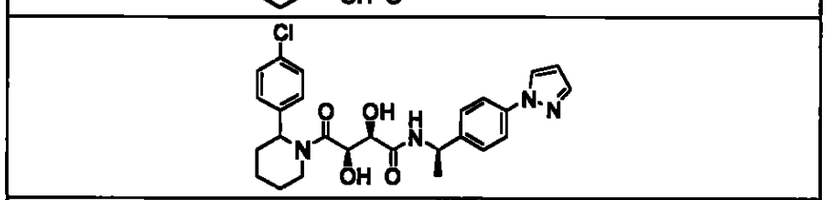












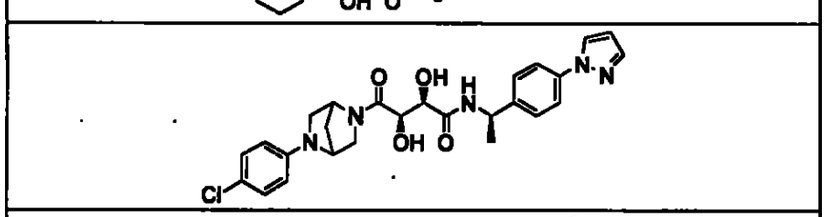
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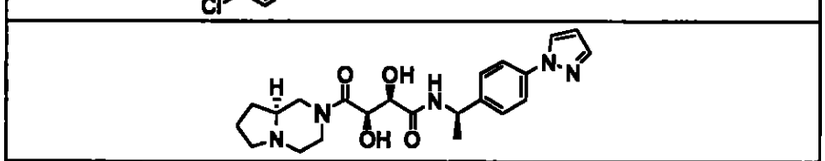


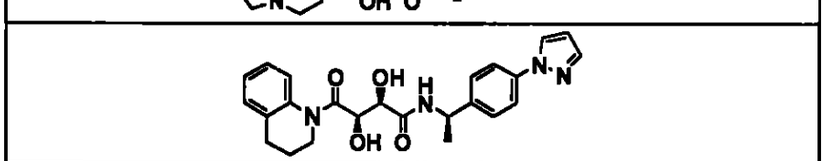


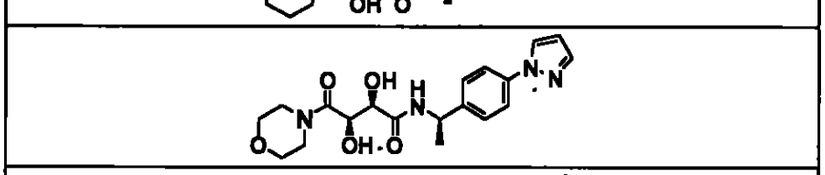


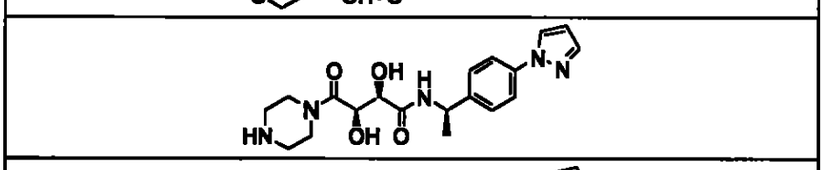


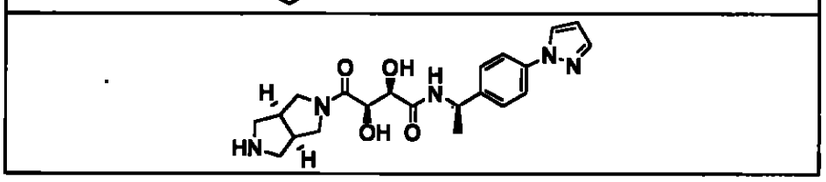


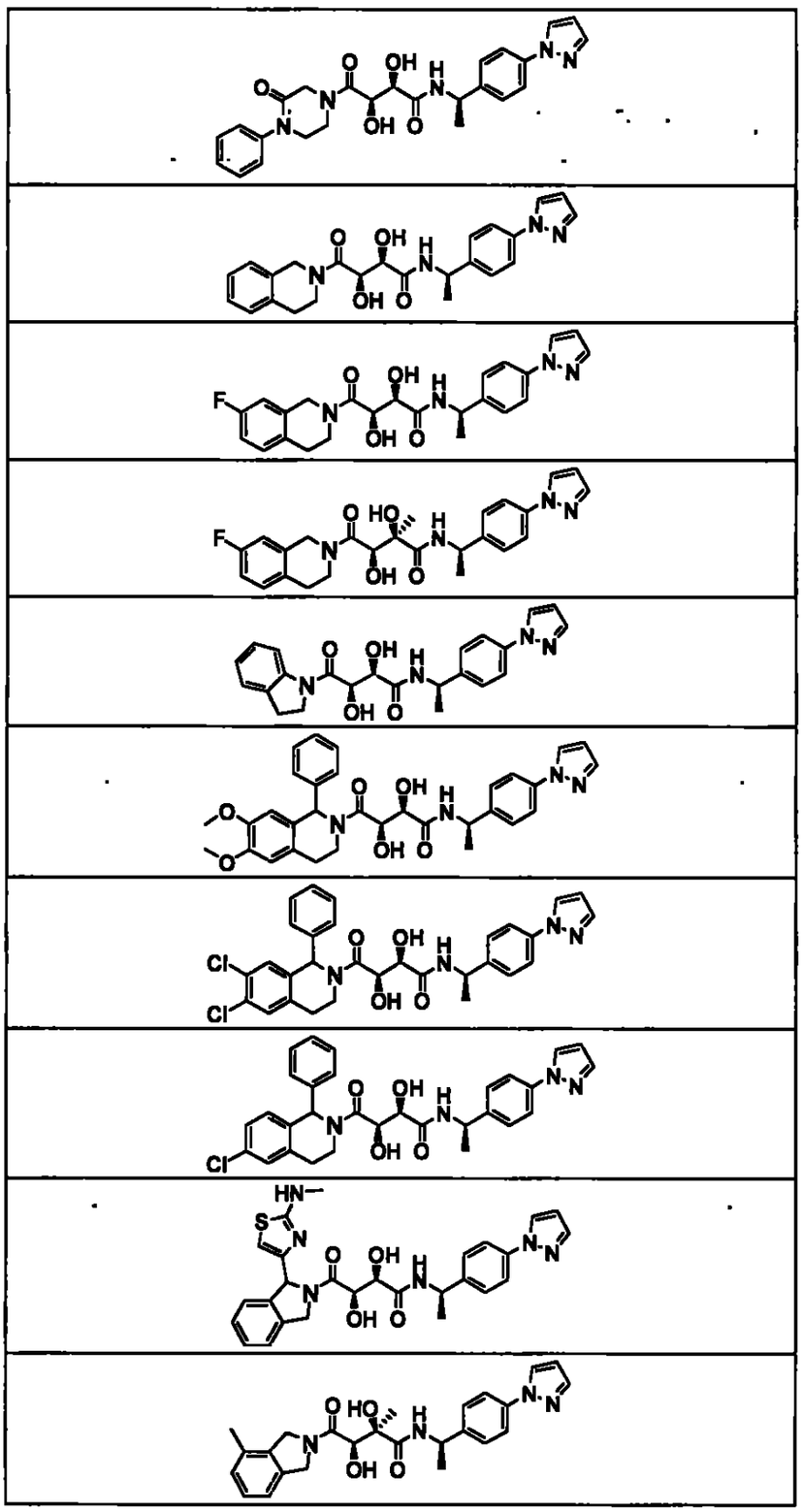




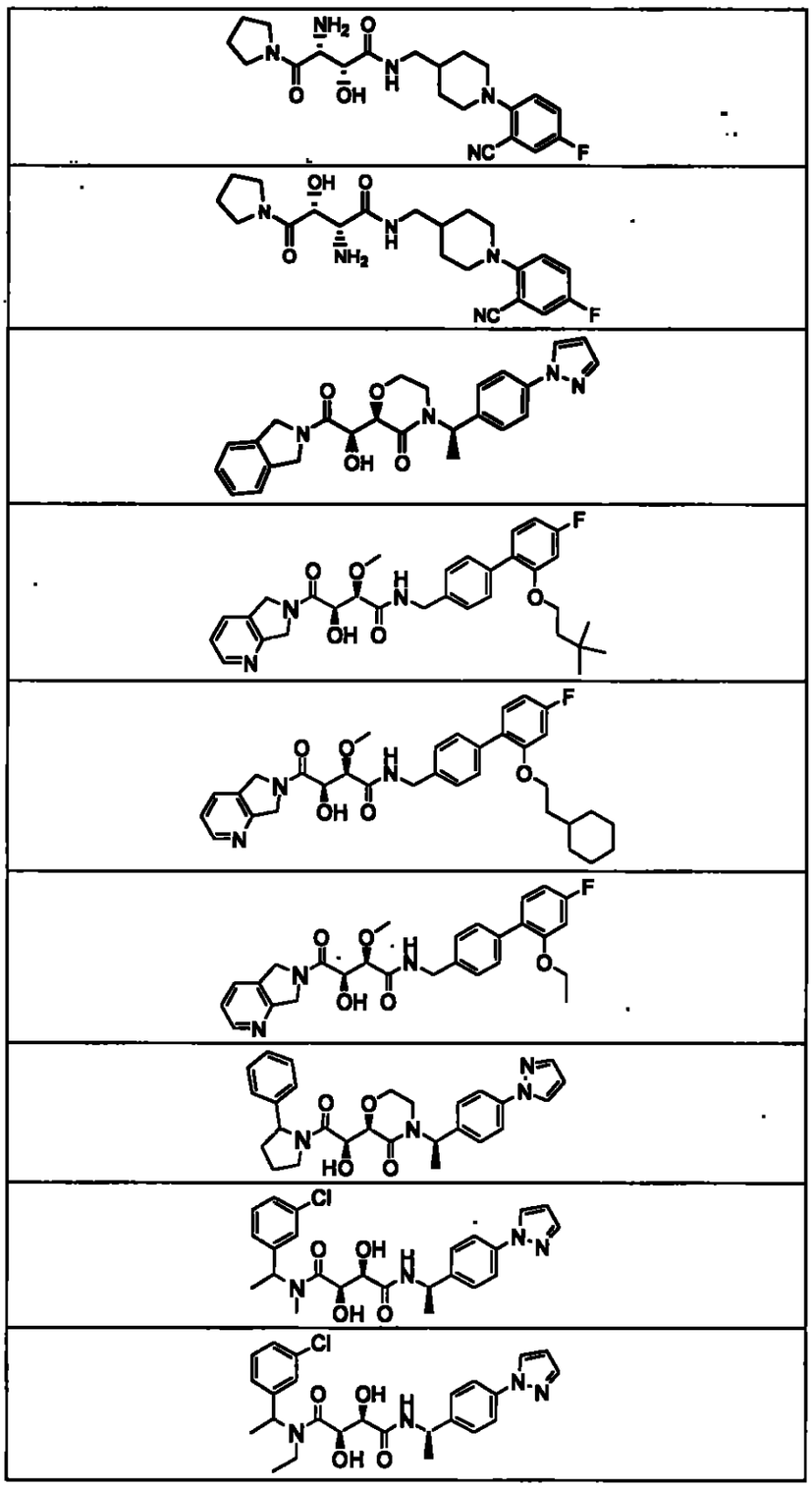


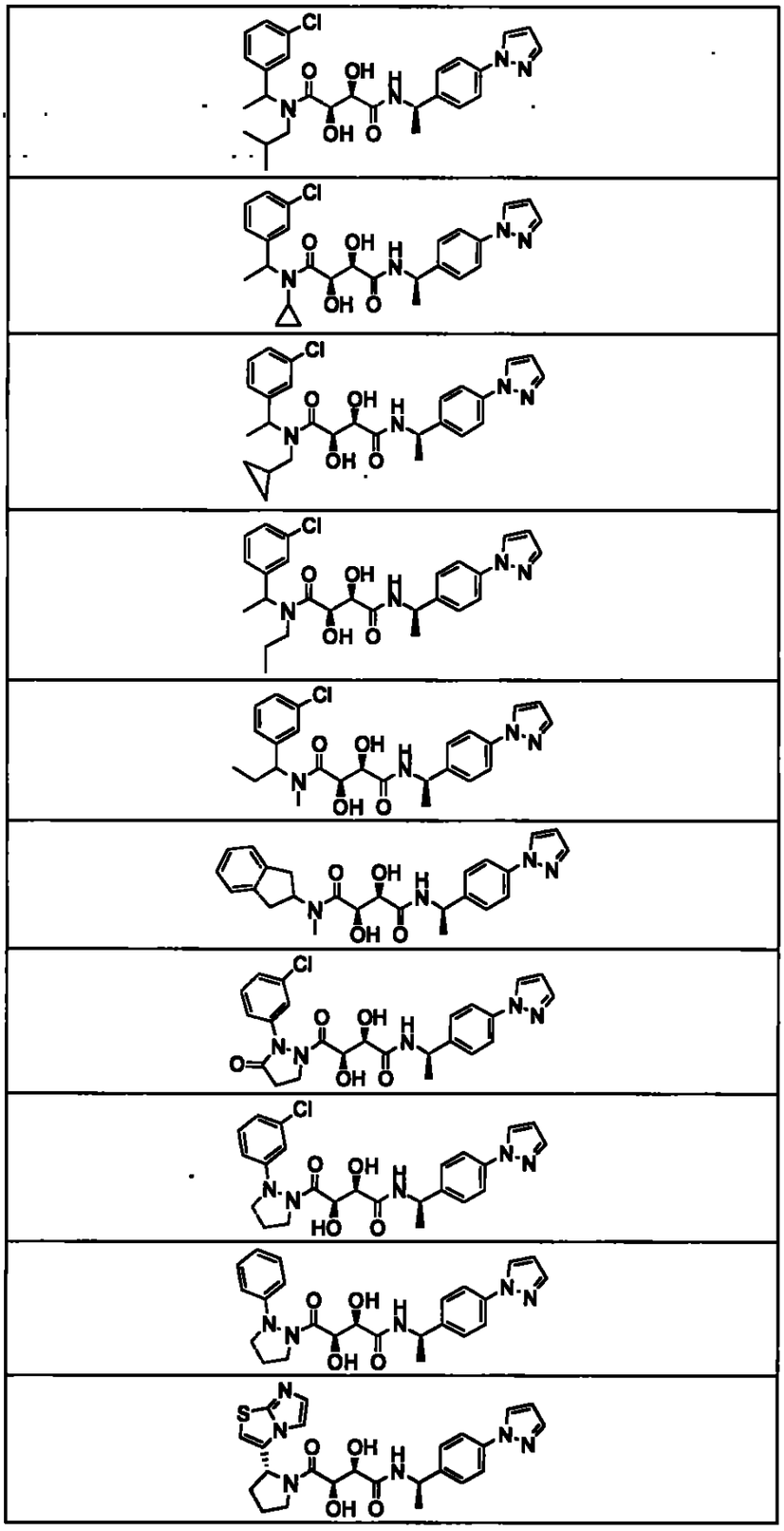


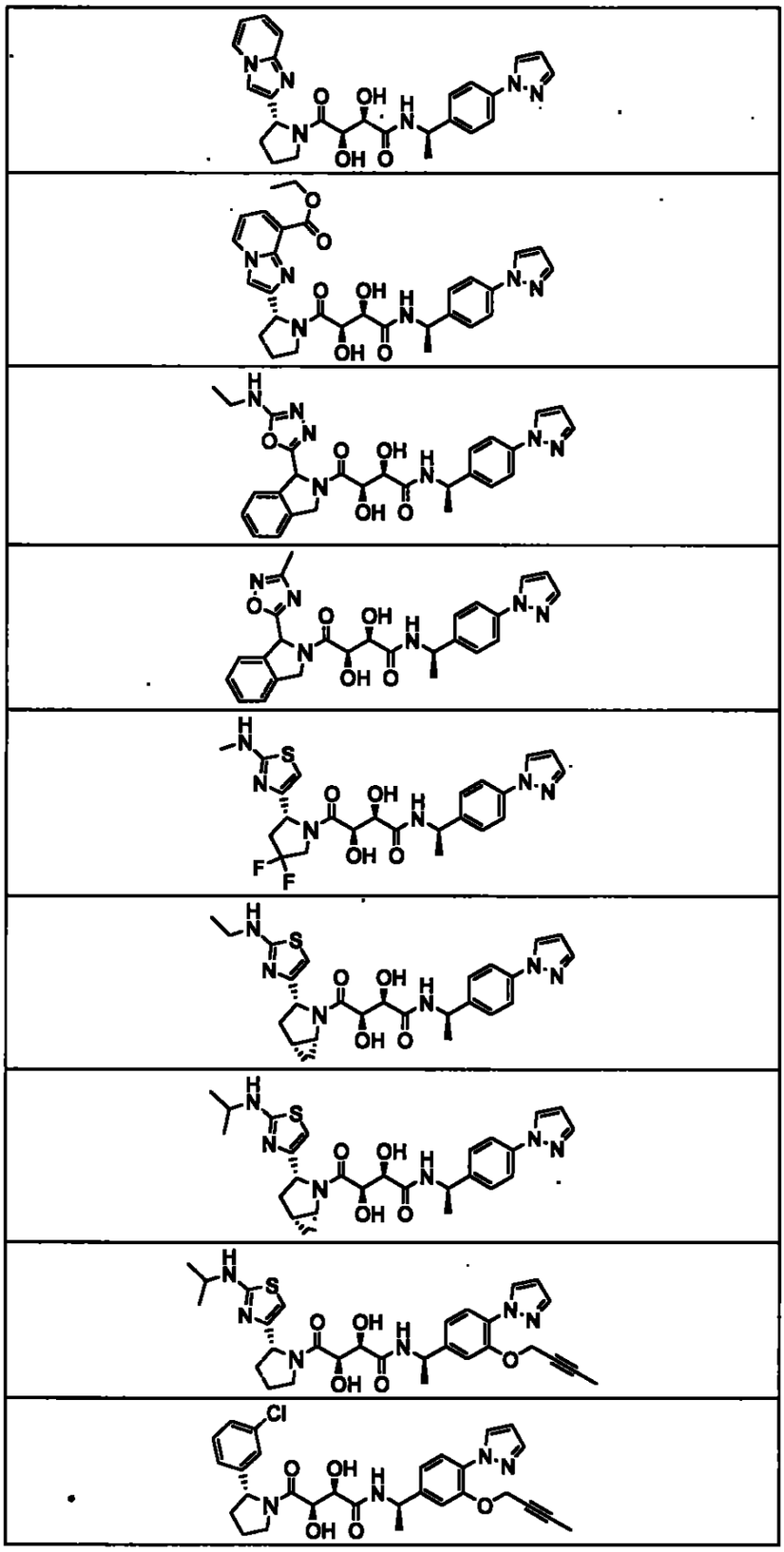




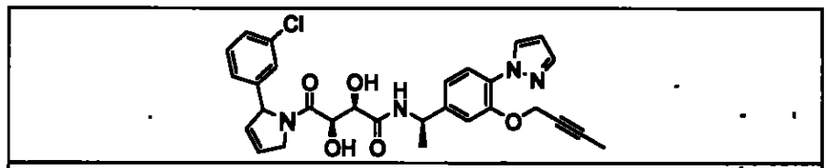
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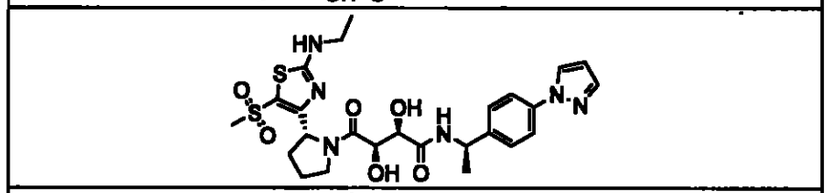


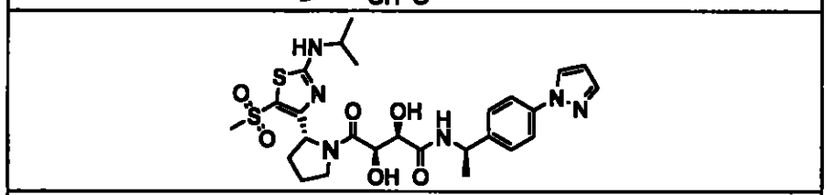


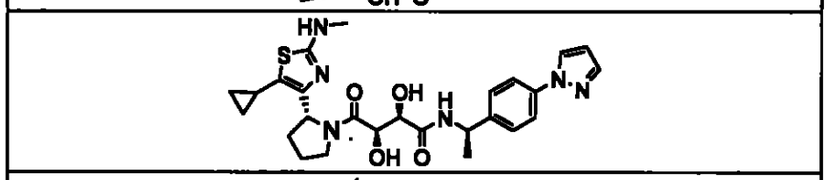


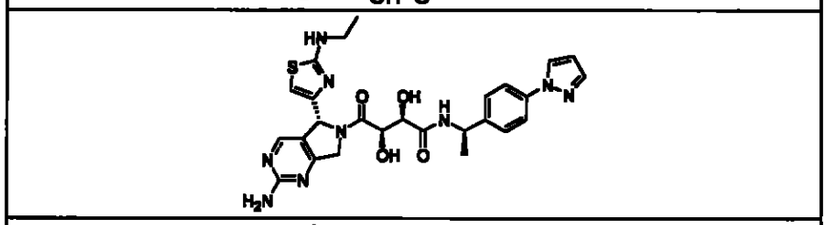
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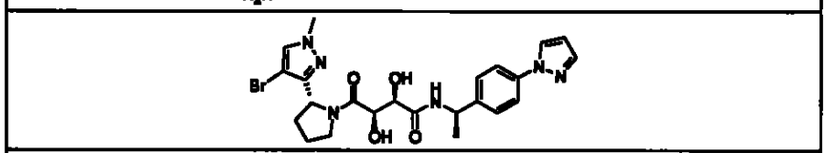


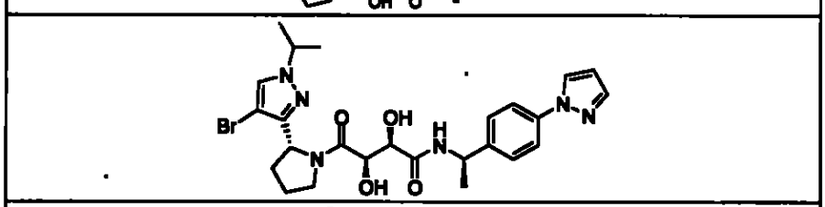


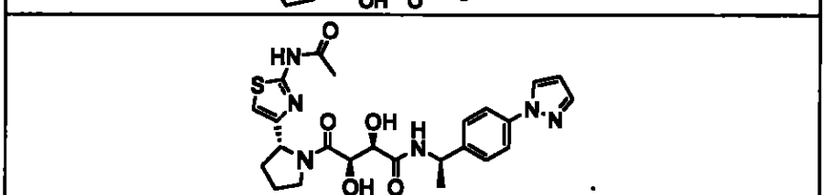


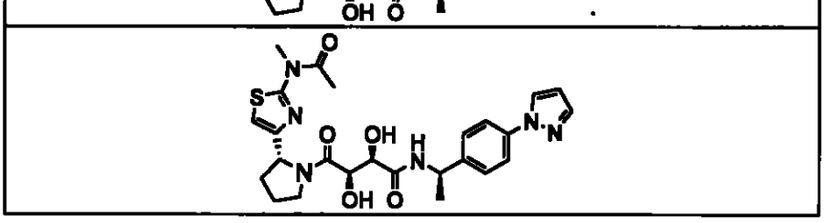


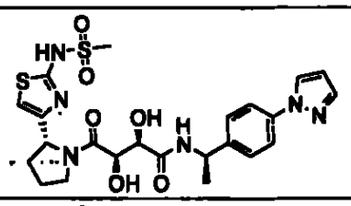
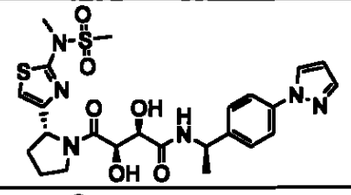
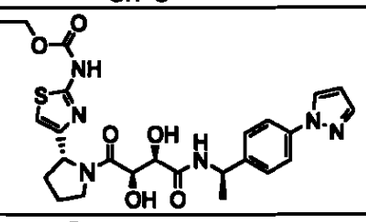
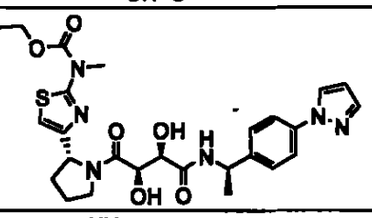
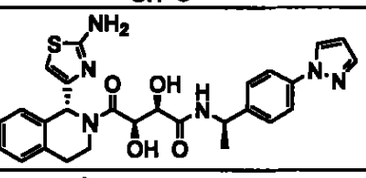
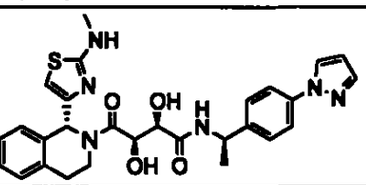
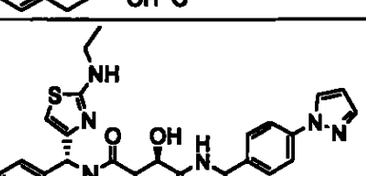
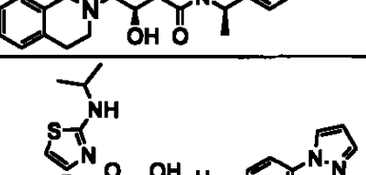


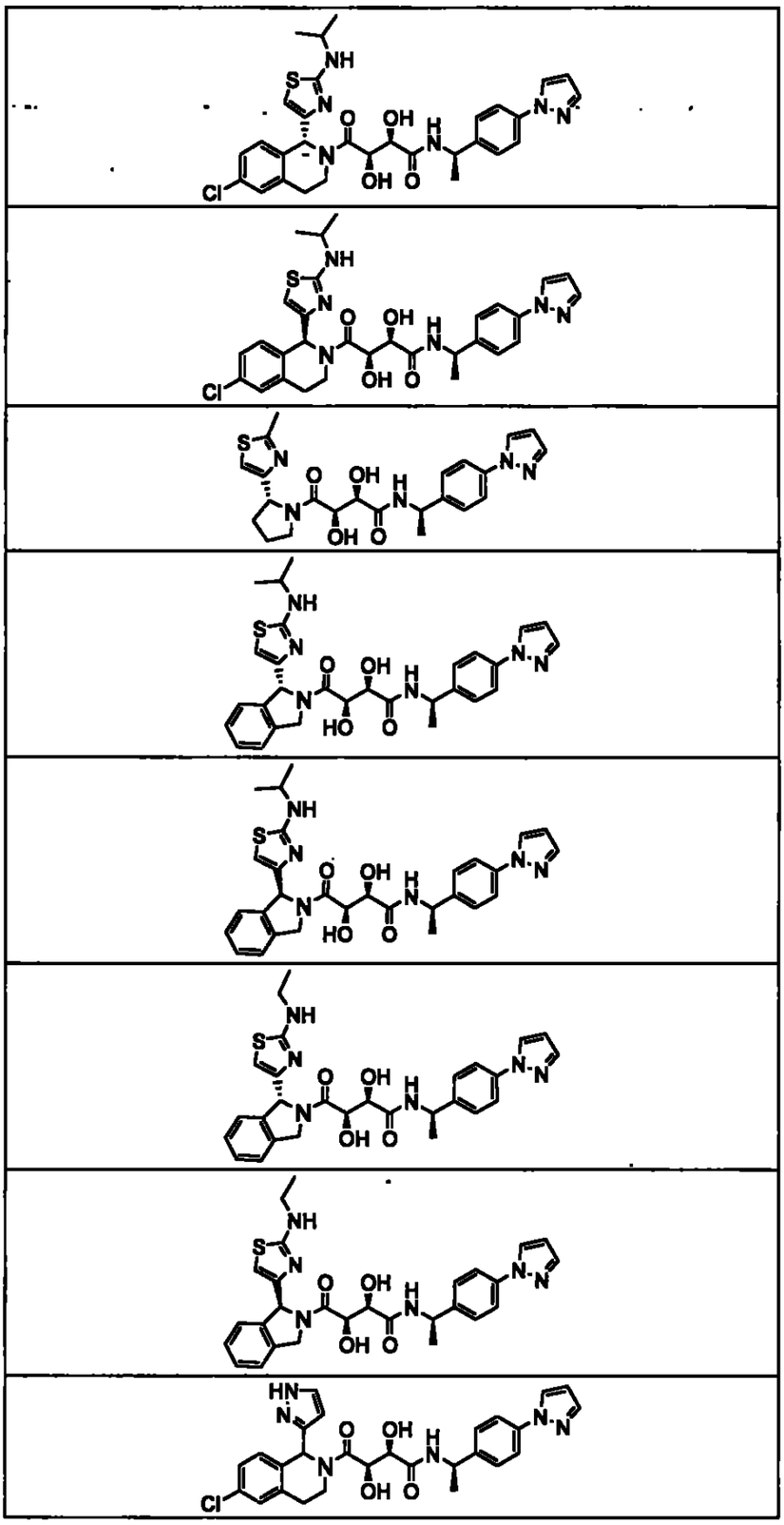




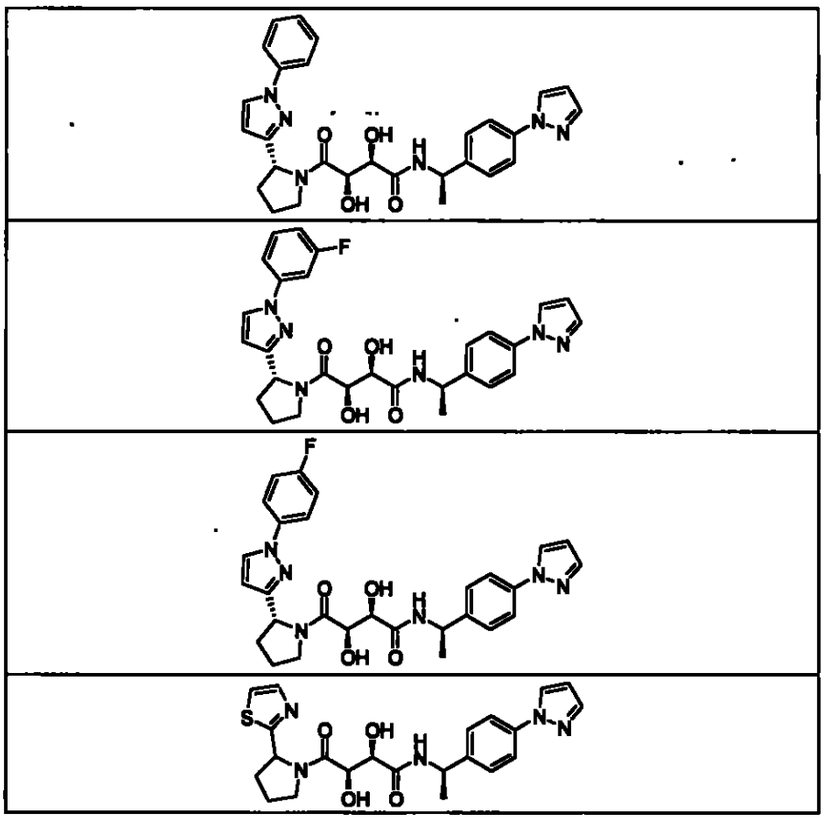




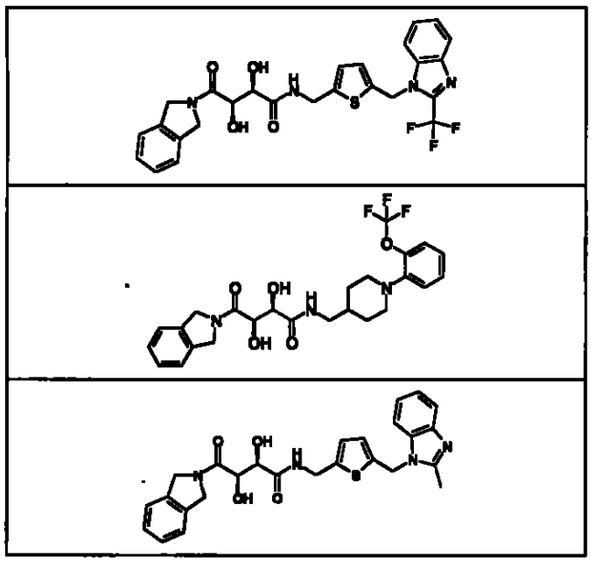











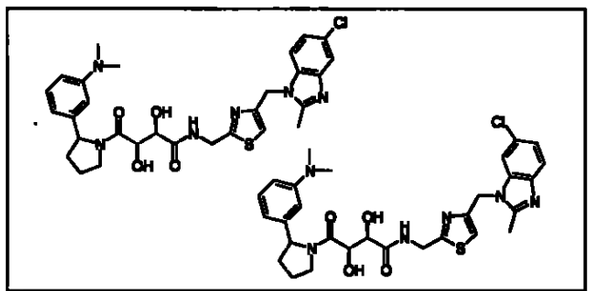
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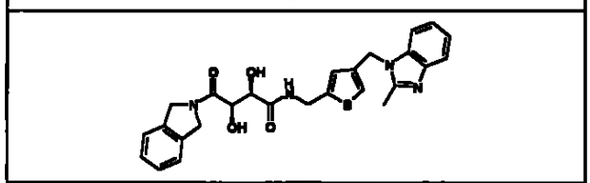


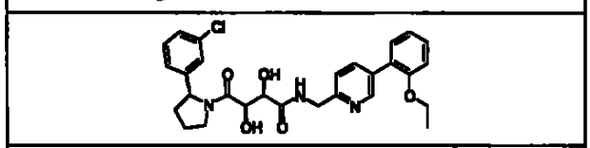
61. El compuesto de la reivindicación 60, seleccionándose dicho compuesto de los compuestos de las estructuras enumeradas a continuación:

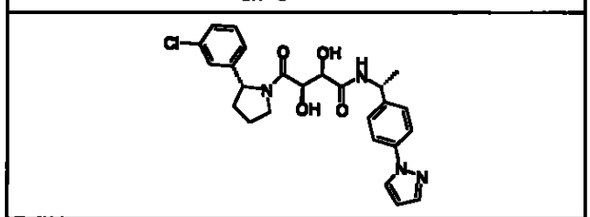


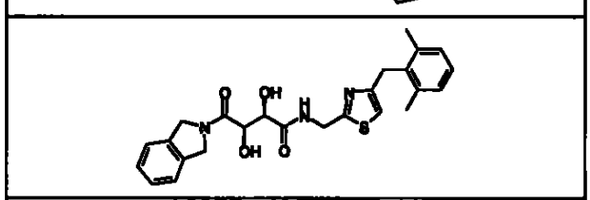
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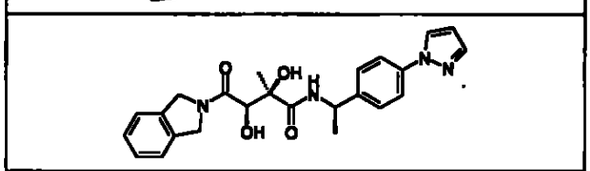


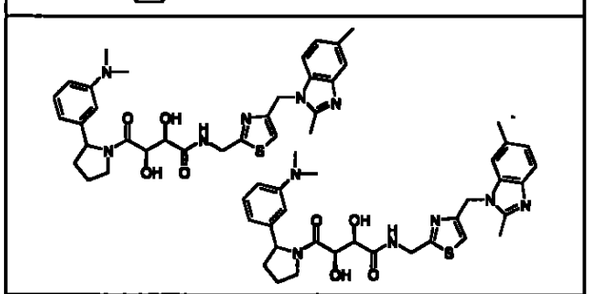


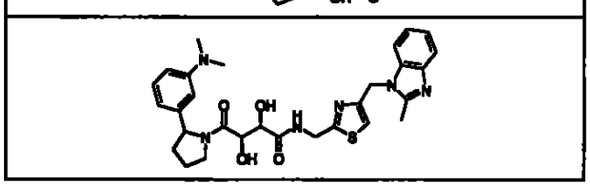




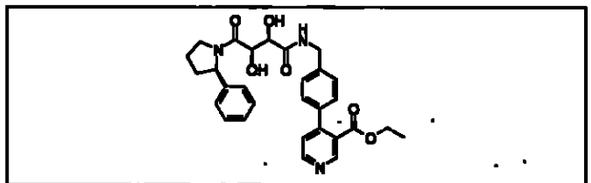


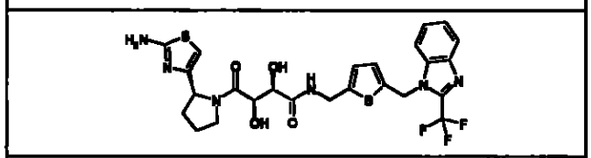


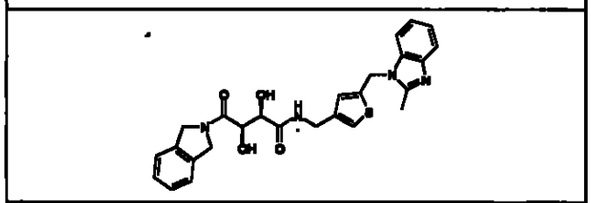


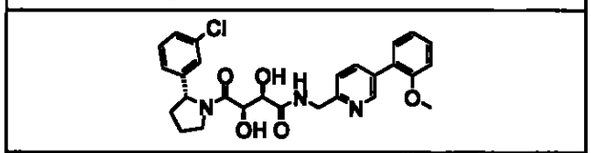


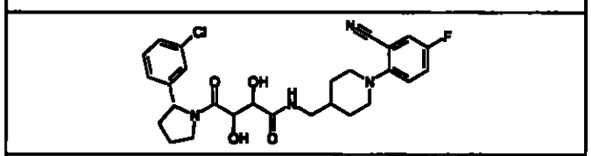
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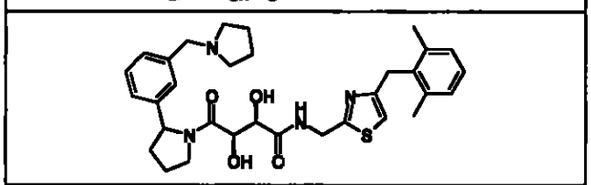


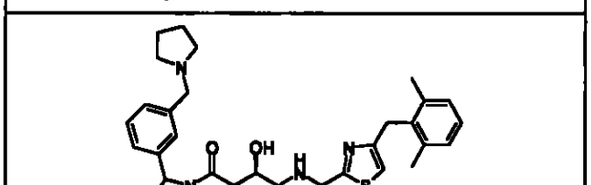


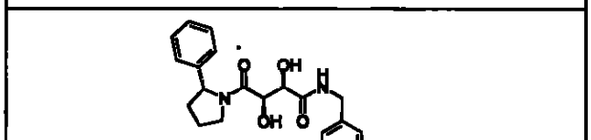


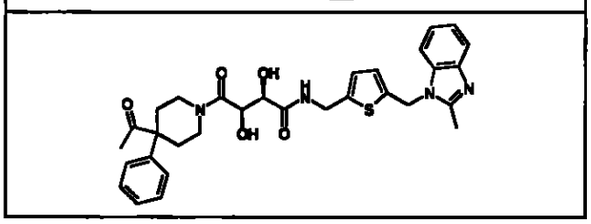


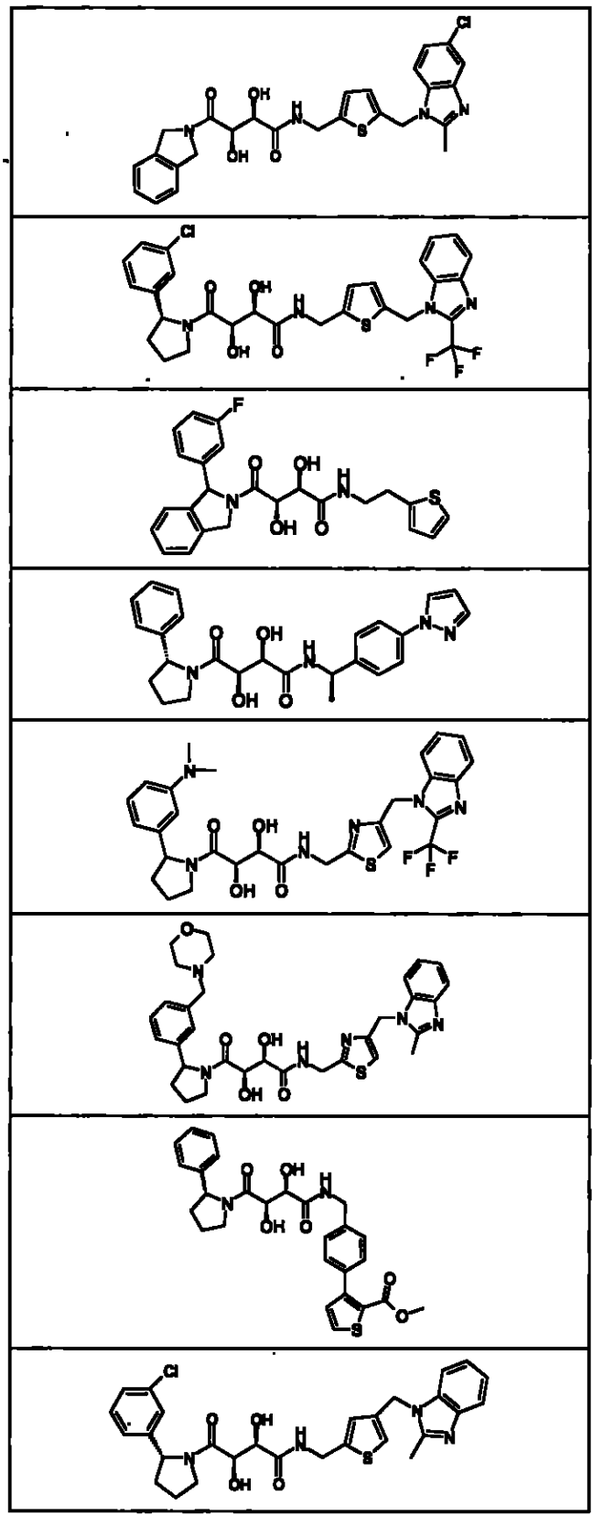


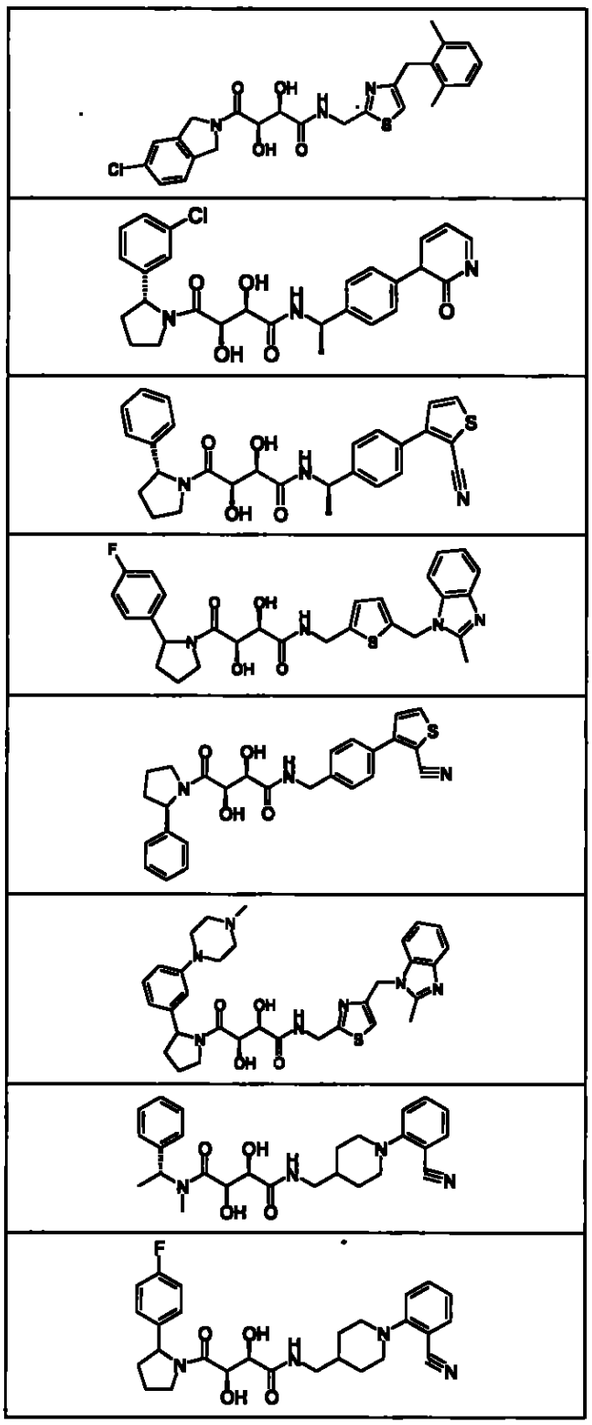






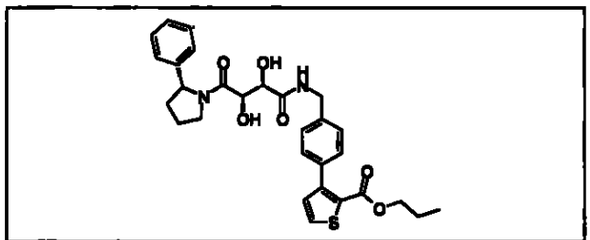


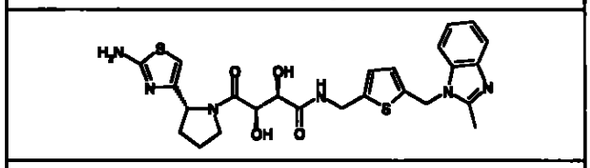


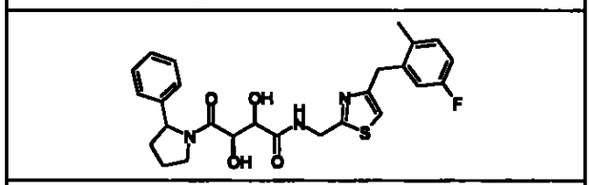


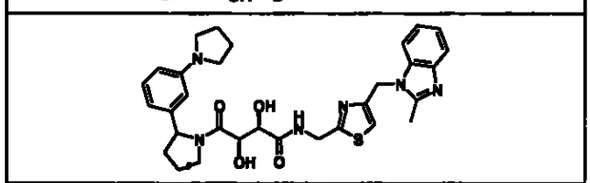
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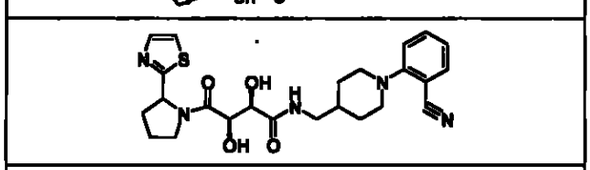
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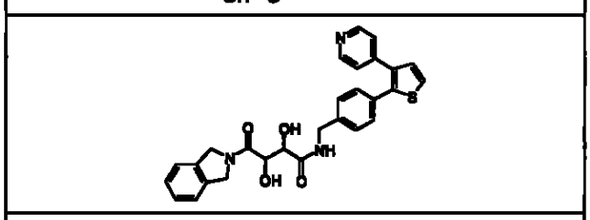


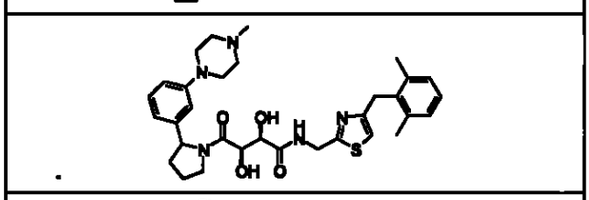


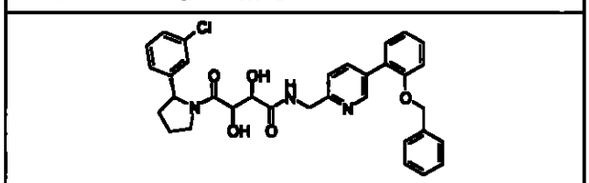


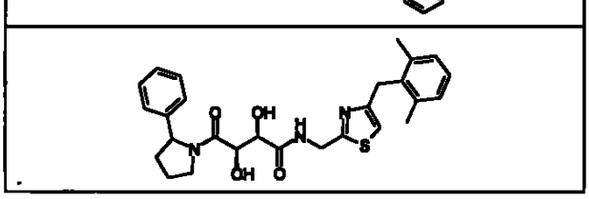




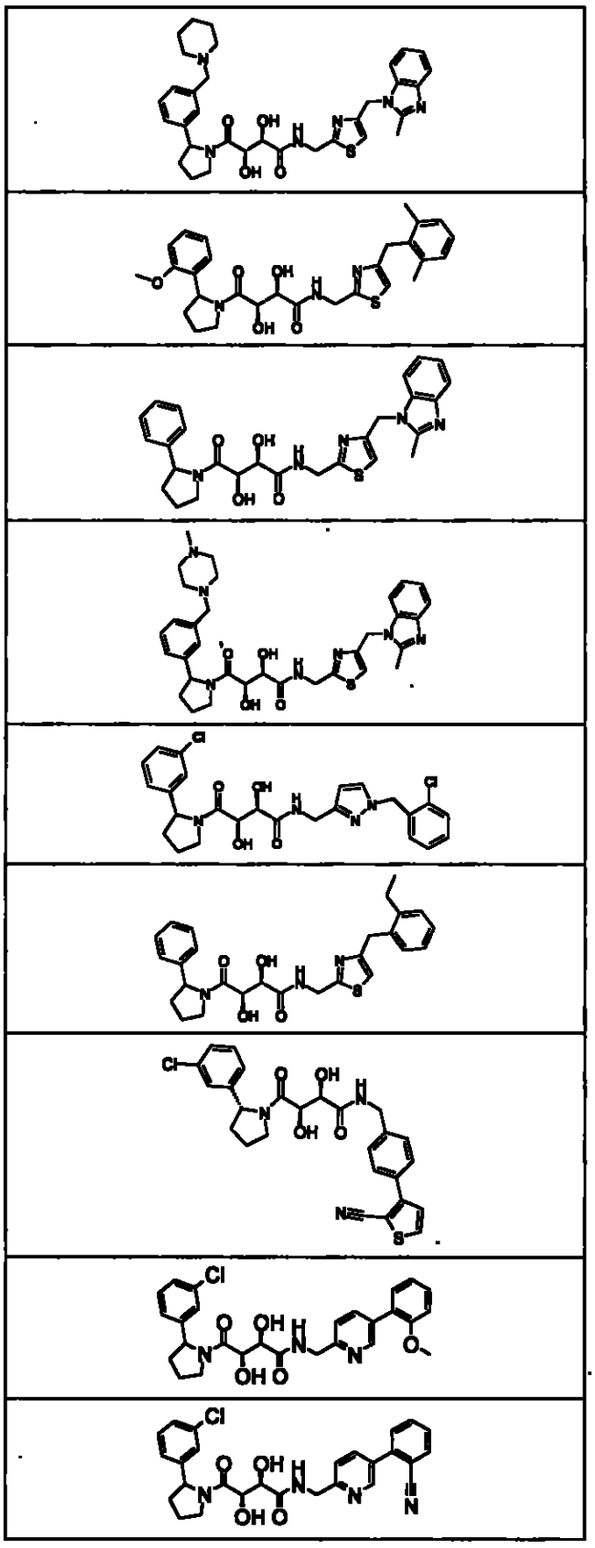




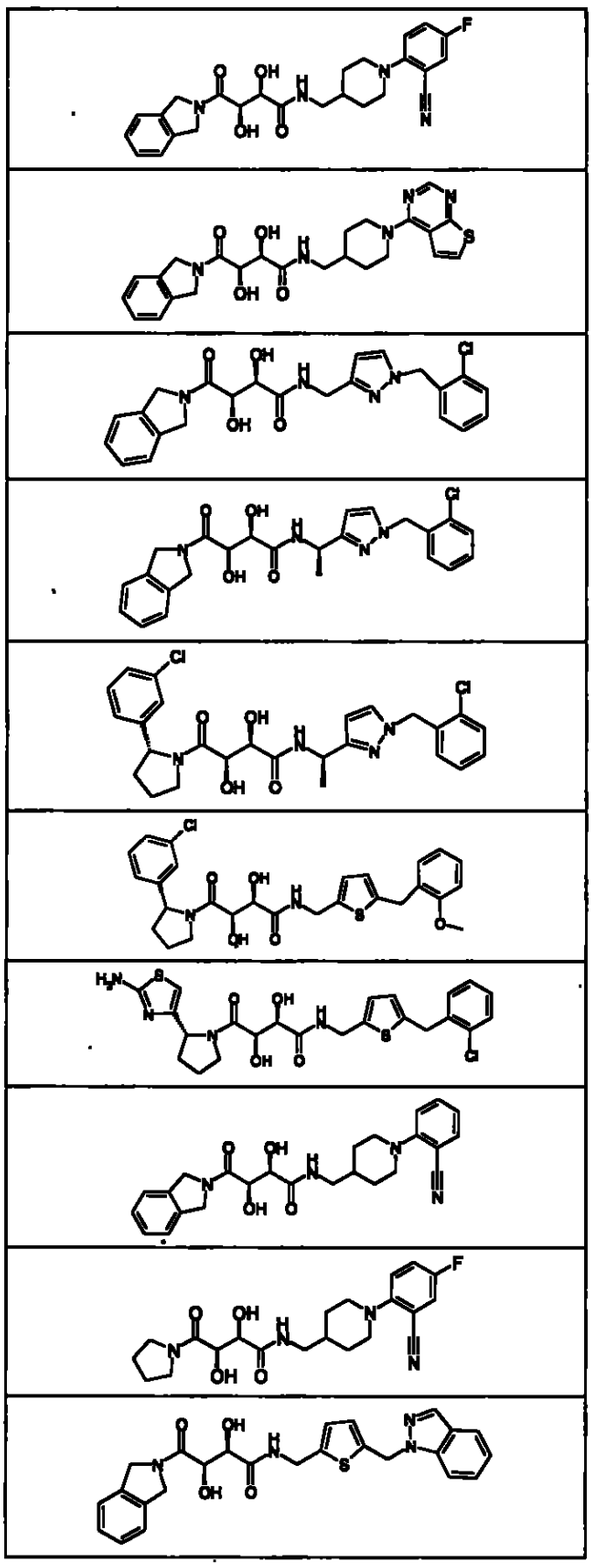


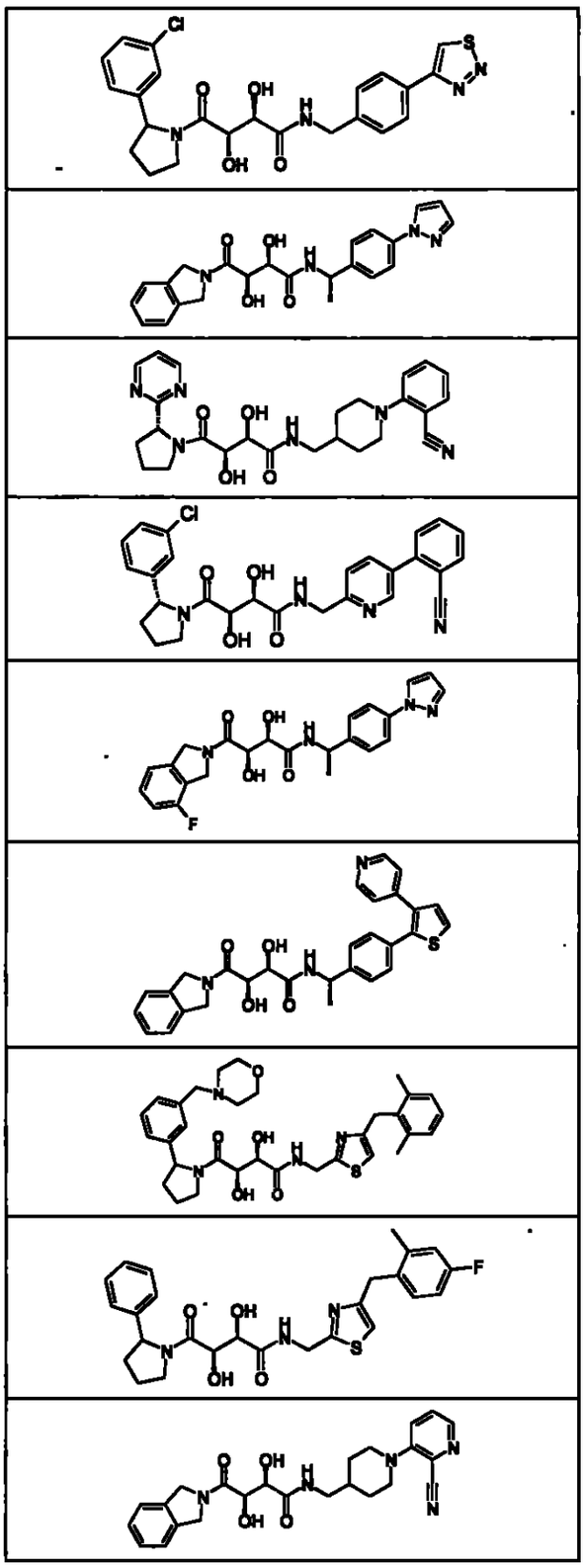


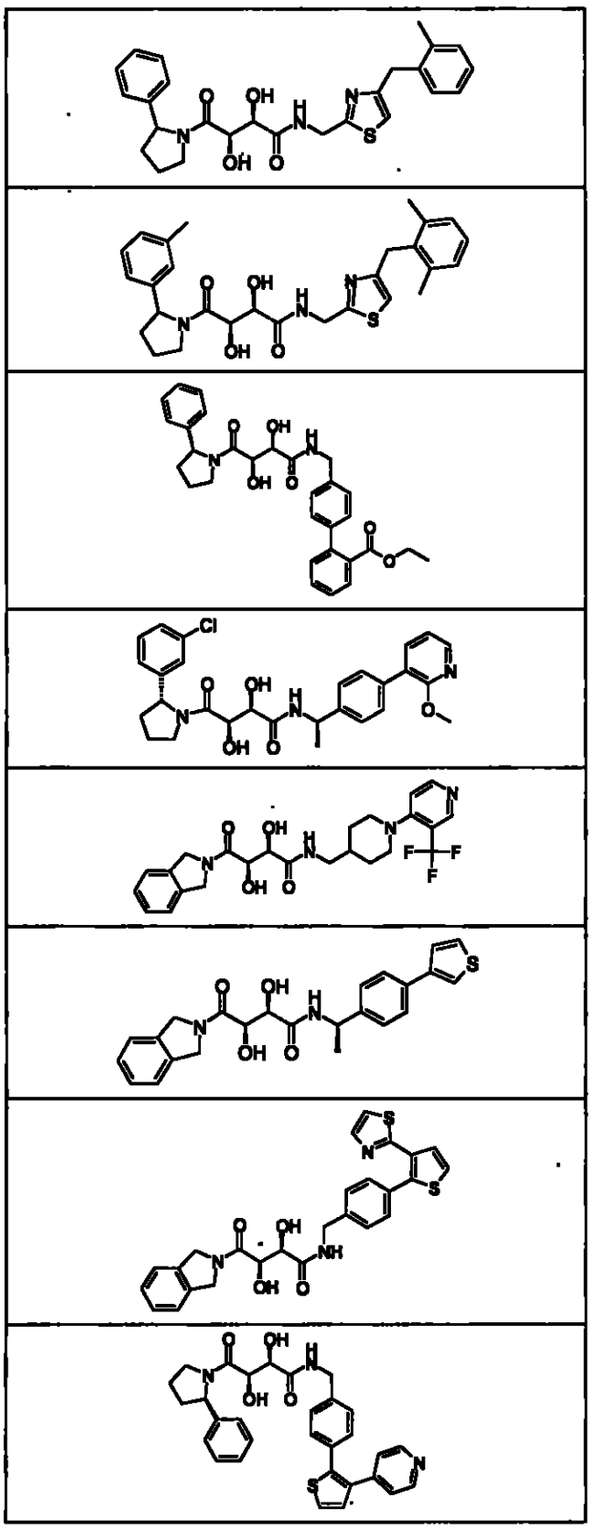
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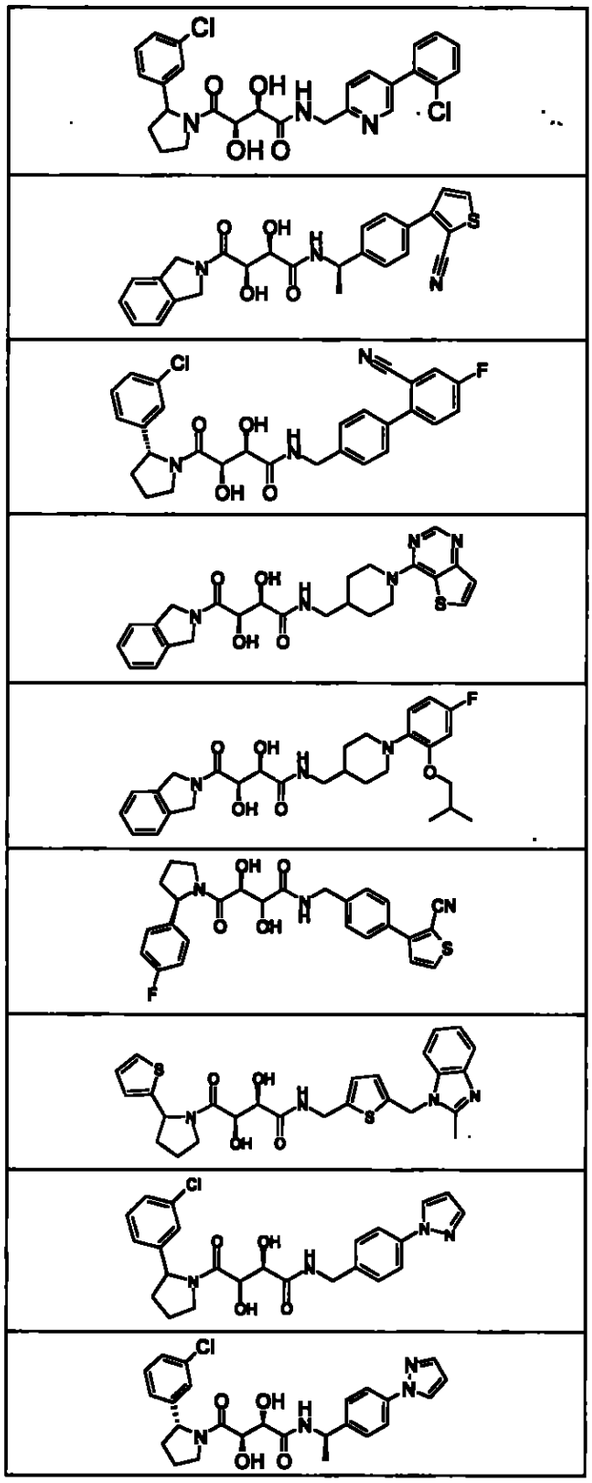


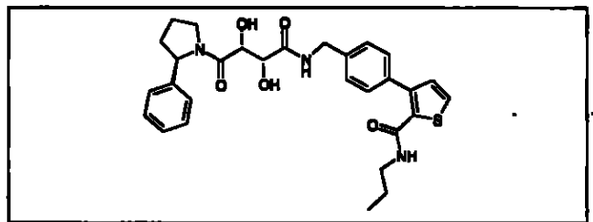
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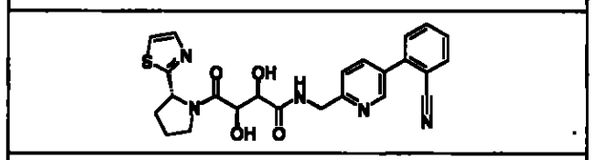


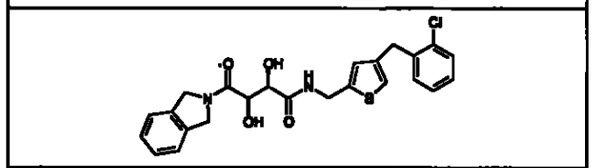


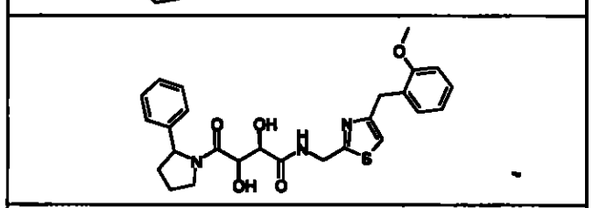


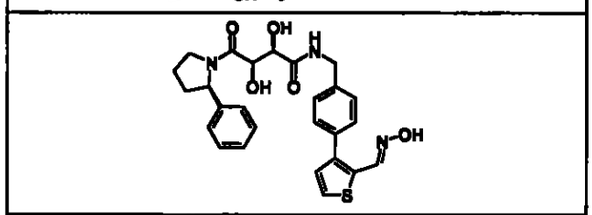


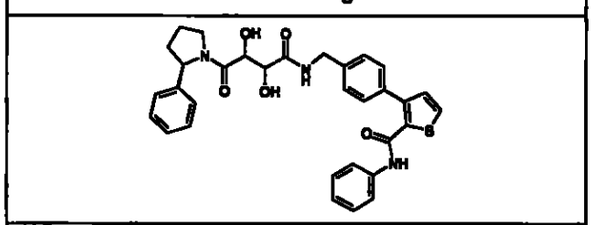


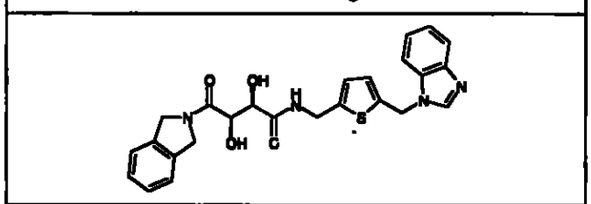


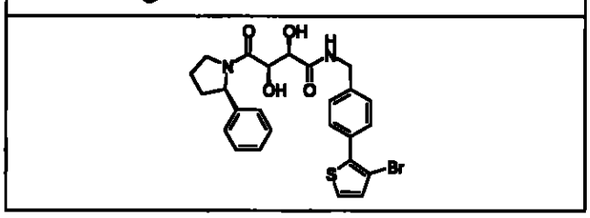




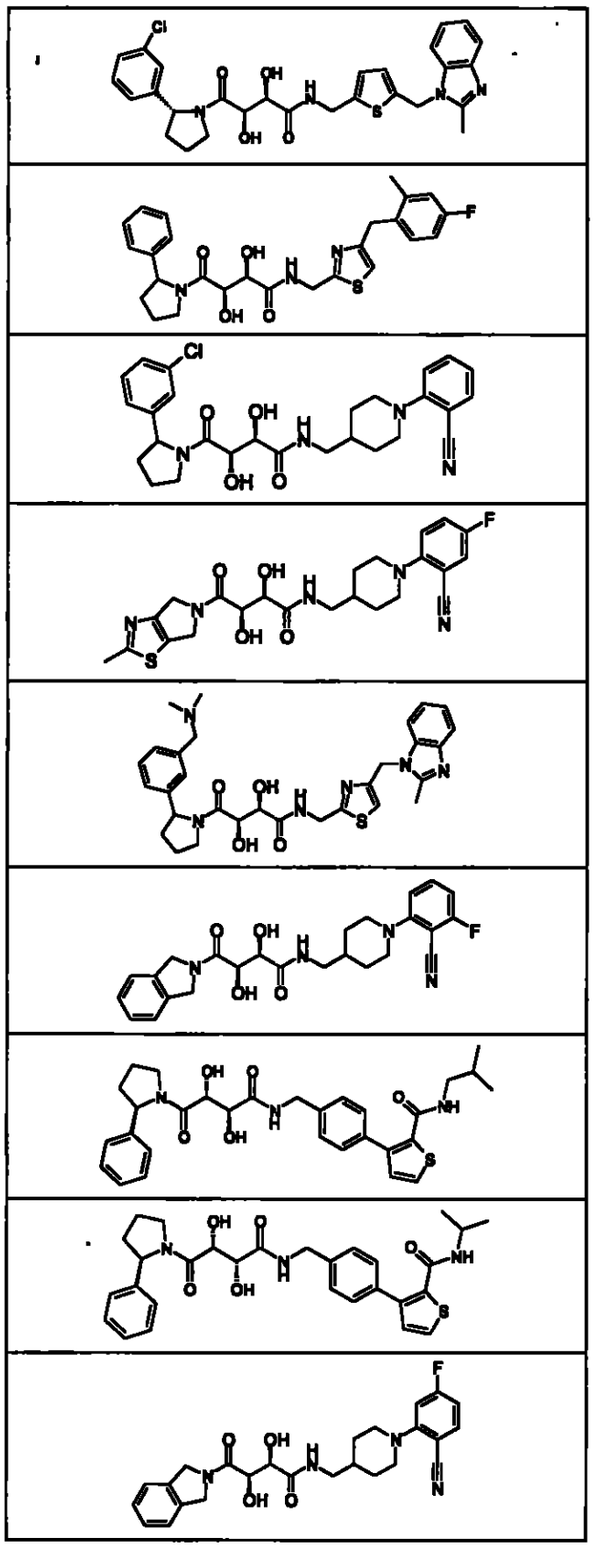


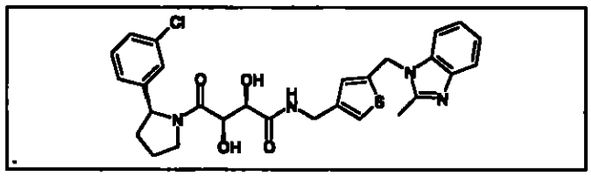


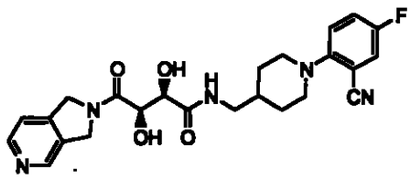


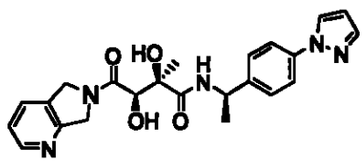


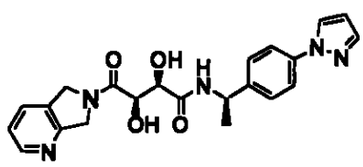
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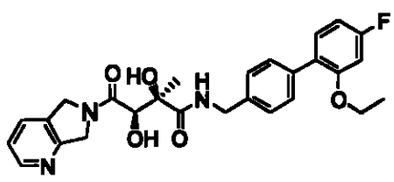


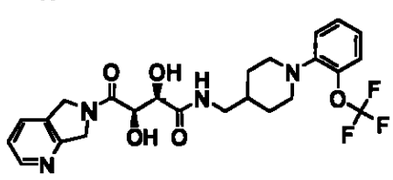


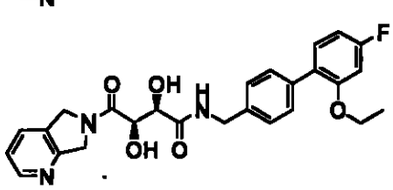


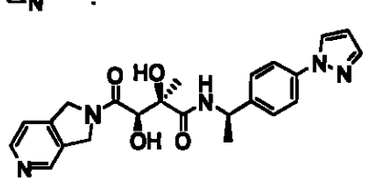


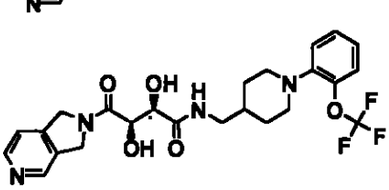






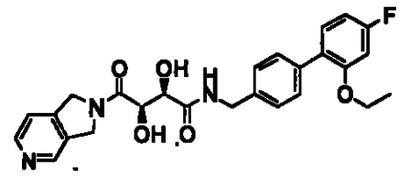


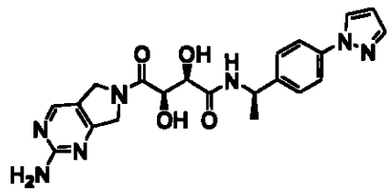


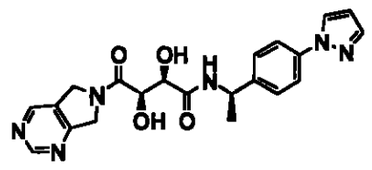


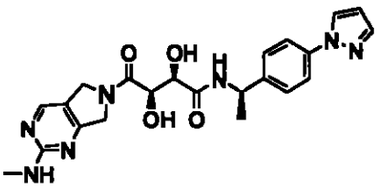


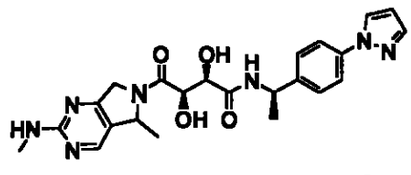
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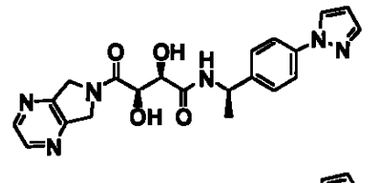


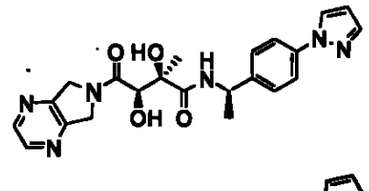


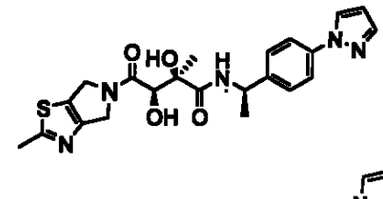


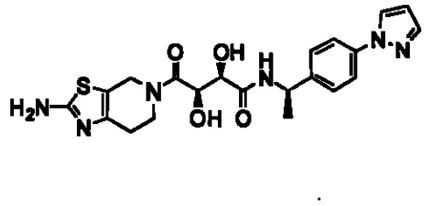


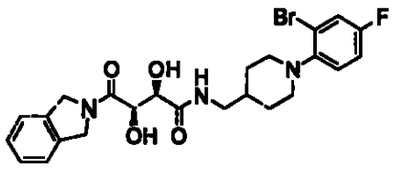


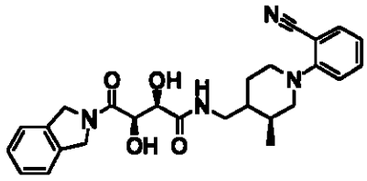


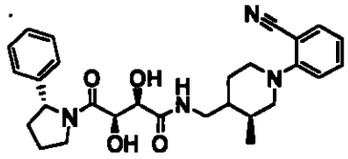


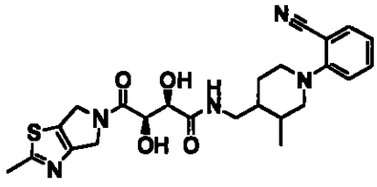


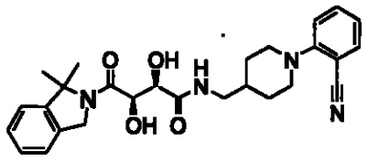


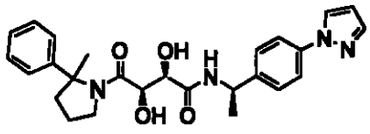


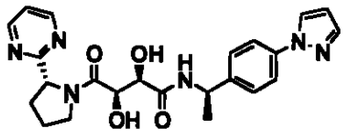


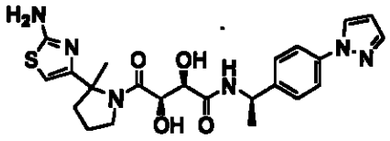


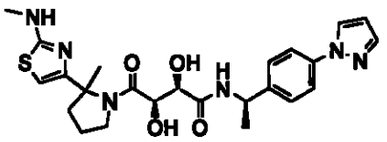


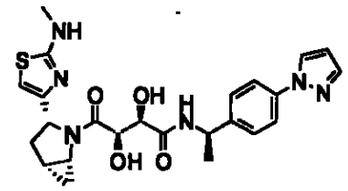


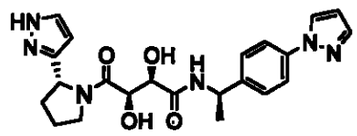


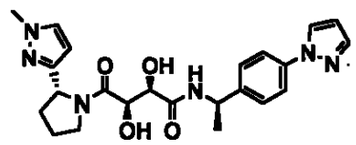


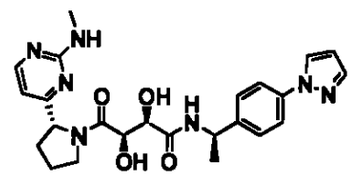


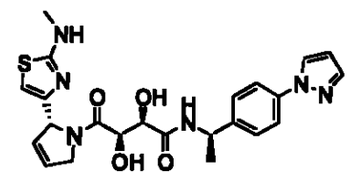


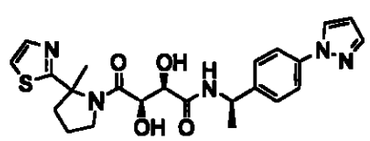


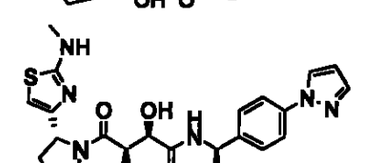


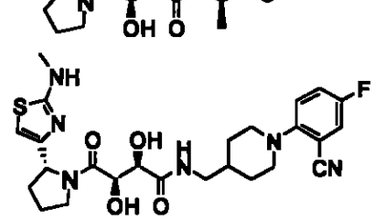


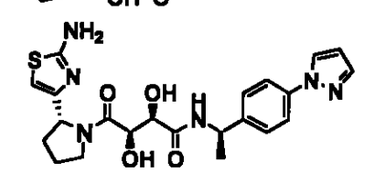


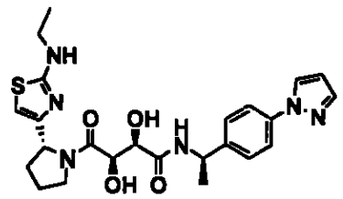


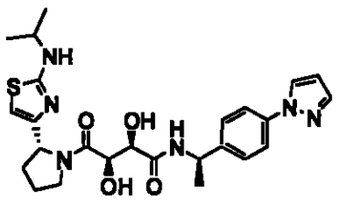


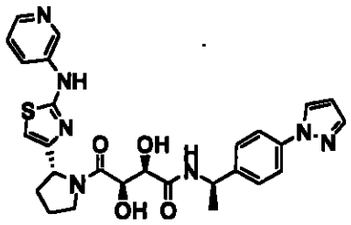


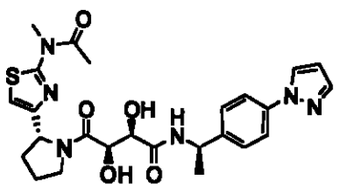


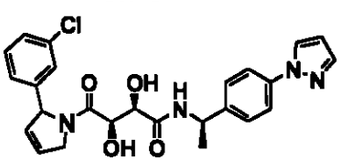


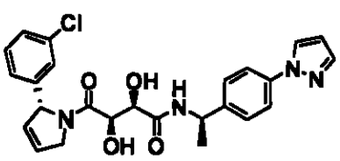


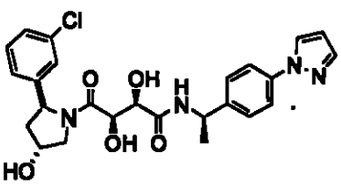


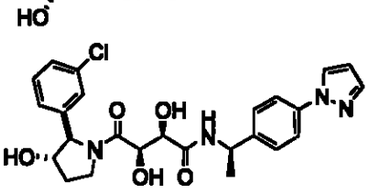


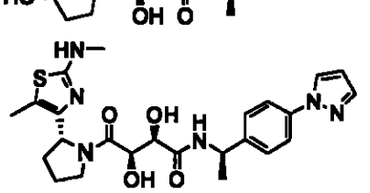


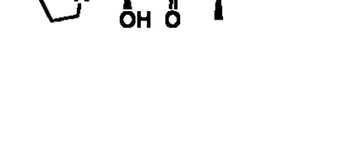


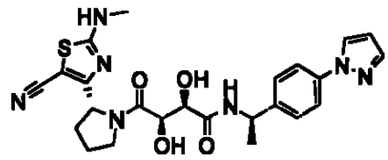


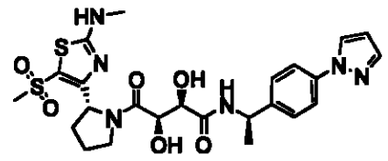


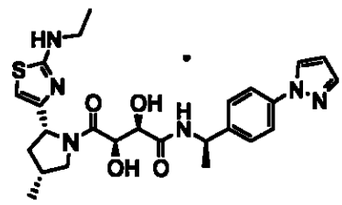


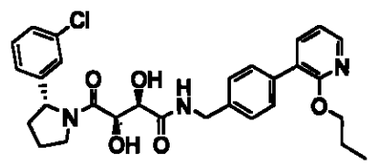


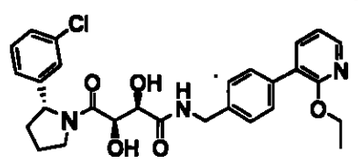


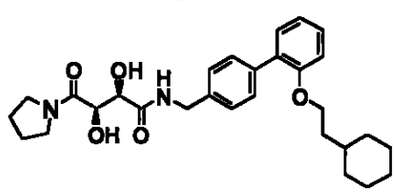


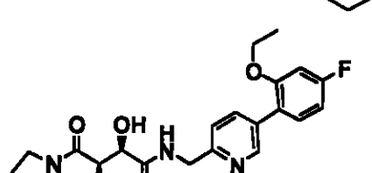


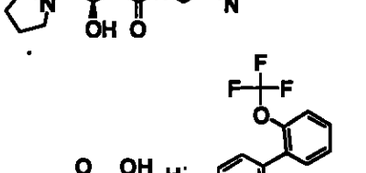


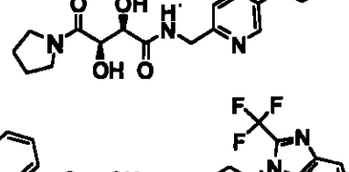


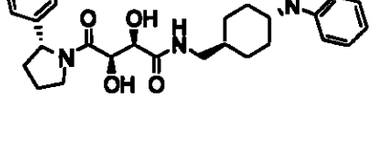


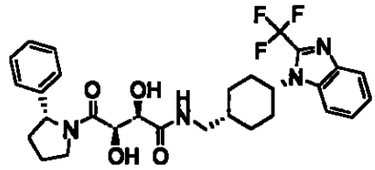


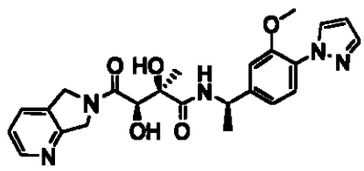


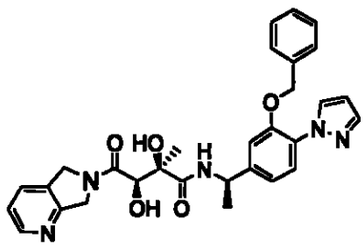


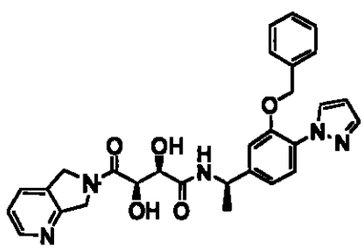


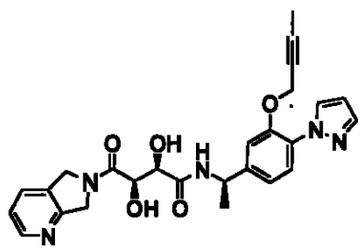


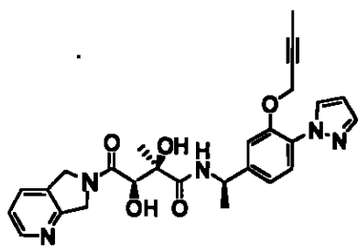


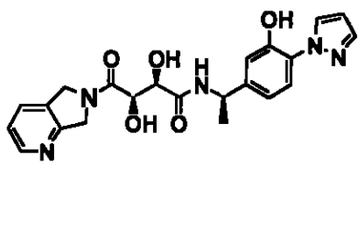


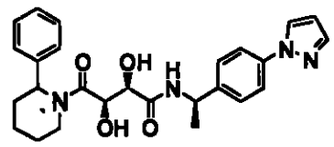


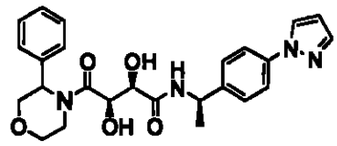


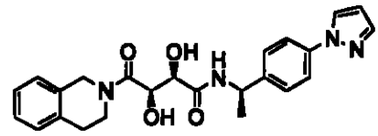


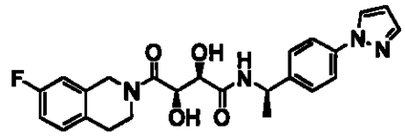


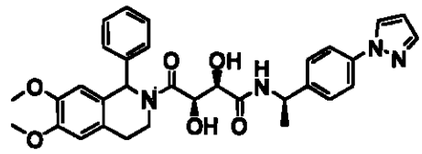


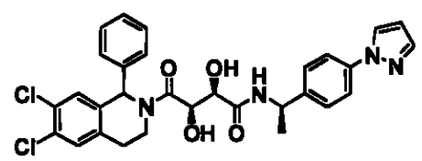


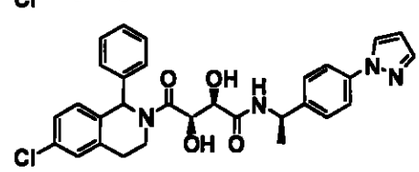


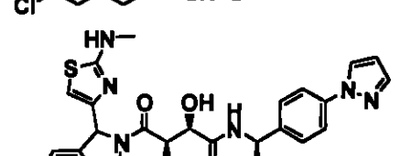


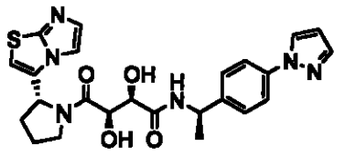


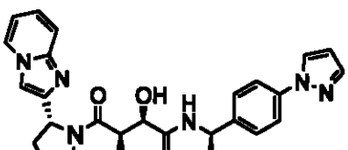


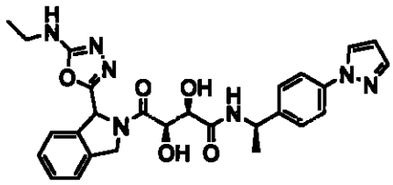


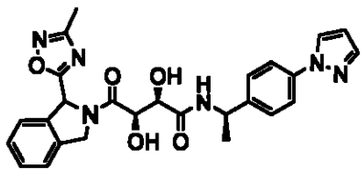


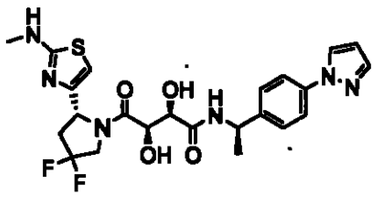


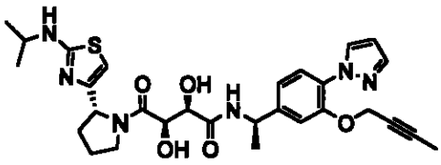


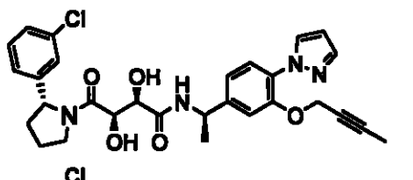


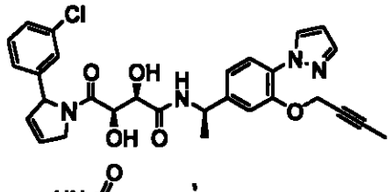


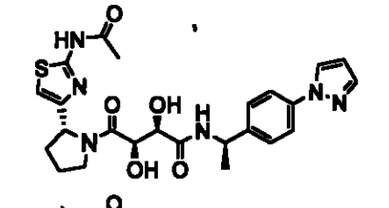


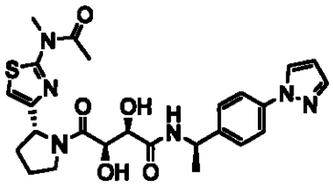


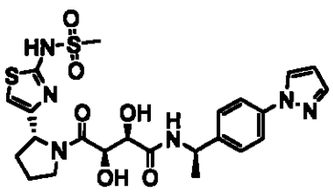


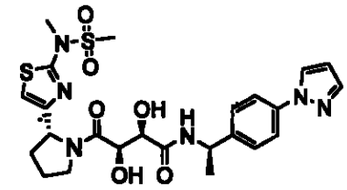


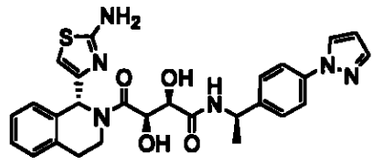


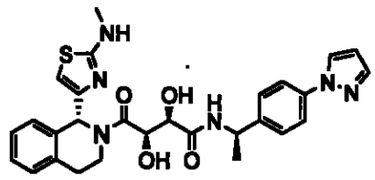


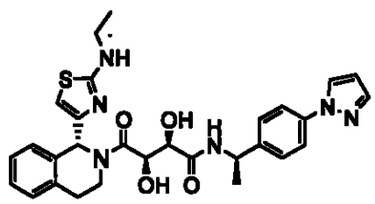


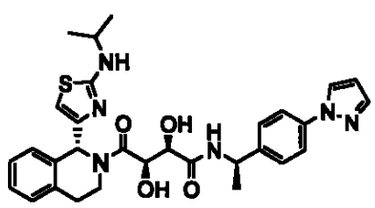


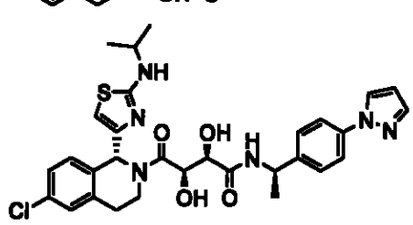


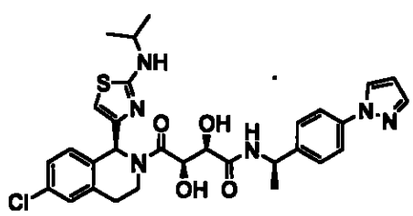


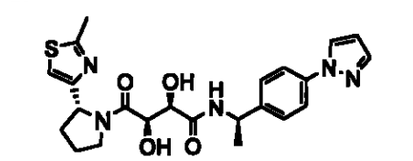


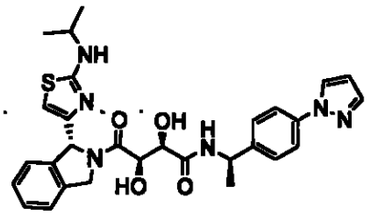


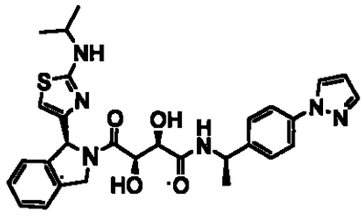


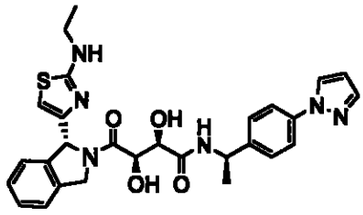


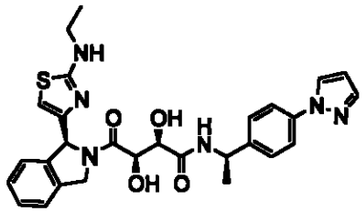


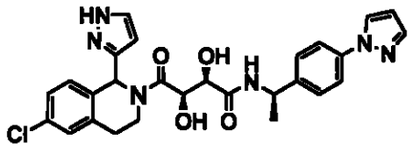


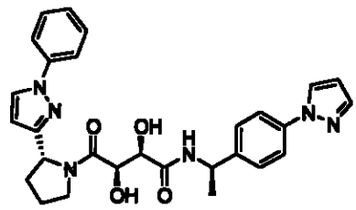


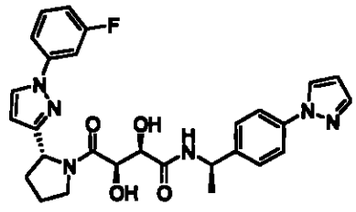


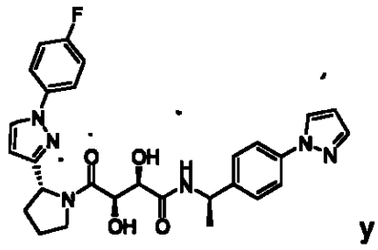




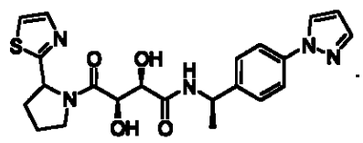




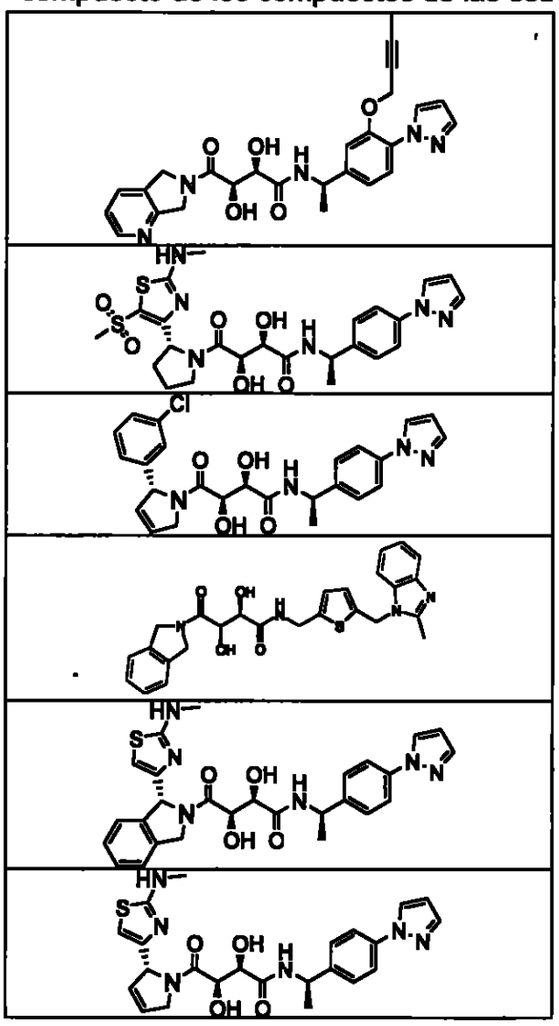


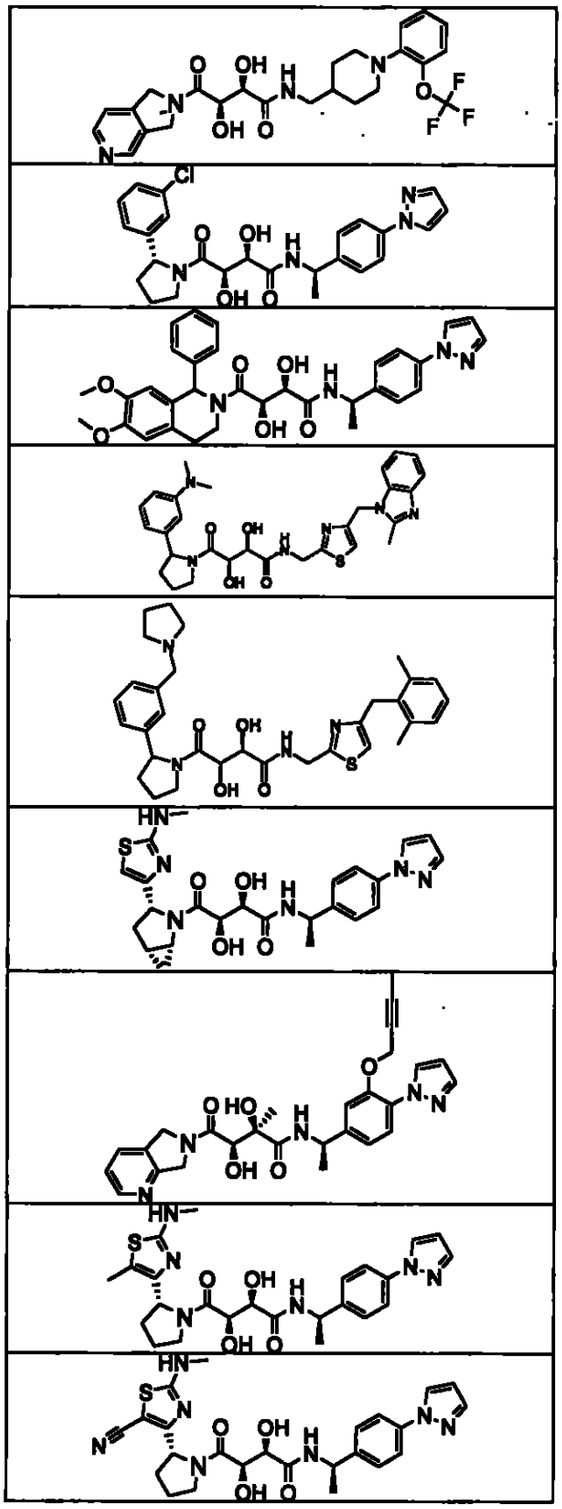


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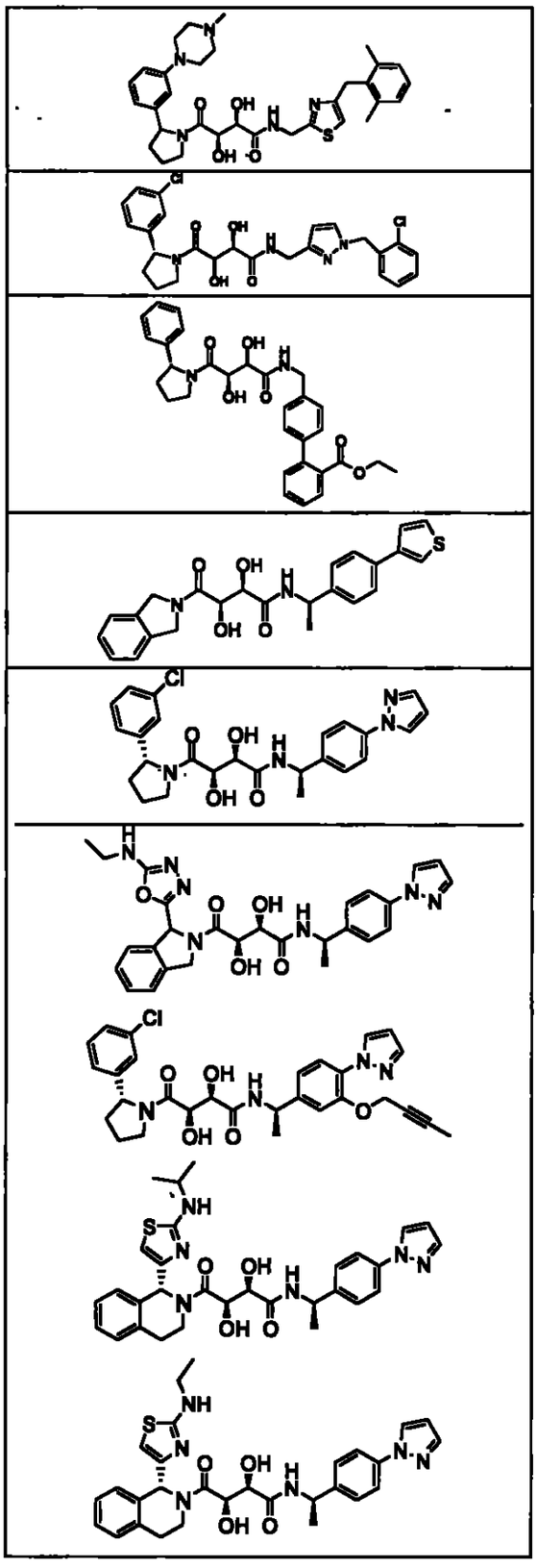


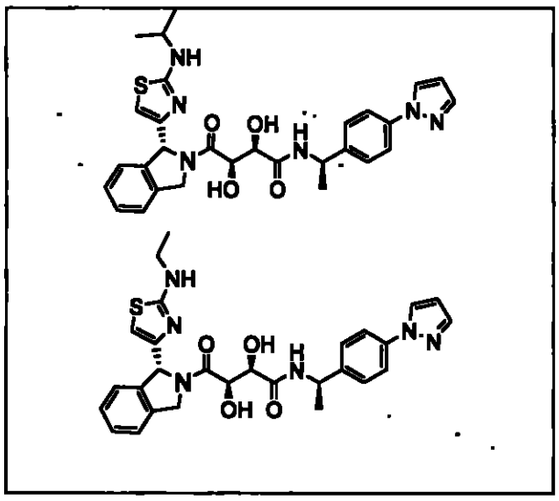
62. El compuesto de la reivindicación 61, seleccionándose dicho compuesto de los compuestos de las estructuras enumeradas a continuación:





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63. Una composición farmacéutica que comprende como componente activo al menos un compuesto de la reivindicación 1.

64. La composición farmacéutica de la reivindicación 1, que comprende adicionalmente al menos un vehículo aceptable para uso farmacéutico.

65. Un método para el tratamiento de trastornos asociados con la enzima convertidora del factor de necrosis tumoral alfa (TACE), el factor de necrosis tumoral alfa (TNF-α), las metaloproteinasas de matriz (MMPs), una desintegrina y metaloproteasas (ADAMs) o cualquier combinación de los mismos, comprendiendo dicho método administrar a un paciente que necesita tal tratamiento una composición farmacéutica que comprende cantidades terapéuticamente efectivas de al menos un compuesto de la reivindicación 1.

66. El uso de un compuesto de la reivindicación 1 para la fabricación de un medicamento para el tratamiento de trastornos asociados con TACE, TNF-α, MMPs, ADAMs o cualquier combinación de los mismos.

67. Un método para preparar una composición farmacéutica para el tratamiento de trastornos asociados con TACE, TNF-α, MMPs, ADAMs o cualquier combinación de los mismos, comprendiendo dicho método poner en

contacto íntimo al menos un compuesto de la reivindicación 1 y al menos un vehículo aceptable para uso farmacéutico.

68. Una composición farmacéutica para el tratamiento de trastornos asociados con TACE, TNF-α, MMP, ADAM o cualquier combinación de los mismos en un sujeto, que comprende administrar al sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

69. Un compuesto de la reivindicación 1 en forma purificada.

70. Un método para el tratamiento de una afección o enfermedad mediada por TACE, MMPs, TNF-α, agrecanasa, o cualquier combinación de los mismos en un sujeto, que comprende: administrar al sujeto que necesita tal tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

71. El método de la reivindicación 70, donde dicha agrecanasa es agrecanasa 1 o agrecanasa 2.

72. Un método para el tratamiento de una afección o enfermedad seleccionada del grupo que consiste en artritis reumatoidea, osteoartritis, periodontitis, gingivitis, úlcera de córnea, crecimiento de tumor sólido e invasión de tumor por metástasis secundarias, glaucoma neovascular, enfermedad intestinal inflamatoria, esclerosis múltiple y psoriasis en un sujeto, que comprende: administrar al sujeto que necesita tal tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

73. Un método para el tratamiento de una afección o enfermedad seleccionada del grupo que consiste en fiebre, trastornos cardiovasculares, hemorragia, coagulación, caquexia, anorexia, alcoholismo, respuesta de fase aguda, infección aguda, shock, reacción injerto versus huésped, enfermedad autoinmune e

infección de VIH en un sujeto, que comprende administrar al sujeto que necesita tal tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

74. Un método para el tratamiento de una afección o enfermedad seleccionado del grupo que consiste en shock séptico, shock hemodinámico, síndrome séptico, lesión de reperfusión pos isquémica, malaria, infección micobacteriana, meningitis, psoriasis, insuficiencia cardíaca congestiva, enfermedades fibróticas, caquexia, rechazo a injerto, cánceres tales como linfoma de células T cutáneas, enfermedades relacionadas con angiogénesis, enfermedades autoinmunes, enfermedades inflamatorias de la piel, enfermedades intestinales inflamatorias tales como enfermedad de Crohn y colitis, osteoartritis y artritis reumatoidea, espondilitis anquilosante, artritis psoriásica, enfermedad de Still en adultos, ureítis, granulomatosis de Wegener, enfermedad de Behcehe, síndrome de Sjogren, sarcoidosis, polimiositis, dermatomiositis, esclerosis múltiple, ciática, síndrome de dolor regional complejo, lesión por radiación, lesión alveolar hiperóxica, enfermedad periodontal, VIH, diabetes mellitus no-insulino dependiente, lupus eritematoso sistémico, glaucoma, sarcoidosis, fibrosis pulmonar idiopática, displasia broncopulmonar, enfermedad retinal, escleroderma, osteoporosis, isquemia renal, infarto de miocardio, accidente cerebrovascular, isquemia cerebral, nefritis, hepatitis, glomerulonefritis, aveolitis fibrosa criptogénica, psoriasis, rechazo a transplante, dermatitis atópica, vasculitis, alergia, rinitis alérgica estacional, obstrucción reversible de las vías aéreas, síndrome de insuficiencia respiratoria de adultos, asma, enfermedad pulmonar obstructiva crónica (COPD) y/o bronquitis en un sujeto, que comprende administrar al sujeto que necesita tal tratamiento una cantidad terapéuticamente efectiva de al menos

un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

75. Un método para el tratamiento de una afección o enfermedad asociados con COPD, que comprende: administrar al sujeto que necesita tal tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

76. Un método para el tratamiento de una afección o enfermedad asociados con artritis reumatoidea, que comprende: administrar al sujeto que necesita tal tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

77. Un método para el tratamiento de una afección o enfermedad asociados con la enfermedad de Crohn, que comprende: administrar al sujeto que necesita tal tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

78. Un método para el tratamiento de una afección o enfermedad asociados con psoriasis, que comprende: administrar al sujeto que necesita tal tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

79. Un método para el tratamiento de una afección o enfermedad asociados con espondilitis anquilosante, que comprende: administrar al sujeto que necesita tal tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

80. Un método para el tratamiento de una afección o enfermedad asociados con ciática, que comprende: administrar al sujeto que necesita tal tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

81. Un método para el tratamiento de una afección o enfermedad asociados con síndrome complejo de dolor regional, que comprende: administrar al sujeto que necesita tal tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

82. Un método para el tratamiento de una afección o enfermedad asociados con artritis psoriásica, que comprende: administrar al sujeto que necesita tal tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo.

83. Un método para el tratamiento de una afección o enfermedad asociados con esclerosis múltiple, que comprende: administrar al sujeto que necesita tal tratamiento una cantidad terapéuticamente efectiva de al menos un compuesto de la reivindicación 1 o una sal aceptable para uso farmacéutico, solvato o isómero del mismo, en combinación con un compuesto seleccionado del grupo que consiste en Abones®, Betaseron, Copaxone u otros compuestos indicados para el tratamiento de la esclerosis múltiple.

84. El método de la reivindicación 71, que comprende además administrar a dicho sujeto una cantidad terapéuticamente efectiva de al menos un medicamento seleccionado del grupo que consiste en fármacos anti-reumáticos modificadores de la enfermedad (DMARDS), NSAIDs, inhibidores de COX-2, inhibidores de COX-1, inmunosupresores, modificadores de la respuesta biológica (BRMs), agentes anti-inflamatorios y antagonistas de H1.

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85. Un método de la reivindicación 73, que comprende además administrar a dicho sujeto una cantidad terapéuticamente efectiva de al menos un medicamento seleccionado del grupo que consiste en DMARDS, NSAIDs, inhibidores de COX-2, inhibidores de COX-1, inmunosupresores, modificadores de la respuesta biológica, agentes anti-inflamatorios y antagonistas de H1.

86. Un método de la reivindicación 75, que comprende además administrar a dicho sujeto una cantidad terapéuticamente efectiva de al menos un medicamento seleccionado del grupo que consiste en DMARDS, NSAIDs, inhibidores de COX-2, inhibidores de COX-1, inmunosupresores, modificadores de la respuesta biológica, agentes anti-inflamatorios y antagonistas de H1.

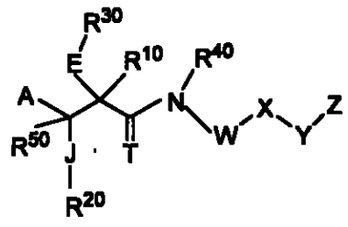
p. SCHERING CORPORATION

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COMPUESTOS PARA EL TRATAMIENTO DE TRASTORNOS INFLAMATORIOS

RESUMEN DE LA INVENCIÓN

La presente invención se refiere a compuestos de Fórmula (I):



(I)

o una sal aceptable para uso farmacéutico, solvato o isómero de los mismos, que puede ser útil para el tratamiento de enfermedades o afecciones mediadas por MMPs, ADAMs, TACE, TNF-α o una combinación de los mismos.

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SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [✓] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [✓]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [✓]
- Descripción de la invención [✓]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [✓]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha 21 de Nov 2006

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1873

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCI

Folio ~~1863~~

2020
Bogotá D.C.,

Doctor(a)
RAISBECK J. IAN
Apoderado(a) y/o Representante de
SCHERING CORPORATION

REFERENCIA	Radicación No.	06 117761
	Solicitud internacional	PCT/US2005/019131
	Fecha inicio fase nacional	02/01/2007
	Trámite	11
	Evento	379
	Actuación	416
	Oficio No.	2382
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 26 DIC. 2006

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

aalvarado