

07-59189

Industria y Comercio
SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIVISIÓN DE NUEVAS CREACIONES

07.59189

SOLICITUD DE PATENTE DE
INVENCION

TITULO: INHIBIDORES HETEROCICLICOS DE ASPARTIL PROTEASA

SOLICITANTE: SCHERING CORPORATION Y PHARMACOPEDIA, INC.

DIRECCIÓN: 3000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530,
E.U.A. y 3000 Eastpark Boulevard, Cranbury, NJ 08512 E.U.A.

AG 1K 31/48, 31/4178, 407D 233/46, 233/88, 239/22, 271/06,
273/00, 401/10, 403/06, 403/12, 407/10, 409/04, 409/14, 413/10,
413/12

APODERADO: J. IAN RAISBECK

BOGOTÁ 12 de Junio de 2007



No. 07-059189- -00000-0000

Fecha: 2007-06-12 16:48:14 Dep. 2020 NUECREACION
Tla. 11 PATENTEIYII Eje: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 827**PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT****ENTRADA EN FASE NACIONAL****P2007/000104****SOLICITUD DE:**

①



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

②

**SOLICITANTE
(71)****Nombre:** SCHERING CORPORATION y
PHARMA COPEIA, INC.
Dirección: 2000 Gallows Hill Road, Kenilworth, NJ 07033-
0530, y 3000 Eastpark Boulevard, Cranbury, NJ 08512 E.U.A.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: Kenilworth y Cranbury E.U.A.**Teléfono:** _____ **Fax:** _____
E-mail: _____**IDENTIFICACIÓN****C.C.** ☐ **NIT** ☐**C.E.** ☐ **Otro** ☐**Cual** _____**Número** _____**REPRESENTANTE
O APODERADO****Nombre:** J. IAN RAISBECK
Dirección: World Trade Center, Torre A, Calle
100 No. 8ª-37 Piso 10.
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com**IDENTIFICACIÓN****C.C.** ☒ **NIT** ☐**C.E.** ☐ **Otro** ☐**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/US2005/020446 **Fecha** Junio 9, 2005**Publicación Internacional No.** WO 2006/065277 **Fecha** Junio 22, 2006

⑥

Título (54) INHIBIDORES HETEROCICLICOS DE ASPARTIL PROTEASA**Clasificación Internacional (51)** A61K 31/48, A61K 31/4178, C07D 233/48, C07D/233/88, C07D
239/22, C07D 271/08, C07D 273/00, C07D 401/10, C07D 403/08, C07D 403/12, C07D 407/10, C07D 409/04,
C07D 409/14, C07D 413/10, C07D 413/12**Prioridad****SI****NO****(33) País de Origen**US**(32) Fecha**Diciembre 13, 2004**(31) Número de Solicitud**11/010.772

⑨

Comprobante de pago No. 07-45.388**Fecha**5 de Junio de 2007

10

ANEXOS

- ☒ 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.
- ☒ Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 06-057.472 Sustitución
- ☐ Documento de cesión del Inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicaciones, dibujos).
- ☒ 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.
- ☒ 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

LISTA DE INVENTORES PCT/US2005/020446

Zhaoning ZHU,
6 Cypress Court, Plainsboro,
NJ 08536
Estados Unidos de America
Nacionalidad: Estadounidense

Brian MCKITTRICK,
14 Millbrook Road, New Vernon,
NJ 07976
Estados Unidos de America
Nacionalidad: Estadounidense

Zhong-Yue SUN,
12 Straton Court, Parlin,
NJ 08859
Estados Unidos de América
Nacionalidad: China

Yuanzan, C. YE,
103 Othen Street, Edison,
NJ 08817
Estados Unidos de América
Nacionalidad: China

J hannes, H. VOIGT,
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Estados Unidos de América
Nacionalidad: Alemania

Corey STRICKLAND,
825 Newmans Lane, Martinsville,
NJ 08836
Estados Unidos de América
Nacionalidad: Estadounidense

Elizabeth, M. SMITH,
166 Grove Street, Verona,
NJ 07044
Estados Unidos de América
Nacionalidad: Canadiense

Andrew STAMFORD,
27 Overlook Road,
Chatham Township,
NJ 07928
Estados Unidos de América
Nacionalidad: Austria

William, J. GREENLEE,
115 Herrick Avenue, Teaneck,
New Jersey 07666
Estados Unidos de América
Nacionalidad: Estadounidense

Robert MAZZOLA,
6 Greenwich Church Road, Stewartsville,
NJ 08886
Estados Unidos de América
Nacionalidad: Estadounidense

John CALDWELL,
86 Upper Lakeview Avenue,
Ringwood, NJ 07456
Estados Unidos de América
Nacionalidad: Estadounidense

Jared CUMMING,
417 Center Street, Garwood,
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Estados Unidos de América
Nacionalidad: Estadounidense

Lingyan WANG,
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East Brunswick, NJ 08816
Estados Unidos de América
Nacionalidad: China

Yusheng WU,
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New York, NY 10016
Estados Unidos de América
Nacionalidad: Estadounidense

Ulrich ISERLOH,
1110 Park Avenue, Apt. 2L,
Hoboken, NJ 07030
Estados Unidos de América
Nacionalidad: Alemana

Tao GUO,
1606 Dahlia Circle,
Dayton, NJ 08810
Estados Unidos de América
Nacionalidad: Estadounidense

Thuy, X., H. LE,
16 Black Gum Drive,
Monmouth Junction, NJ 08852
Estados Unidos de América
Nacionalidad: Estadounidense

Kurt, W. SAI NZ,
508 Linden Place,
Cranford, NJ 07016
Estados Unidos de América
Nacionalidad: Estadounidense

Suresh, D. BABU,
1407 Aspen Drive,
Plainsboro, NJ 08536
Estados Unidos de América
Nacionalidad: Estadounidense

Rachael, C. HUNTER,
27 Chestnut Street,
Princeton, NJ 08542
Estados Unidos de América
Nacionalidad: Británica

Michelle, L. MORRIS,
10 Carla Way,
Lawrenceville, NJ 08648
Estados Unidos de América
Nacionalidad: Estadounidense

Huizhong GU,
22 Cotoneaster Court,
Monmouth Junction, NJ 08852
Estados Unidos de América
Nacionalidad: Estadounidense

Gang QIAN,
59 Colleen Court,
Kendall Park, NJ 08824
Estados Unidos de América
Nacionalidad: China

Dawit TADESSE,
U-15 Avon Drive,
East Windsor, NJ 08520
Estados Unidos de América
Nacionalidad: Estadounidense

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-058189- -00000-0000

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Tra. 11 PATENTEIYI Evs: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 827

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

MIT : 900176089-2

RECIBO OFICIAL DE CAJA : 07 - 45,388
FECHA : JUNIO 5 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBECK	CONSIGNACION	BANCO POPULAR	050-00110-6	67535363	05/06/2007	6,757,000.00

***** CONCEPTO *****

CANT. REENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 30005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
	TOTAL :	\$ 482,000.00

SOM: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Nueva solicitud de Patente de Invención titulada: "INHIBIDORES
HETEROCICLICOS DE ASPARTIL PROTEASA"
Solicitantes: Schering Corporation y Pharmacopela Inc.

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.

Comer no

File # 74293031



**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 Marguerite 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
confrontación. Bogotá 5 septiembre, 2003.

copia archivo, para
Marlén Neira
MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

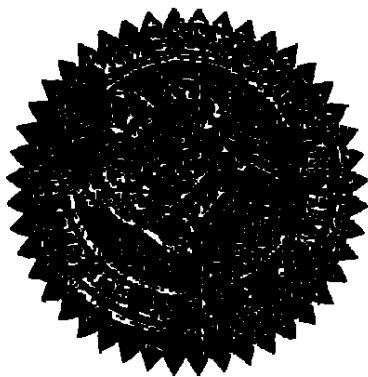
APOSTILLE

(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



John E McCormac

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER - TORRE C
CALLE 100 No. 8A-55 Piso 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 838-8200
Fax: +57-1 838-8201

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
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. Hazer, Senior Legal Director

Date/Fecha:

August 7, 2003

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

OLARTERAISBECK

OLARTE RAISBECK & FRIER, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER - TORRE C
CALLE 100 No. 8A-55 Piso 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 838-8200
Fax: +57-1 838-8201

www.olarteraisbeck.com

Notarial Certification

On this date, August 7, 2003

The undersigned Notary Public certifies:

1. That Edward H. Maser

of legal age and domiciled in

119 Glenwood 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.S.A., 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

maser de edad y domiciliado

suscribió el documento que antecede.

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

4. Que

con sede principal ubicada en

New Jersey 07033-0530, U.S.A., está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentran 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):

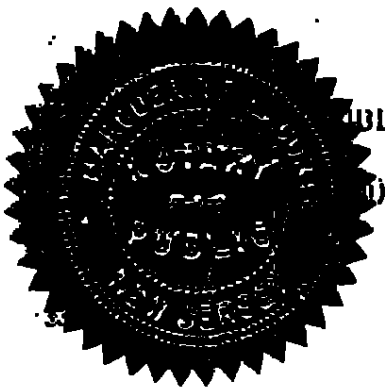
PUBLIC (Signature):

Marguerite La Corte

Marguerite La Corte

Notary Public of New Jersey.

My Commission Expires October 7, 2003



PODER DE REPRESENTACIÓN DE PHARMACOPEIA, INC.

PHARMACOPEIA, INC, una compañía con oficinas principales en el número 300 Eastpark Boulevard, por el presente otorga a Carlos R. Olarte y a Ana María Frieri, poder relacionado con patentes, modelos de utilidad y diseños industriales.

Firmado /cargo: Michael G. Lenahan, Vicepresidente Ejecutivo y Asesor General el 17 de septiembre de 2003.

Ciudad, país: Cranbury, Nueva Jersey, Estados Unidos de América.

Este poder de representación es nuestra autorización para presentar una solicitud de patente titulada:

"3,4- Di-sustituido Ciclobuteno-1,2- Diones como CXC antagonistas receptores de chemokina"

("3,4- Di-substituted Cyclobutene-1,2- Diones as CXC chemokine receptor antagonists)."

CERTIFICACION NOTARIAL

El 17 de septiembre de 2003 la suscrita notaria Salma Cuadrado certifica que:

1. Michael G. Lenahan, de Pharmacoepia, Inc. mayor y domiciliada en el Estado de Nueva Jersey, Estados Unidos, firmó el documento anterior

2 en su caracter de Vicepresidente Ejecutivo/Asesor General de Pharmacoepia, Inc.

3- Pharmacoepia, Inc. tiene sede principal en el no. 3000 Eastpark Boulevard Cranbury, Nueva Jersey, 08512, Estados Unidos.

4. El otorgante y tiene la capacidad legal para firmar el instrumento.

5. El otorgante firmó el instrumento anterior basado en los siguientes documentos: Este poder de representación es nuestra autorización para presentar una solicitud de patente titulada:

"3,4- Di-sustituido Ciclobuteno-1,2- Diones como CXC antagonistas receptores de chemokina"

("3,4- Di-substituted Cyclobutene-1,2- Diones as CXC chemokine receptor antagonists)."

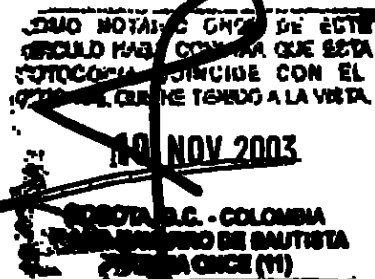
Firma de la Notaria Salma Cuadrado-

Sello en alto relieve y otro azul de Salma Cuadrado - notario público de Nueva Jersey. Sus funciones vencen el junio __- 200_- ilegible. Sello en alto relieve

Es traducción del inglés con copia para la traductora. Bogotá, octubre 28- 2003

Marlén Neira Castro
MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés

Resolución No. 2117 del 7 Oct 1987



OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
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TELEPHONE: +57-1 838-6200
Fax: +57-1 838-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned, Michael G. Lenahan of
PHARMACOPEDIA, INC.

domiciled in
3000 Eastpark Boulevard
Cranbury, New Jersey, 08512
U.S.A.

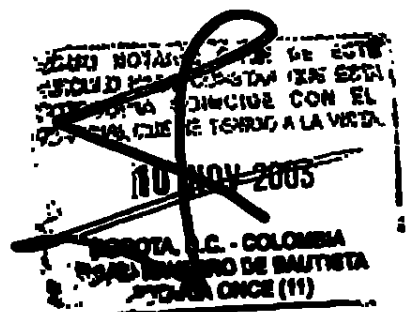
by means of these presents hereby grants to Carlos R. Olarte and/or Ana María Frieri full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs in the Republic of Colombia, to which end it empowers them 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.



X Signature/Title: Michael G. Lenahan, Executive Vice President and General Counsel
X Date/Fecha: September 17, 2003

X City/Country/Ciudad/Pais: Cranbury, New Jersey, USA

**THIS POWER OF ATTORNEY IS OUR
AUTHORIZATION TO FILE A PATENT APPLICATION
ENTITLED: "3,4-DI-SUBSTITUTED CYCLOBUTENE-1,2-DIONES AS CXK CHROMOKINE
RECEPTOR ANTAGONISTS"**



Poder

El suscrito,

domiciliado en

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.

OLARTE RAISBECK

OLARTE RAISBECK & FRIER, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER - TORRE C
CALLE 100 No. 8A-55 Piso 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 838-8200
Fax +57-1 838-8201

www.olarteraisbeck.com

Notarial Certification

On this date, September 17, 2003,

The undersigned Notary Public certifies:
Michael G. Lenahan of

1. That PHARMACOPEIA, INC.

of legal age and domiciled in the state
of New Jersey, U.S.A.,
signed the foregoing document.

2. That the grantor has executed the foregoing
document as Executive VP and Gen. Counsel
of Pharmacopeia, Inc.

3. That PHARMACOPEIA, INC.
having its principal place of business located in
1000 Eastpark Boulevard Cranbury,
New Jersey, 08512, U.S.A.
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):

THIS POWER OF ATTORNEY IS OUR
AUTHORIZATION TO FILE A PATENT APPLICATION
ENTITLED: "3,4-DI-SUBSTITUTED CYCLOBUTENE-1,2-DIONES AS CXCR1 CHEMOKINE
RECEPTOR ANTAGONISTS"

X NOTARY PUBLIC (Signature):

X SEAL (optional)

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

maior de edad y domiciliado

suscribió el documento que antecede.

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

4. Que

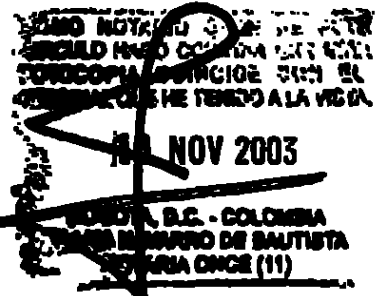
con sede principal ubicada en

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
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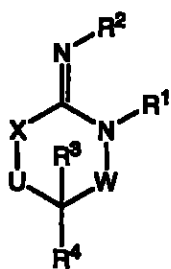
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(54) Title: HETEROCYCLIC ASPARTYL PROTEASE INHIBITORS



(I)

(57) Abstract: Disclosed are compounds of the formula (I) a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, wherein W is a bond, -C(=S)-, -S(O)-, -S(O)-, -C(=O)-, -O-, -C(R)(R')-, -N(R)- or -C(=N(R'))-; X is -O-, -N(R)- or -C(R)(R')-; provided that when X is -O-, U is not -O-, -S(O)-, -S(O)2-, -C(=O)- or -C(=NR5)-; U is a bond, -S(O)-, -S(O)2-, -C(=O)-, -O-, -P(O)(OR')-, -C(=NR)-, -C(R)(R')-, or -N(R)-; wherein b is 1 or 2; provided that when W is -S(O)-, -S(O)2-, -O-, or -N(R5)-, U is not -S(O)-, -S(O)2-, -O-, or -N(R)-; provided that when X is -N(R)- and W is -S(O)-, -S(O)2-, -O-, or -N(R)-, then U is not a bond; and R1, R2, R3, R4, R5, R6, and R7 are as defined in the specification; and pharmaceutical compositions comprising the compounds of formula (I). Also disclosed is the method of inhibiting aspartyl protease, and in particular, the methods of treating cardiovascular diseases, cognitive and neurodegenerative diseases, and the methods of inhibiting of Human Immunodeficiency Virus, plasmodium, cathepsin D and protozoal

enzymes. Also disclosed are methods of treating cognitive or neurodegenerative diseases using the compounds of formula I in combination with a cholinesterase inhibitor or a muscarinic m1 agonist or m2 antagonist.

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HETEROCYCLIC ASPARTYL PROTEASE INHIBITORS

10

FIELD OF THE INVENTION

15 This invention relates to heterocyclic aspartyl protease inhibitors, pharmaceutical compositions comprising said compounds, their use in the treatment of cardiovascular diseases, cognitive and neurodegenerative diseases, and their use as inhibitors of the Human Immunodeficiency Virus, plasmepsins, cathepsin D and protozoal enzymes.

BACKGROUND

20 Eight human aspartic proteases of the A1 (pepsin-like) family are known to date: pepsin A and C, renin, BACE, BACE 2, Napsin A, cathepsin D in pathological conditions.

25 The role of renin-angiotensin system (RAS) in regulation of blood pressure and fluid electrolyte has been well established (Opert, S, et al. N Engl J Med 1974; 291:381-401/446-57). The octapeptide Angiotensin-II, a potent vasoconstrictor and stimulator for release of adrenal aldosterone, was processed from the precursor decapeptide Angiotensin-I, which in turn was processed from angiotensinogen by the renin enzyme. Angiotensin-II was also found to play roles in vascular smooth muscle
30 cell growth, inflammation, reactive oxygen species generation and thrombosis, influence atherogenesis and vascular damage. Clinically, the benefit of interruption of the generation of angiotensin-II through antagonism of conversion of angiotensin-I has been well known and there are a number of ACE inhibitor drugs on the market. The blockade of the earlier conversion of angiotensinogen to angiotensin-I, i.e. the
35 inhibition of renin enzyme, is expected to have similar but not identical effects. Since renin is an aspartyl protease whose only natural substrate is angiotensinogen, it is

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believed that there would be less frequent adverse effect for controlling high blood pressure and related symptoms regulated by angiotensin-II through its inhibition.

Another protease, Cathepsin-D, is involved in lysosomal biogenesis and protein targeting, and may also be involved in antigen processing and presentation of peptide fragments. It has been linked to numerous diseases including, Alzheimer's, disease, connective tissue disease, muscular dystrophy and breast cancer.

Alzheimer's disease (AD) is a progressive neurodegenerative disease that is ultimately fatal. Disease progression is associated with gradual loss of cognitive function related to memory, reasoning, orientation and judgment. Behavioral changes including confusion, depression and aggression also manifest as the disease progresses. The cognitive and behavioral dysfunction is believed to result from altered neuronal function and neuronal loss in the hippocampus and cerebral cortex. The currently available AD treatments are palliative, and while they ameliorate the cognitive and behavioral disorders, they do not prevent disease progression. Therefore there is an unmet medical need for AD treatments that halt disease progression.

Pathological hallmarks of AD are the deposition of extracellular β -amyloid ($A\beta$) plaques and intracellular neurofibrillary tangles comprised of abnormally phosphorylated protein tau. Individuals with AD exhibit characteristic $A\beta$ deposits, in brain regions known to be important for memory and cognition. It is believed that $A\beta$ is the fundamental causative agent of neuronal cell loss and dysfunction which is associated with cognitive and behavioral decline. Amyloid plaques consist predominantly of $A\beta$ peptides comprised of 40 – 42 amino acid residues, which are derived from processing of amyloid precursor protein (APP). APP is processed by multiple distinct protease activities. $A\beta$ peptides result from the cleavage of APP by β -secretase at the position corresponding to the N-terminus of $A\beta$, and at the C-terminus by γ -secretase activity. APP is also cleaved by α -secretase activity resulting in the secreted, non-amyloidogenic fragment known as soluble APP.

An aspartyl protease known as BACE-1 has been identified as the β -secretase activity responsible for cleavage of APP at the position corresponding to the N-terminus of $A\beta$ peptides.

Accumulated biochemical and genetic evidence supports a central role of $A\beta$ in the etiology of AD. For example, $A\beta$ has been shown to be toxic to neuronal cells in

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vitro and when injected into rodent brains. Furthermore inherited forms of early-onset AD are known in which well-defined mutations of APP or the presenilins are present. These mutations enhance the production of A β and are considered causative of AD.

5 Since A β peptides are formed as a result β -secretase activity, inhibition of BACE-1 should inhibit formation of A β peptides. Thus inhibition of BACE-1 is a therapeutic approach to the treatment of AD and other cognitive and neurodegenerative diseases caused by A β plaque deposition.

Human Immunodeficiency virus (HIV), is the causative agent of acquired immune deficiency syndrome (AIDS). It has been clinically demonstrated that 10 compounds such as Indinavir, ritonavir and saquinavir which are inhibitors of the HIV aspartyl protease result in lowering of viral load. As such, the compounds described herein would be expected to be useful for the treatment of AIDS. Traditionally, a major target for researchers has been HIV-1 protease, an aspartyl protease related to renin.

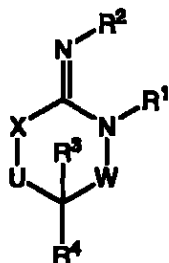
15 In addition, Human T-cell leukemia virus type I (HTLV-I) is a human retrovirus that has been clinically associated with adult T-cell leukemia and other chronic diseases. Like other retroviruses, HTLV-I requires an aspartyl protease to process viral precursor proteins, which produce mature virions. This makes the protease an attractive target for inhibitor design. (Moore, et al. Purification of HTLV-I Protease and Synthesis of Inhibitors for the treatment of HTLV-I Infection 55th Southeast 20 Regional Meeting of the American Chemical Society, Atlanta, GA, US November 16-19, 2003 (2003), 1073. CODEN: 69EUCH Conference, AN 2004:137641 CAPLUS.)

Plasmeprins are essential aspartyl protease enzymes of the malarial parasite. Compounds for the inhibition of aspartyl proteases plasmeprins, particularly I, II, IV 25 and HAP, are in development for the treatment of malaria. (Freire, et al. WO 2002074719. Na Byoung-Kuk, et al. Aspartic proteases of Plasmodium vivax are highly conserved in wild isolates Korean Journal of Parasitology (2004 June), 42(2) 61-6. Journal code: 9435800) Furthermore, compounds used to target aspartyl proteases plasmeprins (e.g. I, II, IV and HAP), have been used to kill malarial 30 parasites, thus treating patients thus afflicted.

SUMMARY OF THE INVENTION

The present invention relates to compounds having the structural formula I

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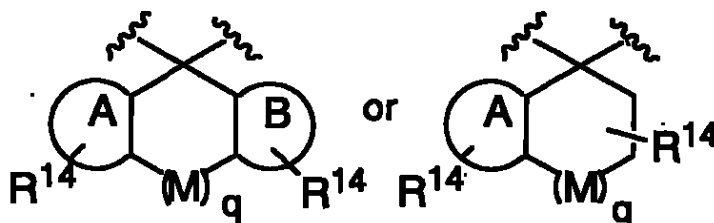
or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, wherein

- W is a bond, $-C(=S)-$, $-S(O)-$, $-S(O)_2-$, $-C(=O)-$, $-O-$, $-C(R^6)(R^7)-$, $-N(R^5)-$ or $-C(=N(R^5))-$;
- X is $-O-$, $-N(R^5)-$ or $-C(R^6)(R^7)-$; provided that when X is $-O-$, U is not $-O-$, $-S(O)-$, $-S(O)_2-$, $-C(=O)-$ or $-C(=NR^5)-$;
- U is a bond, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-O-$, $-P(O)(OR^{15})-$, $-C(=NR^5)-$, $-(C(R^6)(R^7))_b-$ or $-N(R^5)-$; wherein b is 1 or 2; provided that when W is $-S(O)-$, $-S(O)_2-$, $-O-$, or $-N(R^5)-$, U is not $-S(O)-$, $-S(O)_2-$, $-O-$, or $-N(R^5)-$; provided that when X is $-N(R^5)-$ and W is $-S(O)-$, $-S(O)_2-$, $-O-$, or $-N(R^5)-$, then U is not a bond;
- R^1 , R^2 and R^5 are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, $-OR^{16}$, $-CN$, $-C(O)R^8$, $-C(O)OR^9$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-C(O)N(R^{11})(R^{12})$, $-S(O)N(R^{11})(R^{12})$, $-S(O)_2N(R^{11})(R^{12})$, $-NO_2$, $-N=C(R^8)_2$ and $-N(R^8)_2$, provided that R^1 and R^5 are not both selected from $-NO_2$, $-N=C(R^8)_2$ and $-N(R^8)_2$;
- R^3 , R^4 , R^6 and R^7 are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, $-CH_2-O-Si(R^9)(R^{10})(R^{16})$, $-SH$, $-CN$, $-OR^9$, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^{11})(R^{12})$, $-SR^{10}$, $-S(O)N(R^{11})(R^{12})$, $-S(O)_2N(R^{11})(R^{12})$, $-N(R^{11})(R^{12})$, $-N(R^{11})C(O)R^8$, $-N(R^{11})S(O)R^{10}$, $-N(R^{11})C(O)N(R^{12})(R^{13})$, $-N(R^{11})C(O)OR^9$ and $-C(=NOH)R^8$; provided that when U is $-O-$ or $-N(R^5)-$, then R^3 , R^4 , R^6 and R^7 are not halo, $-SH$, $-OR^9$, $-SR^{10}$, $-S(O)N(R^{11})(R^{12})$, $-S(O)_2N(R^{11})(R^{12})$, $-N(R^{11})(R^{12})$, $-N(R^{11})C(O)R^8$, $-N(R^{11})S(O)R^{10}$, $-N(R^{11})C(O)N(R^{12})(R^{13})$, or $-N(R^{11})C(O)OR^9$; provided that when W is $-O-$ or $-N(R^5)-$, then R^3 and R^4 are not halo, $-SH$, $-OR^9$, $-SR^{10}$, $-S(O)N(R^{11})(R^{12})$, $-S(O)_2N(R^{11})(R^{12})$, $-N(R^{11})(R^{12})$, $-N(R^{11})C(O)R^8$, $-N(R^{11})S(O)R^{10}$, $-N(R^{11})C(O)N(R^{12})(R^{13})$, or $-N(R^{11})C(O)OR^9$;

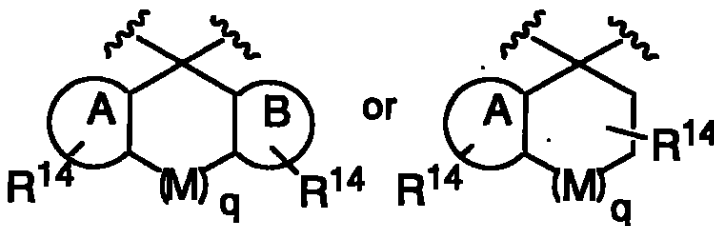
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and provided that when X is $-N(R^5)-$, W is $-C(O)-$ and U is a bond, R^3 and R^4 are not halo, $-CN$, $-SH$, $-OR^9$, $-SR^{10}$, $-S(O)N(R^{11})(R^{12})$ or $-S(O)_2N(R^{11})(R^{12})$; or R^3 , R^4 , R^6 and R^7 , together with the carbon to which they are attached, form a 3-7 membered cycloalkyl group optionally substituted by R^{14} or a 3-7 membered cycloalkylether optionally substituted by R^{14} ;

or R^3 and R^4 or R^6 and R^7 together with the carbon to which they are attached, are combined to form multicyclic groups such as



- 10 wherein M is $-CH_2-$, S, $-N(R^{10})-$ or O, A and B are independently aryl or heteroaryl and q is 0, 1 or 2 provided that when q is 2, one M must be a carbon atom and when q is 2, M is optionally a double bond; and with the proviso that when R^3 , R^4 , R^6 and R^7 form said multicyclic groups



- 15 then adjacent R^3 and R^4 or R^6 and R^7 groups cannot be combined to form said multicyclic groups;

R^8 is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, $-OR^{16}$, $-N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$ and $-N(R^{15})C(O)OR^{16}$;

R^9 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;

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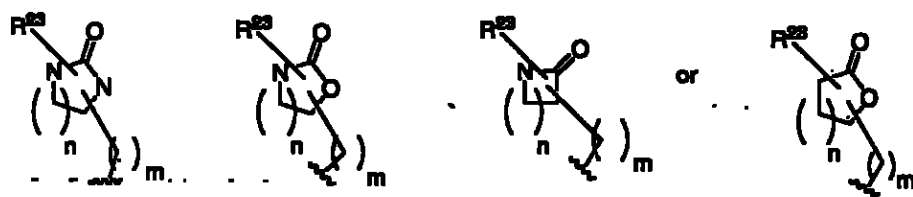
R^{10} is independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and $-N(R^{15})(R^{16})$;

R^{11} , R^{12} and R^{13} are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, $-C(O)R^8$, $-C(O)OR^8$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-C(O)N(R^{15})(R^{16})$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$ and $-CN$;

R^{14} is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, $-CN$, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$ and $-N(R^{15})C(O)OR^{15}$;

R^{15} , R^{16} and R^{17} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, arylheterocycloalkyl, R^{18} -alkyl, R^{18} -cycloalkyl, R^{18} -cycloalkylalkyl, R^{18} -heterocycloalkyl, R^{18} -heterocycloalkylalkyl, R^{18} -aryl, R^{18} -arylalkyl, R^{18} -heteroaryl and R^{18} -heteroarylalkyl; or

R^{15} , R^{16} and R^{17} are



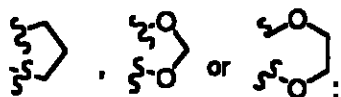
wherein R^{23} numbers 0 to 5 substituents, m is 0 to 6 and n is 1 to 5;

R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, $-NO_2$, halo, heteroaryl, HO-alkoxyalkyl, $-CF_3$, $-CN$, alkyl-CN, $-C(O)R^{19}$, $-C(O)OH$, $-C(O)OR^{19}$, $-C(O)NHR^{20}$, $-C(O)NH_2$, $-C(O)NH_2-C(O)N(alkyl)_2$, $-C(O)N(alkyl)(aryl)$, $-C(O)N(alkyl)(heteroaryl)$, $-SR^{19}$, $-S(O)_2R^{20}$, $-S(O)NH_2$, $-S(O)NH(alkyl)$, $-S(O)N(alkyl)(alkyl)$, $-S(O)NH(aryl)$, $-S(O)_2NH_2$, $-S(O)_2NHR^{19}$, $-S(O)_2NH(heterocycloalkyl)$, $-S(O)_2N(alkyl)_2$, $-S(O)_2N(alkyl)(aryl)$, $-OCF_3$, $-OH$, $-OR^{20}$, $-O$ -heterocycloalkyl, $-O$ -cycloalkylalkyl, $-O$ -

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heterocycloalkylalkyl, $-\text{NH}_2$, $-\text{NHR}^{20}$, $-\text{N}(\text{alkyl})_2$, $-\text{N}(\text{arylalkyl})_2$, $-\text{N}(\text{arylalkyl})$ -
 (heteroarylalkyl), $-\text{NHC}(\text{O})\text{R}^{20}$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NH}(\text{alkyl})$,
 $-\text{NHC}(\text{O})\text{N}(\text{alkyl})(\text{alkyl})$, $-\text{N}(\text{alkyl})\text{C}(\text{O})\text{NH}(\text{alkyl})$, $-\text{N}(\text{alkyl})\text{C}(\text{O})\text{N}(\text{alkyl})(\text{alkyl})$,
 $-\text{NHS}(\text{O})_2\text{R}^{20}$, $-\text{NHS}(\text{O})_2\text{NH}(\text{alkyl})$, $-\text{NHS}(\text{O})_2\text{N}(\text{alkyl})(\text{alkyl})$, $-\text{N}(\text{alkyl})\text{S}(\text{O})_2\text{NH}(\text{alkyl})$
 5 and $-\text{N}(\text{alkyl})\text{S}(\text{O})_2\text{N}(\text{alkyl})(\text{alkyl})$;

or two R^{18} moieties on adjacent carbons can be linked together to form



R^{18} is alkyl, cycloalkyl, aryl, arylalkyl or heteroarylalkyl;

R^{20} is alkyl, cycloalkyl, aryl, halo substituted aryl, arylalkyl, heteroaryl or

10 heteroarylalkyl;

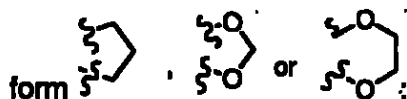
and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl,
 heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl
 groups in R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are
 independently unsubstituted or substituted by 1 to 5 R^{21} groups independently

15 selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl,
 cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl,
 heteroarylalkyl, halo, $-\text{CN}$, $-\text{OR}^{15}$, $-\text{C}(\text{O})\text{R}^{15}$, $-\text{C}(\text{O})\text{OR}^{15}$, $-\text{C}(\text{O})\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{SR}^{15}$,
 $-\text{S}(\text{O})\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{CH}(\text{R}^{15})(\text{R}^{16})$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{C}(=\text{NOR}^{15})\text{R}^{16}$,
 $-\text{P}(\text{O})(\text{OR}^{15})(\text{OR}^{16})$, $-\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{alkyl}-\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$, $-\text{CH}_2$ -
 20 $\text{N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{CH}_2-\text{R}^{16}$, $-\text{CH}_2\text{N}(\text{R}^{15})(\text{R}^{16})$,
 $-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{N}(\text{R}^{16})(\text{R}^{17})$,
 $-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$,
 $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{OR}^{16}$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{OR}^{16}$, $-\text{S}(\text{O})\text{R}^{15}$, $=\text{NOR}^{15}$, $-\text{N}_3$, $-\text{NO}_2$ and $-\text{S}(\text{O})_2\text{R}^{15}$;
 and wherein each of the alkyl, cycloalkenyl, cycloalkyl, cycloalkylalkyl,

25 heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl,
 alkenyl and alkynyl groups in R^{21} are independently unsubstituted or substituted by 1
 to 5 R^{22} groups independently selected from the group consisting of alkyl, cycloalkyl,
 cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, halo, $-\text{CF}_3$, $-\text{CN}$,
 $-\text{OR}^{15}$, $-\text{C}(\text{O})\text{R}^{15}$, $-\text{C}(\text{O})\text{OR}^{15}$, $-\text{alkyl}-\text{C}(\text{O})\text{OR}^{15}$, $\text{C}(\text{O})\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{SR}^{15}$,
 30 $-\text{S}(\text{O})\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{C}(=\text{NOR}^{15})\text{R}^{16}$, $-\text{P}(\text{O})(\text{OR}^{15})(\text{OR}^{16})$,
 $-\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{alkyl}-\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{R}^{16}$,
 $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{CH}_2-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{N}(\text{R}^{16})(\text{R}^{17})$,

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$-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2N(R^{15})C(O)N(R^{16})(R^{17})$,
 $-N(R^{15})C(O)OR^{16}$, $-CH_2N(R^{15})C(O)OR^{16}$, $-N_3$, $=NOR^{16}$, $-NO_2$, $-S(O)R^{16}$ and $-S(O)_2R^{16}$;
 or two R^{21} or two R^{22} moieties on adjacent carbons can be linked together to



- 5 and when R^{21} or R^{22} are selected from the group consisting of
 $-C(=NOR^{16})R^{16}$, $-N(R^{15})C(O)R^{16}$, $-CH_2N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$,
 $-N(R^{15})S(O)_2R^{16}$, $-CH_2N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$,
 $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2N(R^{15})C(O)N(R^{16})(R^{17})$,
 $-N(R^{15})C(O)OR^{16}$ and $-CH_2N(R^{15})C(O)OR^{16}$, R^{15} and R^{16} together can be a C_2 to C_4
 10 chain wherein, optionally, one, two or three ring carbons can be replaced by $-C(O)-$
 or $-N(H)-$ and R^{15} and R^{16} , together with the atoms to which they are attached, form a
 5 to 7 membered ring, optionally substituted by R^{23} ;

- R^{23} is 1 to 5 groups independently selected from the group consisting of alkyl,
 alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl,
 15 heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, $-CN$, $-OR^{24}$,
 $-C(O)R^{24}$, $-C(O)OR^{24}$, $-C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$,
 $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, $-alkyl-N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$,
 $-CH_2N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2N(R^{24})S(O)_2R^{25}$,
 $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$,
 20 $-CH_2N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ and
 $-S(O)_2R^{24}$; and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl,
 heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl
 groups in R^{23} are independently unsubstituted or substituted by 1 to 5 R^{27} groups
 independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl,
 25 aryl, heteroaryl, halo, $-CF_3$, $-CN$, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, $alkyl-C(O)OR^{24}$,
 $C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$,
 $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, $-alkyl-N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$,
 $-CH_2N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2N(R^{24})S(O)_2R^{25}$,
 $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$,
 30 $-CH_2N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ and
 $-S(O)_2R^{24}$;

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R^{24} , R^{25} and R^{26} are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, R^{27} -alkyl, R^{27} -cycloalkyl, R^{27} -cycloalkylalkyl, R^{27} -heterocycloalkyl, R^{27} -heterocycloalkylalkyl, R^{27} -aryl, R^{27} -arylalkyl, R^{27} -heteroaryl and R^{27} -heteroarylalkyl;

R^{27} is 1-5 substituents independently selected from the group consisting of alkyl, aryl, arylalkyl, $-\text{NO}_2$, halo, $-\text{CF}_3$, $-\text{CN}$, alkyl-CN, $-\text{C}(\text{O})\text{R}^{28}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^{28}$, $-\text{C}(\text{O})\text{NHR}^{29}$, $-\text{C}(\text{O})\text{N}(\text{alkyl})_2$, $-\text{C}(\text{O})\text{N}(\text{alkyl})(\text{aryl})$, $-\text{C}(\text{O})\text{N}(\text{alkyl})(\text{heteroaryl})$, $-\text{SR}^{28}$, $-\text{S}(\text{O})_2\text{R}^{29}$, $-\text{S}(\text{O})\text{NH}_2$, $-\text{S}(\text{O})\text{NH}(\text{alkyl})$, $-\text{S}(\text{O})\text{N}(\text{alkyl})(\text{alkyl})$, $-\text{S}(\text{O})\text{NH}(\text{aryl})$, $-\text{S}(\text{O})_2\text{NH}_2$, $-\text{S}(\text{O})_2\text{NHR}^{29}$, $-\text{S}(\text{O})_2\text{NH}(\text{aryl})$, $-\text{S}(\text{O})_2\text{NH}(\text{heterocycloalkyl})$, $-\text{S}(\text{O})_2\text{N}(\text{alkyl})_2$, $-\text{S}(\text{O})_2\text{N}(\text{alkyl})(\text{aryl})$, $-\text{OH}$, $-\text{OR}^{29}$, $-\text{O-heterocycloalkyl}$, $-\text{O-cycloalkylalkyl}$, $-\text{O-heterocycloalkylalkyl}$, $-\text{NH}_2$, $-\text{NHR}^{29}$, $-\text{N}(\text{alkyl})_2$, $-\text{N}(\text{arylalkyl})_2$, $-\text{N}(\text{arylalkyl})(\text{heteroarylalkyl})$, $-\text{NHC}(\text{O})\text{R}^{29}$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NH}(\text{alkyl})$, $-\text{NHC}(\text{O})\text{N}(\text{alkyl})(\text{alkyl})$, $-\text{N}(\text{alkyl})\text{C}(\text{O})\text{NH}(\text{alkyl})$, $-\text{N}(\text{alkyl})\text{C}(\text{O})\text{N}(\text{alkyl})(\text{alkyl})$, $-\text{NHS}(\text{O})_2\text{R}^{29}$, $-\text{NHS}(\text{O})_2\text{NH}(\text{alkyl})$, $-\text{NHS}(\text{O})_2\text{N}(\text{alkyl})(\text{alkyl})$, $-\text{N}(\text{alkyl})\text{S}(\text{O})_2\text{NH}(\text{alkyl})$ and $-\text{N}(\text{alkyl})\text{S}(\text{O})_2\text{N}(\text{alkyl})(\text{alkyl})$;

R^{28} is alkyl, cycloalkyl, arylalkyl or heteroarylalkyl; and

R^{29} is alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

provided that when W is $-\text{C}(\text{O})-$ and U is a bond, R^1 is not optionally substituted phenyl, and that when U is $-\text{C}(\text{O})-$ and W is a bond, R^5 is not optionally substituted phenyl;

provided that neither R^1 nor R^5 is $-\text{C}(\text{O})$ -alkyl-azetidinone or alkyl di-substituted with $(-\text{COOR}^{15}$ or $-\text{C}(\text{O})\text{N}(\text{R}^{15})(\text{R}^{16}))$ and $(-\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, or $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{OR}^{16})$;

provided that when R^1 is methyl, X is $-\text{N}(\text{R}^5)-$, R^2 is H, W is $-\text{C}(\text{O})-$ and U is a bond, (R^3, R^4) is not (H, H), (phenyl, phenyl), (H, phenyl), (benzyl, H), (benzyl, phenyl), (i-butyl, H), (i-butyl, phenyl), (OH-phenyl, phenyl), (halo-phenyl, phenyl), or (CH₃O-phenyl, NO₂-phenyl); and when W is a bond and U is $-\text{C}(\text{O})-$, (R^3, R^4) is not (H, H), (phenyl, phenyl), (H, phenyl), (benzyl, H), (benzyl, phenyl), (i-butyl, H), (i-butyl, phenyl), (OH-phenyl, phenyl), (halo-phenyl, phenyl), or (CH₃O-phenyl, NO₂-phenyl);

provided that when X is $-\text{N}(\text{R}^5)-$, R^1 and R^5 are each H, W is $-\text{C}(\text{O})-$ and U is a bond, (R^3, R^4) is not (optionally substituted phenyl, optionally substituted benzyl), (optionally substituted phenyl, heteroarylalkyl) or (heteroaryl, heteroarylalkyl);

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provided that when U is a bond, W is $-\text{C}(\text{O})-$, and R^3 and R^4 form a ring with the carbon to which they are attached, R^1 is not 2- CF_3 -3-CN-phenyl;

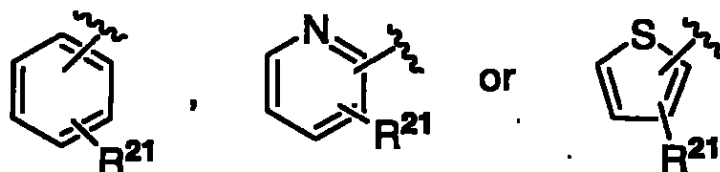
provided that when X is $-\text{N}(\text{R}^5)-$, U is $-\text{O}-$ and W is a bond or $-\text{C}(\text{R}^6)(\text{R}^7)-$, (R^3, R^4) is not (H, - $\text{NHC}(\text{O})$ -alkyl-heteroaryl) or (H, alkyl- $\text{NHC}(\text{O})$ -alkyl-heteroaryl); and

5 provided that when X is $-\text{N}(\text{R}^5)-$, R^1 and R^5 are not -alkylaryl-aryl- SO_2 - $\text{N}(\text{R}^{15})(\text{R}^{16})$ wherein R^{15} is H and R^{16} is heteroaryl;

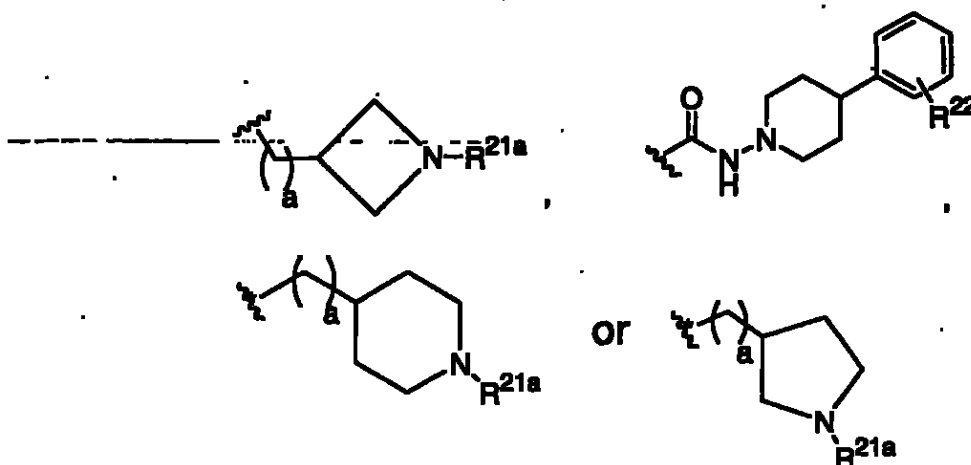
provided that when R^1 is R^{21} -aryl or R^{21} -arylalkyl, wherein R^{21} is $-\text{OCF}_3$, $-\text{S}(\text{O})\text{CF}_3$, $-\text{S}(\text{O})_2\text{CF}_3$, $-\text{S}(\text{O})\text{alkyl}$, $-\text{S}(\text{O})_2\text{alkyl}$, $-\text{S}(\text{O})_2\text{CHF}_2$, $-\text{S}(\text{O})_2\text{CF}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{SF}_5$ or $-\text{S}(\text{O})_2\text{NR}^{15}\text{R}^{16}$;

10 wherein R^{15} and R^{16} are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, R^{18} -alkyl, R^{18} -cycloalkyl, R^{18} -heterocycloalkyl, R^{18} -aryl and R^{18} -heteroaryl; U is a bond or $-\text{CH}_2$; and X is $-\text{N}(\text{R}^5)-$; then R^5 is H;

15 provided that when U is a bond, R^3 and R^4 are alkyl,



where R^{21} is halo, -CN, alkyl, alkoxy, haloalkyl or haloalkoxy, or R^3 and R^4 , together with the carbon to which they are attached, form a 3-7 membered cycloalkyl group, and R^1 is



20

where a is 0 to 6 and R^{22} is alkyl, alkoxy, halo, -CN, -OH, $-\text{NO}_2$ or haloalkyl;

27

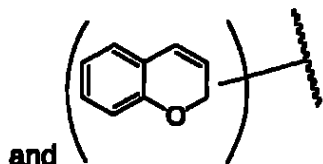
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then R^{21a} is not H, $-C(O)_2R^{15}$, wherein R^{15} is selected from the group consisting of alkyl, cycloalkyl and alkyl substituted with phenyl, alkyl or alkyl- R^{22} , wherein R^{22} is selected from the group consisting of

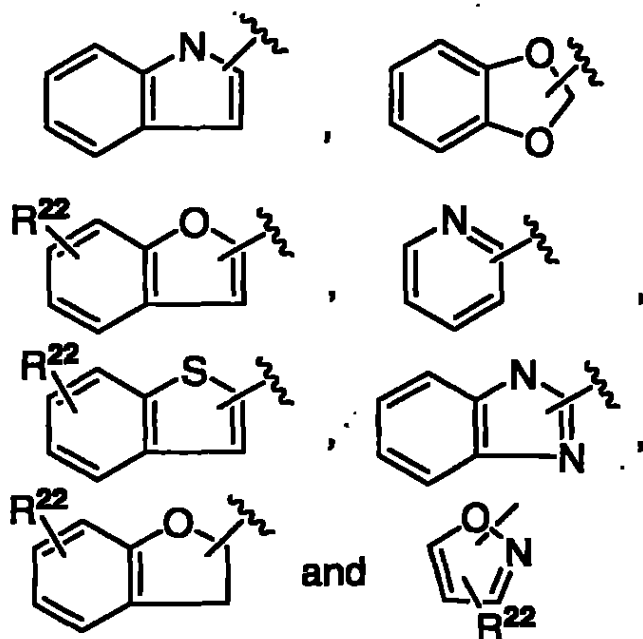
phenyl,

5

phenyl substituted with alkyl,



wherein R^{22} is selected from the group consisting of H, methoxy, nitro, oxo, -OH, halo and alkyl,



10

In another aspect, the invention relates to a pharmaceutical composition comprising at least one compound of formula I and a pharmaceutically acceptable carrier.

15

In another aspect, the invention comprises the method of inhibiting aspartyl protease comprising administering at least one compound of formula I to a patient in need of such treatment.

More specifically, the invention comprises: the method of treating a cardiovascular disease such as hypertension, renal failure, or a disease modulated by renin inhibition; the method of treating Human Immunodeficiency Virus; the method of treating a cognitive or neurodegenerative disease such as Alzheimer's Disease;

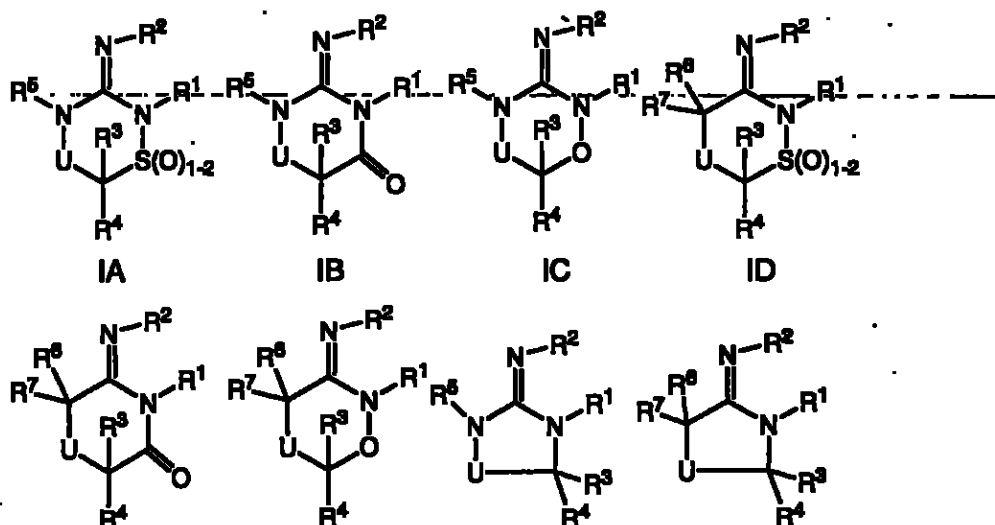
the method of inhibiting plasmepsins I and II for treatment of malaria; the method of inhibiting Cathepsin D for the treatment of Alzheimer's Disease, breast cancer, and ovarian cancer; and the method of inhibiting protozoal enzymes, for example inhibition of plasmodium falciparum, for the treatment of fungal infections. Said method of treatment comprise administering at least one compound of formula I to a patient in need of such treatment. In particular, the invention comprises the method of treating Alzheimer's disease comprising administering at least one compound of formula I to a patient in need of such treatment.

In another aspect, the invention comprises the method of treating Alzheimer's disease comprising administering to a patient in need of such treatment a combination of at least one compound of formula I and a cholinesterase inhibitor or a muscarinic m_1 agonist or m_2 antagonist.

In a final aspect, the invention relates to a kit comprising in separate containers in a single package pharmaceutical compositions for use in combination, in which one container comprises a compound of formula I in a pharmaceutically acceptable carrier and a second container comprises a cholinesterase inhibitor or a muscarinic m_1 agonist or m_2 antagonist in a pharmaceutically acceptable carrier, the combined quantities being an effective amount to treat a cognitive disease or neurodegenerative disease such as Alzheimer's disease.

DETAILED DESCRIPTION:

Compounds of formula I wherein X, W and U are as defined above include the following independently preferred structures:



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IE

IF

IG

IH

In compounds of formulas IA to IF, U is preferably a bond or $-C(R^6)(R^7)-$. In compounds of formula IG and IH, U is preferably $-C(O)-$.

It will be understood that since the definition of R^1 is the same as the definition of R^5 , when X is $-N(R^5)-$, compounds of formula I wherein W is a bond and U is a bond, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-O-$, $-C(R^6)(R^7)-$ or $-N(R^5)-$ are equivalent to compounds of formula I wherein U is a bond and W is a bond, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-O-$, $-C(R^6)(R^7)-$ or $-N(R^5)-$.

More preferred compounds of the invention are those of formula IB wherein U is a bond or those of formula IB wherein U is $-C(R^6)(R^7)-$.

Another group of preferred compounds of formula I is that wherein R^2 is H.

R^3 , R^4 , R^6 and R^7 are preferably selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, $-CH_2O-Si(R^9)(R^{10})(R^{10})$, $-SH$, $-CN$, $-OR^9$, $-C(O)R^9$, $-C(O)OR^9$, $-C(O)N(R^{11})(R^{12})$, $-SR^{10}$, $-S(O)N(R^{11})(R^{12})$, $-S(O)_2N(R^{11})(R^{12})$, $-N(R^{11})(R^{12})$, $-N(R^{11})C(O)R^9$, $-N(R^{11})S(O)R^{10}$, $-N(R^{11})C(O)N(R^{12})(R^{13})$, $-N(R^{11})C(O)OR^9$ and $-C(=NOH)R^9$.

R^3 , R^4 , R^6 and R^7 are preferably selected from the group consisting of aryl, heteroaryl, heteroarylalkyl, arylalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkyl and cycloalkylalkyl.

In a group of preferred compounds

U is a bond or $-C(O)-$;

W is a bond or $-C(O)-$;

X is $-N(R^5)-$;

R^1 is H, alkyl, R^{21} -alkyl, arylalkyl, R^{21} -arylalkyl, cycloalkylalkyl, R^{21} -cycloalkylalkyl, heterocycloalkylalkyl or R^{21} -heterocycloalkylalkyl,

R^2 is H;

R^3 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21} -alkyl, R^{21} -cycloalkylalkyl, R^{21} -cycloalkyl, R^{21} -aryl or R^{21} -arylalkyl;

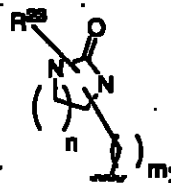
R^4 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21} -alkyl, R^{21} -cycloalkylalkyl, R^{21} -cycloalkyl, R^{21} -aryl or R^{21} -arylalkyl;

R^6 is H, alkyl, R^{21} -alkyl, arylalkyl, R^{21} -arylalkyl, cycloalkylalkyl, R^{21} -cycloalkylalkyl, heterocycloalkylalkyl or R^{21} -heterocycloalkylalkyl;

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R^6 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21} -alkyl, R^{21} -cycloalkylalkyl, R^{21} -cycloalkyl, R^{21} -aryl or R^{21} -arylalkyl;

R^7 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21} -alkyl, R^{21} -cycloalkylalkyl, R^{21} -cycloalkyl, R^{21} -aryl or R^{21} -arylalkyl;



5 R^{15} , R^{16} and R^{17} is H, R^{18} -alkyl, alkyl or
 R^{21} is alkyl, aryl, halo, $-OR^{15}$, $-NO_2$, $-C(O)R^{15}$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$ or
 $-CH(R^{15})(R^{16})$;

n is 1;

m is 1;

10 R^{18} is $-OR^{20}$

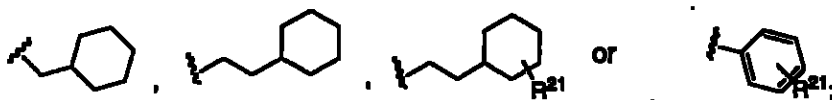
R^{20} is aryl;

and

R^{23} is alkyl.

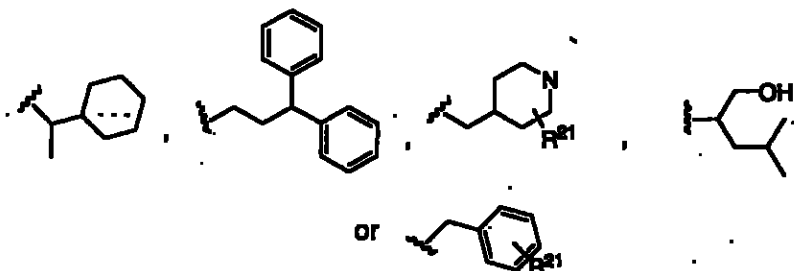
In a group of preferred compounds

15 R^3 , R^4 , R^6 and R^7 are



and

R^1 and R^5 is H, CH_3 ,



20

In an additional group of preferred compounds;

U is a bond or $-C(O)-$;

W is a bond or $-C(O)-$;

X is $-N(R^5)-$;

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R^1 is H, alkyl, R^{21} -alkyl, arylalkyl, R^{21} -arylalkyl, cycloalkylalkyl, R^{21} -cycloalkylalkyl, heterocycloalkylalkyl or R^{21} -heterocycloalkylalkyl,

R^2 is H;

5 R^3 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21} -alkyl, R^{21} -cycloalkylalkyl, R^{21} -cycloalkyl, R^{21} -aryl, R^{21} -arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21} -heteroarylalkyl, R^{21} -heteroaryl, R^{21} -heterocycloalkyl or R^{21} -heterocycloalkylalkyl;

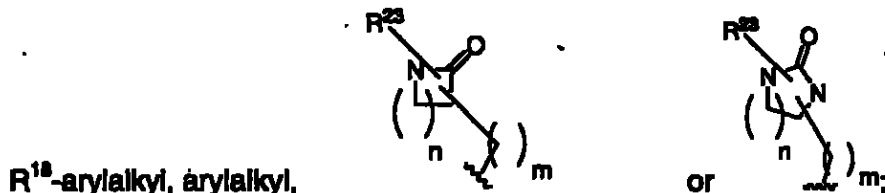
10 R^4 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21} -alkyl, R^{21} -cycloalkylalkyl, R^{21} -cycloalkyl, R^{21} -aryl, R^{21} -arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21} -heteroarylalkyl, R^{21} -heteroaryl, R^{21} -heterocycloalkyl or R^{21} -heterocycloalkylalkyl;

R^5 is H, alkyl, R^{21} -alkyl, arylalkyl, R^{21} -arylalkyl, cycloalkylalkyl, R^{21} -cycloalkylalkyl, heterocycloalkylalkyl or R^{21} -heterocycloalkylalkyl;

15 R^6 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21} -alkyl, R^{21} -cycloalkylalkyl, R^{21} -cycloalkyl, R^{21} -aryl, R^{21} -arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21} -heteroarylalkyl, R^{21} -heteroaryl, R^{21} -heterocycloalkyl or R^{21} -heterocycloalkylalkyl;

20 R^7 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21} -alkyl, R^{21} -cycloalkylalkyl, R^{21} -cycloalkyl, R^{21} -aryl, R^{21} -arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21} -heteroarylalkyl, R^{21} -heteroaryl, R^{21} -heterocycloalkyl or R^{21} -heterocycloalkylalkyl;

R^{15} , R^{16} and R^{17} is H, cycloalkyl, cycloalkylalkyl, R^{18} -alkyl, alkyl, aryl, R^{18} -aryl,



25 n is 1 or 2;

m is 0 or 1;

R^{18} is $-OR^{20}$ or halo;

R^{20} is aryl or halo substituted aryl;

R^{21} is alkyl, aryl, heteroaryl, R^{22} -alkyl, R^{22} -aryl, R^{22} -heteroaryl, halo, heterocycloalkyl, $-N(R^{15})(R^{16})$, $-OR^{15}$, $-NO_2$, $-C(O)R^{15}$, $-N(R^{15})C(O)R^{16}$,

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$-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$ or $-CH(R^{15})(R^{16})$;

R^{22} is $-OR^{16}$ or halo

and

5 R^{23} is H or alkyl.

It is noted that the carbons of formula I may be replaced with 1 to 3 silicon atoms so long as all valency requirements are satisfied.

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

10 "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
15 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. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, heptyl, nonyl and decyl. R^{21} -substituted alkyl groups include fluoromethyl, trifluoromethyl and cyclopropylmethyl.
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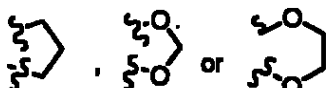
"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2
25 to about 12 carbon atoms in the chain; and more preferably about 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.
30

"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

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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, 3-methylbutynyl, n-pentynyl, and decynyl.

"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 substituents (e.g., R^{18} , R^{21} , R^{22} , etc.) which may be the same or different, and are as defined herein or two substituents on adjacent carbons can be linked together to form



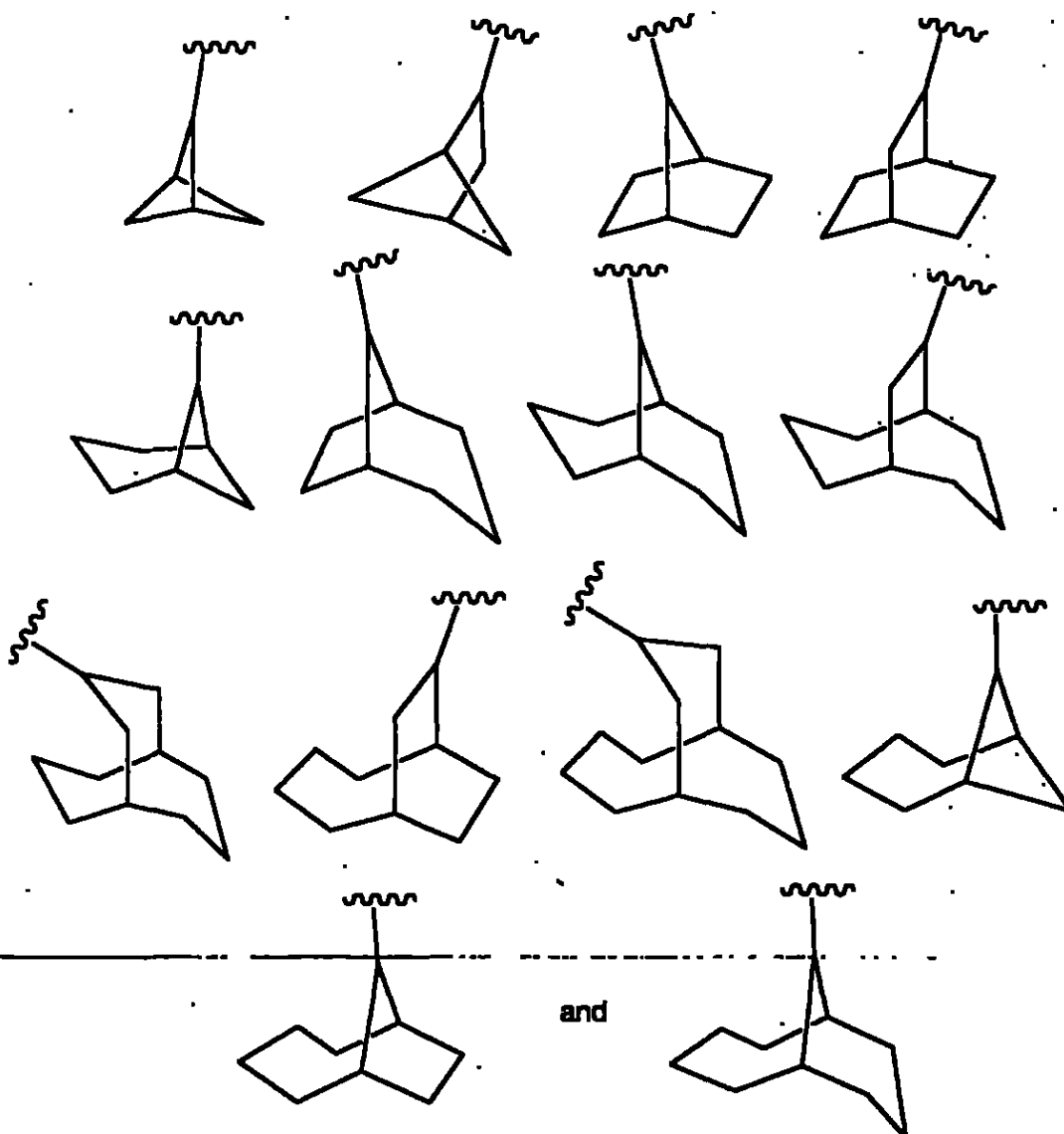
Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"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 to eight 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 R^{21} 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, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidinyl, pyrrolopyridyl, imidazopyridyl, isoquinolyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

"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 R^{21} 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-decalin, norbornyl, adamantyl and the like. Further non-limiting examples of cycloalkyl include

5



"Cycloalkylether" means a non-aromatic ring of 3 to 7 members comprising an oxygen atom and 2 to 7 carbon atoms. Ring carbon atoms can be substituted, provided that substituents adjacent to the ring oxygen do not include halo or

10

substituents joined to the ring through an oxygen, nitrogen or sulfur atom.

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"Cycloalkenyl" 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 which contains at least one carbon-carbon double bond. The cycloalkenyl ring can be optionally substituted with one or more R^{21} substituents which may be the same or different, and are as defined above. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornenyl.

"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 14 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 atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system.

Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic azaheterocyclenyl groups include 1,2,3,4-tetrahydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridine, 1,4,5,6-tetrahydropyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolyl, 2-pyrazolyl, and the like. Non-limiting examples of suitable oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, fluorodihydrofuranyl, and the like. Non-limiting example of a suitable multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Non-limiting examples of suitable monocyclic thiaheterocyclenyl rings include dihydrothiophenyl, dihydrothiopyranyl, and the like.

"Halo" means fluoro, chloro, bromo, or iodo groups. Preferred are fluoro, chloro or bromo, and more preferred are fluoro and chloro.

"Haloalkyl" means an alkyl as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halo group defined above.

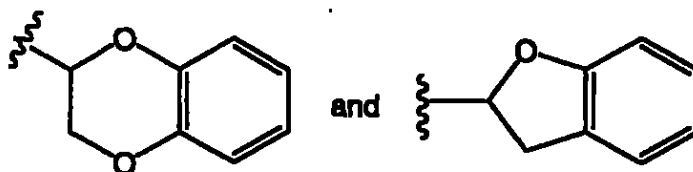
- 20 -

"Heterocyclyl" (or heterocycloalkyl) means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which 1-3, preferably 1 or 2 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. The heterocyclyl can be optionally substituted by one or more R^{21} 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, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"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.

"Arylcycloalkyl" means a group derived from a fused aryl and cycloalkyl as defined herein. Preferred arylcycloalkyls are those wherein aryl is phenyl and cycloalkyl consists of about 5 to about 6 ring atoms. The arylcycloalkyl can be optionally substituted by 1-5 R^{21} substituents. Non-limiting examples of suitable arylcycloalkyls include indanyl and 1,2,3,4-tetrahydronaphthyl and the like. The bond to the parent moiety is through a non-aromatic carbon atom.

"Arylheterocycloalkyl" means a group derived from a fused aryl and heterocycloalkyl as defined herein. Preferred arylcycloalkyls are those wherein aryl is phenyl and heterocycloalkyl consists of about 5 to about 6 ring atoms. The arylheterocycloalkyl can be optionally substituted by 1-5 R^{21} substituents. Non-limiting examples of suitable arylheterocycloalkyls include



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The bond to the parent moiety is through a non-aromatic carbon atom.

Similarly, "heteroarylalkyl", "cycloalkylalkyl" and "heterocycloalkylalkyl" mean a heteroaryl-, cycloalkyl- or heterocycloalkyl-alkyl- group in which the heteroaryl, cycloalkyl, heterocycloalkyl and alkyl are as previously described. Preferred groups contain a lower alkyl group. The bond to the parent moiety is through the alkyl.

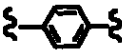
"Acyl" means an H-C(O)-, alkyl-C(O)-, alkenyl-C(O)-, alkynyl-C(O)- or cycloalkyl-C(O)- group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and cyclohexanoyl.

"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, n-butoxy and heptoxy. The bond to the parent moiety is through the ether oxygen.

"Alkoxyalkyl" means a group derived from an alkoxy and alkyl as defined herein. The bond to the parent moiety is through the alkyl.

"Arylalkenyl" means a group derived from an aryl and alkenyl as defined herein. Preferred arylalkenyls are those wherein aryl is phenyl and the alkenyl consists of about 3 to about 6 atoms. The arylalkenyl can be optionally substituted by one or more R²⁷ substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

"Arylalkynyl" means a group derived from a aryl and alkynyl as defined herein. Preferred arylalkynyls are those wherein aryl is phenyl and the alkynyl consists of about 3 to about 6 atoms. The arylalkynyl can be optionally substituted by one or more R²⁷ substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

The suffix "ene" on alkyl, aryl, heterocycloalkyl, etc. indicates a divalent moiety, e.g., -CH₂CH₂- is ethylene, and  is para-phenylene.

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

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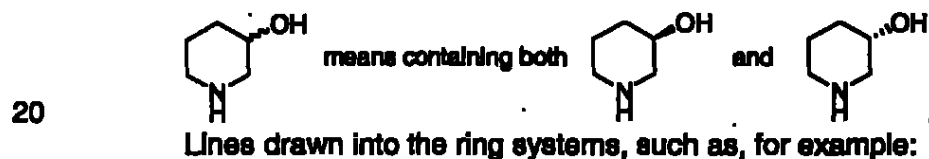
Substitution on a cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, or heteroarylalkyl moiety includes substitution on the ring portion and/or on the alkyl portion of the group.

When a variable appears more than once in a group, e.g., R^8 in $-N(R^8)_2$, or a variable appears more than once in the structure of formula I, e.g., R^{15} may appear in both R^1 and R^3 , the variables can be the same or different.

With reference to the number of moieties (e.g., substituents, groups or rings) in a compound, unless otherwise defined, the phrases "one or more" and "at least one" mean that there can be as many moieties as chemically permitted, and the determination of the maximum number of such moieties is well within the knowledge of those skilled in the art. With respect to the compositions and methods comprising the use of "at least one compound of formula I," one to three compounds of formula I can be administered at the same time, preferably one.

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.

The wavy line ~~~ as a bond generally indicates a mixture of, or either of, the possible isomers, e.g., containing (R)- and (S)- stereochemistry. For example,



Indicate that the indicated line (bond) may be attached to any of the substitutable ring carbon atoms.

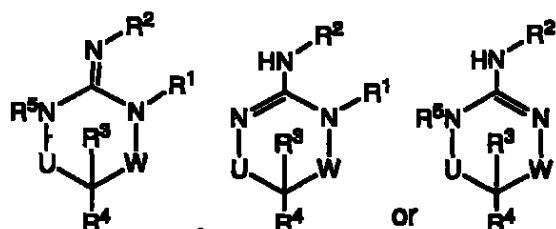
25 As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom, unless stated otherwise. For example:

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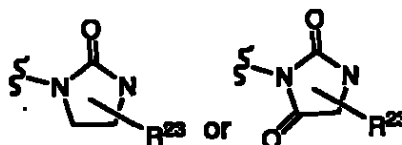


It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples, structural formulae, and any Tables herein is assumed to have the hydrogen atom or atoms to satisfy the valences.

- 5 Those skilled in the art will recognize that certain compounds of formula I are tautomeric, and all such tautomeric forms are contemplated herein as part of the present invention. For example, a compound wherein X is $-N(R^5)-$ and R^1 and R^5 are each H can be represented by any of the following structures:



- 10 When R^{21} and R^{22} are, for example, $-N(R^{15})C(O)N(R^{16})(R^{17})$ and R^{15} and R^{16}



form a ring, the moiety formed, is, for example,

- 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
 15 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) Volume 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
 20 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

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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 ethanulates, methanulates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H₂O.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting aspartyl protease and/or inhibiting BACE-1 and thus producing the desired therapeutic effect in a suitable patient.

The compounds of formula I 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. Acids (and bases) which are generally considered suitable for the formation of pharmaceutically useful salts from basic (or acidic) pharmaceutical compounds are discussed, for example, by 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; In *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website); and P. Heinrich Stahl, Camille G. Wermuth (Eds.), *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (2002) Int'l. Union of Pure and Applied Chemistry, pp. 330-331. These disclosures are incorporated herein by reference thereto.

Exemplary acid addition salts include acetates, adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates,

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citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, methyl sulfates, 2-naphthalenesulfonates, nicotines, nitrates, oxalates, pamoates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propanates, salicylates, succinates, sulfates, sulfonates (such as those mentioned herein), tartarates, thiocyanates, toluenesulfonates (also known as tosylates), undecanoates, and the like.

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, aluminum salts, zinc salts, salts with organic bases (for example, organic amines) such as benzathines, diethylamine, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, piperazine, phenylcyclohexylamine, choline, tromethamine, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl 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.

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. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for

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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, 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

Compounds of formula I can be made using procedures known in the art. Preparative methods for preparing starting materials and compounds of formula I are shown below as general reaction schemes (Method A, Method B, etc.) followed by specific procedures, but those skilled in the art will recognize that other procedures can also be suitable. In the Schemes and in the Examples below, the following abbreviations are used:

methyl: Me; ethyl: Et; propyl: Pr; butyl: Bu; benzyl: Bn; tertiary butyloxycarbonyl: Boc or BOC

high pressure liquid chromatography: HPLC

liquid chromatography mass spectroscopy: LCMS

room temperature: RT or rt

day: d; hour: h; minute: min

retention time: R_t

microwave: μW

saturated: sat.; anhydrous: anhyd.

1-hydroxybenzotriazole: HOBT

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride: EDCI

ethyl acetate: EtOAc

Benzyloxycarbonyl: CBZ

[1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)]: Selectfluor

1,8-diazabicyclo[5.4.0]undec-7-ene: DBU

tetrahydrofuran: THF; N,N-dimethylformamide: DMF; methanol: MeOH; diethyl

ether: Et₂O; acetic acid: AcOH; acetonitrile: MeCN; trifluoroacetic acid: TFA;

dichloromethane: DCM; dimethoxyethane: DME; diphenylphosphinoferrocene (dppf);

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n-butyllithium: n-BuLi; lithium diisopropylamide: LDA

1-hydroxy-7-azabenzotriazole: HOAt

4-N,N-dimethylaminopyridine: DMAP; diisopropylethylamine: DIEA;

N-methylmorpholine: NMM

5 Microporous Toluene sulfonic acid resin (MP-TsOH resin)

tris-(2-aminoethyl)aminomethyl polystyrene (PS-trisamine)

methylisocyanate polystyrene (PS-NCO)

Saturated (sat.); anhydrous. (anhyd); room temperature (rt); hour (h);

Minutes (Min), Retention Time (R_t); molecular weight (MW); milliliter (mL); gram10 (g), milligram (mg); equivalent (eq); day (d); microwave (μ W); microliter (μ L);

All NMR data were collected on 400 MHz NMR spectrometers unless otherwise indicated. LC-Electrospray-Mass spectroscopy with a C-18 column and 5% to 95% MeCN in water as the mobile phase was used to determine the molecular mass and retention time. The tables contain the compounds with retention

15 time/observed MW and/or NMR data.

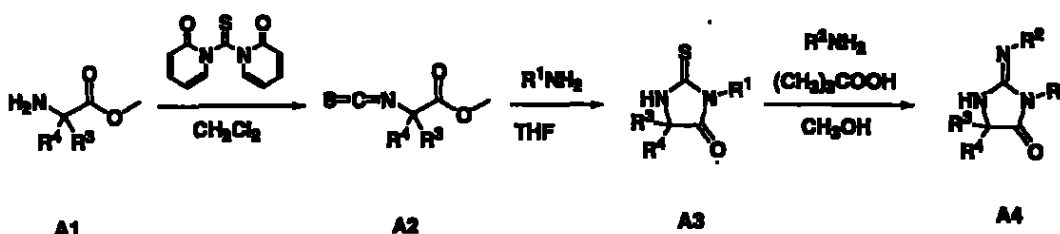
For internal consistency in the reaction schemes shown in Methods A to DF, the product of each method is shown as structure A4, B4, C3, etc., wherein certain variables are as defined for that method, but it will be apparent that, for example, A4 has the same structure as C3. That is, different methods can be used to prepare

20 similar compounds.

The compounds in 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. The tables contain the compounds with observed m/e values from mass spectroscopy and/or NMR

25 data. These compounds can be obtained with synthetic methods similar to those listed in the last column using appropriate reagents.

Method A



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Method A, Step 1:

To a solution of A1 ($R^3 = \text{CH}_3$ & $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (10 mmol, 1 eq) in 30ml of anhyd. CH_2Cl_2 was added thiocarbonyl dipyrldone (1.2 eq). After stirring overnight the solution was diluted with CH_2Cl_2 , washed with 1N HCl, H_2O (2x),
5 and a saturated aqueous NaCl solution (2x). The organic solution was dried over Na_2SO_4 , filtered and concentrated. The crude material was purified via flash chromatography to afford A2 ($R^3 = \text{CH}_3$ & $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$).

Method A, Step 2:

A solution of 3,5-difluorobenzyl amine (0.15 mmol, 1.5 eq) in THF (0.15
10 mL) was added to a solution of A2 ($R^3 = \text{CH}_3$ & $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (0.1 mmol, 1 eq) in anhydrous CH_2Cl_2 (1 mL). The reaction mixture was refluxed overnight. The reaction solution was added to MP-TsOH resin (2–3 eq) and diluted with CH_3CN . The suspension was agitated overnight. The mixture was filtered and the filtrate was concentrated to afford A3 ($R^1 = 3,5\text{-difluorobenzyl}$, $R^3 = \text{CH}_3$, & R^4
15 $= \text{CH}_2\text{CH}(\text{CH}_3)_2$).

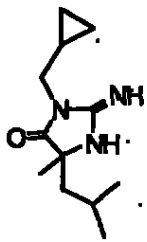
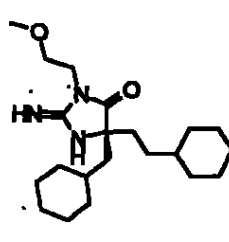
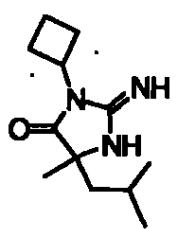
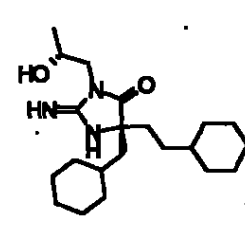
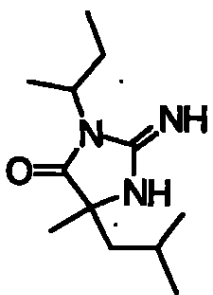
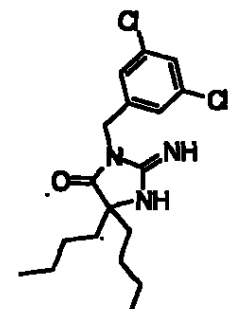
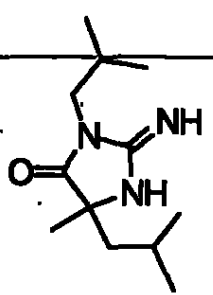
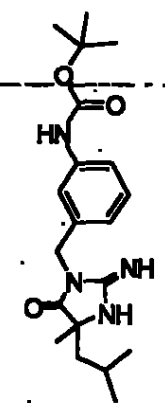
Method A, Step 3:

To a solution of A3 ($R^1 = 3,5\text{-difluorobenzyl}$, $R^3 = \text{CH}_3$, & $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (10 mg) in CH_3OH (1 mL) was added NH_4OH (0.44 mL) and *t*-butyl hydrogen peroxide (0.1 mL) and the reaction mixture was agitated for 2 d.
20 The solution was concentrated, the resulting residue was dissolved in CH_3OH (1.2 mL) and was treated with sulfonic acid resin. The suspension was agitated overnight and the resin was washed with CH_3OH (4 x 10 min) before it was treated with 2 N NH_3 in CH_3OH for 1 h. The suspension was filtered and the
25 filtrate was concentrated to give the crude material which was purified by preparative HPLC/LCMS eluting with a $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ gradient to afford A4 ($R^1 = 3,5\text{-difluorobenzyl}$, $R^2 = \text{H}$, $R^3 = \text{CH}_3$, & $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$). NMR (CD_3OD): δ 8.9, m, 3H; δ 4.8–4.9, m; δ 1.75, d, 2H; δ 1.5, m, 1H; δ 1.42, s, 3H; δ 0.85, d, 3H; δ 0.65, d, 3H. ES_LCMS (*m/e*) 296.1.

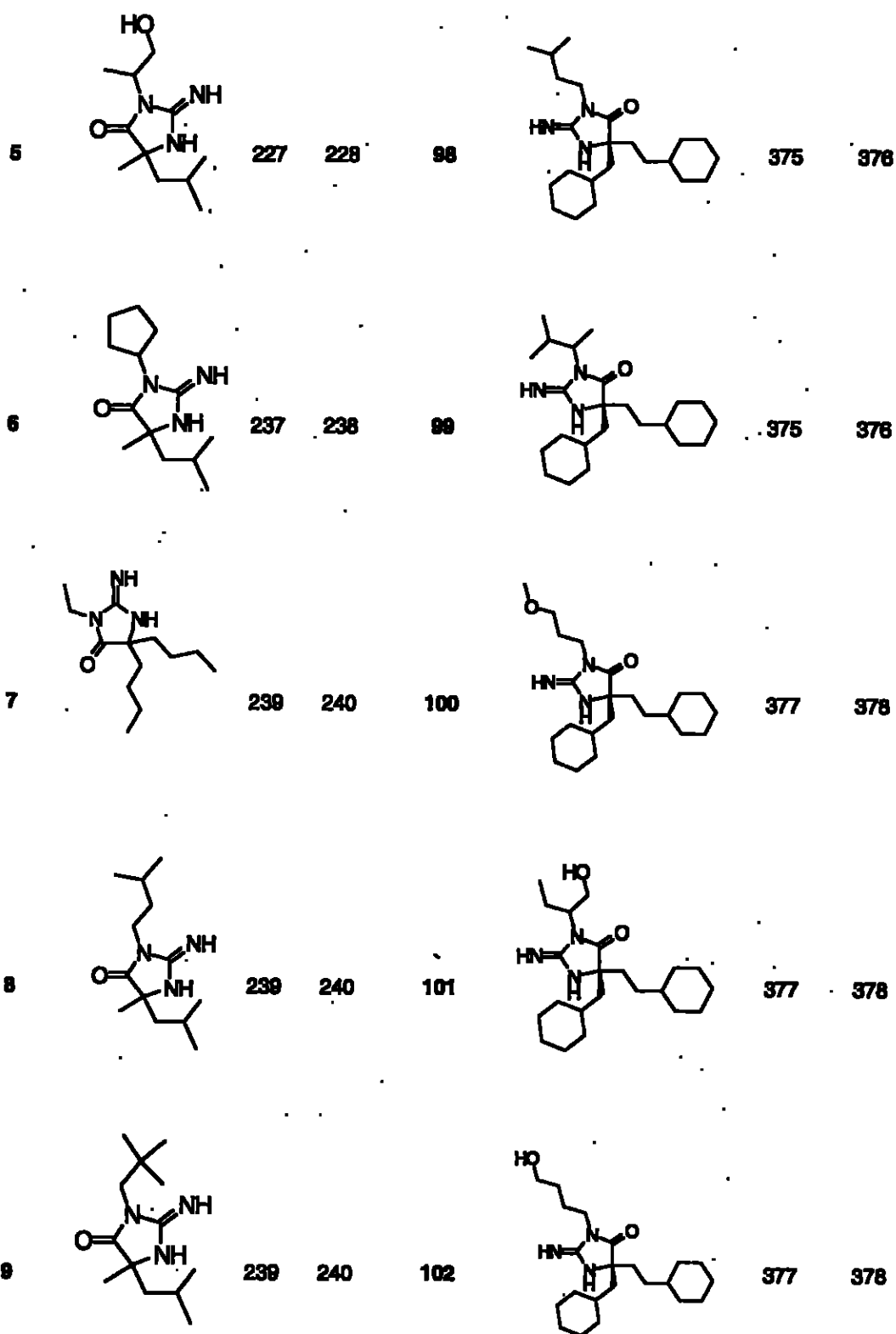
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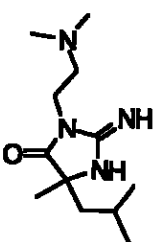
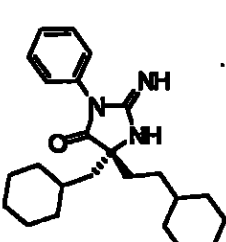
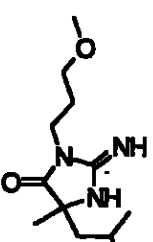
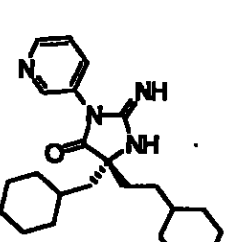
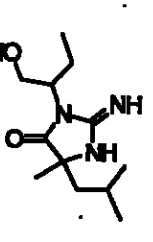
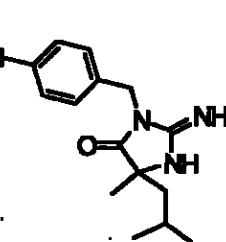
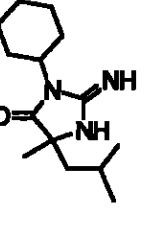
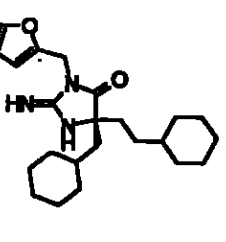
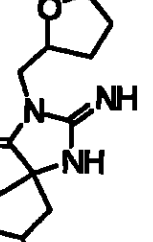
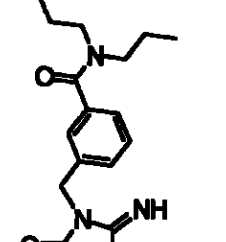
The following compounds were synthesized using similar methods:

- 29 -

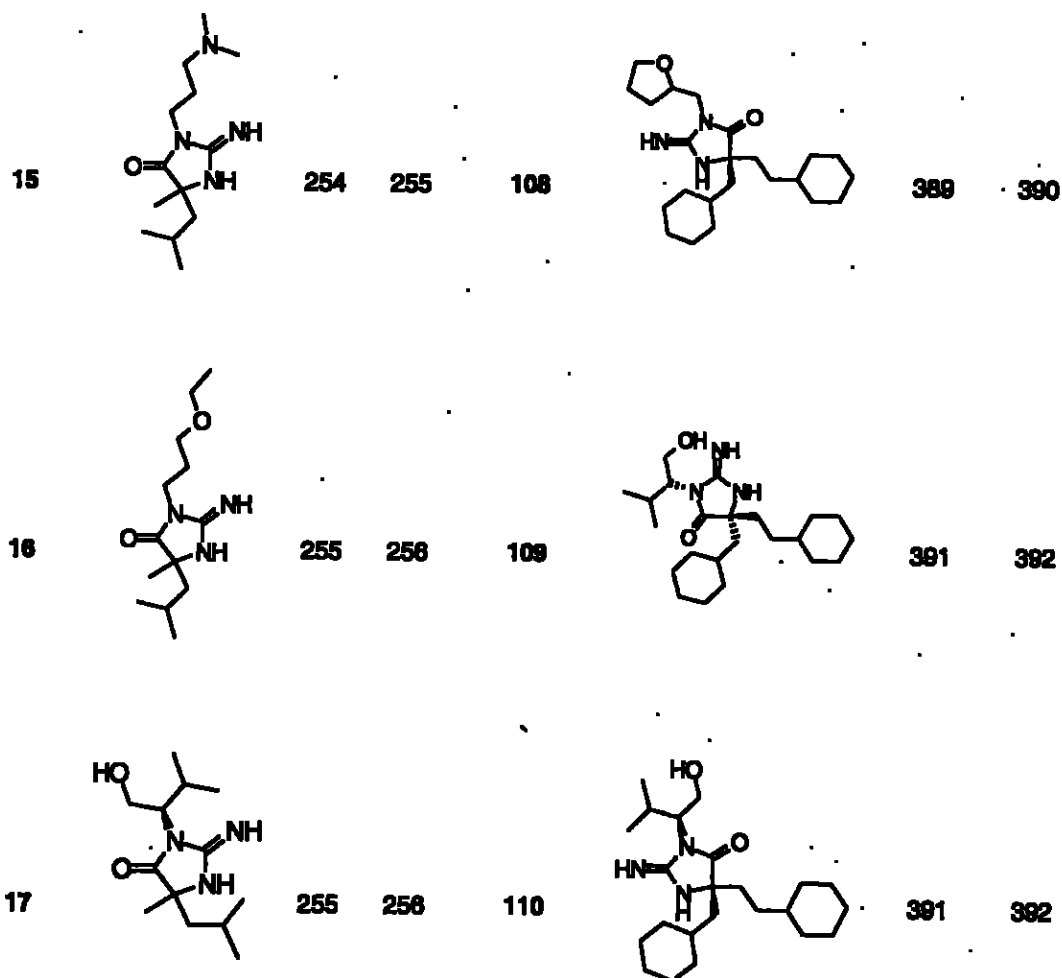
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1		223	224	94		383	384
2		223	224	95		383	384
3		225	226	96		389	370
4		225	226	97		374	375

- 30 -

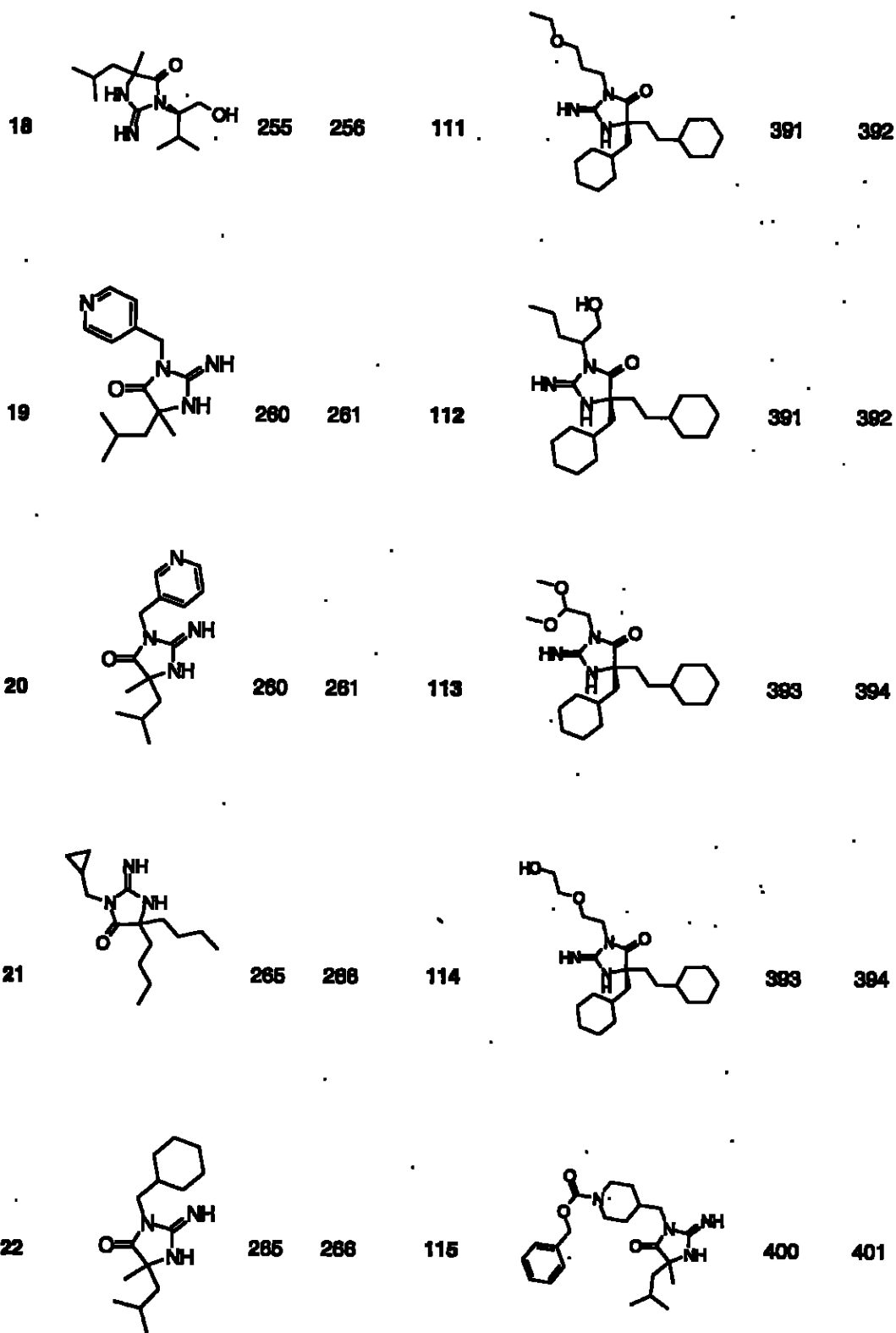


10		240	241	103		381	382
11		241	242	104		382	383
12		241	242	105		385	386
13		251	252	106		385	386
14		253	254	107		386	387

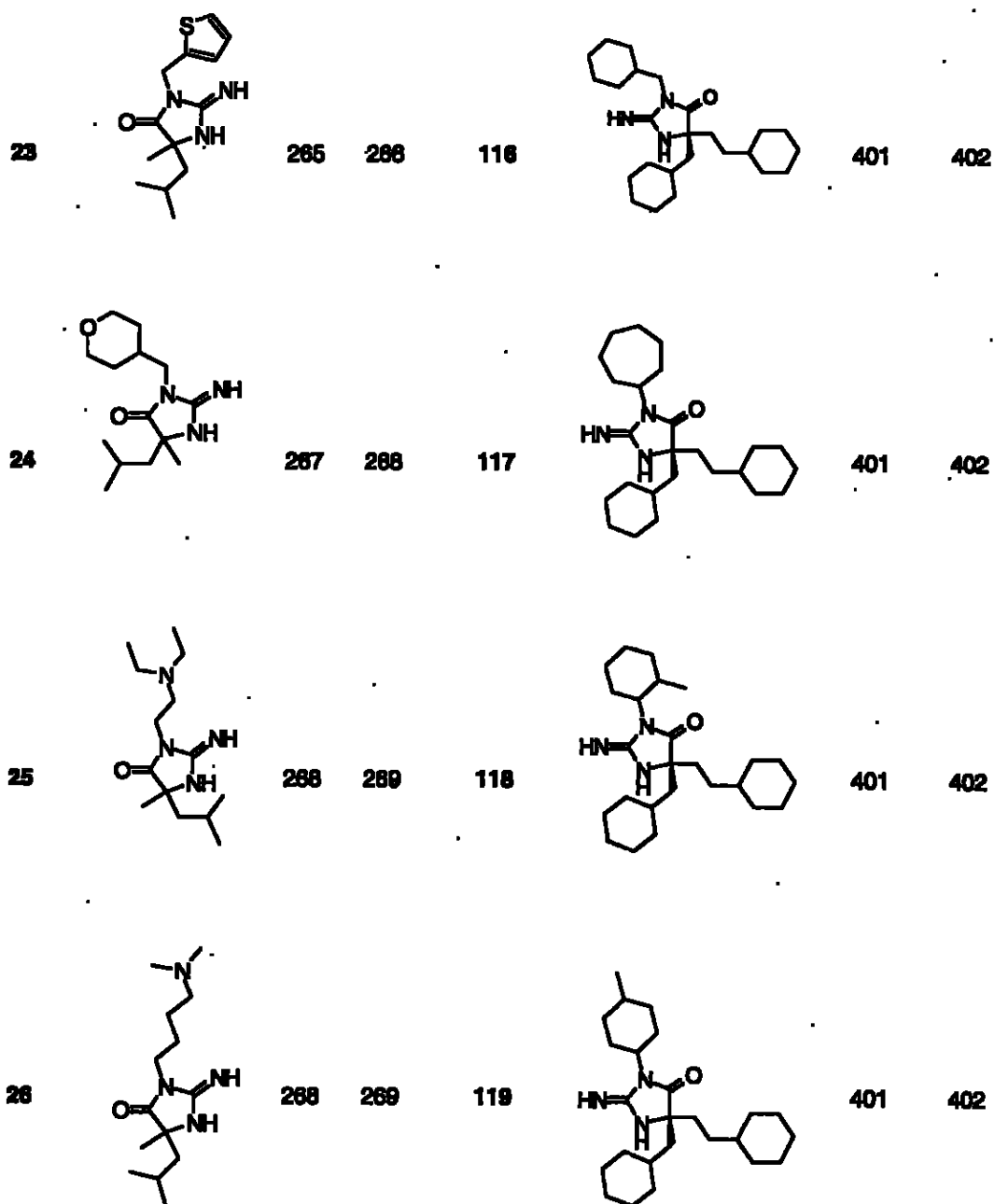
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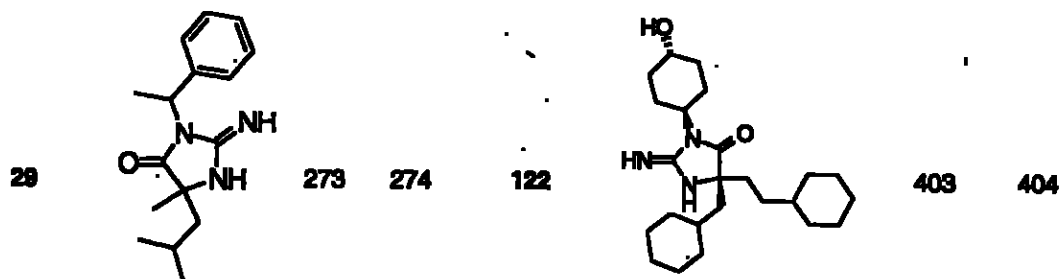
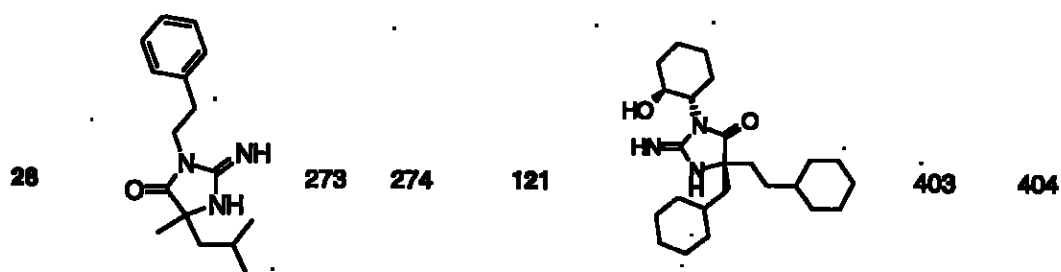
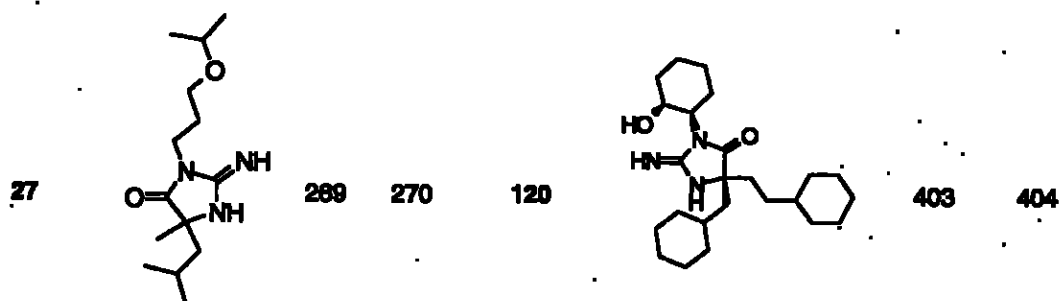


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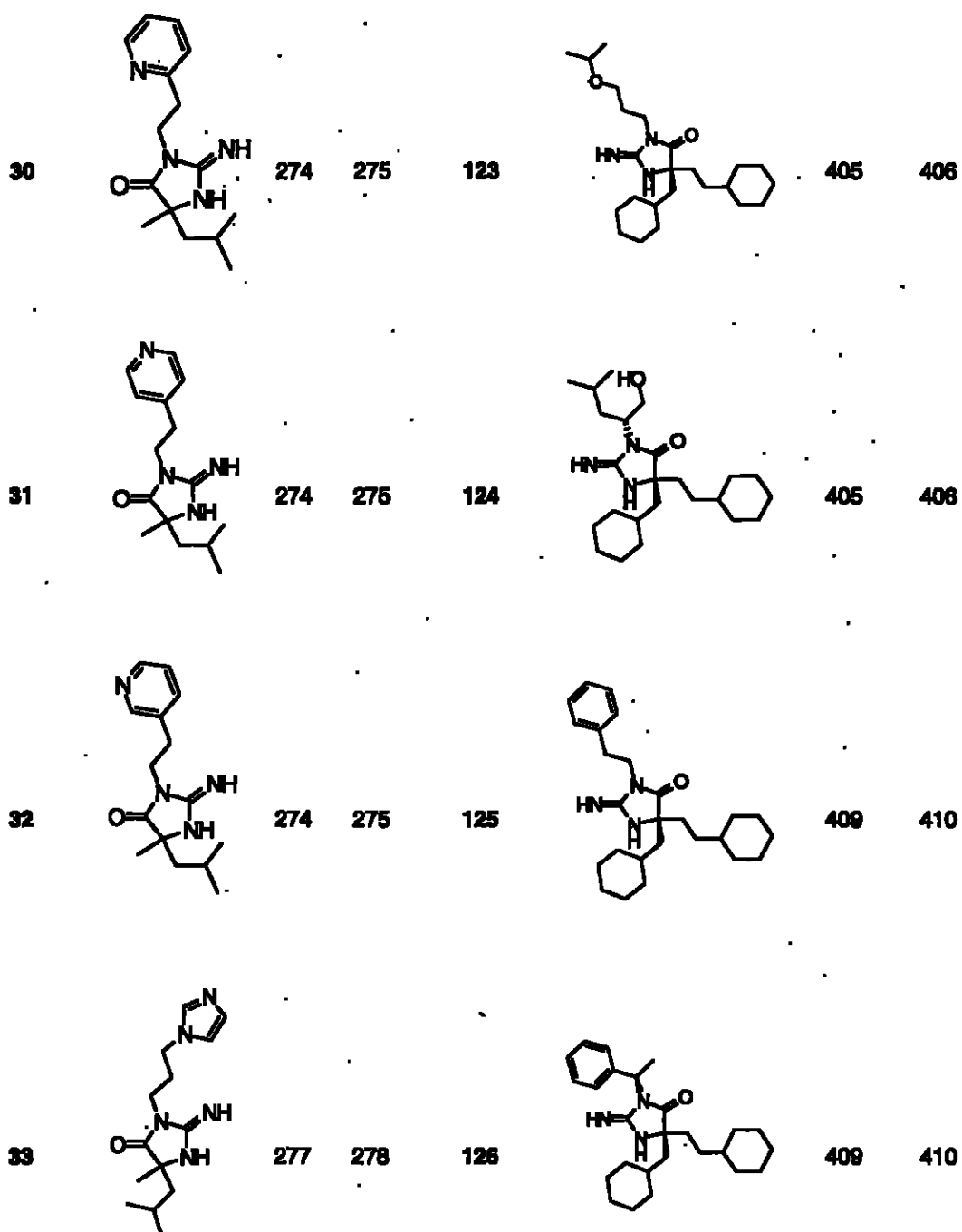


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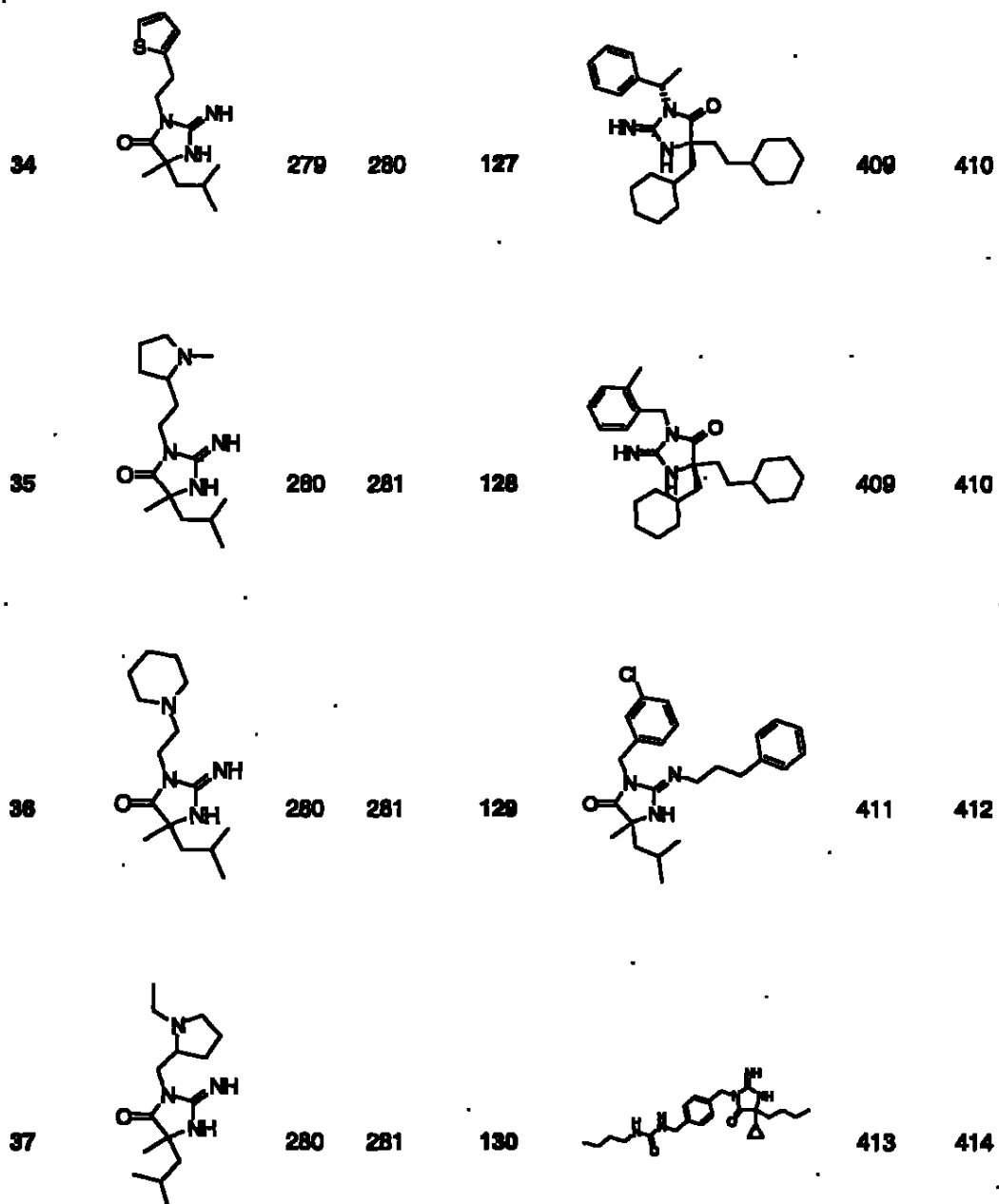




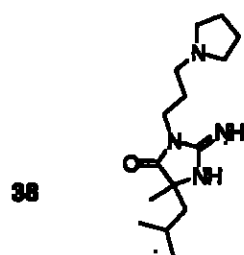
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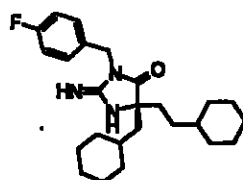


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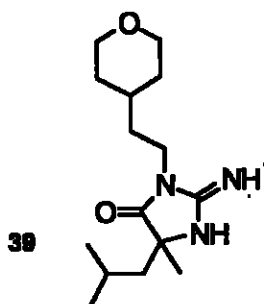


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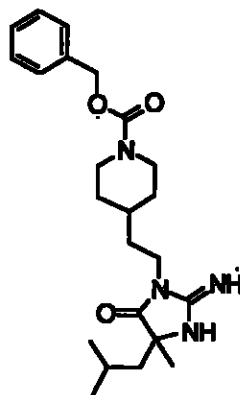


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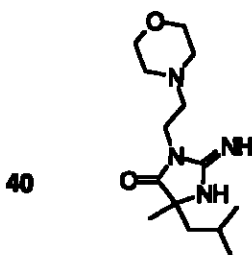


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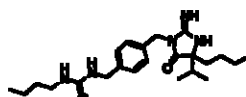


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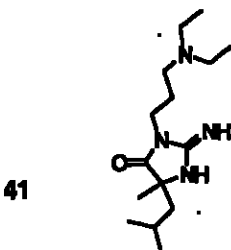


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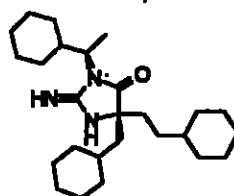


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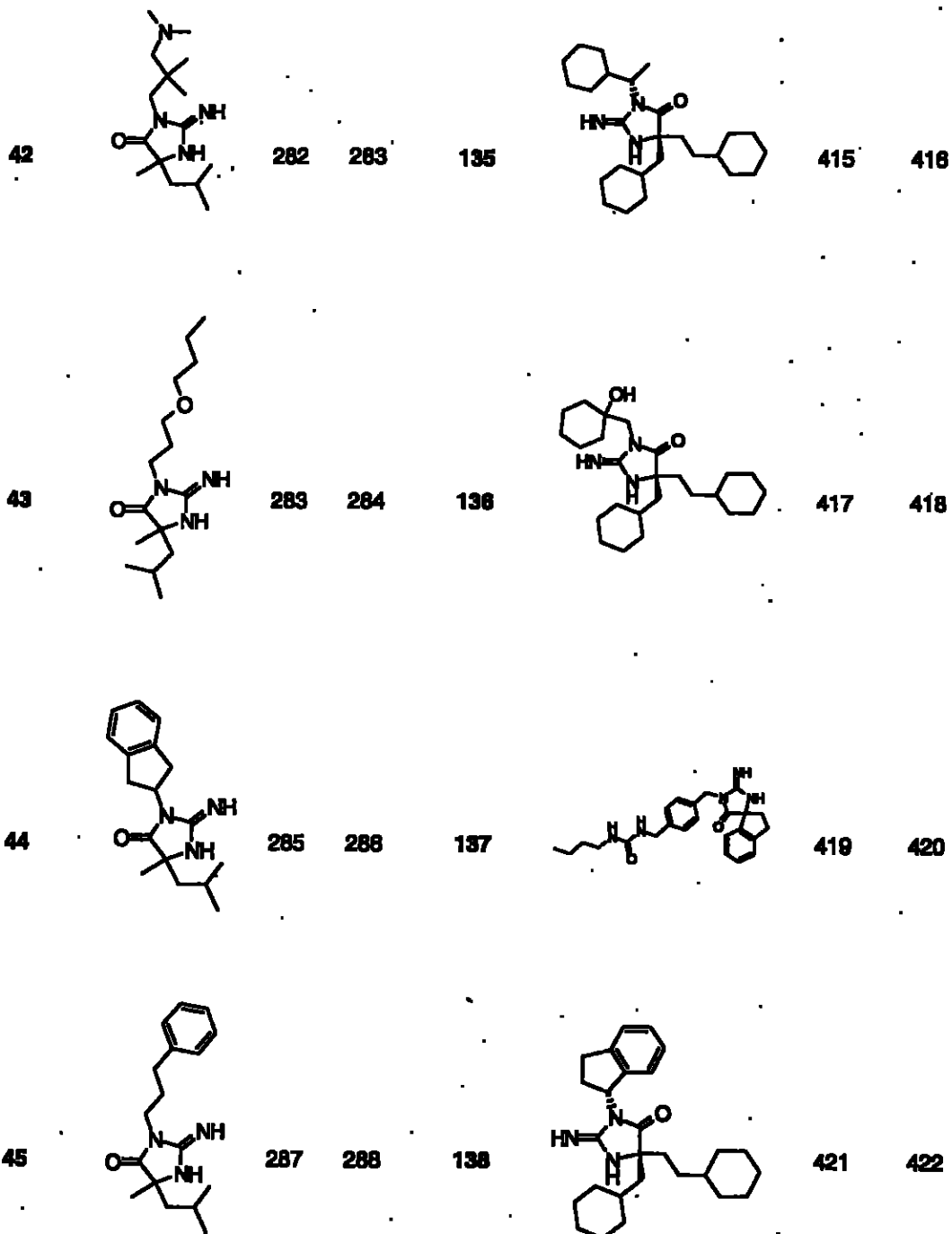
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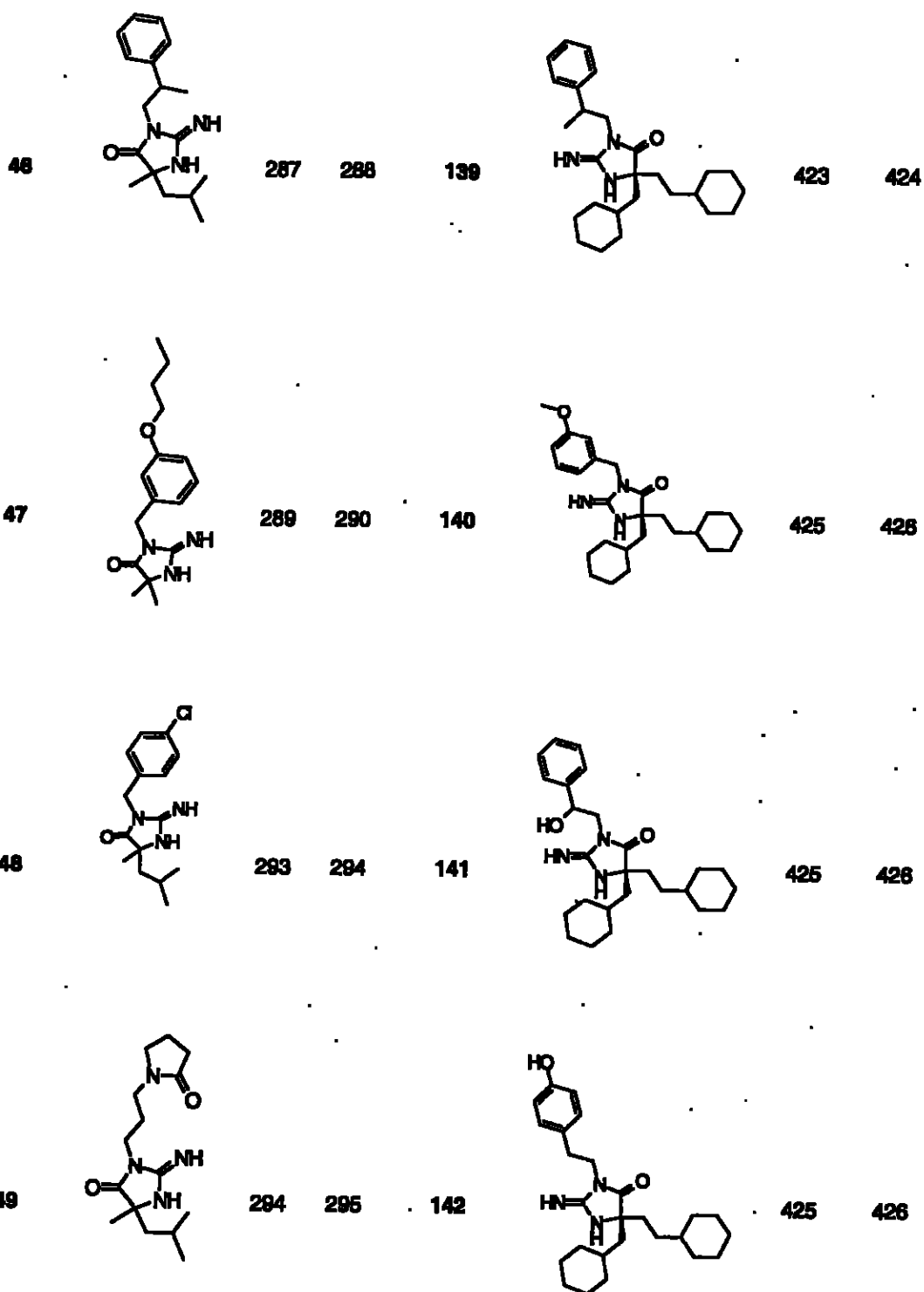
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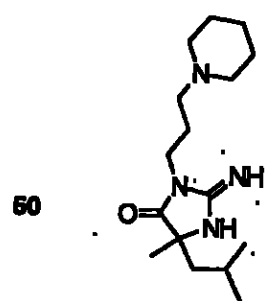
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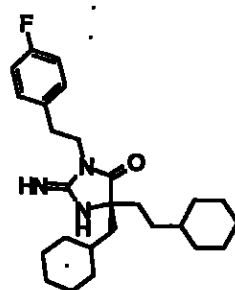
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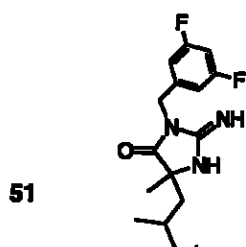
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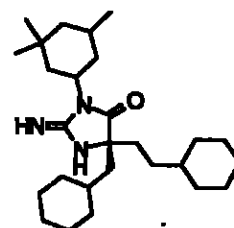
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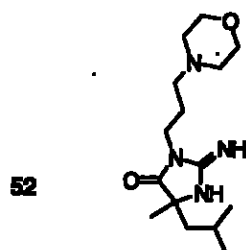
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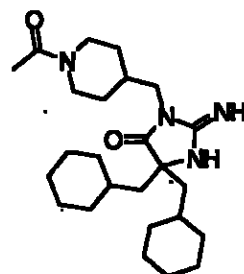
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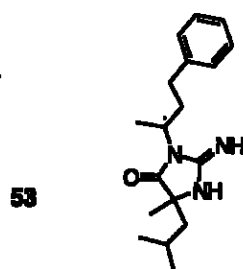
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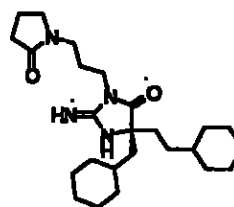
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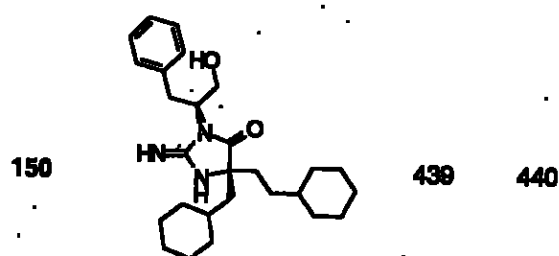
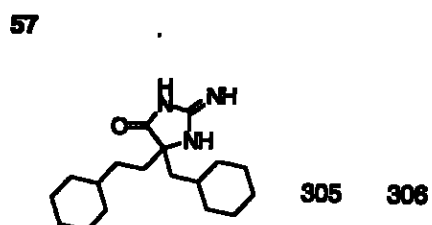
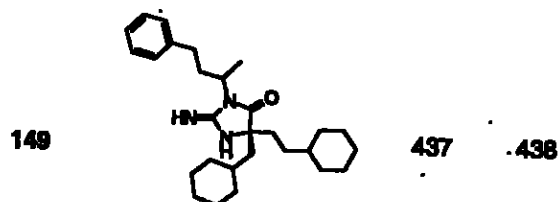
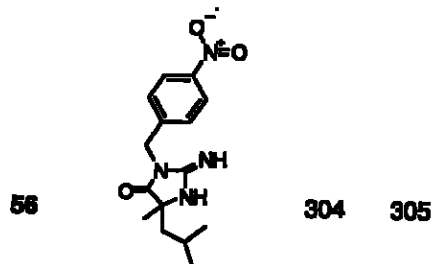
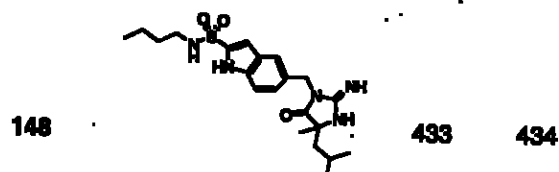
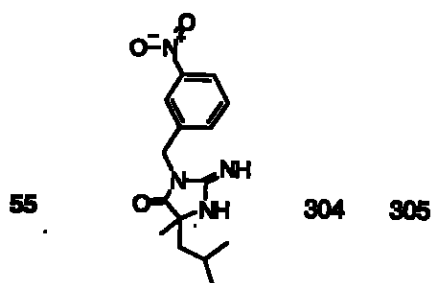
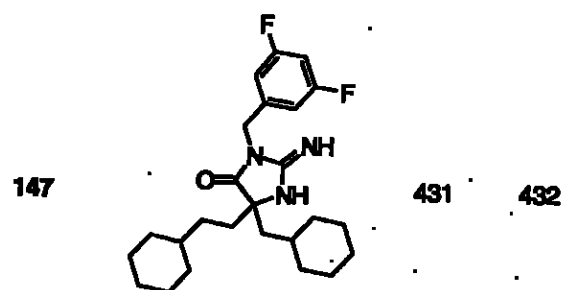
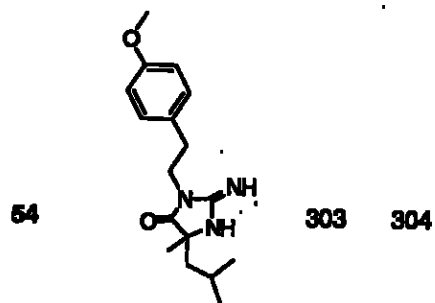


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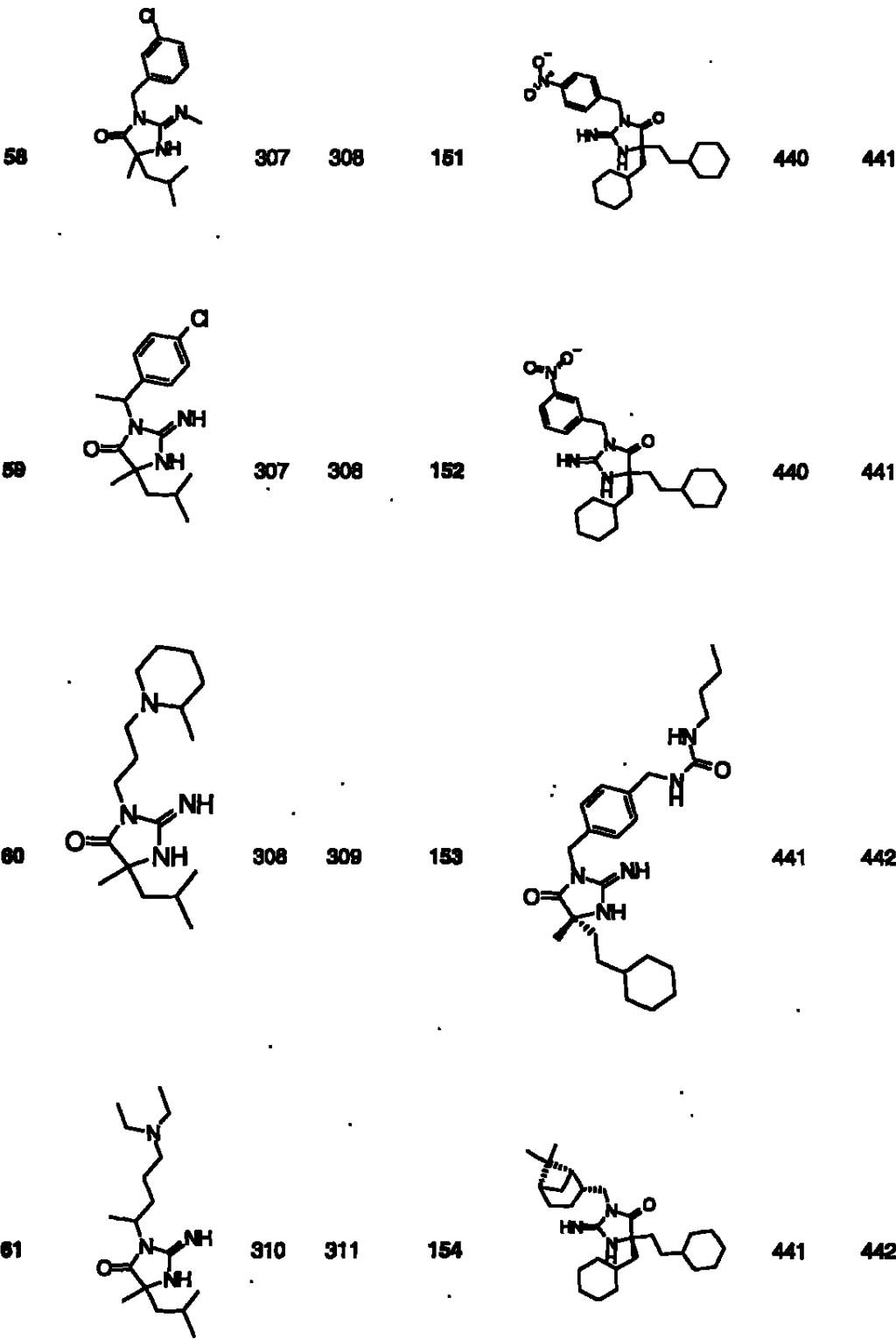
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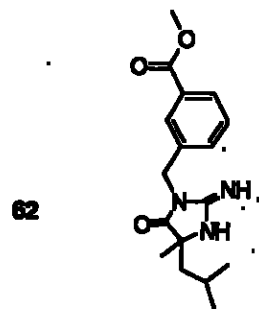


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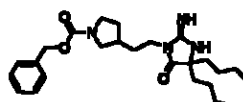
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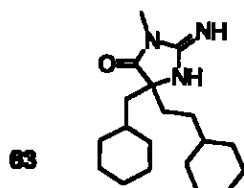


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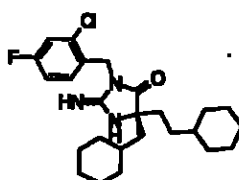


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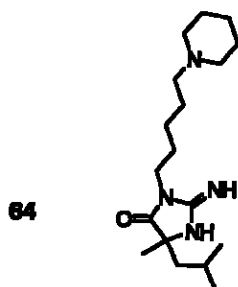


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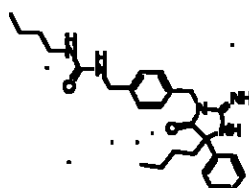


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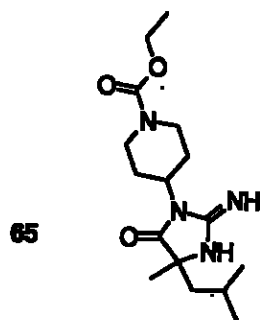


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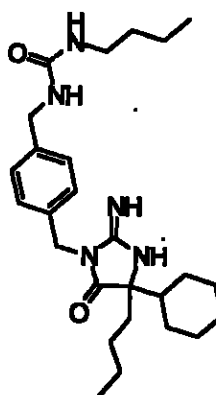


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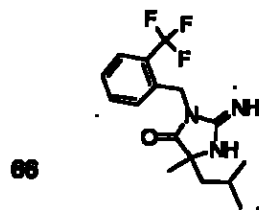
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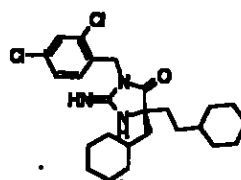
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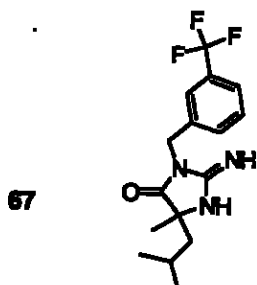
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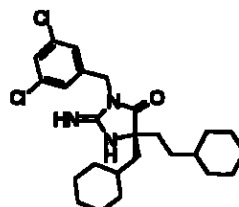
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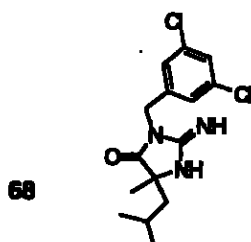
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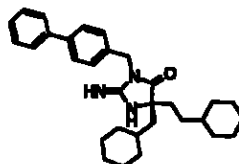
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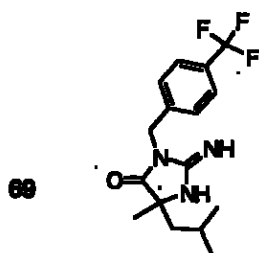
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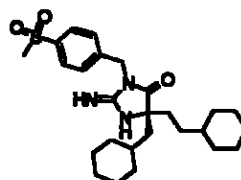
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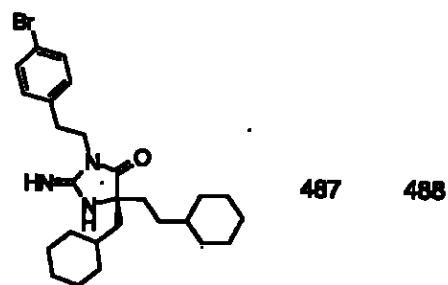
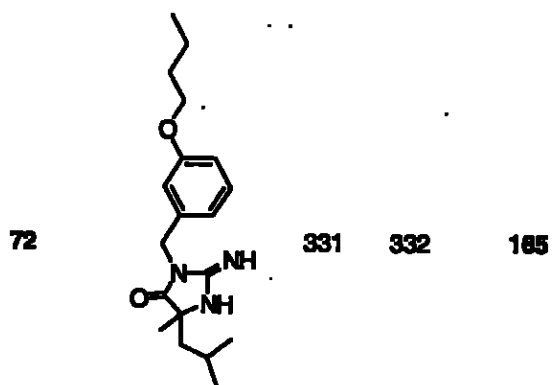
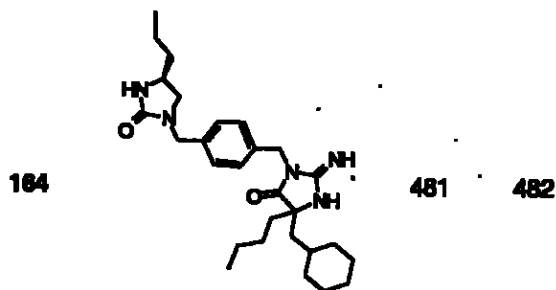
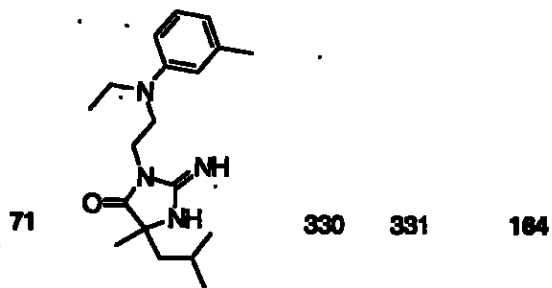
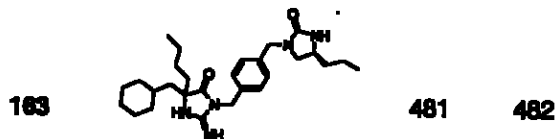
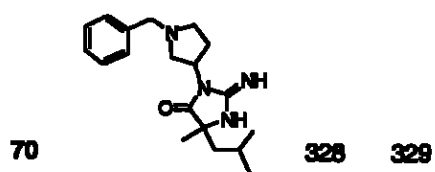


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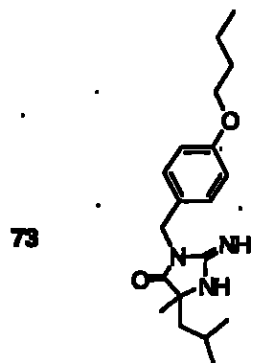
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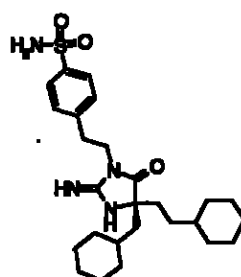
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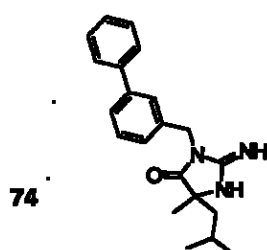
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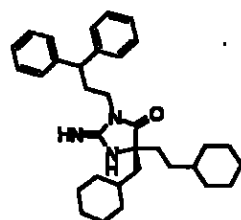
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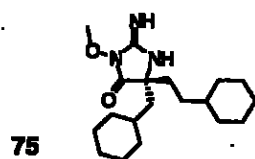
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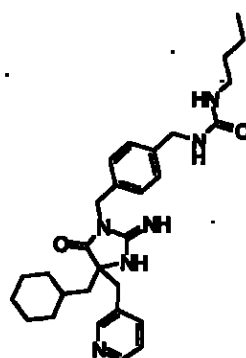
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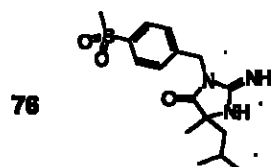
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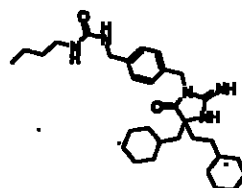
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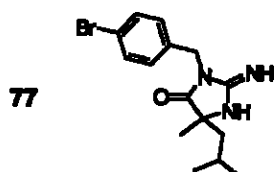
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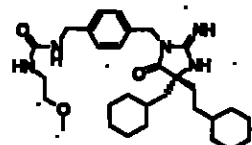
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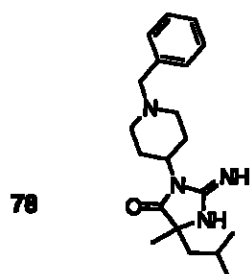
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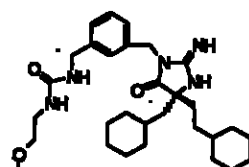
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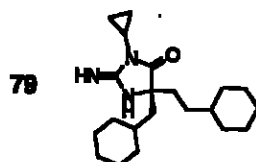
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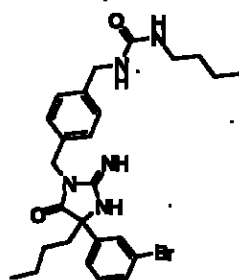
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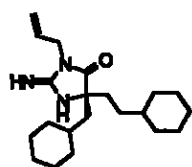


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- 49 -

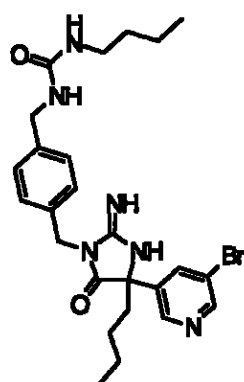


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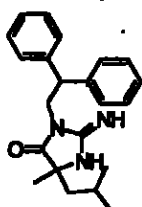
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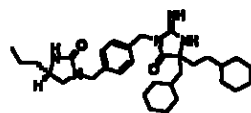


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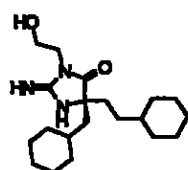
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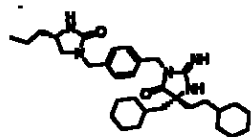


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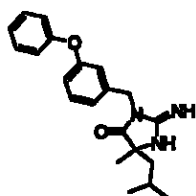
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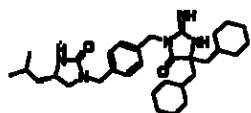


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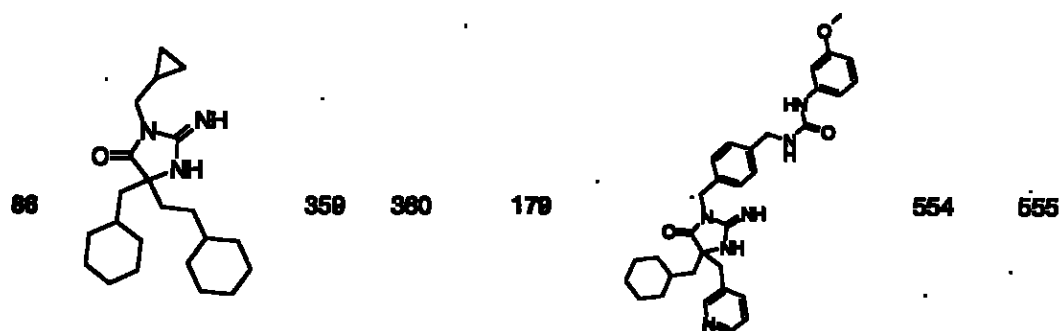
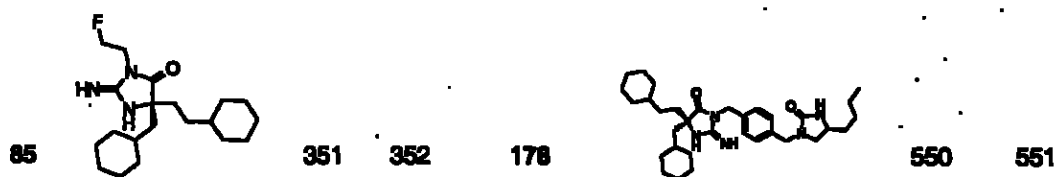
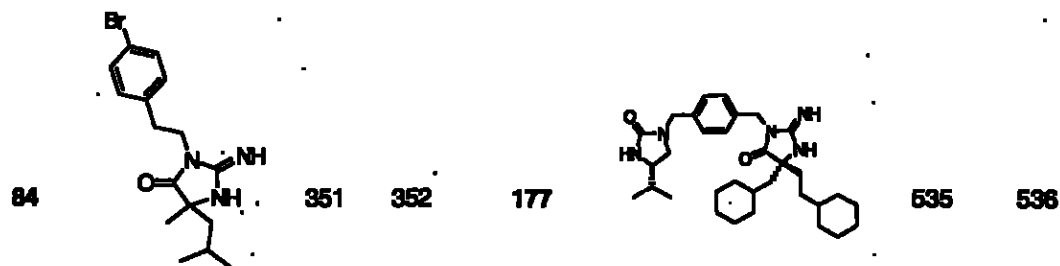


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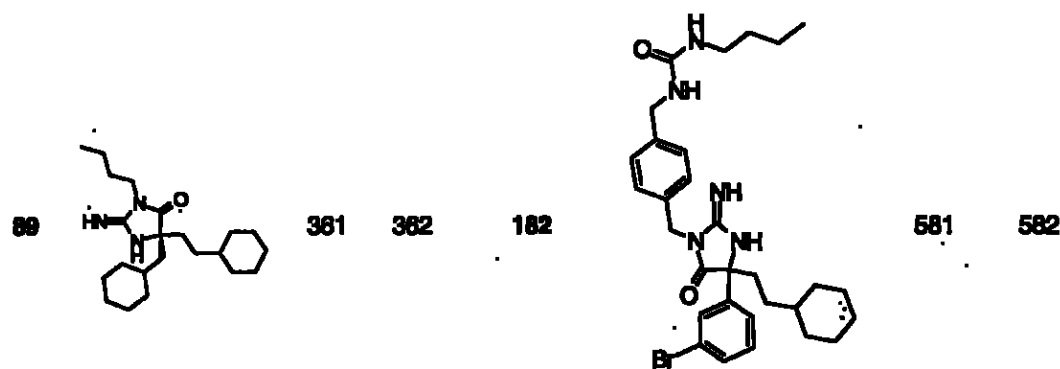
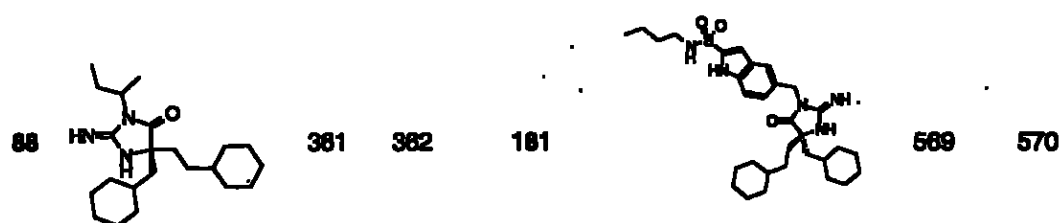
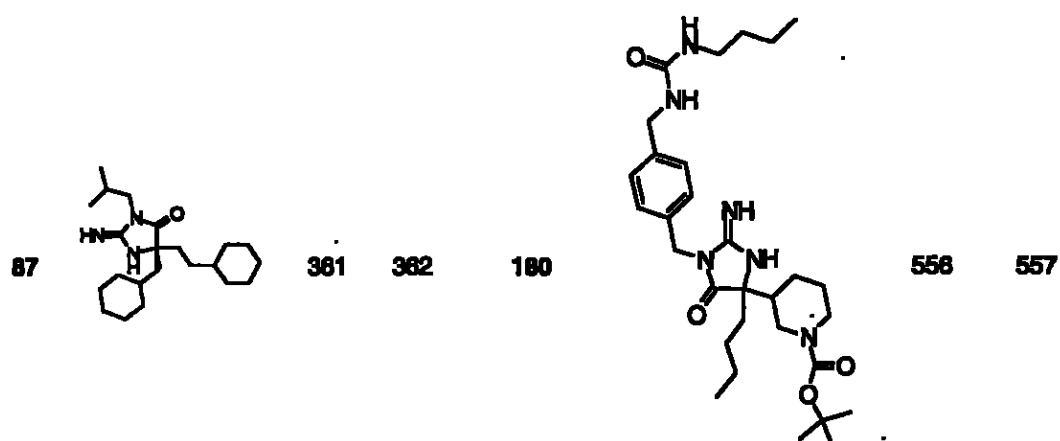
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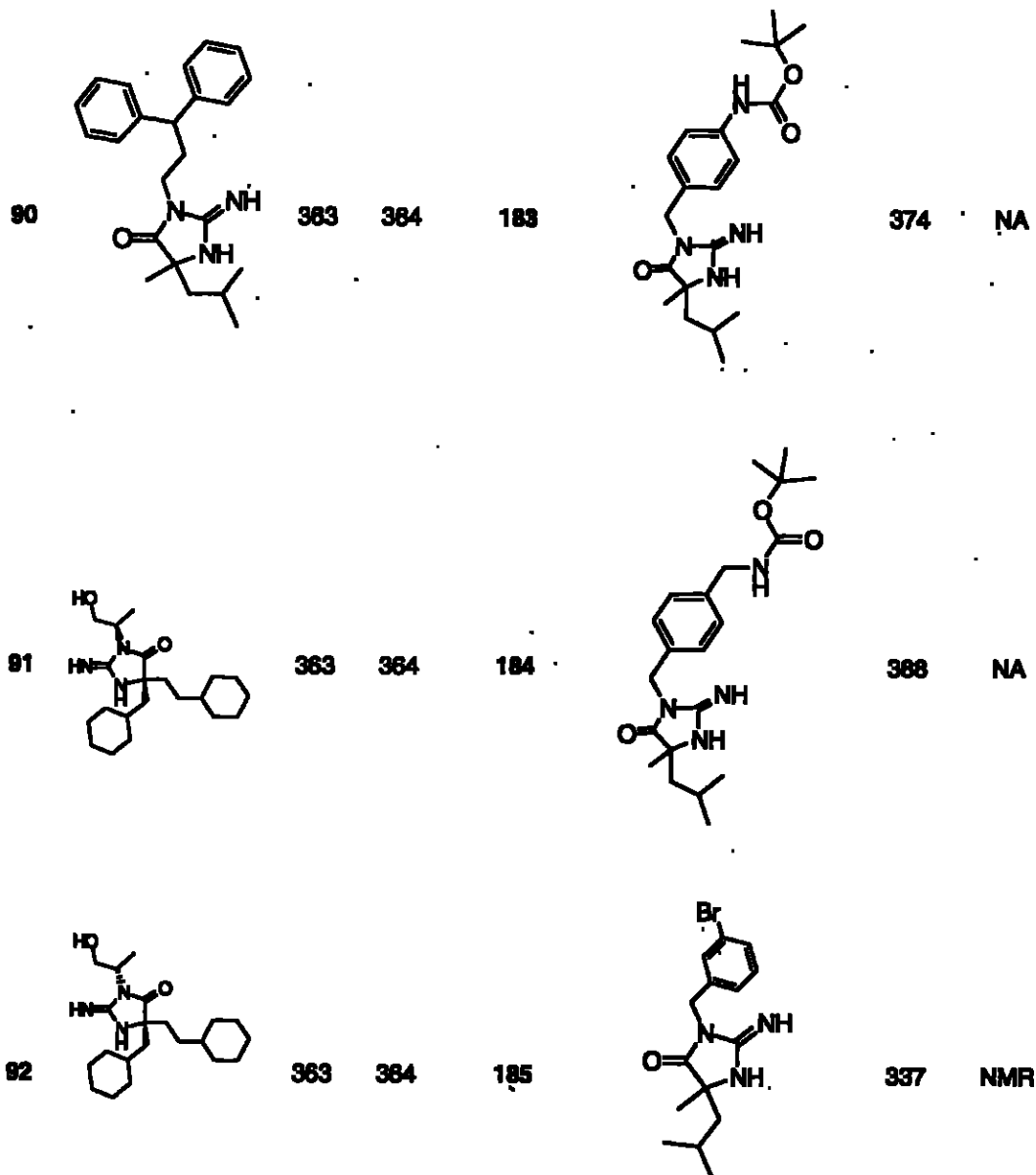


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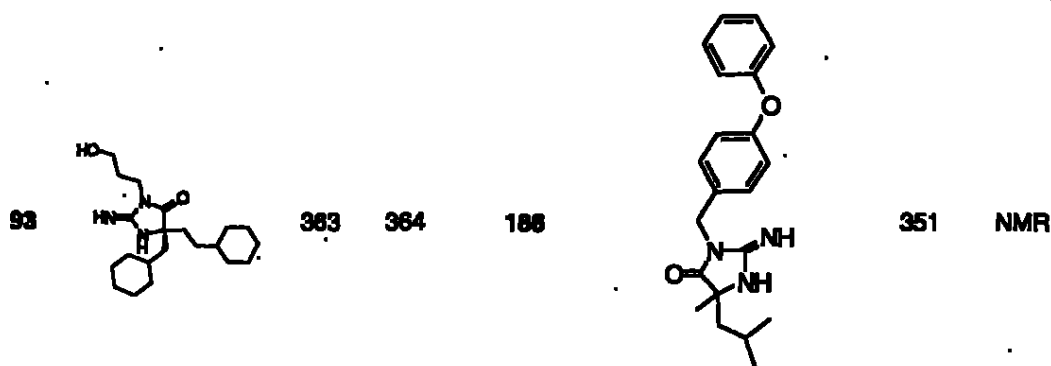
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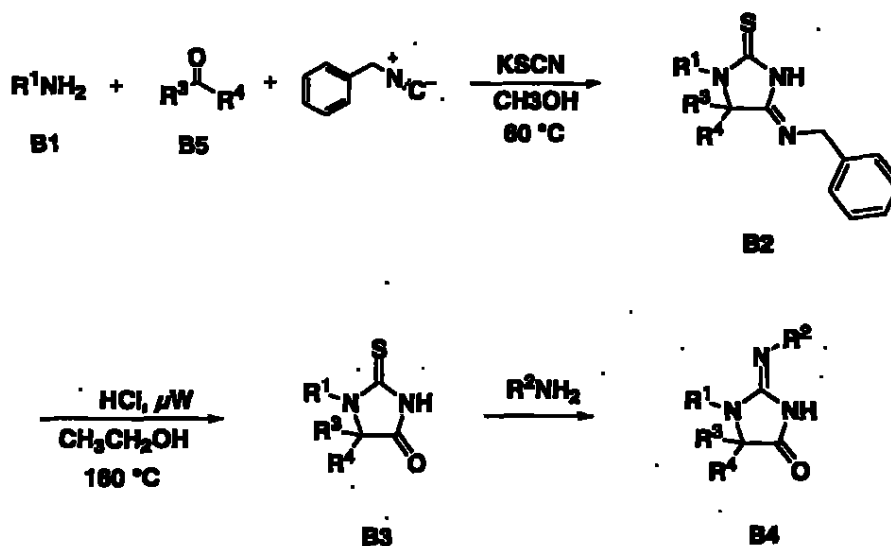


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Method B



5 A modified literature procedure was used (Ugi, I. *Angew. Chem.* 1962, 74 9-22).

Method B, Step 1:

To a solution of B1 (HCl salt, R¹ = 3-chlorophenethyl) (1.1 g, 5.73 mmol) in anhydrous CH₃OH (15 mL) was added potassium thiocyanate (0.56 g, 5.73 mmol). The reaction mixture was heated to 80 °C for 1 h. The suspension was filtered and the filtrate was added to B5 (R³=Me, R⁴=ⁱBu) (0.72 mL, 5.73 mmol) and benzyl isocyanide (0.77 mL, 6.3 mmol). The mixture was stirred overnight before the solution was concentrated and the residue was purified via flash

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- 54 -

chromatography eluting with ethyl acetate in hexane to yield 0.28 g of B2 ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, and $R^1 = 3\text{-Chlorophenethyl}$).

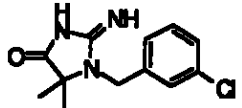
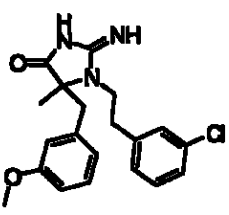
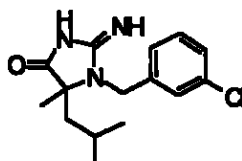
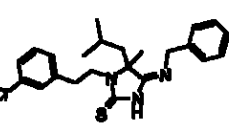
Method B, Step 2:

- 5 A solution of 40% concentrated HCl in $\text{CH}_3\text{CH}_2\text{OH}$ was added to B2 ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, and $R^1 = 3\text{-Chlorophenethyl}$) and the solution was heated in a microwave at 160 °C for 30 min. The solution was concentrated and purified via reverse phase preparative HPLC eluting with a $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (with 0.1% formic acid) gradient to afford B3 ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, and $R^1 =$
10 3-Chlorophenethyl).

Method B, Step 3:

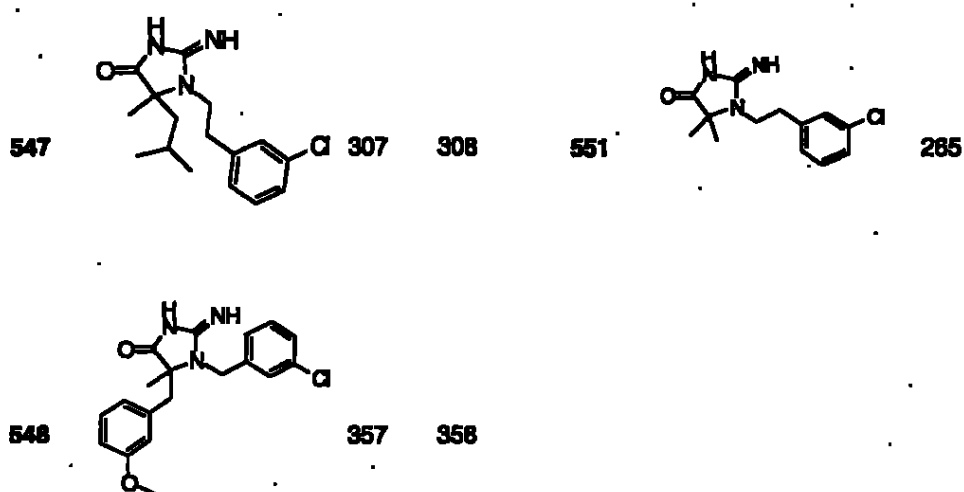
- Compound B4 ($R^2 = \text{H}$, $R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, and $R^1 = 3\text{-Chlorophenethyl}$) was prepared from B3 ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, and $R^1 =$
15 3-Chlorophenethyl) following a procedure similar to Method A, Step 3.
NMR(CD_3OD): δ 8.1, br, 1H; δ 7.35, s, 1H; δ 7.25, m, 3H; δ 3.6, m, 1H; δ 3.4, m, 1 H; δ 3.0, m, 1H; δ 2.8, m, 1 H; δ 1.75, m, 1H; δ 1.6, m, 1H; δ 1.35, m, 1H; δ 1.2 s, 3H; δ 0.8, m, 6H. ES_LCMS (m/e): 308.1

- 20 The following compounds were prepared using similar methods

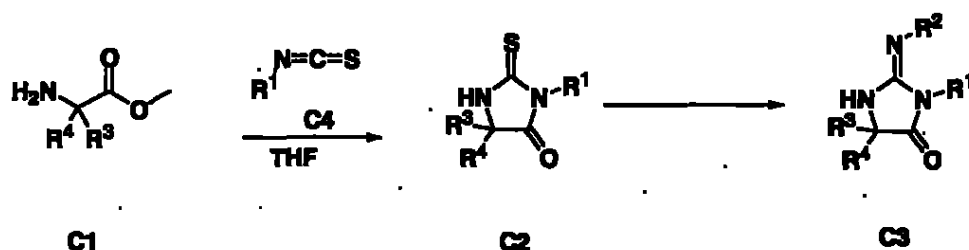
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
545		251	252	549		371	372
546		283	284	550		413	

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- 55 -



Method C



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Method C, Step 1:

A solution of C1 ($R^3 = R^4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) (50 mg, 0.25 mmol) and C4 ($R^1 = 3\text{-chlorophenyl}$) (38 μL , 0.26 mmol) was refluxed overnight. Trisamine resin (2 eq) and polystyrene isocyanate resin (2 eq) was added and the mixture was agitated. After 3 h, the suspension was filtered and the resin was washed with CH_2Cl_2 (3x) and CH_3OH (3x). The filtrate was concentrated to afford C2 ($R^1 = 3\text{-Cl-C}_6\text{H}_4$, $R^3 = R^4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) (60 mg, 68%).

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Method C, Step 2:

Compound C3 ($R^1 = 3\text{-Cl-C}_6\text{H}_4$, $R^2 = \text{H}$, $R^3 = R^4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) was prepared from C2 ($R^1 = 3\text{-Cl-C}_6\text{H}_4$, $R^3 = R^4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) following a

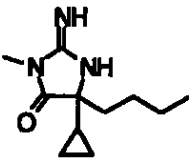
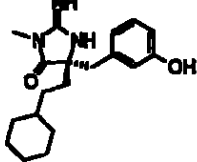
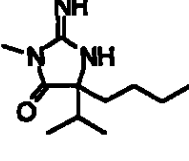
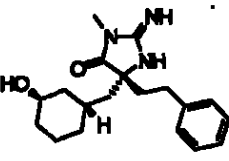
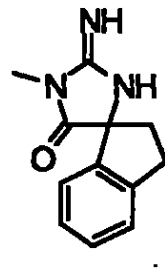
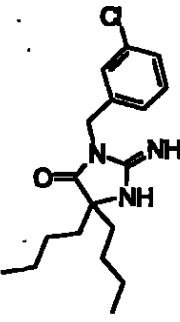
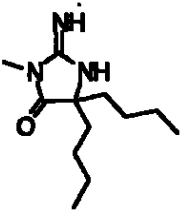
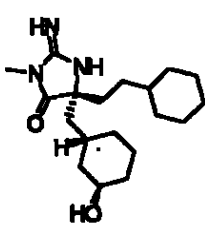
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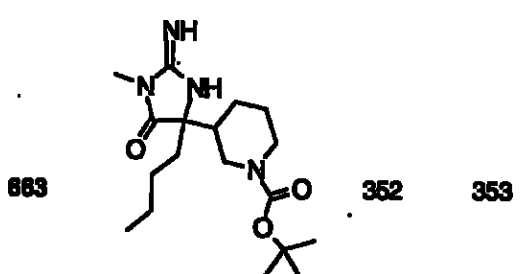
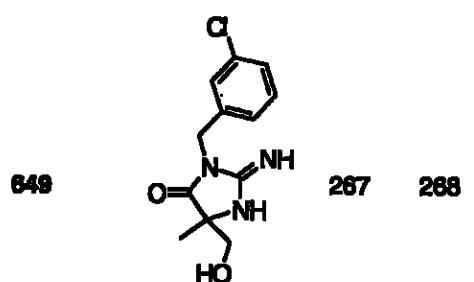
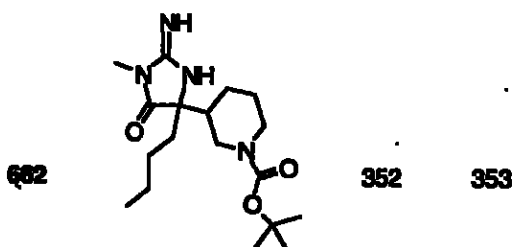
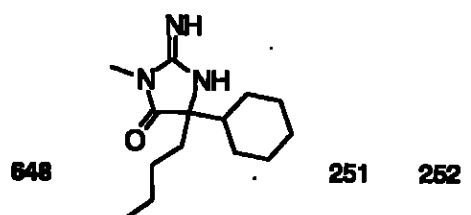
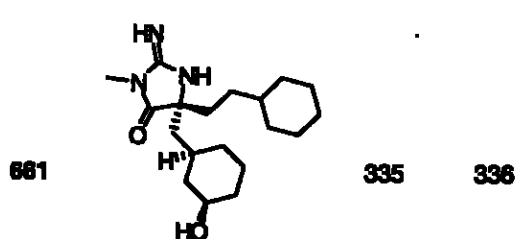
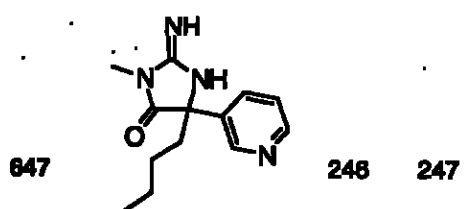
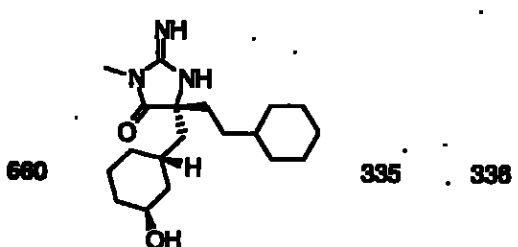
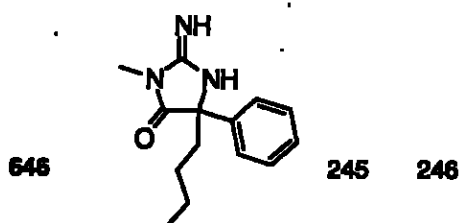
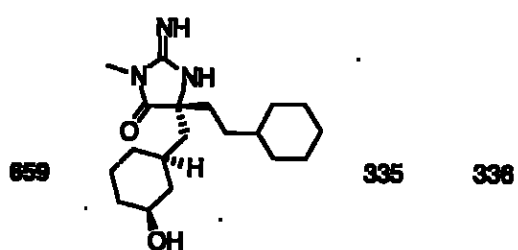
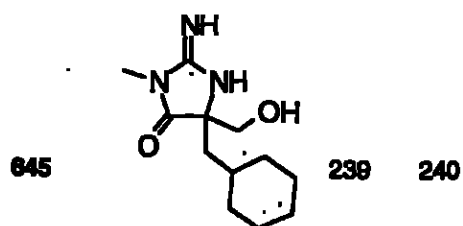
procedure similar to Method A, Step 3. NMR(CDCl₃): δ 7.4, m, 2H; δ 7.2, m, 2H; δ 5.0, s, 2H; δ 1.7, m, 4H; δ 1.1, m, 8H; δ 0.7, m, 6H. ES-LCMS (m/e): 336.1.

The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
641		209	210	655		329	330
642		211	212	656		329	330
643		215	216	657		335	336
644		225	228	658		335	336

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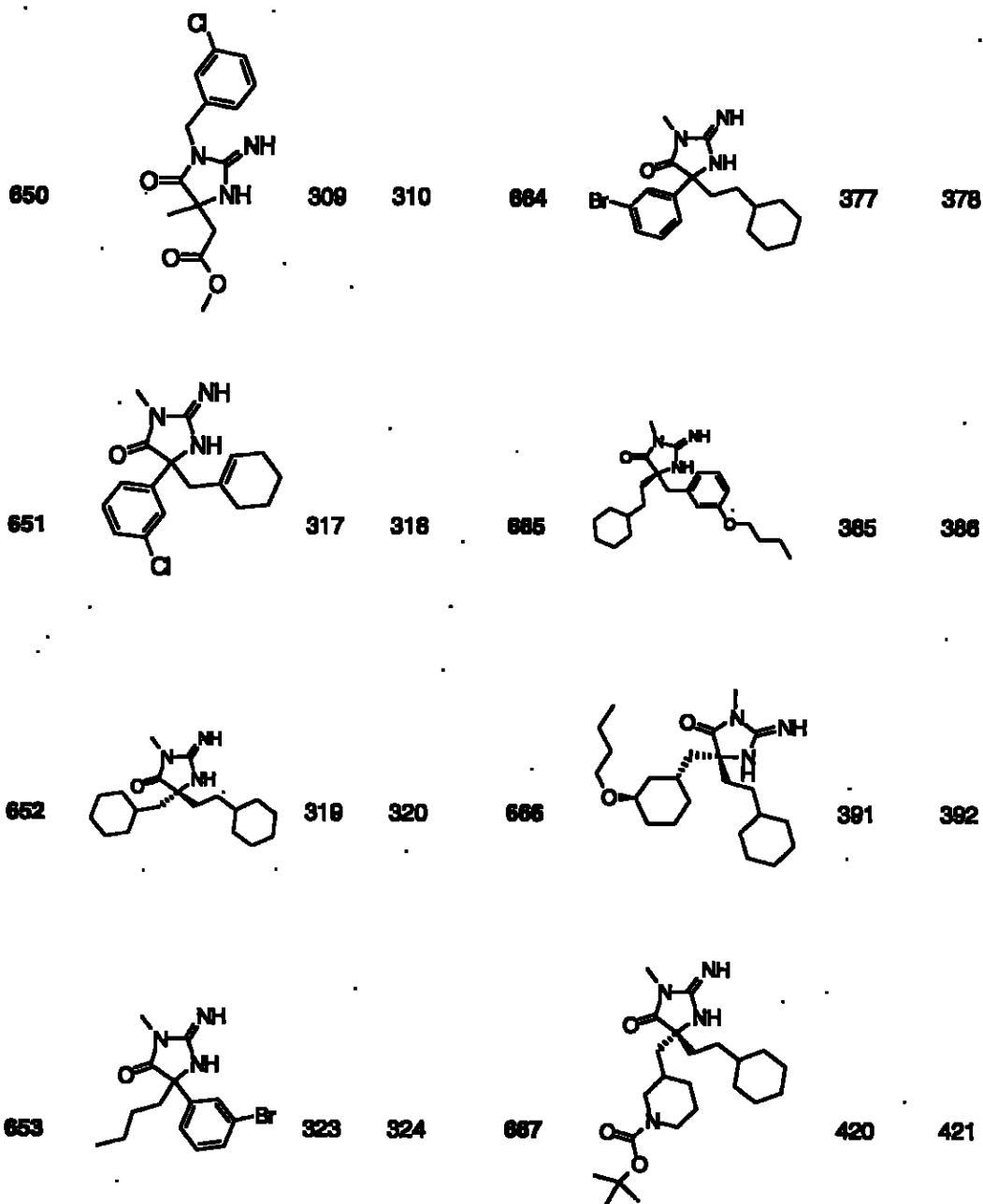
- 57 -

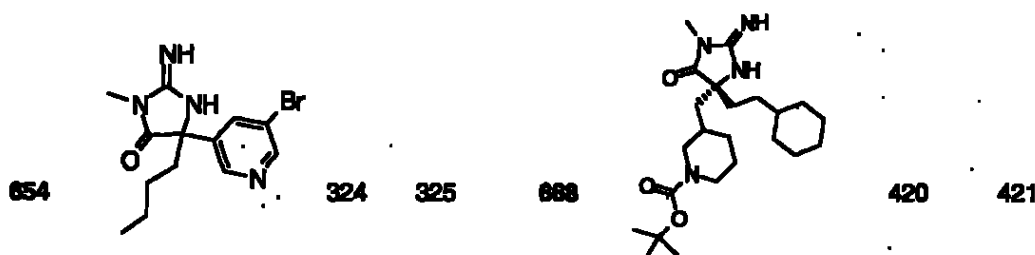


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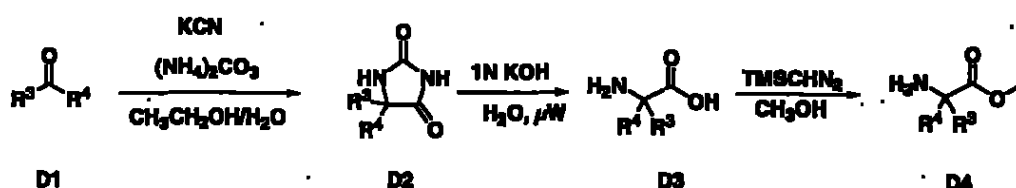
73

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Method D



Method D, Step 1:

A mixture of D1 ($R^3 = R^4 = \text{CH}_2\text{C}_6\text{H}_5$) (20 g), potassium cyanide (40 g) and ammonium carbonate (15 g) in ethanol (100 mL) and H_2O (200 mL) was heated in a sealed flask at 130 °C overnight to yield 25 g of D2 ($R^3 = R^4 = \text{CH}_2\text{C}_6\text{H}_5$) after filtration followed by washing with water.

Method D, Step 2:

A solution of 2 N KOH (3eq) was added to D2 ($R^3 = R^4 = \text{CH}_2\text{C}_6\text{H}_5$) (1 eq) and irradiated via microwave at 185 °C for 3h followed by addition of concentrated HCl to the solution until a pH = 2–3 was obtained. The solid was filtered and washed with water to afford D3 ($R^3 = R^4 = \text{CH}_2\text{C}_6\text{H}_5$).

Method D, Step 3:

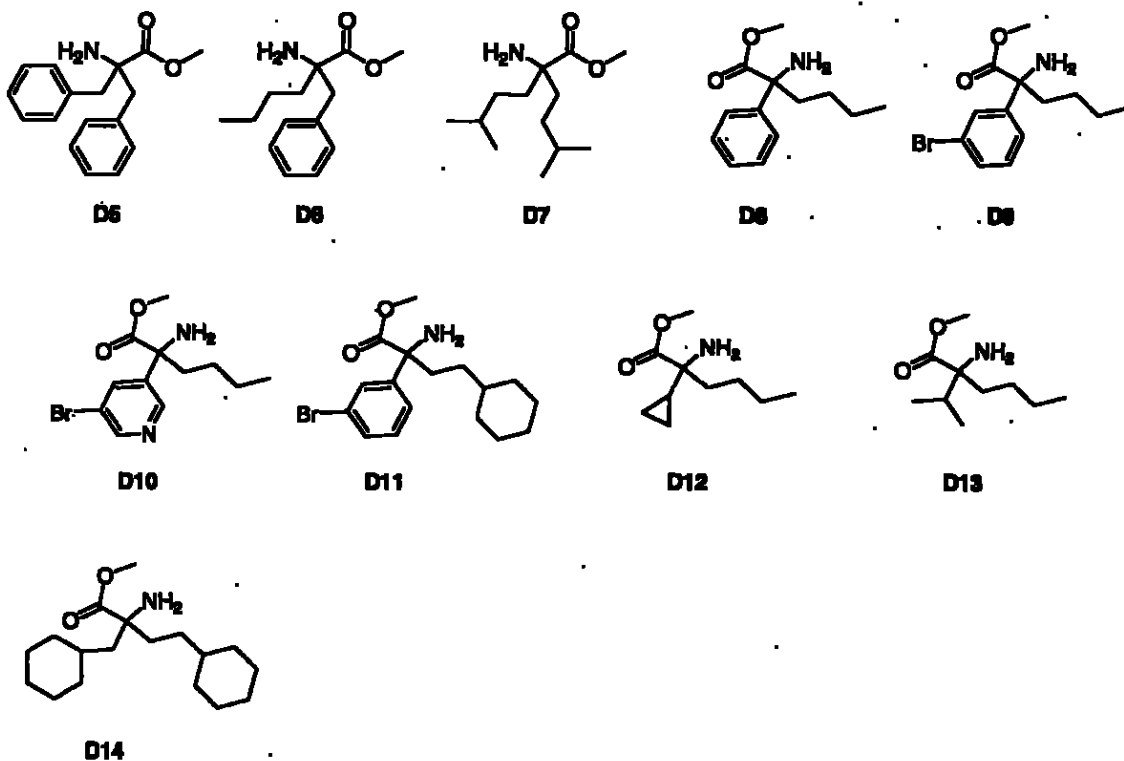
A solution of trimethylsilyldiazomethane in hexane (2 N) (2 eq) was added drop wise to a solution of D3 ($R^3 = R^4 = \text{CH}_2\text{C}_6\text{H}_5$) (1 eq) in anhydrous CH_3OH (30 mL). After 1 h, an additional 2 eq of trimethylsilyldiazomethane in hexane (2 N) was added and the reaction was stirred for 20 minutes before it was concentrated. The residue was dissolved in a 0.2 N HCl solution (25 mL) and

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- 60 -

washed with ether (3x). A saturated solution of Na_2CO_3 was added to the aqueous phase until the pH of the solution was basic. The solution was extracted with ethyl acetate (3x). The organic extracts were combined, dried over Na_2SO_4 , and concentrated to afford D4 ($\text{R}^3 = \text{R}^4 = \text{CH}_2\text{C}_6\text{H}_5$).

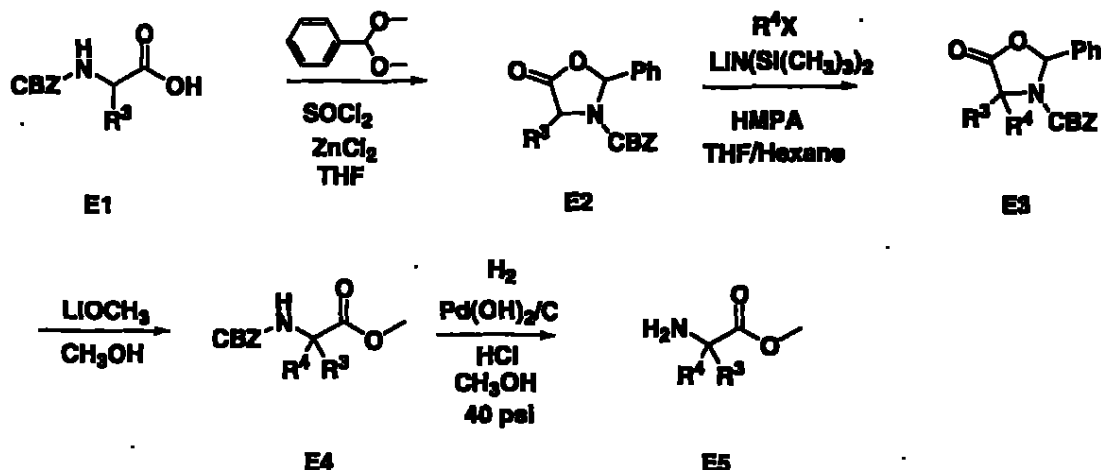
5 The following amino esters were prepared using a similar method.



Method E

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**Method E, Step 1:**

- 5 Thionyl chloride (0.47, 6.38 mmol) was added drop wise to a solution of E1 (R³ = CH₂CH₂C₆H₅) (2g, 6.38 mmol) and benzaldehyde dimethyl acetal (0.96 mL, 6.38 mmol) in anhydrous THF at 0 °C under N₂. After 5 min, ZnCl₂ (0.87 g, 6.38 mmol) was added and the reaction mixture was stirred at 0 °C. After 3 h, an additional amount of ZnCl₂ (0.18 g, 1.28 mmol) and thionyl chloride (0.1 mL, 1.28 mmol) were added and stirred for 1 h at 0 °C. The reaction mixture was
- 10 poured into a stirred suspension of ice/H₂O. The mixture was stirred occasionally until the ice melted. The aqueous solution was extracted with ether (3x). The combined organic extracts were washed with H₂O (3x), a sat. aqueous solution of NaHCO₃ (1x), and H₂O (2x). The organic solution was dried over
- 15 Na₂SO₄, filtered and concentrated. The crude material was purified via flash chromatography eluting with ethyl acetate in hexane to yield compound E2 (R³ = CH₂CH₂C₆H₅).

Method E, Step 2:

- 20 A solution of lithium hexamethyldisilazide in hexane (1.0 M, 1.65 mL, 1.64 mmol) was added drop wise to a solution of E2 (R³ = CH₂CH₂C₆H₅) (600 mg, 1.49 mmol) and HMPA (0.85 mL) in THF (6.5 mL) cooled at -78 °C under N₂. After 15 min, isobutyl iodide (0.52 mL, 4.48 mmol) was added drop wise and the reaction mixture was stirred at -78 °C for 3 h. The reaction was warmed to -65
- 25 °C, stirred for 2 h and warmed to rt overnight. The reaction solution was poured

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- 62 -

into a mixture of sat. NaHCO_3 (aq)/ether/ice. The aqueous layer was extracted with ether (3x). The organic extracts were combined and washed with brine (2x). The organic solution was dried over Na_2SO_4 , filtered and concentrated. The crude material was purified via flash chromatography eluting with ethyl acetate in hexane to yield compound E3 ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$).

Method E, Step 3:

A solution of lithium methoxide (1 N in CH_3OH) (0.36 mL, 0.36 mmol) was added to compound E3 ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$). The reaction mixture was shaken at rt for 50 min. An additional 0.55 eq of lithium methoxide were added. After 2.5 h, a sat. aqueous solution of NaHSO_3 (0.75 mL) and ethyl acetate (3 mL) was added to the reaction mixture and shaken for 15 min. The suspension was filtered. The resulting white solid was washed with a sat. aqueous solution of NaHSO_3 (1x) and ethyl acetate (1x). The aqueous phase of the filtrate was separated and extracted with ethyl acetate (2x). The organic extracts were combined and washed with a sat. aqueous solution of NaHSO_3 (8x). The organic solution was dried over Na_2SO_4 , filtered and concentrated to afford E4 ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (109 mg, 87%).

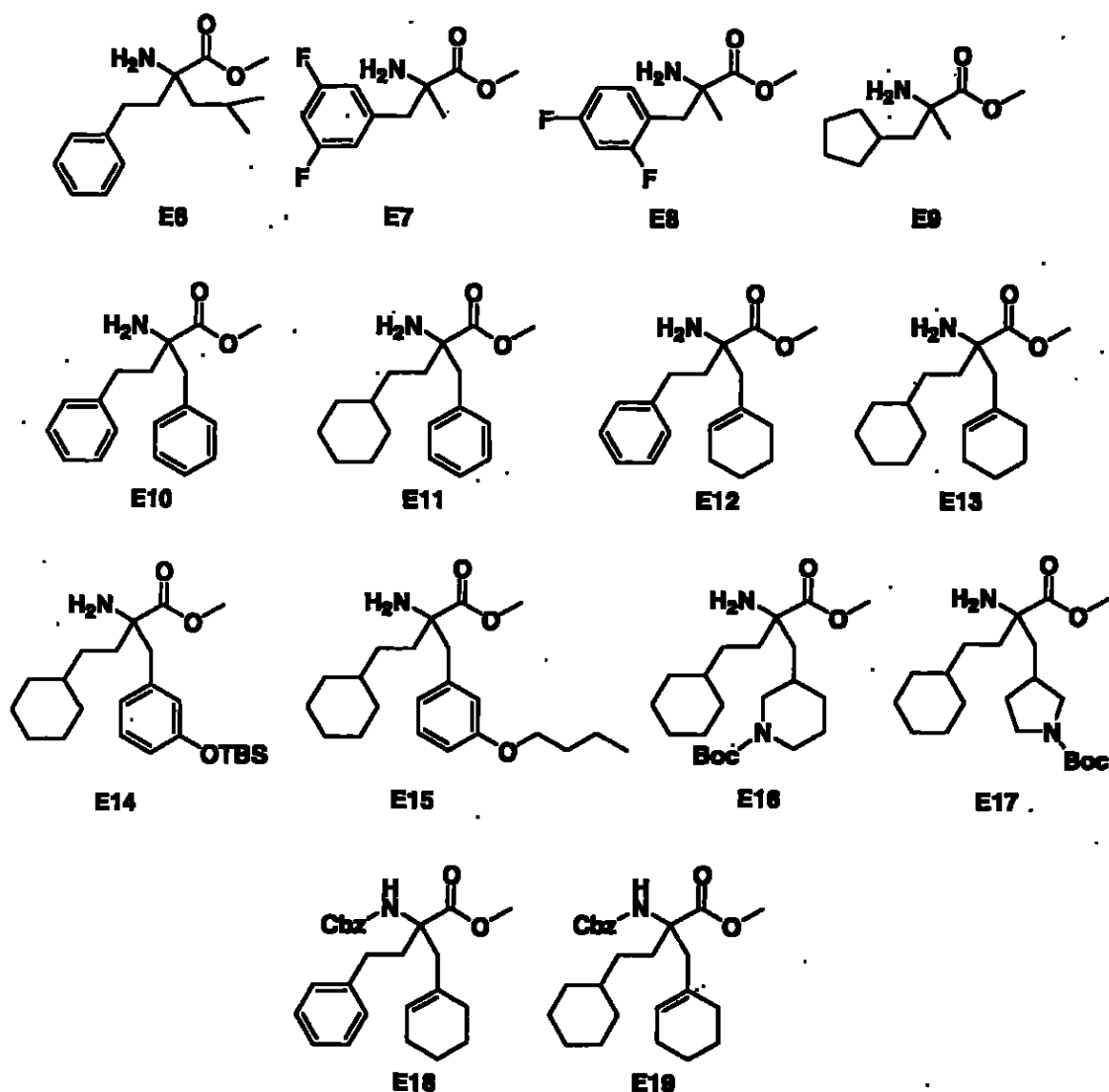
Method E, Step 4:

To a solution of E4 ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (109 mg, 0.28 mmol) in CH_3OH (4 mL) was added 1 N HCl (0.28 mL, 0.28 mmol) and 20% palladium hydroxide on carbon (22 mg). The reaction mixture was hydrogenated at 40 psi. After 2.5 h, the reaction was filtered and the catalyst was washed with CH_3OH (3x). The filtrate was concentrated to afford E5 ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (78 mg, 96%).

The following aminoesters were prepared using similar method.

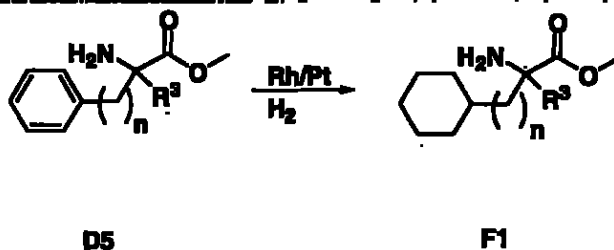
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- 63 -



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Method F

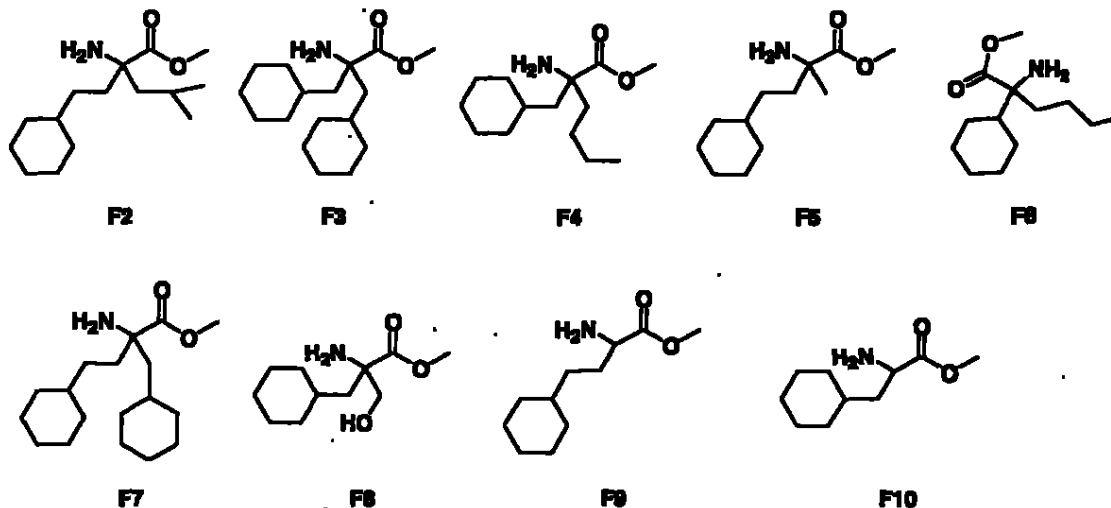


A 500 mL methanol solution of 20 g of D5 (R^3 = benzyl, n = 1) with 1.5 eq of HCl was hydrogenated with 1 g of Rh/C (5% w/w) and 2 g of Pt/C (5% w/w) at 60 psi for 2 days. The solid was filtered and washed with excessive methanol.

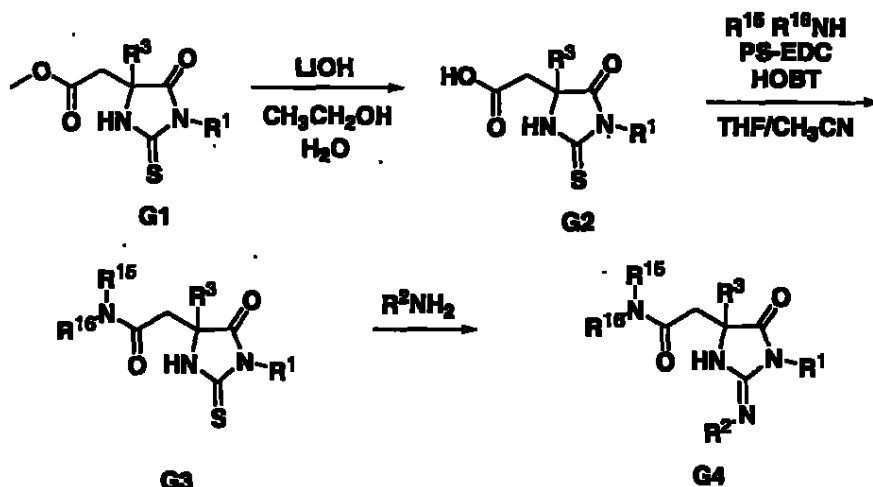
The combined solution was evaporated to give 20 g of F1 ($R^3 =$ cyclohexylmethyl, $n = 1$) as HCl salt.

The following amino esters were examples prepared using similar method.

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Method G



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Method G, Step 1:

To a solution of G1 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$ and $R^3 = \text{CH}_3$) (400 mg, 1.23 mmol, generated following a procedure similar to Method C, Step 1) in ethanol (5 mL) was added lithium hydroxide monohydrate (100 mg, 2.45 mmol) in H_2O (0.5

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- 65 -

5 mL). After 2.5 h, another portion of lithium hydroxide monohydrate (100 mg, 2.45 mmol) was added. After 5.5 h, the reaction mixture was diluted with H₂O (15 mL) and extracted with ether (2x). A solution of 30% HCl was added to the aqueous phase until its pH = 1 to 2. The solution was saturated with NaCl and extracted with ethyl acetate (3x). The organic solution was dried over Na₂SO₄, filtered and concentrated to afford G2 (R¹ = CH₂(3-ClC₆H₄) and R³ = CH₃) (357 mg, 93%).

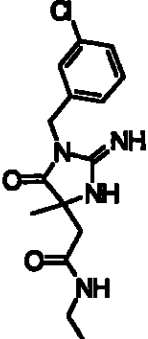
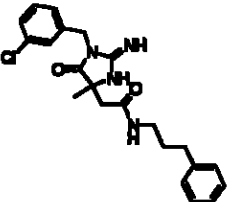
Method G, Step 2:

10 A solution of benzyl amine (1.2 eq) was added to G2 (R¹ = CH₂(3-ClC₆H₄) and R³ = CH₃) (1 eq), HOBT (1.5 eq) and polystyrene EDC resin (94 mg, 1.53 mmol/g, 3eq) in 1:1 THF:CH₃CN (1 mL). The reaction mixture was shaken overnight at rt. Trisamine resin (85 mg, 3.38 mmol/g, 6 eq) and isocyanate resin (100 mg, 1.47 mmol/g, 3 eq) was added. After 6 h, the suspension was filtered and the filtrate was concentrated to afford G3 (R¹ = CH₂(3-ClC₆H₄), R³ = CH₃, R¹⁵ = CH₂C₆H₅ and R¹⁸ = H).

Method G, Step 3:

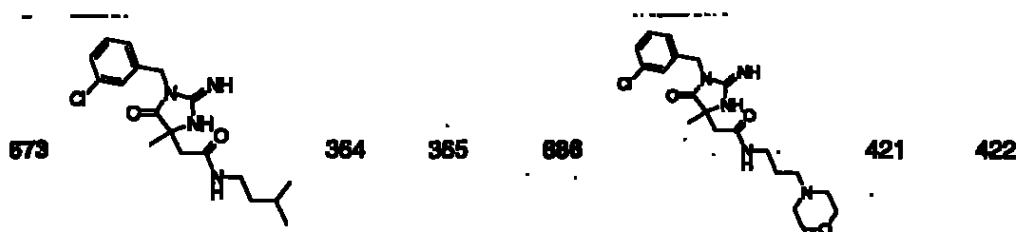
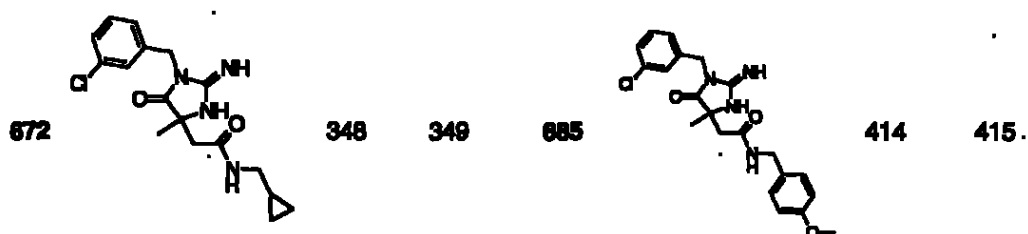
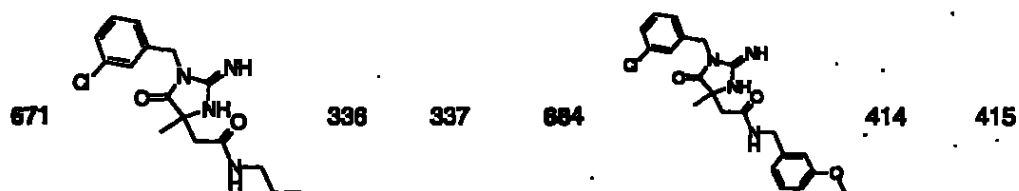
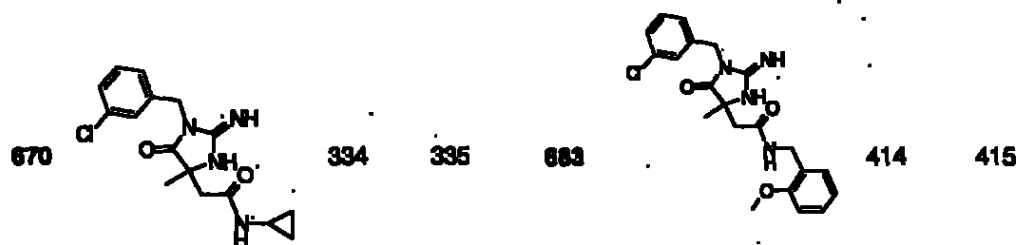
20 Compound G4 (R¹ = CH₂(3-ClC₆H₄), R² = H, R₃ = CH₃, R¹⁵ = CH₂C₆H₅ and R¹⁸ = H) was prepared from G3 (R¹ = CH₂(3-ClC₆H₄), R³ = CH₃, R¹⁵ = CH₂C₆H₅ and R¹⁸ = H) following a procedure similar to Method A, Step 3.

The following compounds were prepared using similar methods.

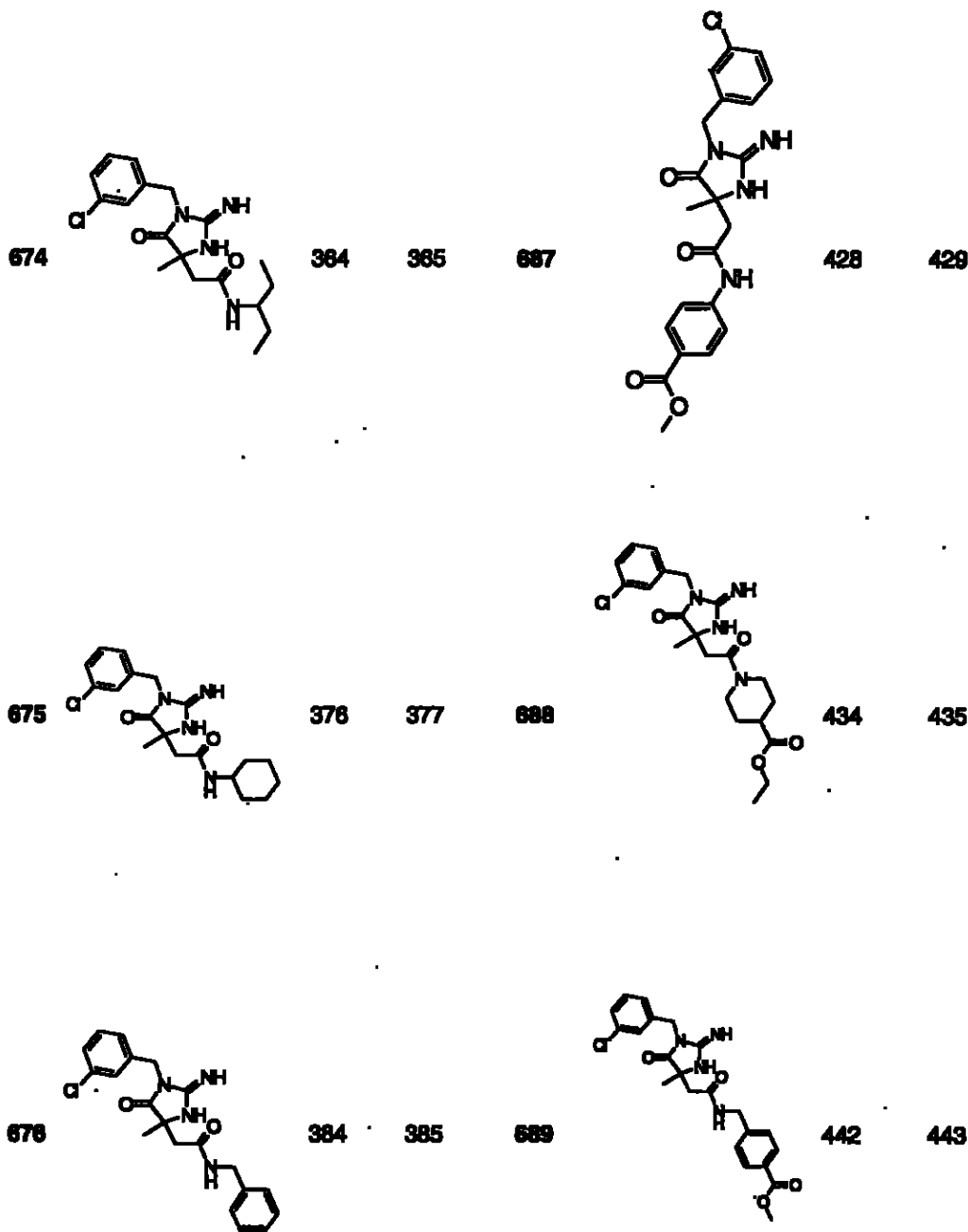
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669		322	323	682		412	413

82
Et

- 68 -

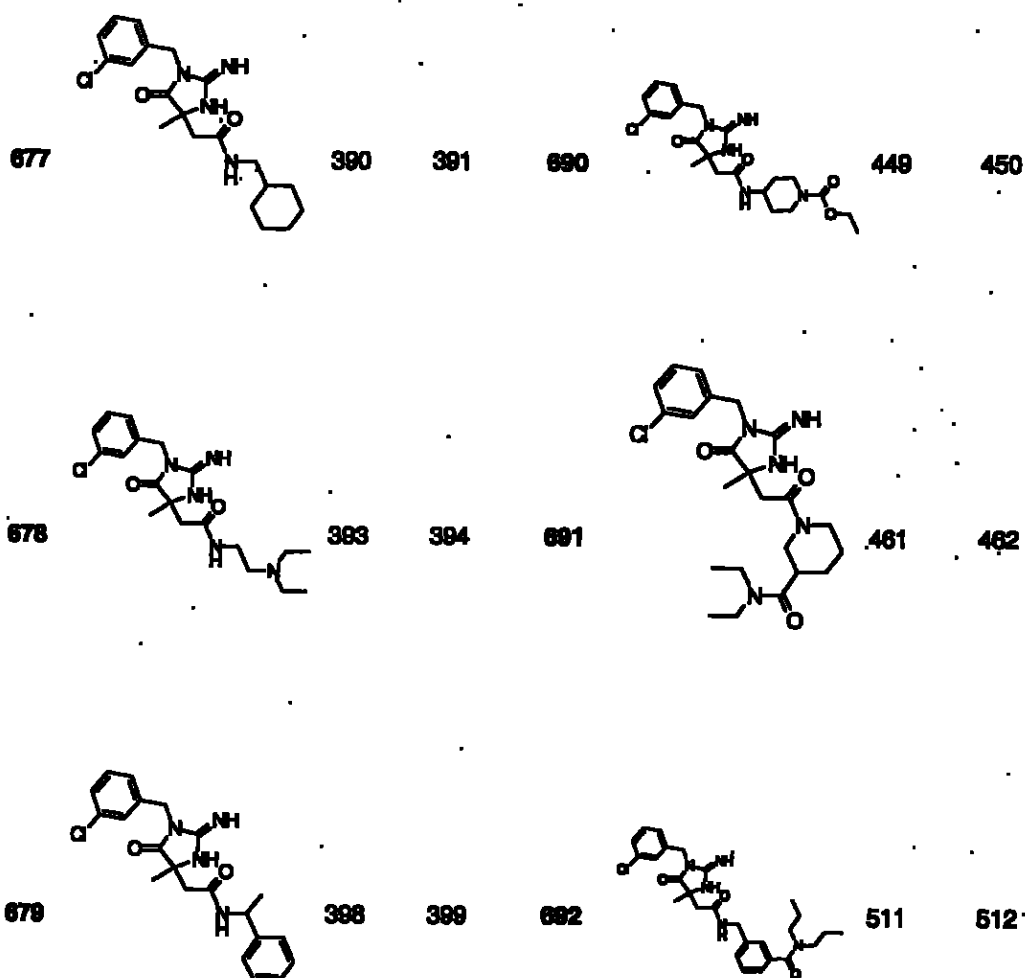


83
82



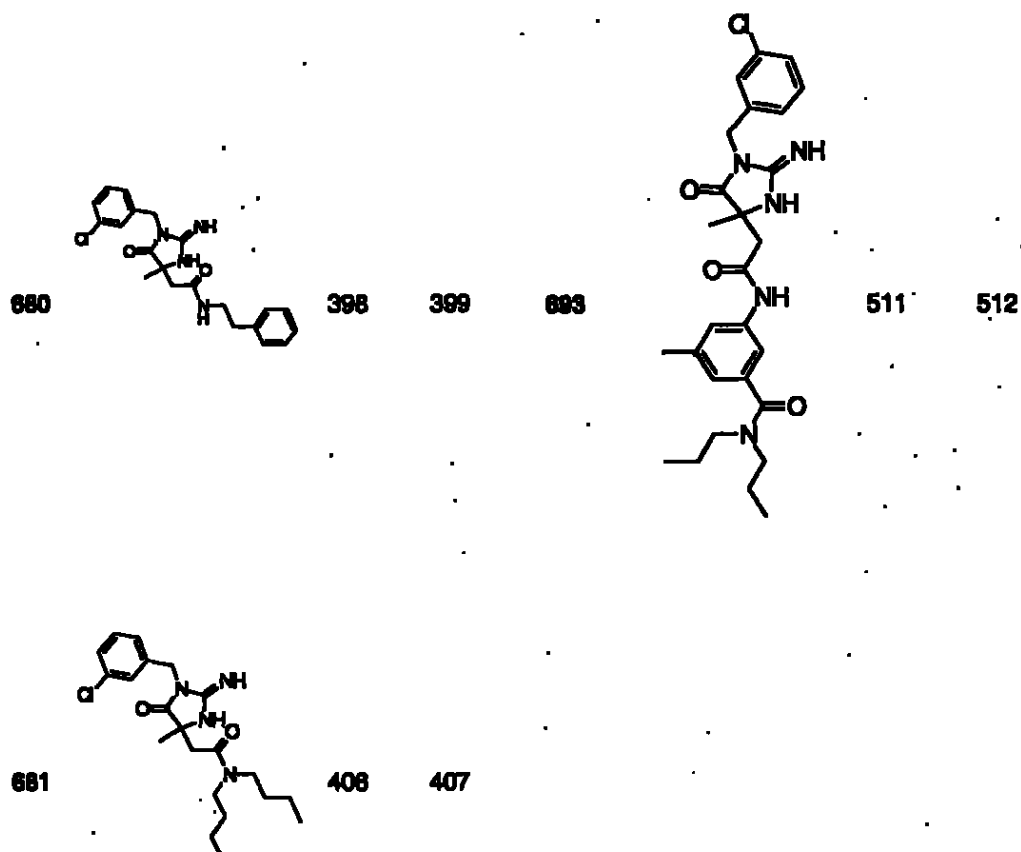
84
83

- 68 -

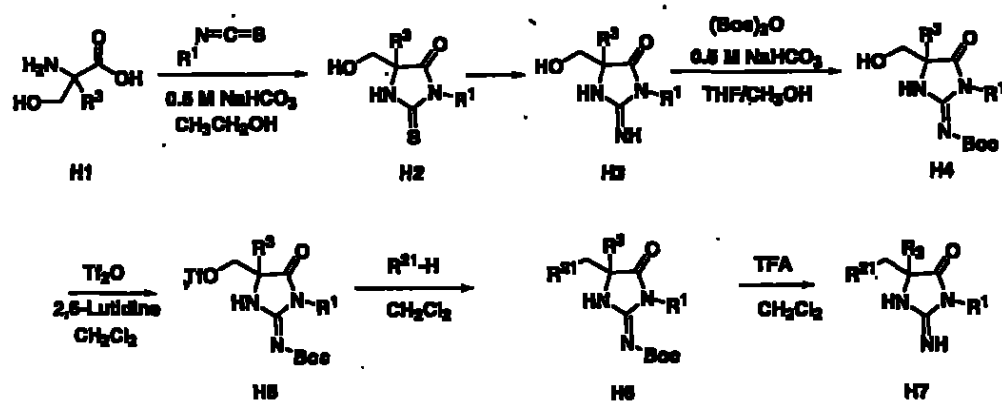


85
84

- 69 -



Method H



5

Method H, Step 1:

To a solution of H1 ($\text{R}^3 = \text{CH}_3$) (5 g, 39 mmol) in a 1:1 mixture of 0.5 M NaHCO_3 : $\text{CH}_3\text{CH}_2\text{OH}$ was added $\text{R}^1\text{-NCS}$ ($\text{R}^1 = 3\text{-chlorobenzyl}$) (11.5 mL, 78

86
85

- 70 -

mmol). The reaction mixture was heated at 50 °C overnight. The reaction was cooled and diluted with water. The aqueous phase was extracted with ethyl acetate (5x). The organic extracts were combined, washed with water (2x) and dried over Na₂SO₄. The solution was filtered and solvent was removed to give a small volume of solution. Hexane was added and the resulting suspension was filtered to yield 6.8 g of a solid H2 (R³ = CH₃, R¹ = CH₂(3-ClC₆H₄)) (61%).

Method H, Step 2:

Compound H3 (R³ = CH₃, R¹ = CH₂(3-ClC₆H₄)) was synthesized from H2 (R³ = CH₃, R¹ = CH₂(3-ClC₆H₄)) following a procedure similar to Method A, Step 3.

Method H, Step 3:

To a solution of crude H3 (R³ = CH₃, R¹ = CH₂(3-ClC₆H₄)) (14 mmol) in a 1:3 mixture of CH₃OH:THF was added 0.5 M NaHCO₃ in H₂O (28 mL, 14 mmol) and di-*tert*-butyl dicarbonate (3.69 g, 16.9 mmol). The reaction was stirred at rt for 2.5 h and then stored at -10 °C overnight. The reaction was diluted with brine and extracted with ethyl acetate (4x). The organic extracts were combined and washed with brine (1x). The organic solution was dried over Na₂SO₄, filtered and concentrated. The crude material was purified via flash chromatography eluting with ethyl acetate in hexane to afford 1.5 g of H4 (R¹ = CH₂(3-ClC₆H₄) and R³ = CH₃).

Method H, Step 4:

A solution of triflic anhydride (128 µL, 0.76 mmol) in CH₂Cl₂ (5 mL) was added drop wise to a solution of H4 (R¹ = CH₂(3-ClC₆H₄) and R³ = CH₃) (200 mg, 0.55 mmol) and 2,6-lutidine (176 µL, 2.18 mmol) at -30 °C. The reaction mixture was stirred for 1.5 h. Water (10 mL) was added at -20 °C and the ice bath was removed. The reaction was stirred until it reached 0 °C. The organic layer was separated, dried over Na₂SO₄, filtered and concentrated to afford 310 mg of H5 (R¹ = CH₂(3-ClC₆H₄) and R³ = CH₃).

Method H, Step 5:

87
86

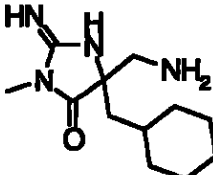
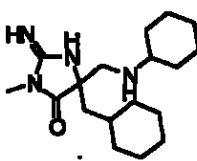
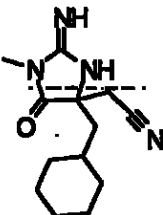
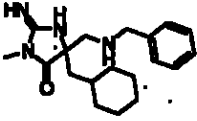
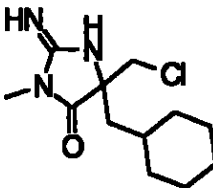
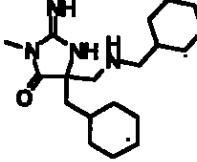
- 71 -

A solution of crude H5 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$ and $R^3 = \text{CH}_3$) (0.11 mmol) and 7N ammonia in-Methanol ($R^{21}\text{-H} = \text{NH}_2\text{-H}$) (10 eq) was stirred overnight at rt. The reaction solution was concentrated. The crude material was purified using reverse phase preparative HPLC eluting with a $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ gradient with 0.1% formic acid to yield H6 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{21} = \text{NH}_2$).

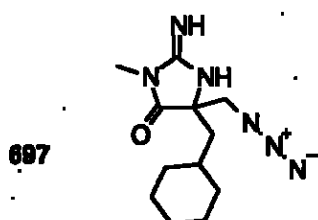
Method H, Step 6:

A solution of 50% trifluoroacetic acid in CH_2Cl_2 (2 mL) was added to H6 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{21} = \text{NH}_2$). After 40 min the solvent was evaporated and residue purified by preparative HPLC/LCMS eluting with a $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ gradient to afford H7 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{21} = \text{NH}_2$). NMR (CDCl_3), δ 7.45, m, 3H; δ 7.35, m, 1H; δ 4.9, m, 2H; δ 3.5, m, 2H; δ 1.65, s, 3H. ES_LCMS (m/e) 267.07.

The following compounds were prepared using similar methods.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
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695		248	249	703		328	329
696		257	258	704		334	335

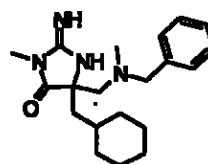
88
87



264

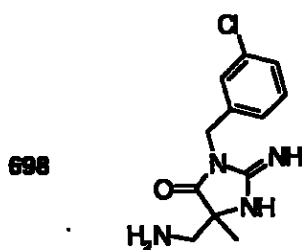
265

705



342

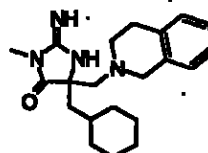
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266

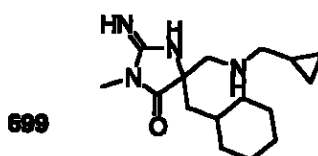
267

706



354

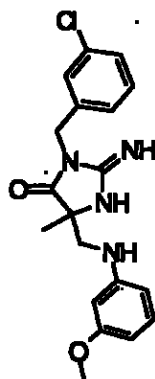
355



292

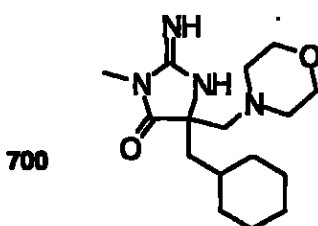
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707



372

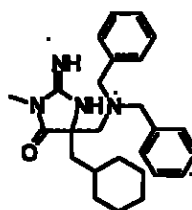
373



308

309

708

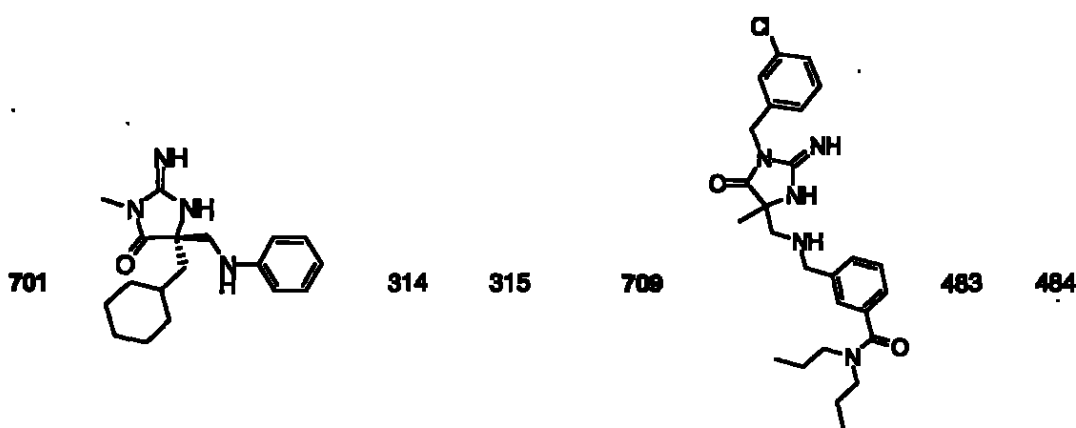


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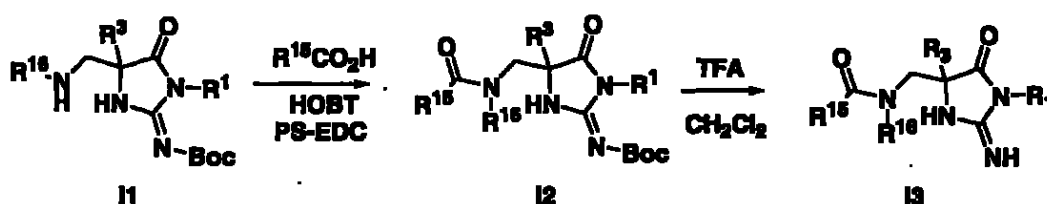
419

89
38

- 73 -



Method I



5 Method I, Step 1:

Diethylaminomethyl polystyrene resin (5 eq) was added to a solution of the formate salt of I1 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$ and $R^{16} = \text{H}$) in CH_2Cl_2 and the suspension was agitated. After 15 min, the mixture was filtered and the resin was washed with CH_2Cl_2 (4x). The filtrate was concentrated to afford the free base I1 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$ and $R^{16} = \text{H}$).

A solution of $R^{16}\text{COOH}$ ($R^{16} = \text{Phenethyl}$) (1.3 eq) was added to a mixture of EDC resin (41 mg, 1.53 mmol/g, 3eq), HOBT (1.5 eq), and the free base of I1 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$ and $R^{16} = \text{H}$) (0.021 mmol) in 1:1 $\text{CH}_3\text{CN}:\text{THF}$. The suspension was agitated overnight. Polystyrene isocyanate resin (45 mg, 3 eq), polystyrene trisamine resin (40 mg, 6 eq) and a 1:1 mixture of $\text{CH}_3\text{CN}:\text{THF}$ (0.5 mL) was added. The mixture was agitated for 6 h. The suspension was filtered and the filtrate was concentrated to afford I2 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{16} = \text{H}$ and $R^{15} = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$).

90
89

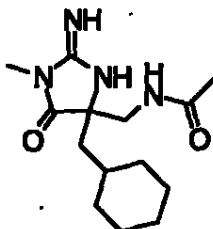
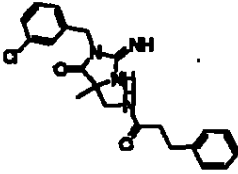
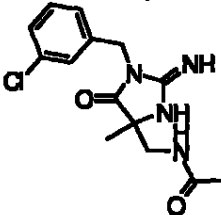
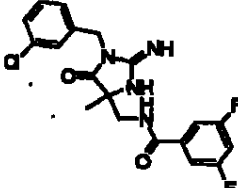
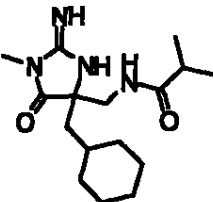
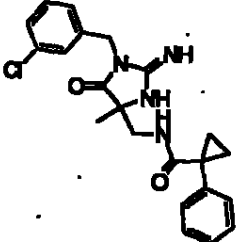
- 74 -

Method I, Step 2:

13 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{18} = \text{H}$ and $R^{15} = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$) was prepared from 12 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{18} = \text{H}$ and $R^{15} = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$) using method similar to method H step 6.

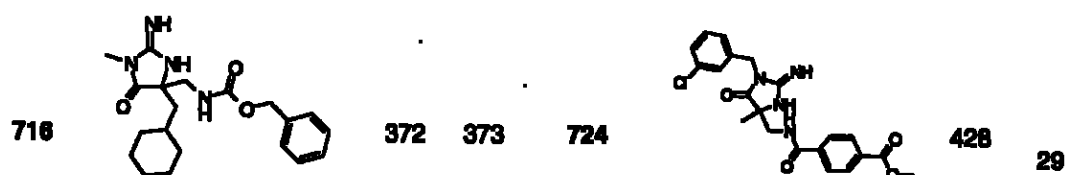
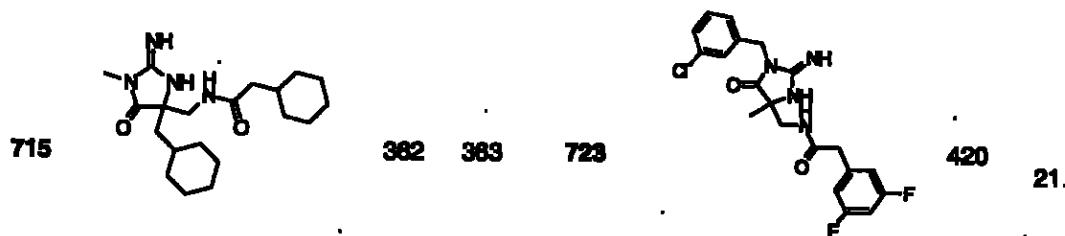
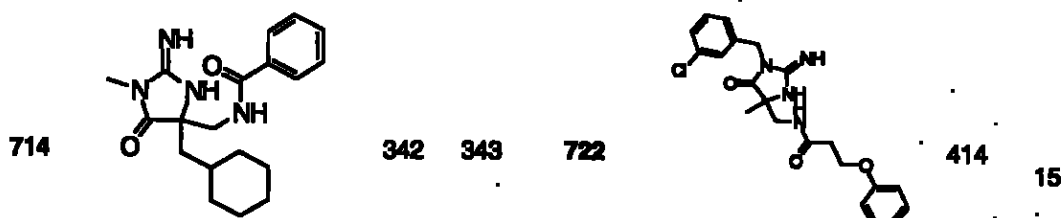
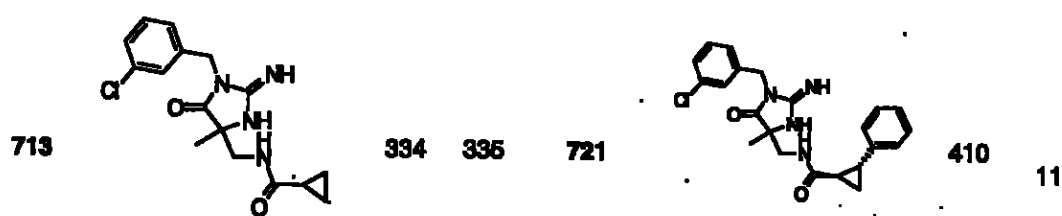
5

The following compounds were prepared using similar method.

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710		280	281	718		398	399
711		308	309	719		406	407
712		308	309	720		410	11

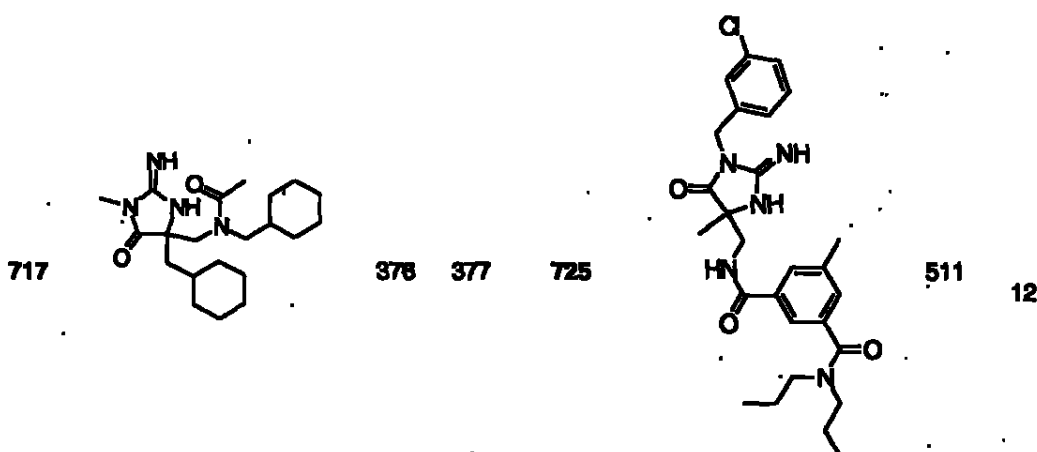
91
90

- 75 -

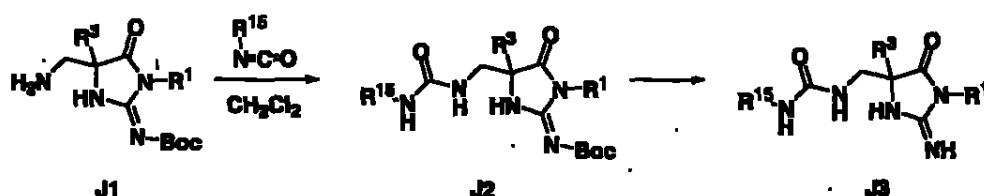


92
91

- 76 -



Method J



5

Method J, Step 1:

Diethylaminomethyl polystyrene resin (5 eq) was added to a solution of J1 (TFA salt, $R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$ and $R^3 = \text{CH}_3$) in CH_2Cl_2 and the suspension was agitated. After 15 min, the mixture was filtered and the resin was washed with CH_2Cl_2 (4x). The filtrate was concentrated to afford the free base. A solution of $R^{15}\text{NCO}$ ($R^{15} = \text{butyl}$) (2 eq) in CH_2Cl_2 was added to the free base of J1 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$ and $R^3 = \text{CH}_3$) (0.021 mmol) in 1:1 $\text{CH}_3\text{CN}:\text{THF}$. The suspension was agitated overnight. Polystyrene isocyanate resin (45 mg, 3 eq), polystyrene trisamine resin (40 mg, 6 eq) and a 1:1 mixture of $\text{CH}_3\text{CN}:\text{THF}$ (0.5 mL) was added. The mixture was agitated for 6 h. The suspension was filtered and the filtrate was concentrated to afford J2 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, and $R^{15} = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$).

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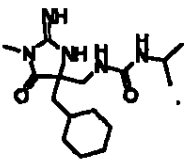
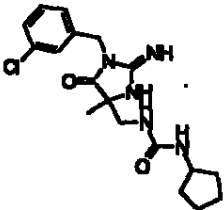
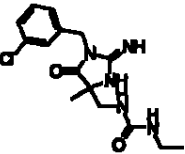
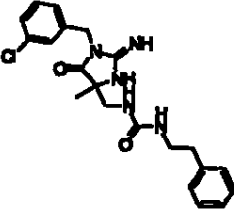
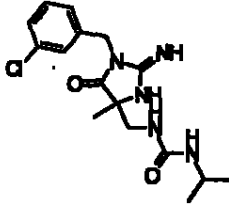
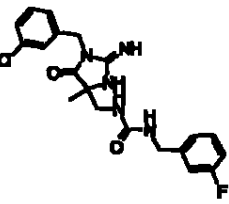
Method J, Step 2:

93
92

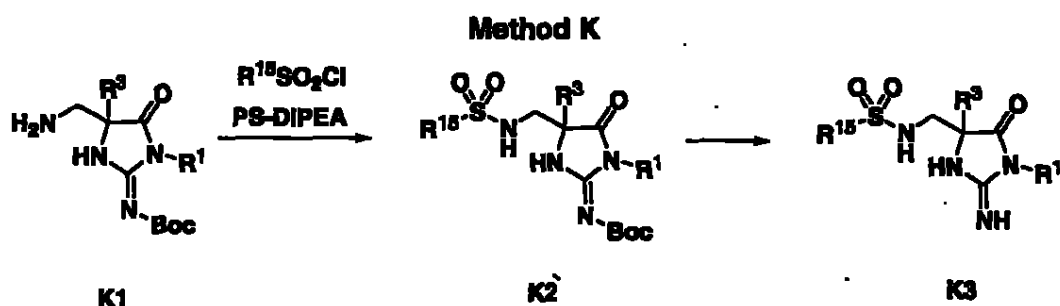
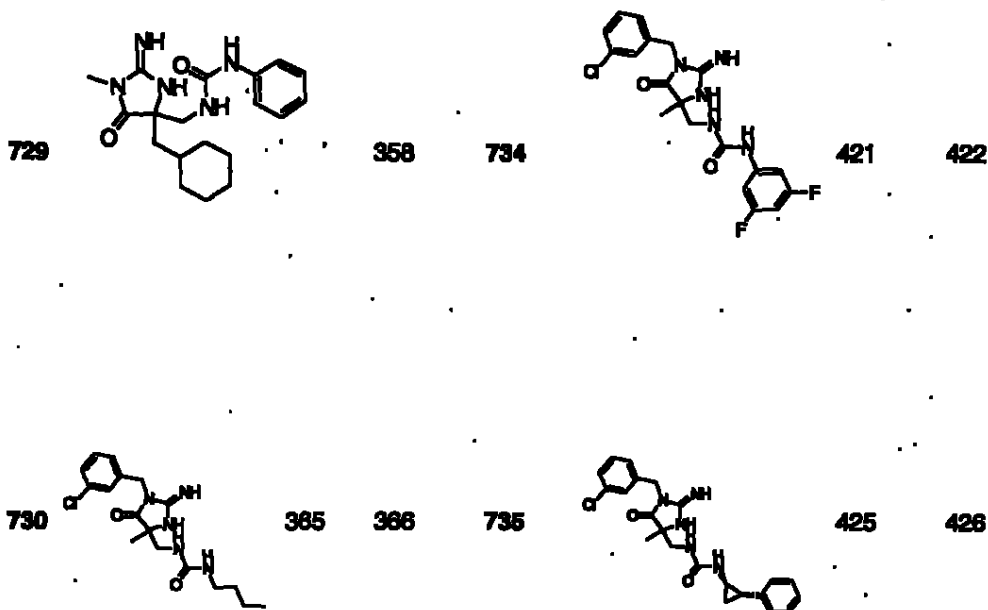
- 77 -

Compound J3 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, and $R^{15} = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) was prepared from J2 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, and $R^{15} = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) following the procedure described in Method H, Step 2.

5 The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
726		323	324	731		377	378
727		337	338	732		413	414
728		352		733		417	418

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5

Method K, Step 1:

A solution of $R^{15}SO_2Cl$ (R^{15} =Propyl)(1.5 eq) was added to a suspension of polystyrene diisopropylethylamine resin (18 mg, 3.45 mmol/g, 3 eq) and the free base of **K1** prepared using method H ($R^1 = CH_2(3-ClC_6H_4)$ and $R^3 = CH_3$) (0.021 mmol) in 1:1 $CH_3CN:THF$. The suspension was agitated overnight.

Polystyrene isocyanate resin (45 mg, 3 eq), polystyrene triamine resin (40 mg, 6 eq) and a 1:1 mixture of $CH_3CN:THF$ (0.5 mL) was added. The mixture was

10

95
94

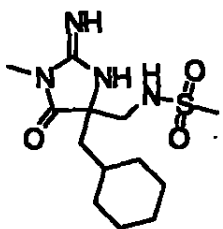
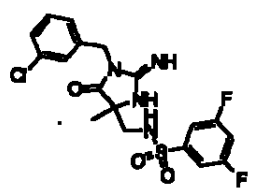
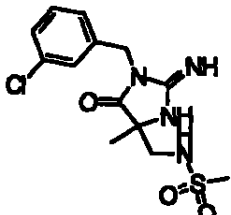
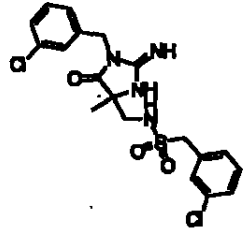
- 79 -

agitated for 6 h. The suspension was filtered and the filtrate was concentrated to afford K2 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, and $R^{15} = \text{CH}_2\text{CH}_2\text{CH}_3$).

Method K, Step 2:

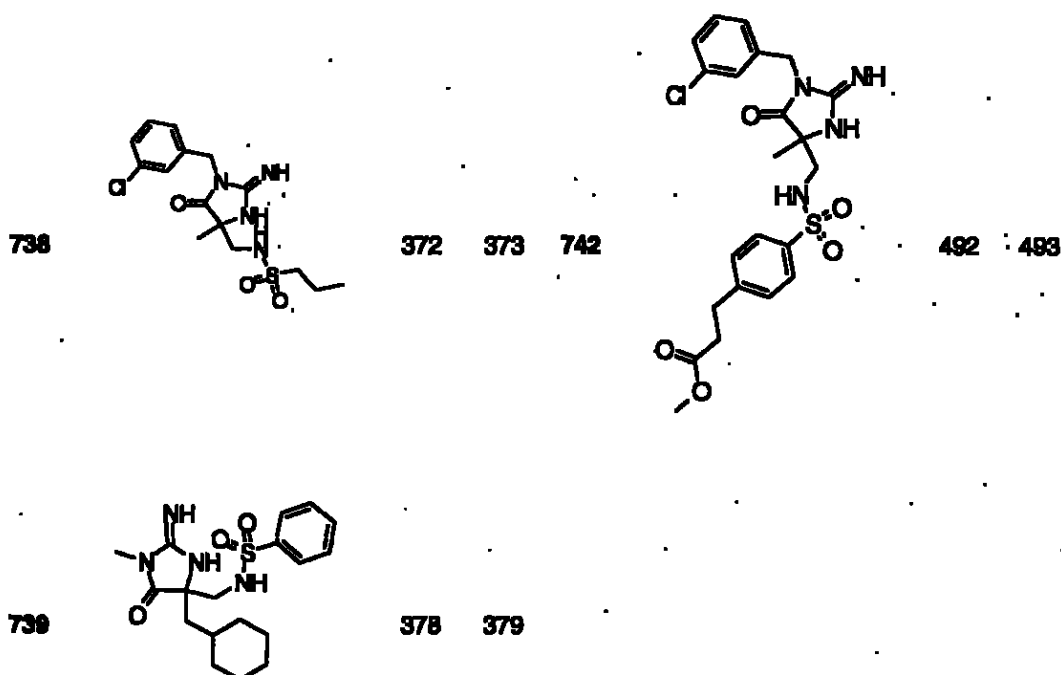
- 5 Compound K3 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, and $R^{15} = \text{CH}_2\text{CH}_2\text{CH}_3$) was prepared from K2 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, and $R^{15} = \text{CH}_2\text{CH}_2\text{CH}_3$) following the procedure described in Method H, Step 6.

The following compounds were prepared using similar method.

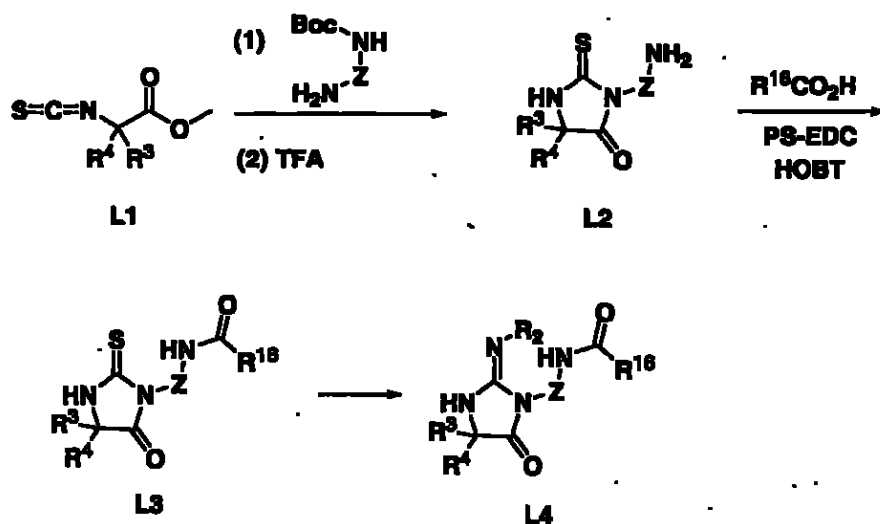
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
736		316	317 740			442	443
737		344	345 741			454	455

96
95

- 80 -



Method L



5

(In the scheme, $-\text{Z-NH-C(=O)R}^{16}$ is equivalent to R^1 substituted by R^{21} , or R^1 substituted by alkyl- R^{22} , wherein R^{21} and R^{22} are $-\text{N(R}^{15})\text{C(=O)R}^{16}$ and R^{15} is H, and wherein Z is optionally substituted alkylene-arylene, alkylene-arylene-

97
96

- 81 -

alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

5

Method L, Step 1:

A solution of L1 ($R^3 = \text{CH}_3$ and $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (1 eq) and Z = -para-methylene-benzyl) (1.05 eq) in CH_2Cl_2 was stirred at rt. The reaction solution was concentrated and purified via flash chromatography. The material was treated with 50% trifluoroacetic acid in CH_2Cl_2 for 30 min. The solution was concentrated. The residue was dissolved in 1 N HCl (10mL) and washed with ether (2x). A saturated solution of Na_2CO_3 in H_2O was added to the aqueous phase until the solution became basic. The solution was extracted with CH_2Cl_2 (3x). The CH_2Cl_2 extracts were combined, dried over Na_2SO_4 , filtered and concentrated to yield L2 ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, Z = para- $(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$).

15

Method L, Step 2:

Compound L3 ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, Z = para- $(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $R^{16} = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) was prepared from L2 ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, Z = para- $(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) following the procedure described in Method I, Step 1.

20

Method L, Step 3:

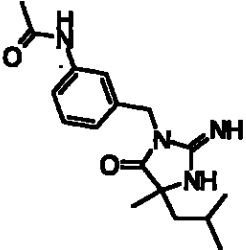
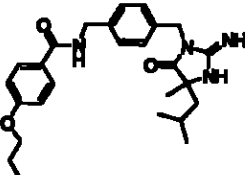
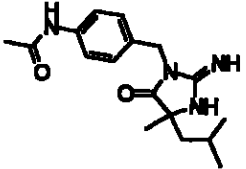
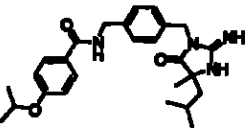
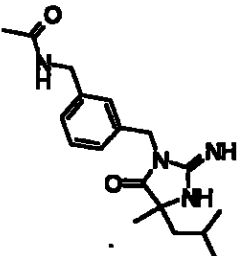
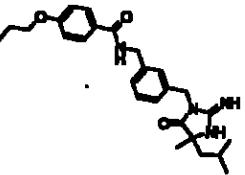
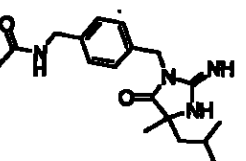
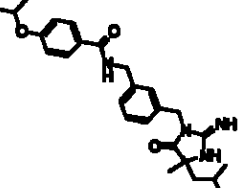
Compound L4 ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, Z = para- $(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $R^1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) was prepared from ($R^3 = \text{CH}_3$, $R^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, Z = para- $(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $R^{16} = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) following the procedure described in Method A, Step 3.

25

The following compounds were prepared using similar method.

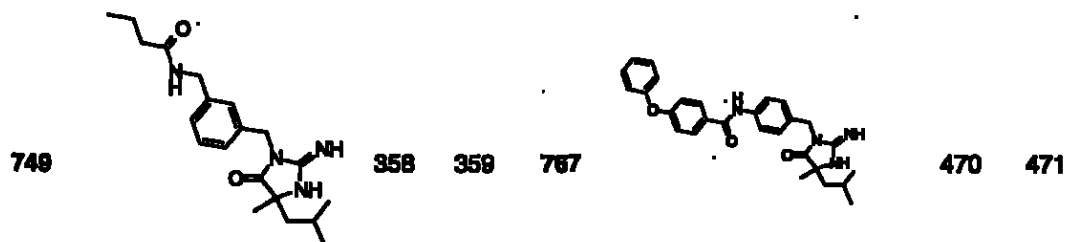
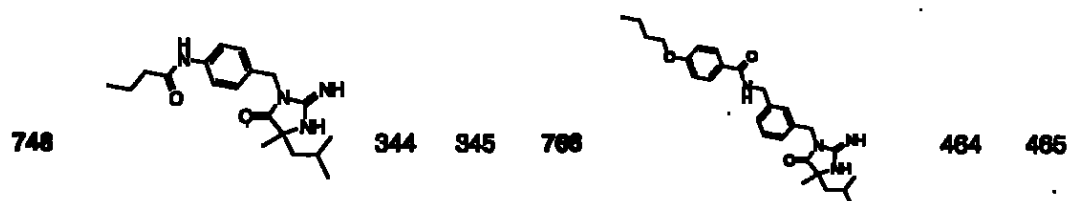
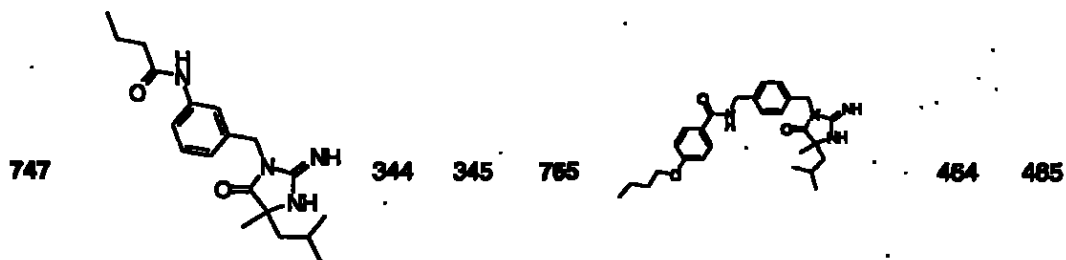
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98
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744		316	317	762		450	451
745		330	331	763		450	451
746		330	331	764		450	451

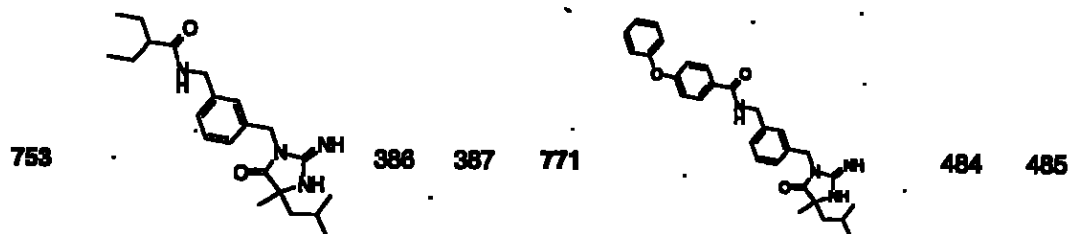
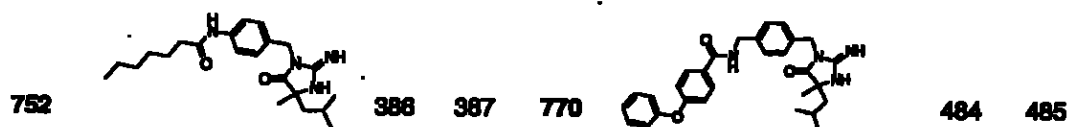
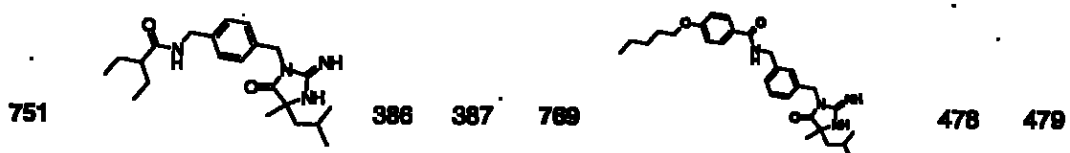
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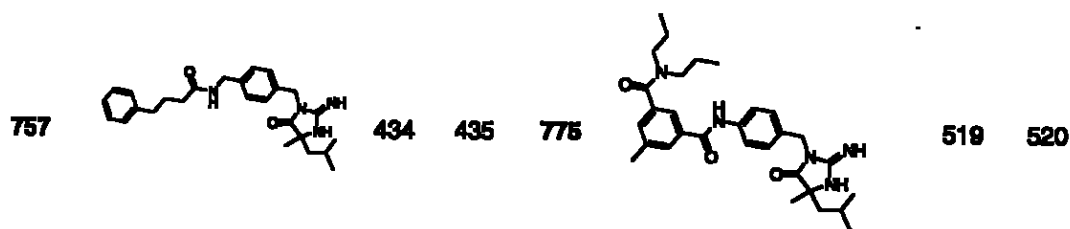
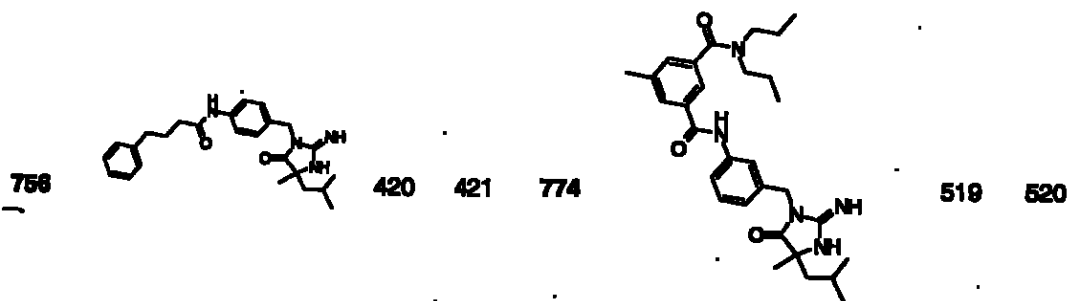
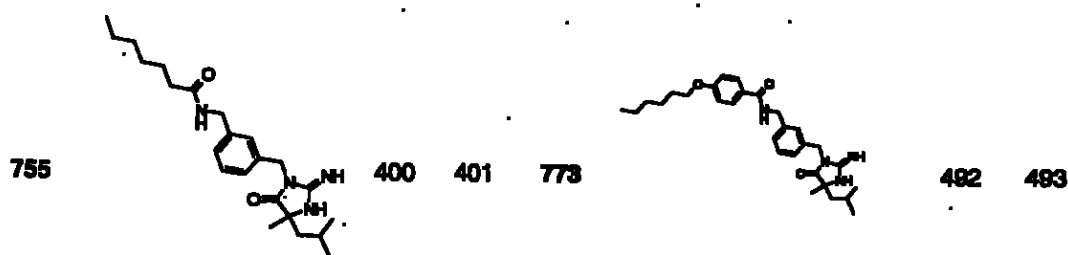
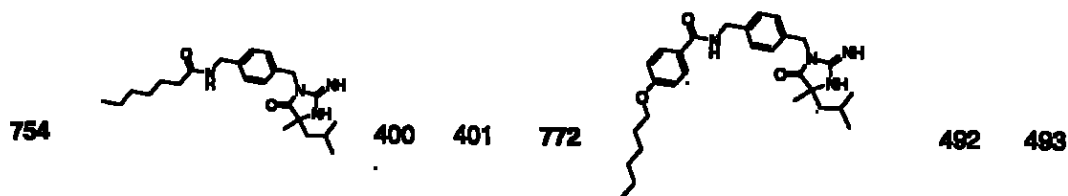
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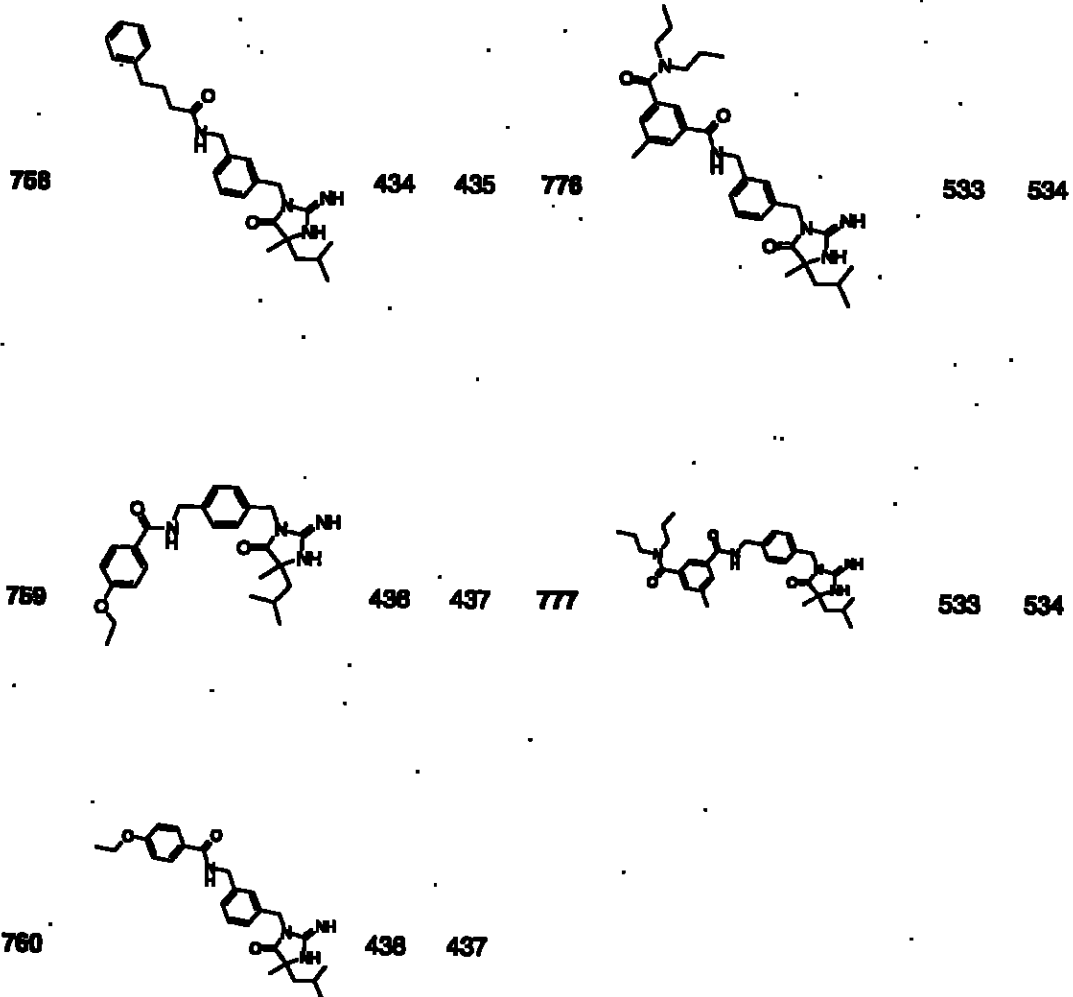


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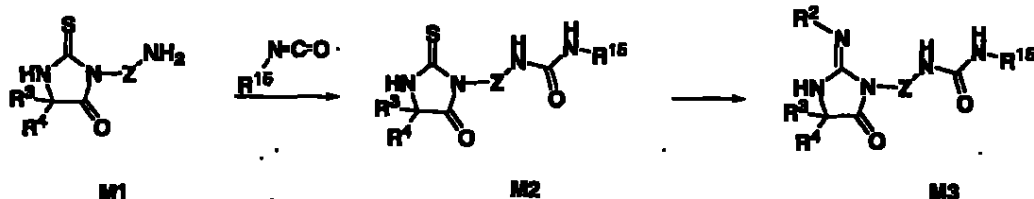
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103
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- 87 -

Method M



(In the scheme, $-\text{Z-NH-C(O)-NHR}^{16}$ is equivalent to R^1 substituted by R^{21} , or R^1 substituted by alkyl- R^{22} , wherein R^{21} and R^{22} are $-\text{N(R}^{16})\text{-C(O)-NHR}^{16}$ and R^{16} is H, and wherein Z is optionally substituted alkylene-arylene, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

Method M, Step 1:

Compound M2 ($\text{R}^3 = \text{CH}_3$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $\text{R}^{16} = 3,4\text{-difluorophenyl}$) was prepared from M1 ($\text{R}^3 = \text{CH}_3$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) following the procedure described in Method J, Step 1.

Method M, Step 2:

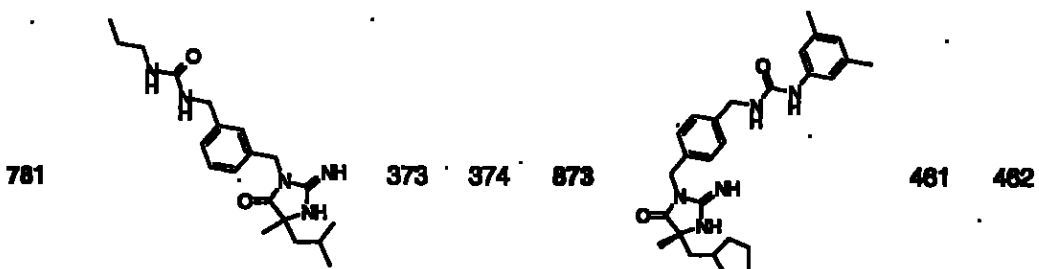
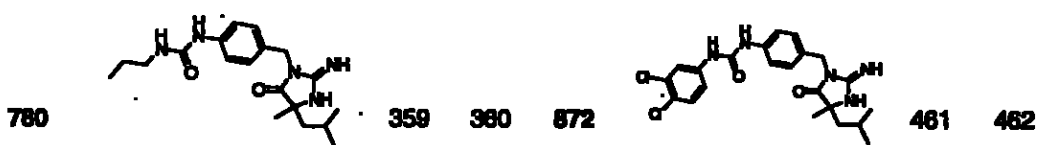
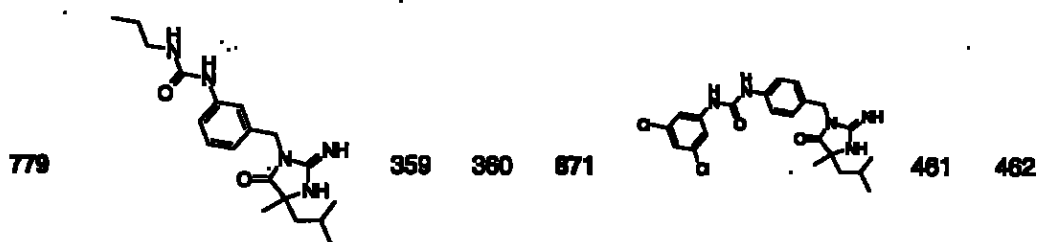
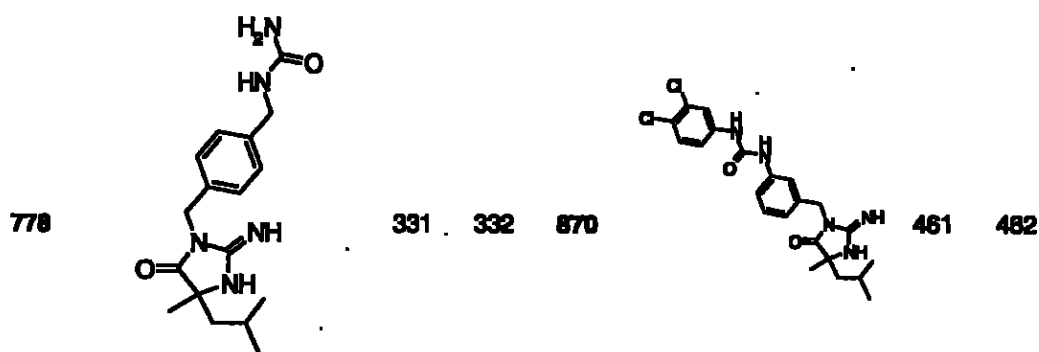
Compound M3 ($\text{R}^3 = \text{CH}_3$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $\text{R}^{16} = 3,4\text{-difluorophenyl}$) was prepared from M2 ($\text{R}^3 = \text{CH}_3$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $\text{R}^{16} = 3,4\text{-difluorophenyl}$) following the procedure described in Method A, Step 3. NMR(CD_3OD) δ 7.45, m, 1H; δ 7.26, m, 4H; 7.24, m, 1H; δ 6.96, m, 1H; δ 4.8, m; δ 4.3, s, 2H; δ 1.69, m, 2H; δ 1.44, m, 1H; δ 1.37, s, 3H; δ 0.8, m, 3H; δ 0.63, m, 3H. ES_LCMS (m/e) 430.27

The following compounds were prepared using similar method.

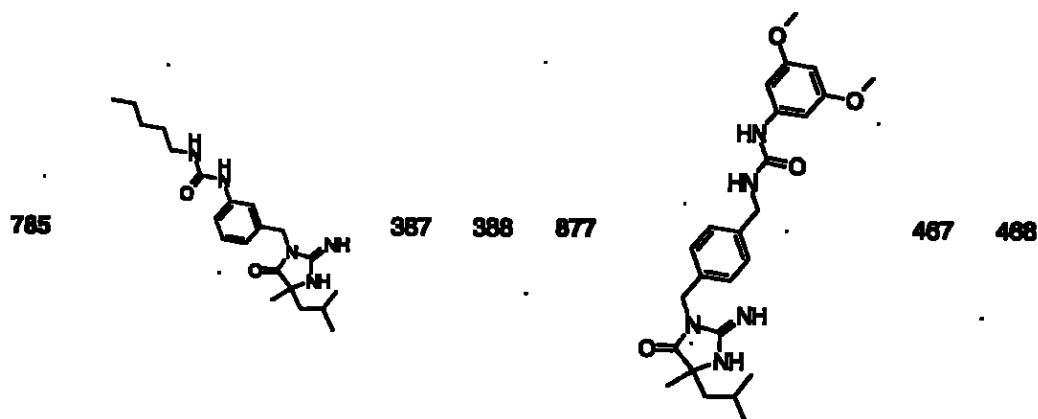
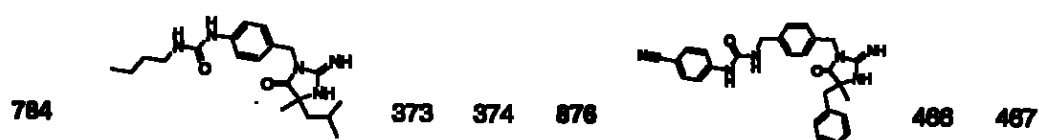
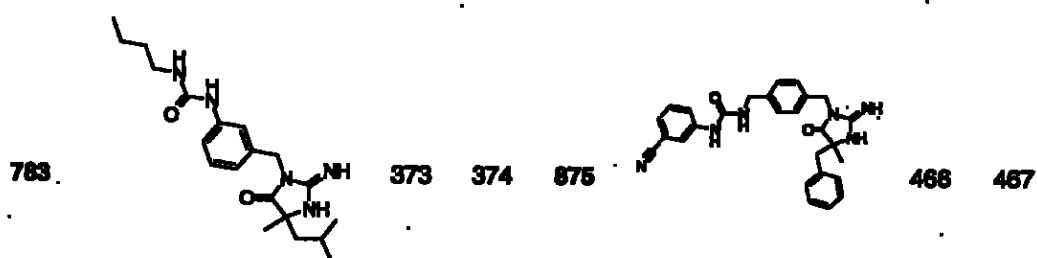
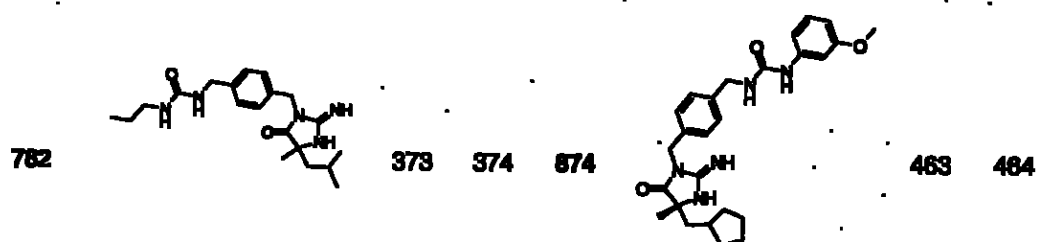
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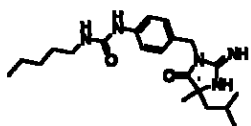


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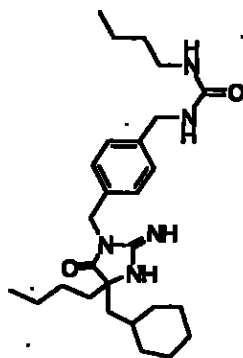
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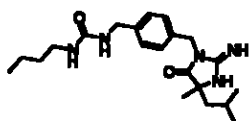
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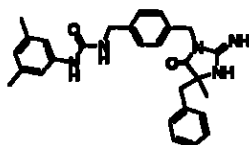
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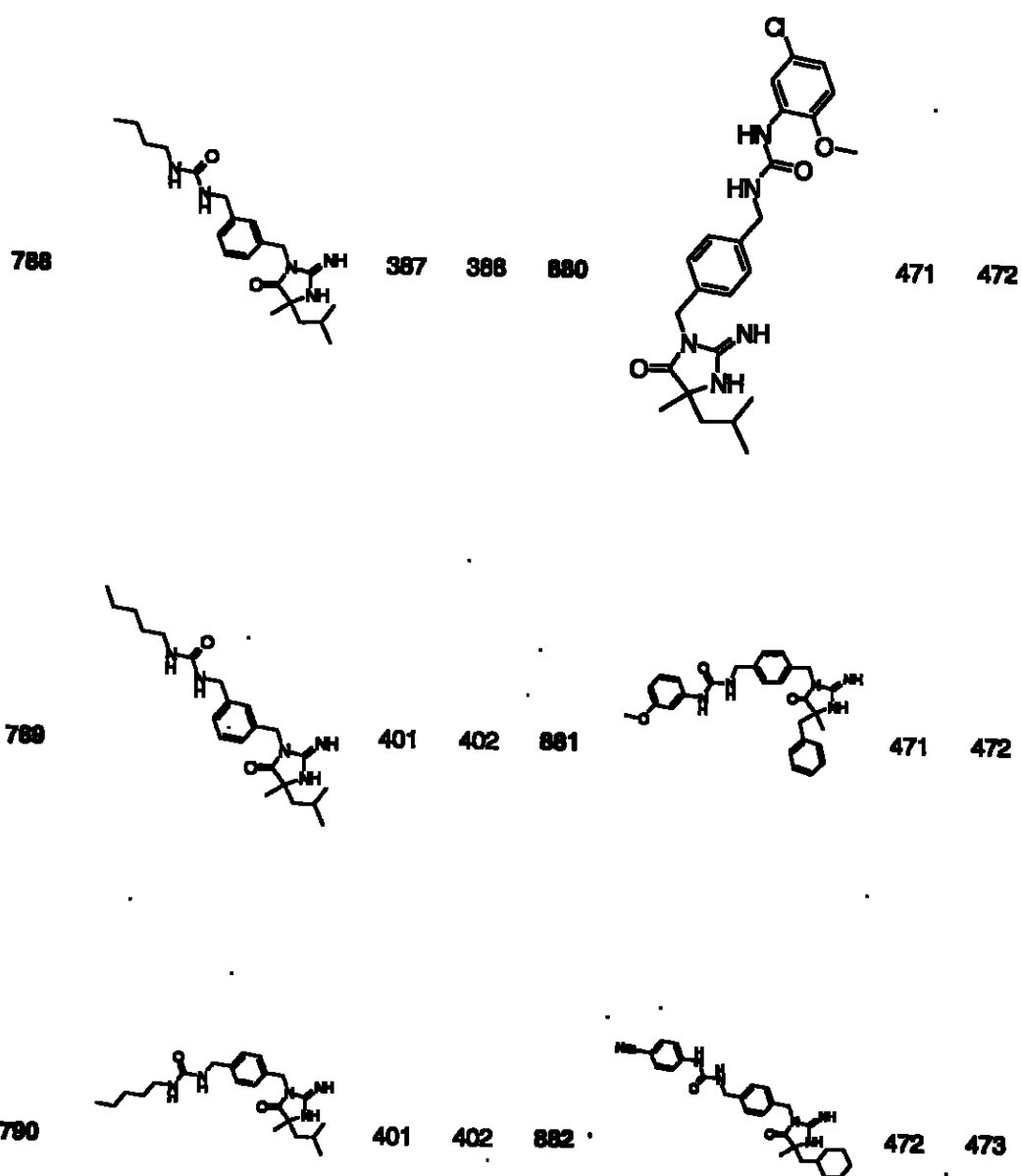


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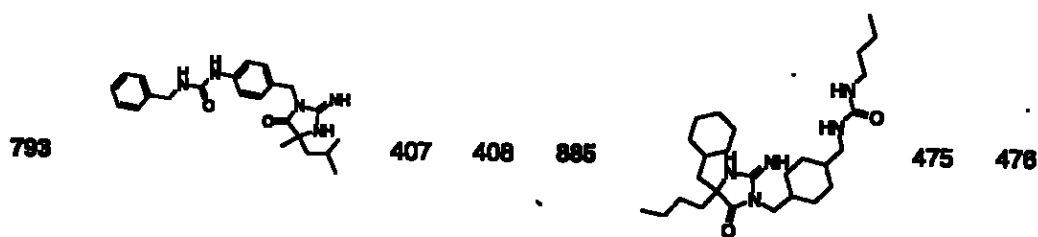
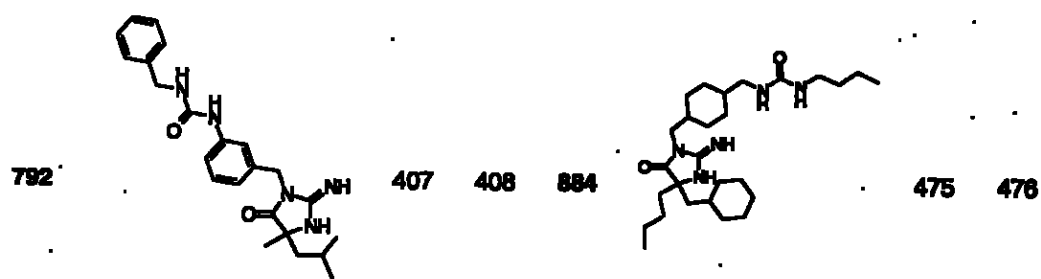
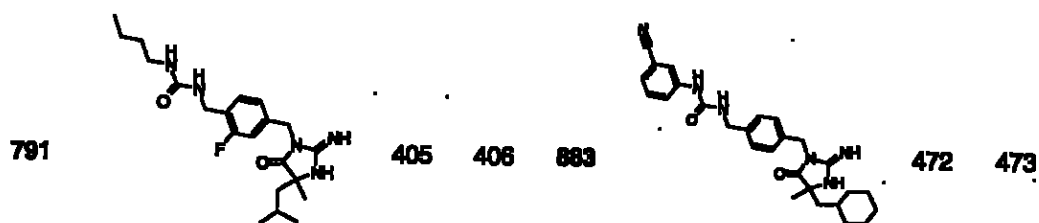
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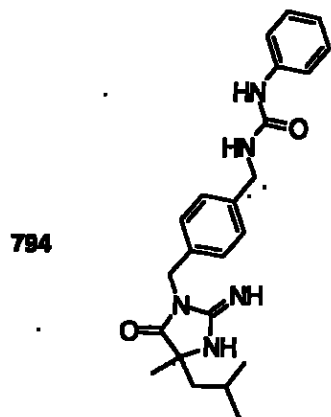


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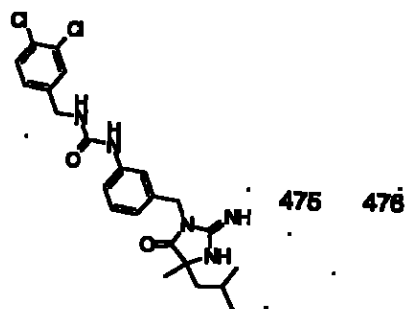


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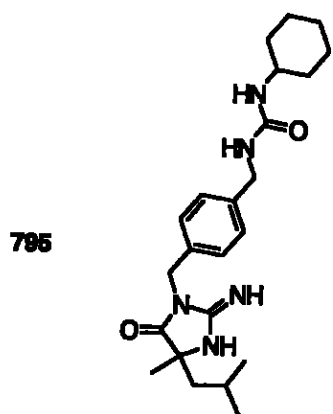
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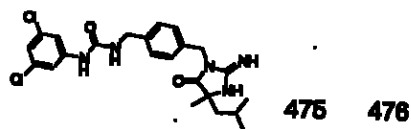
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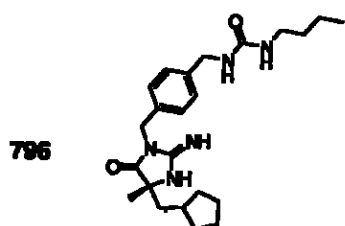
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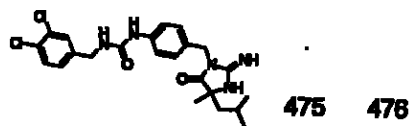
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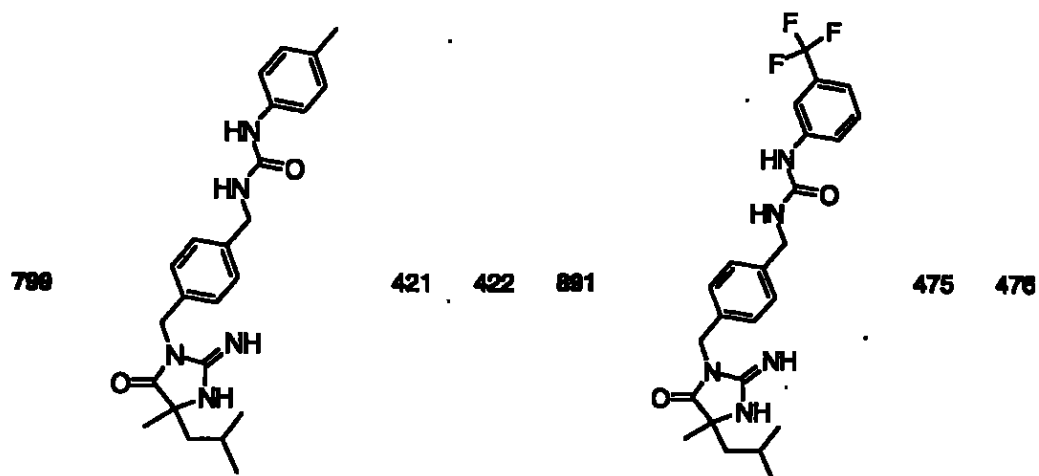
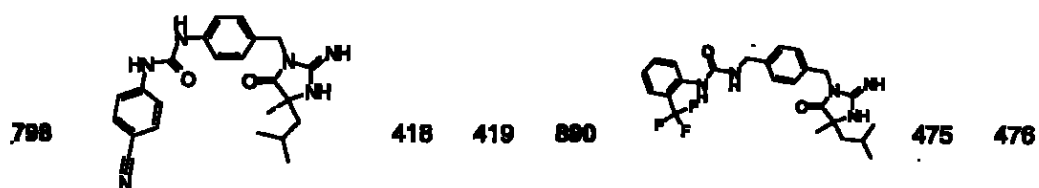
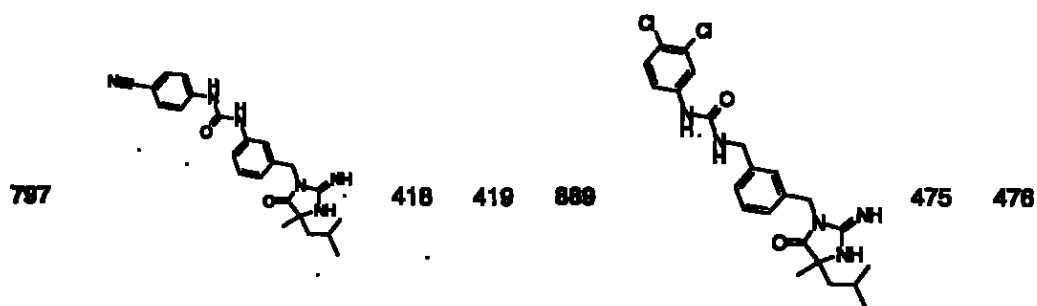
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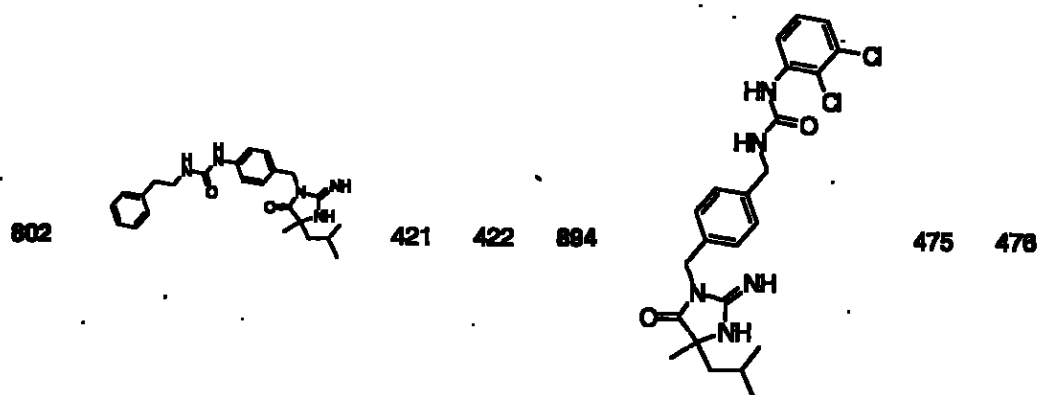
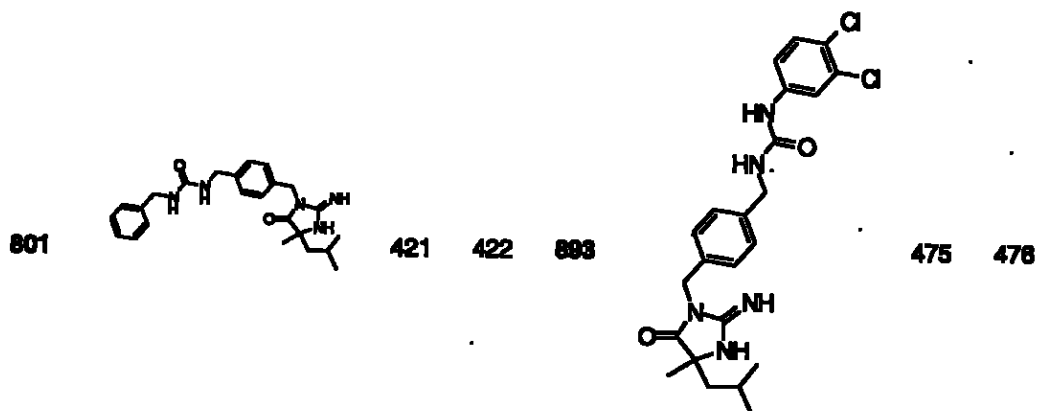
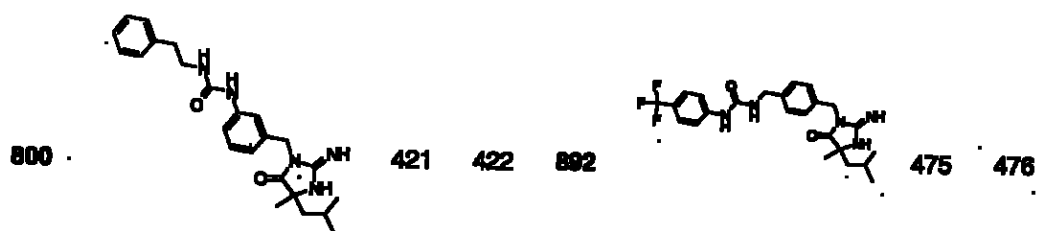


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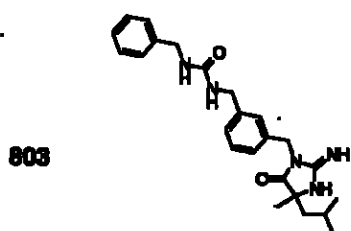
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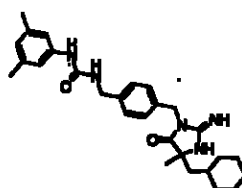


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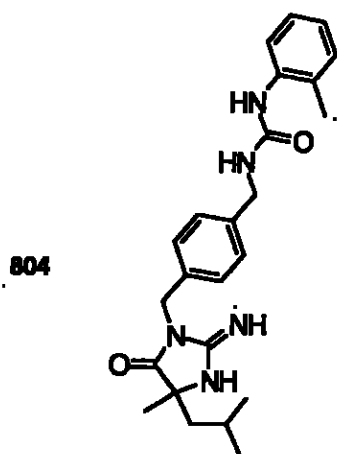
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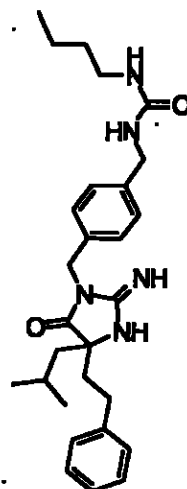
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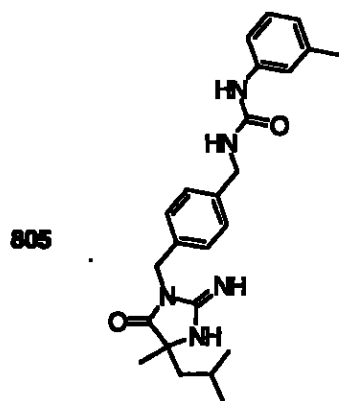
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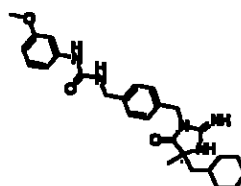
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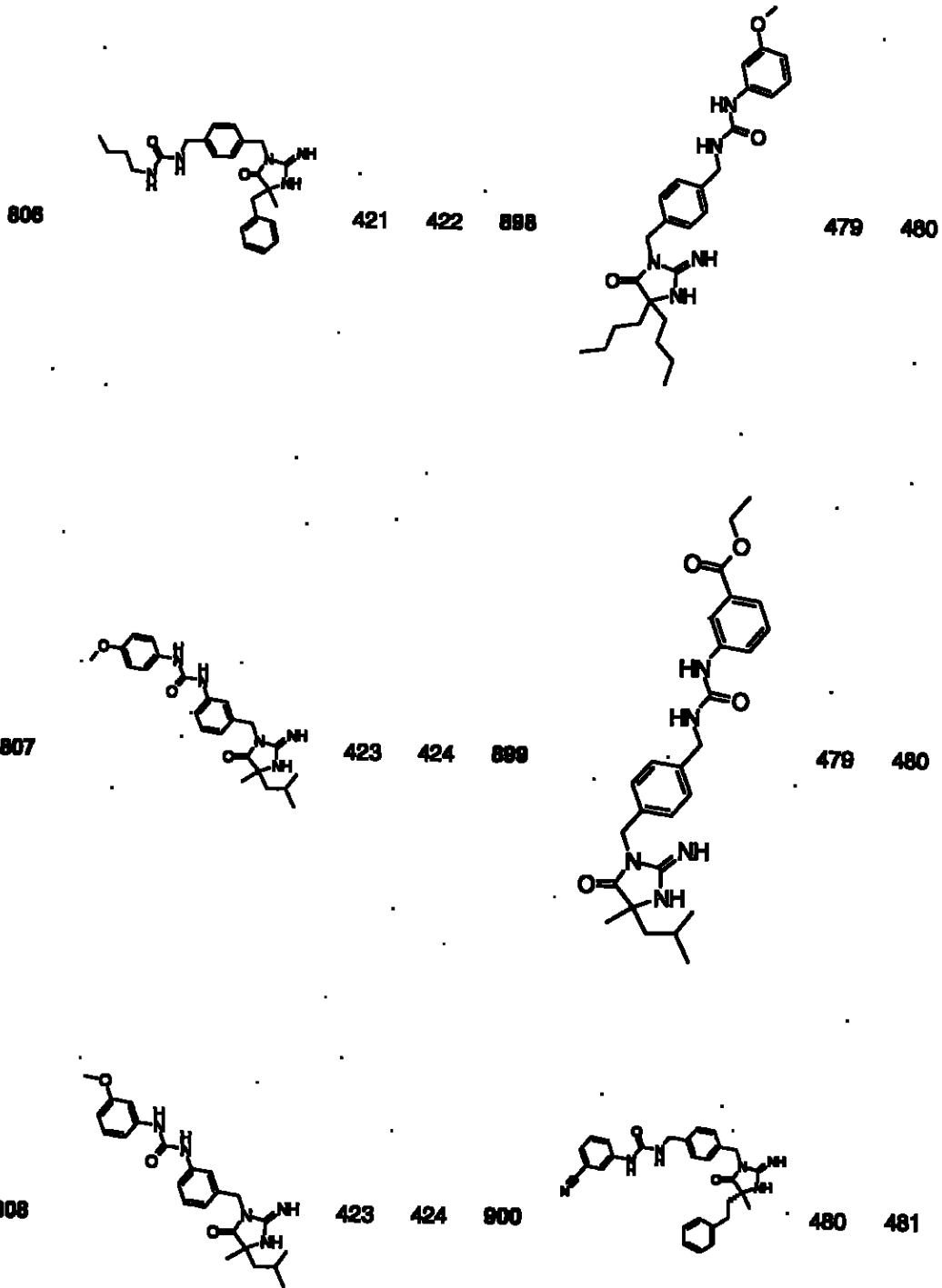


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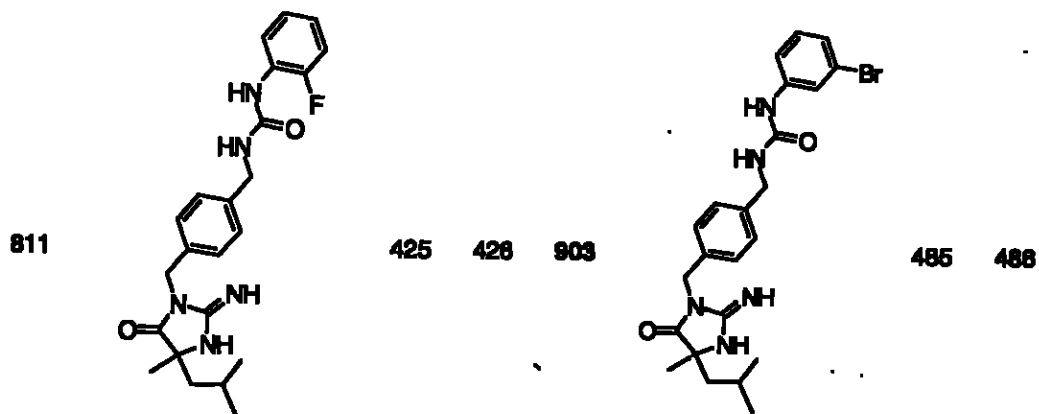
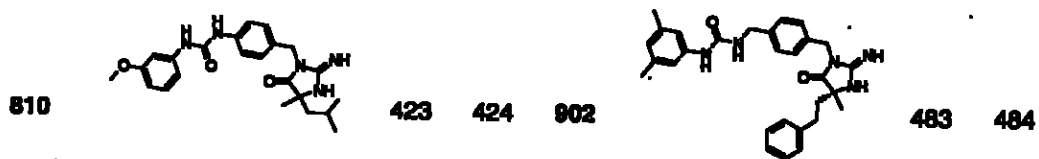
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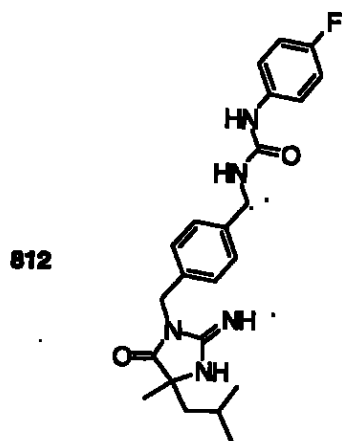
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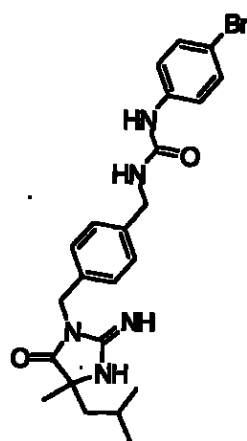


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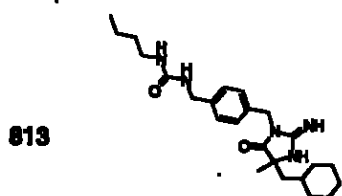
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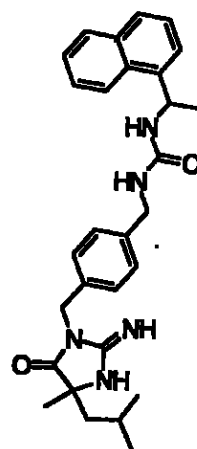
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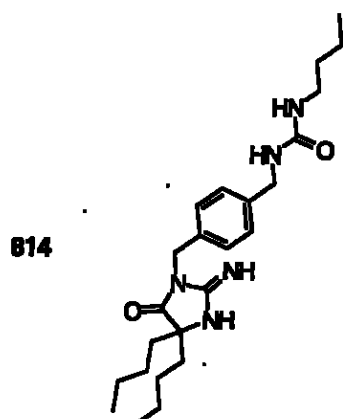
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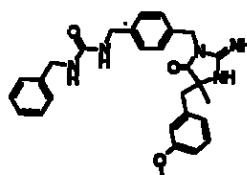
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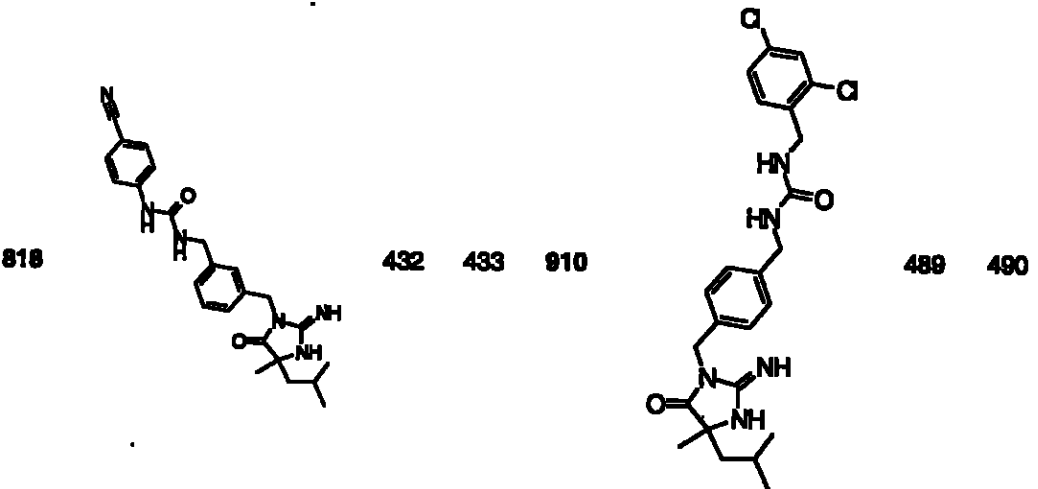
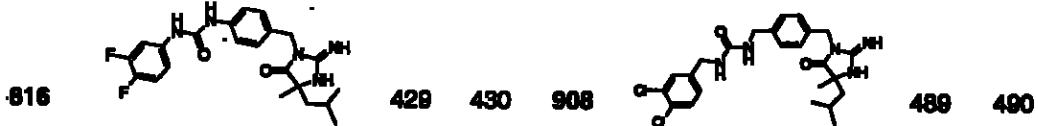
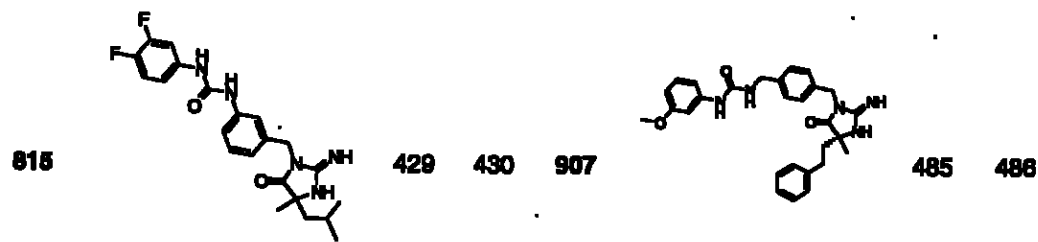


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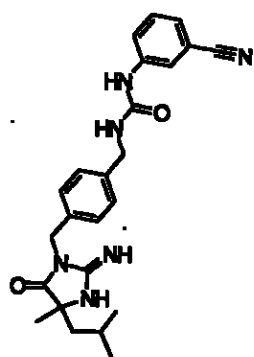
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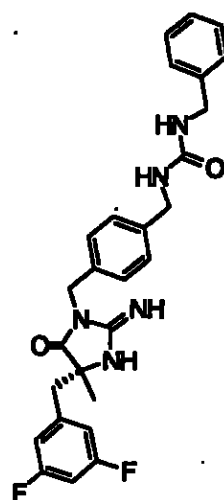
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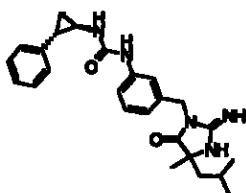
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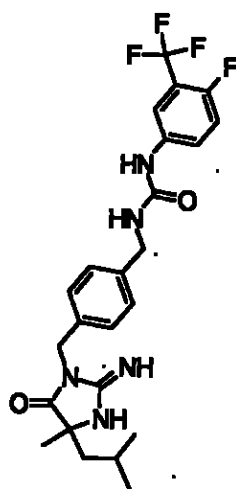
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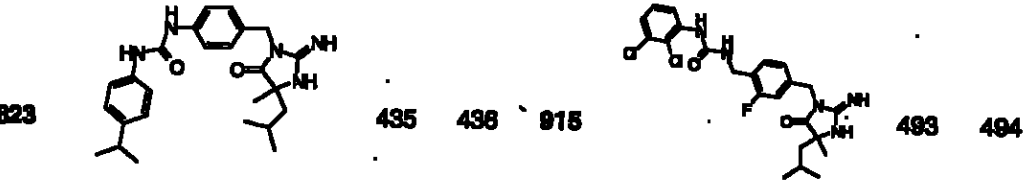
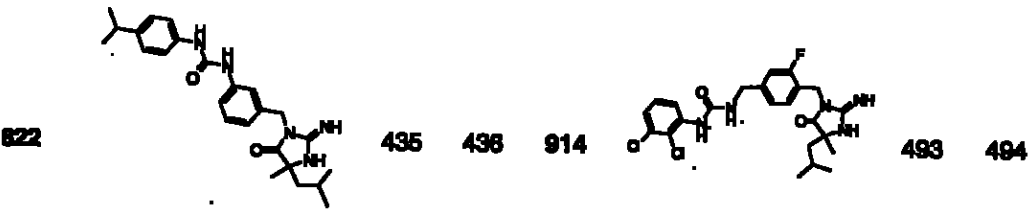
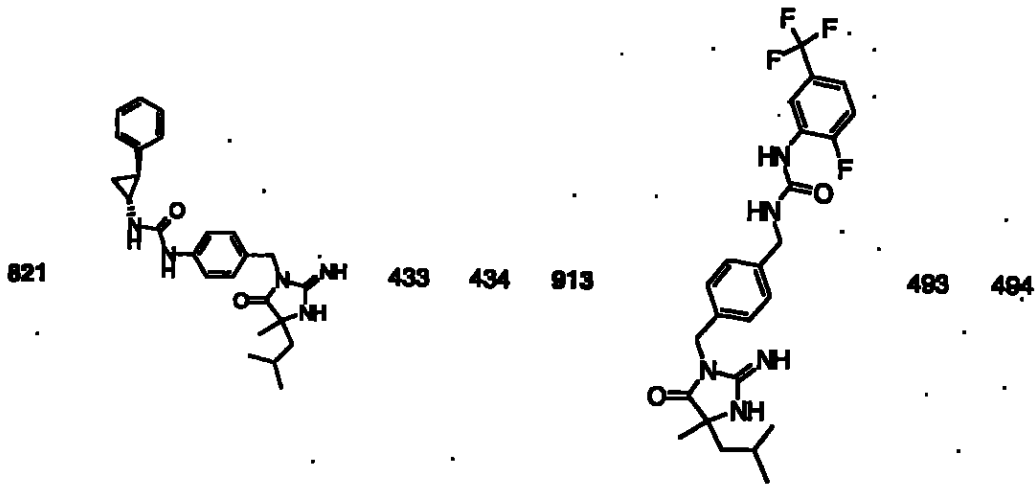
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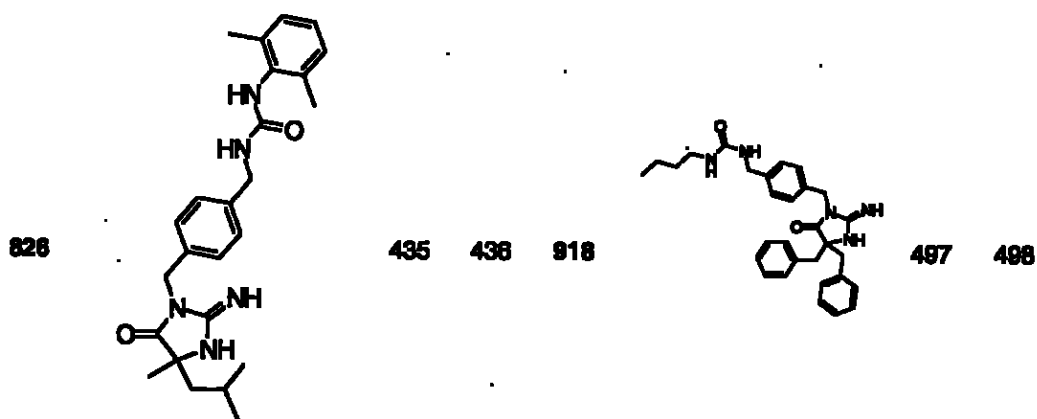
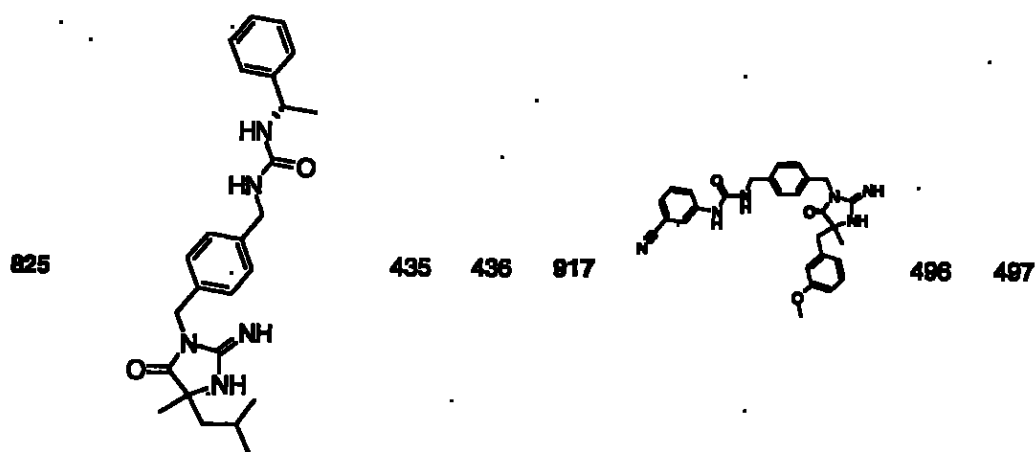
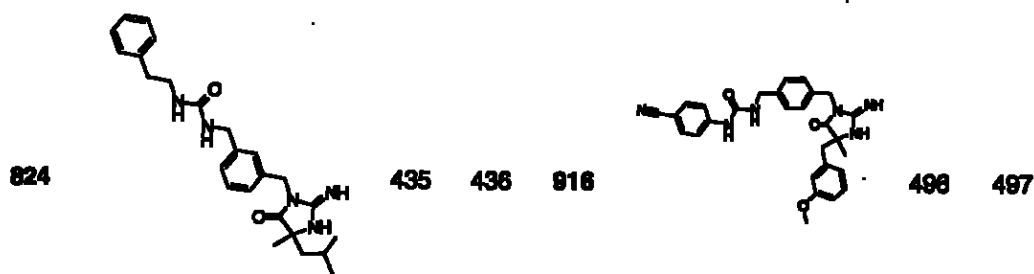
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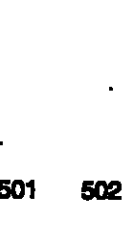
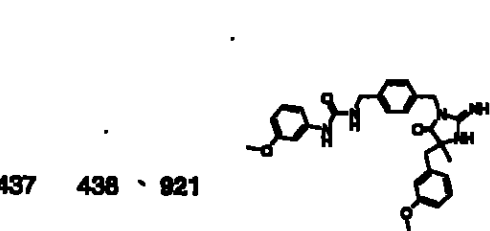
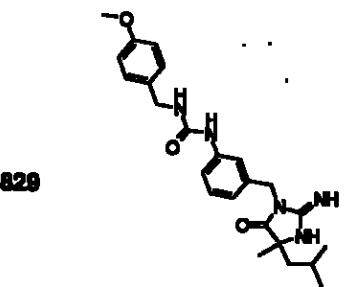
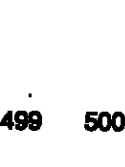
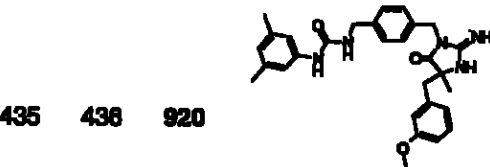
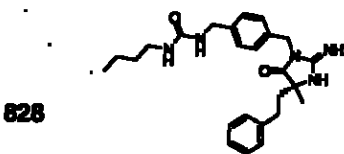
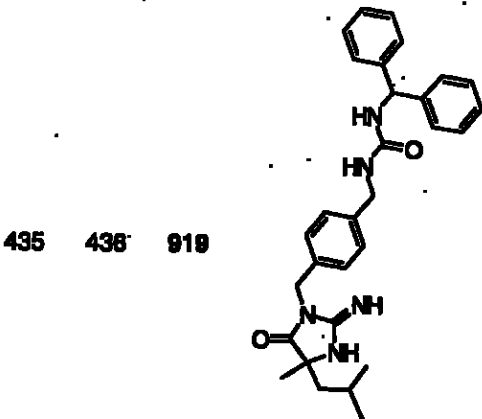
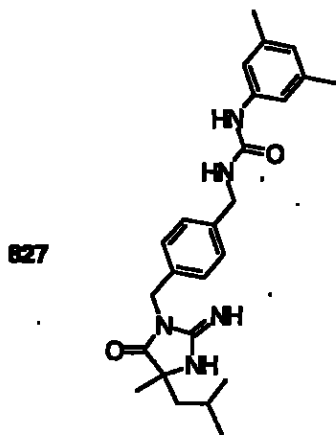
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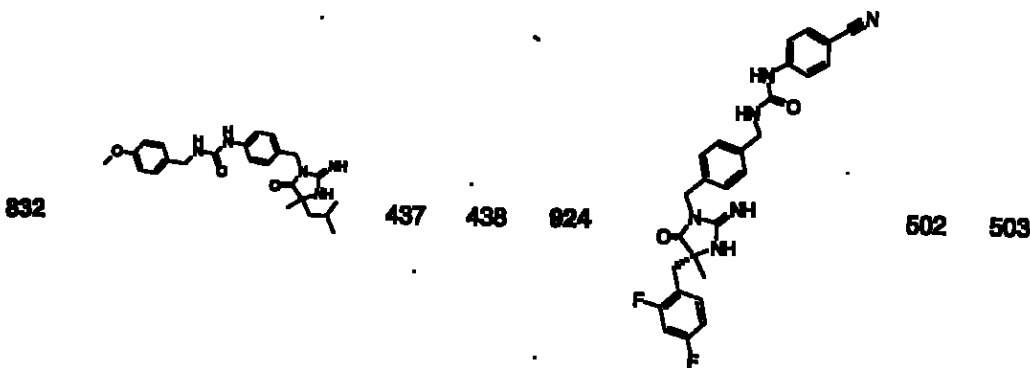
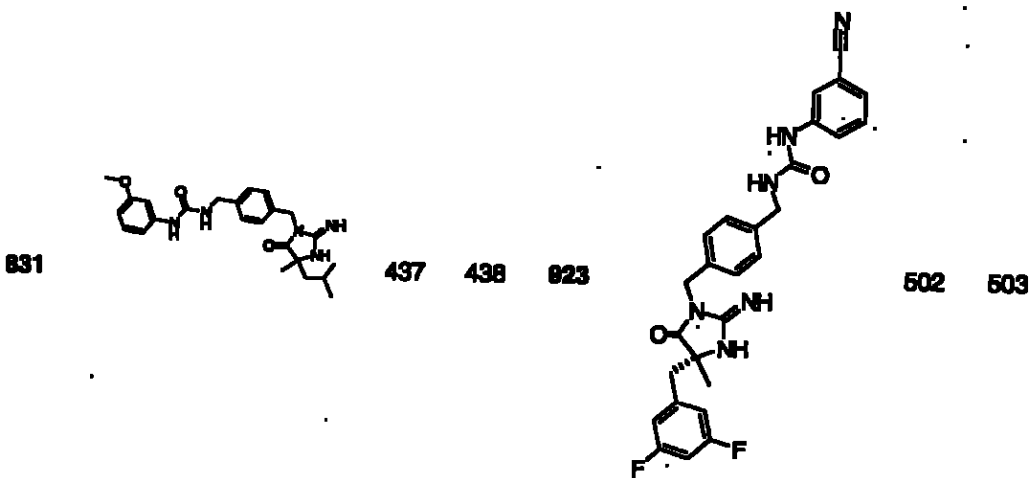
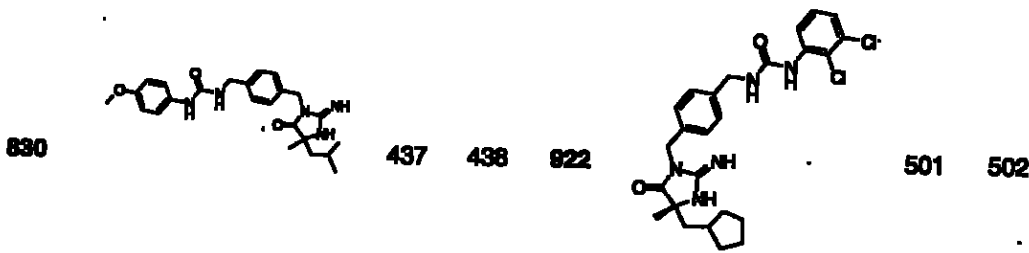
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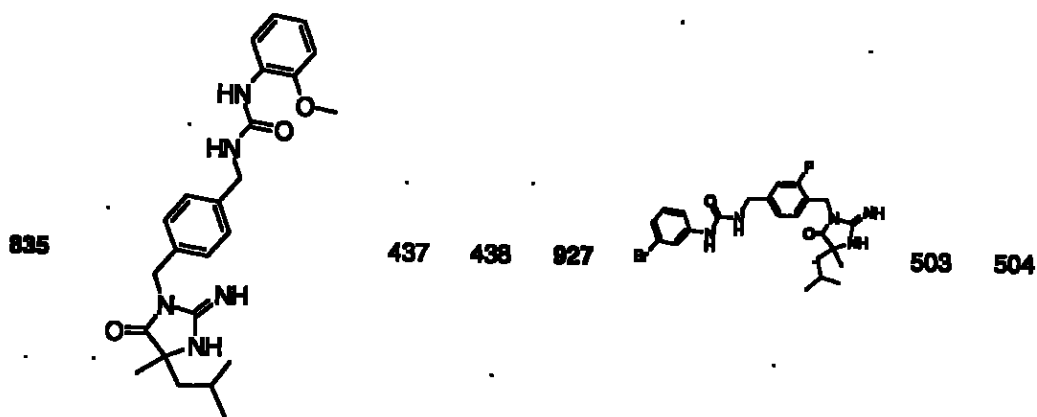
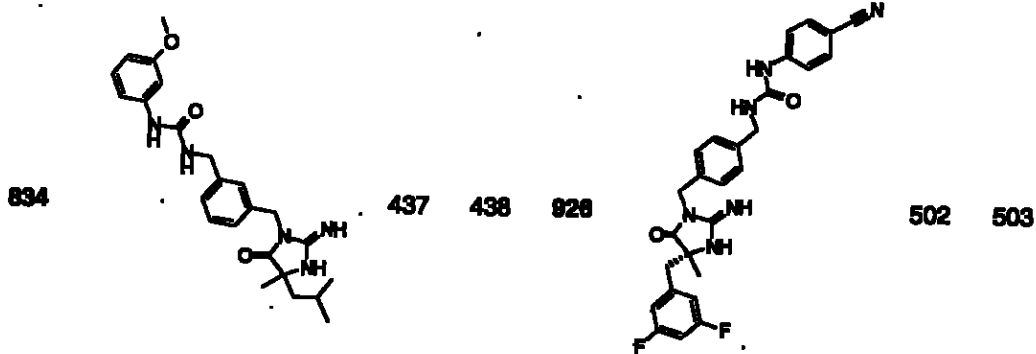
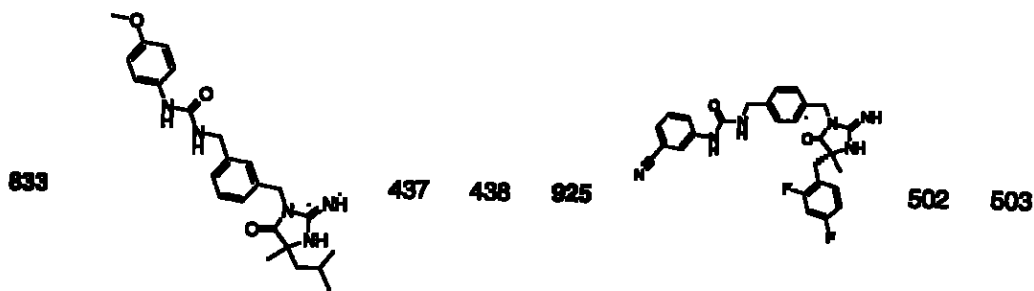
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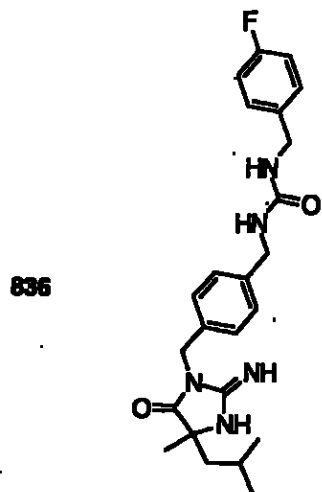


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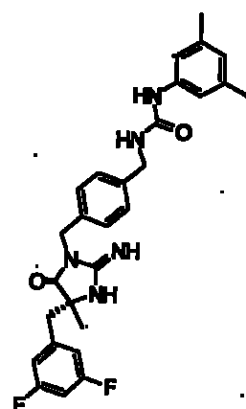


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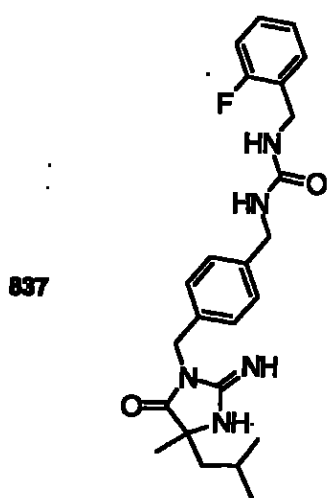
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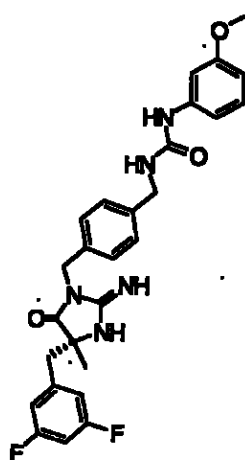
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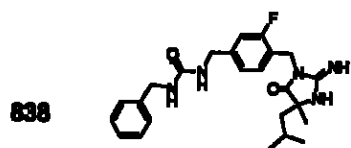
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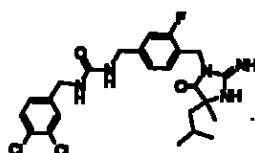
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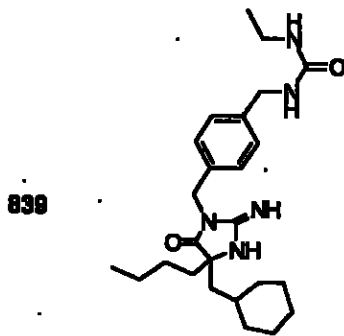


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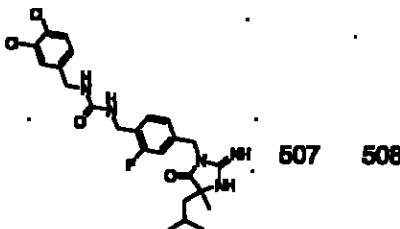


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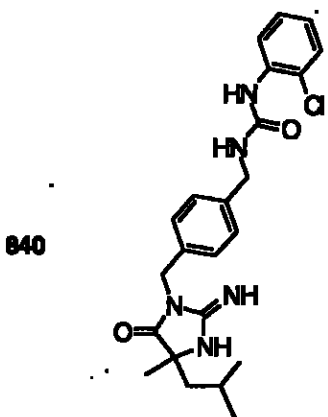
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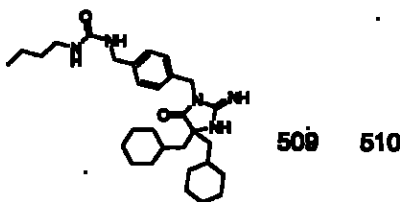
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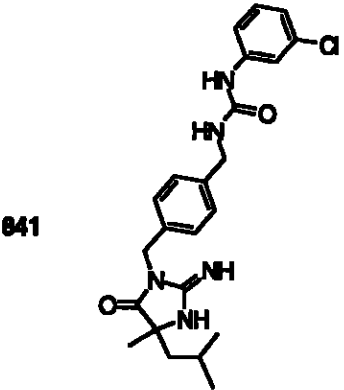
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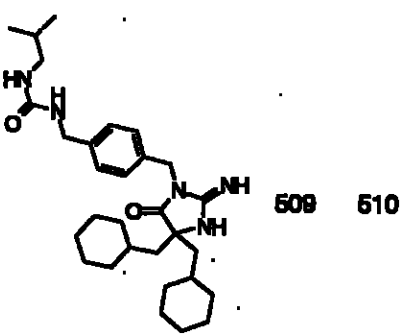
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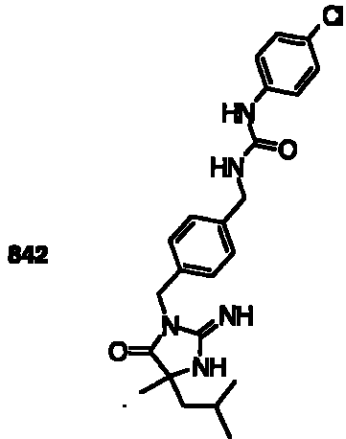


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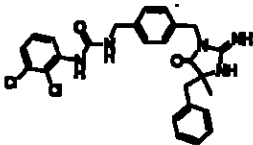


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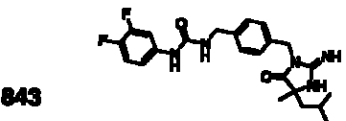
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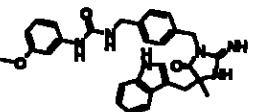
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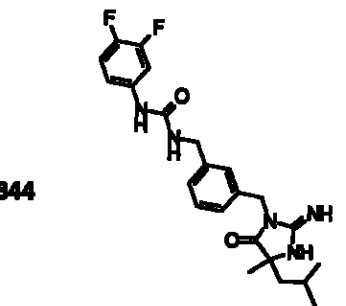
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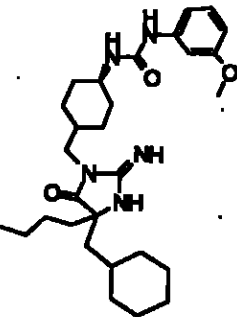
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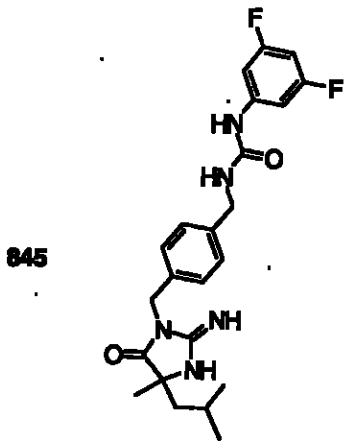


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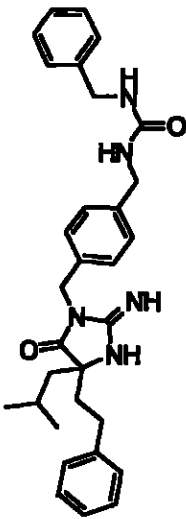


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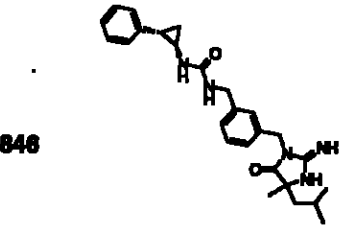
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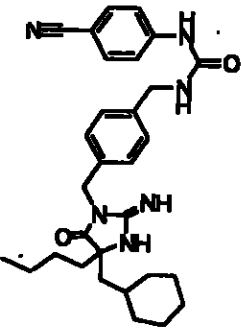
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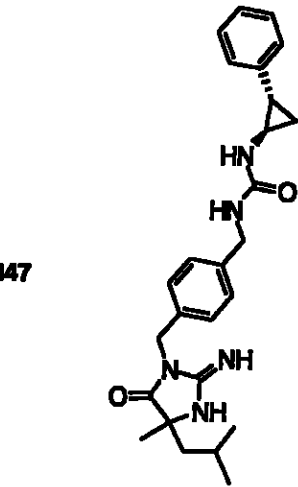
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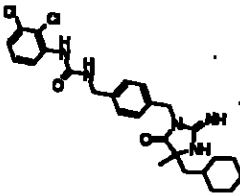
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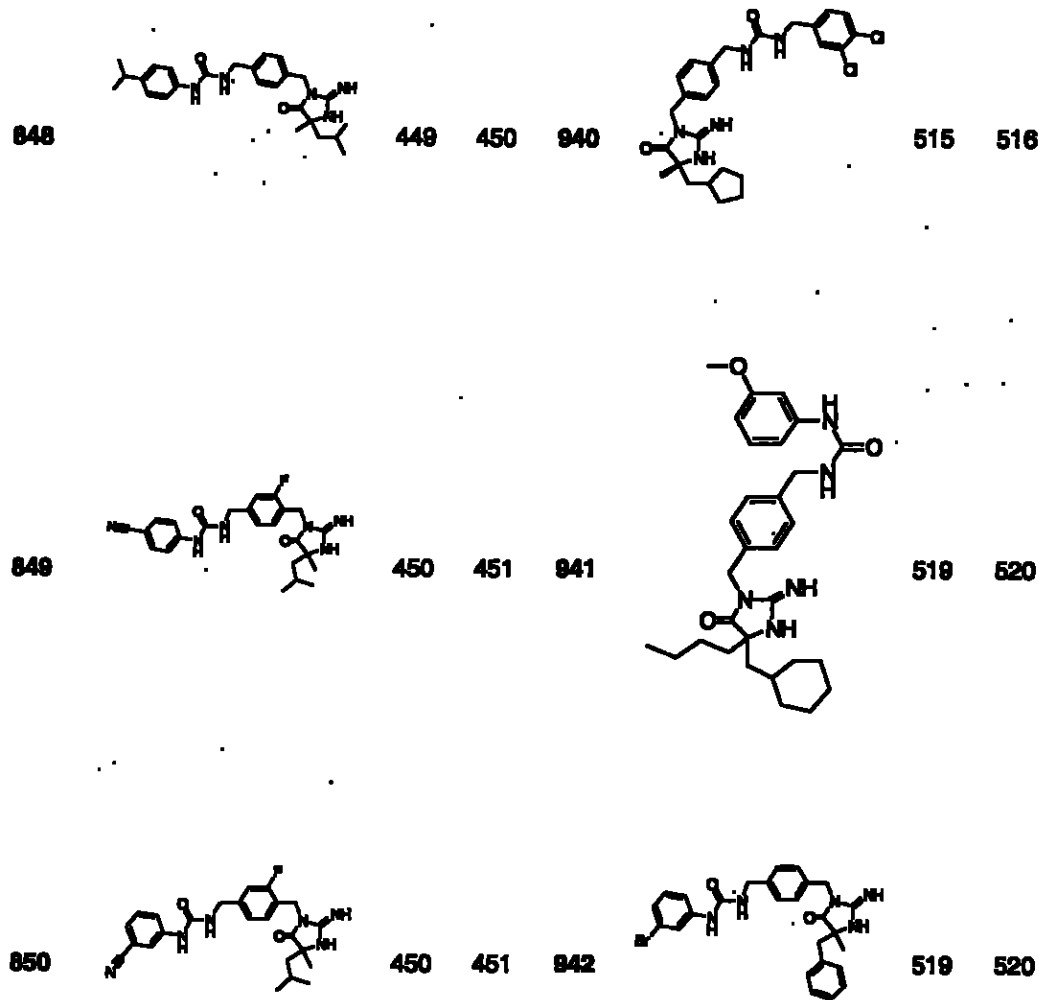


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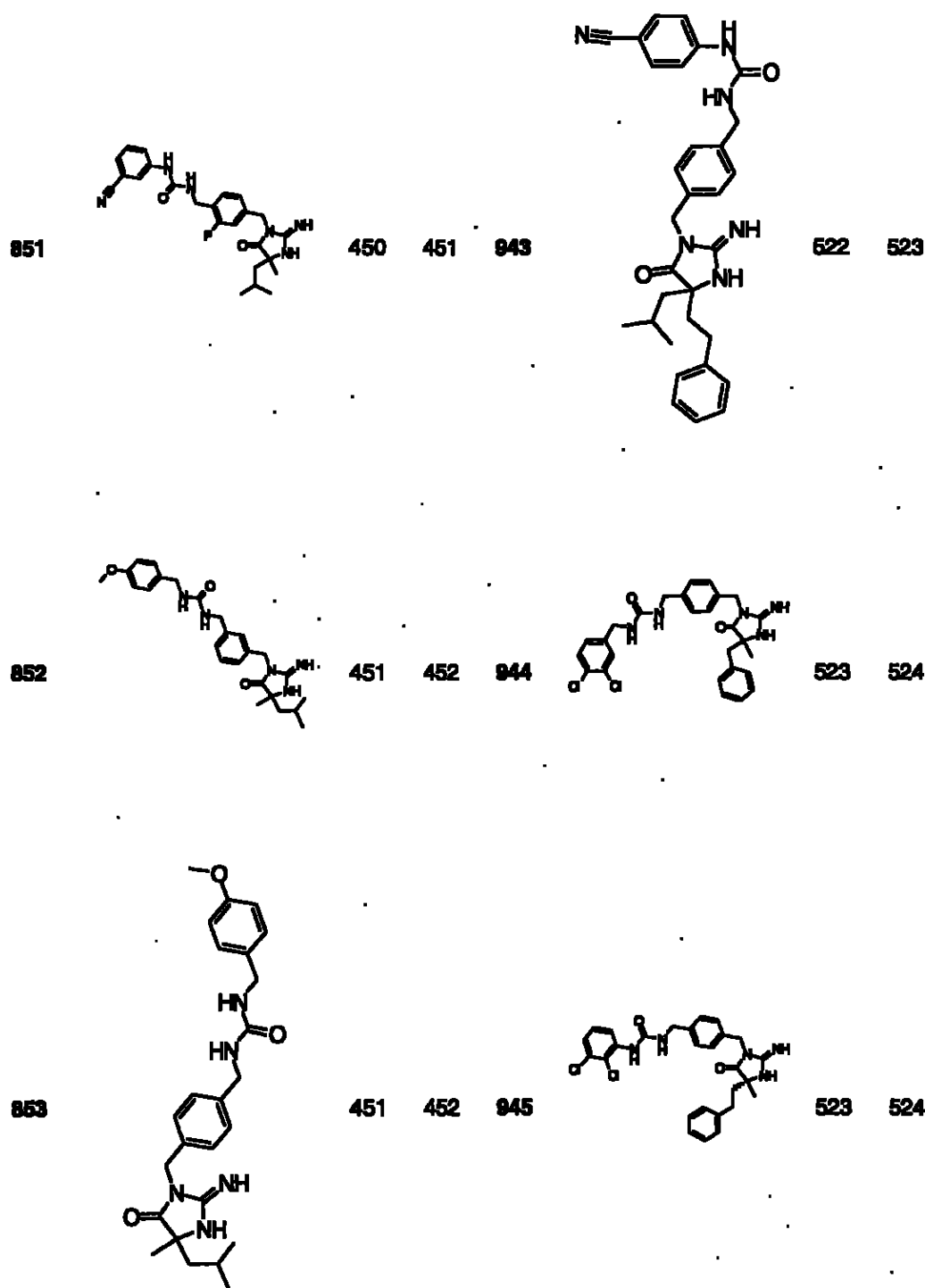
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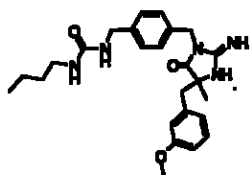
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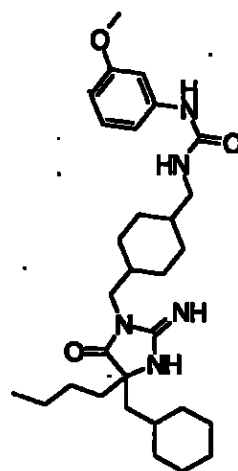
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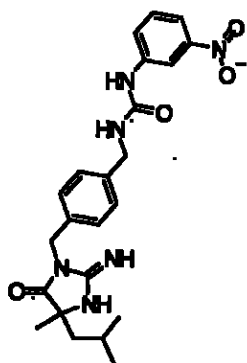
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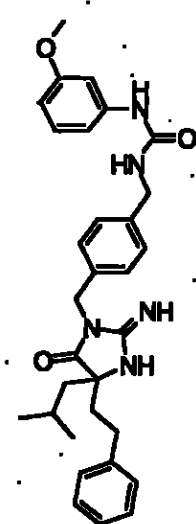
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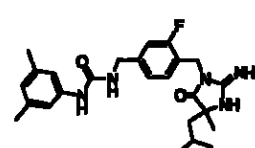
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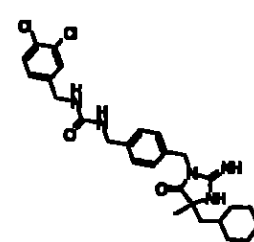
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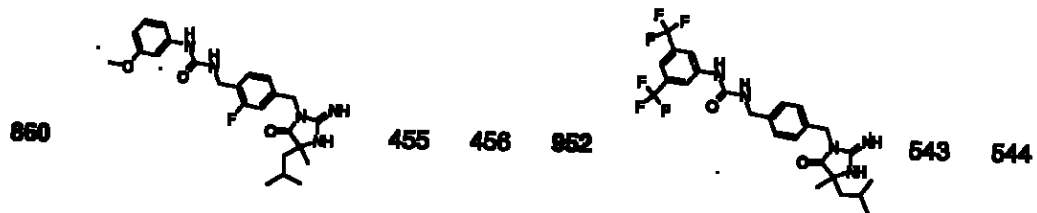
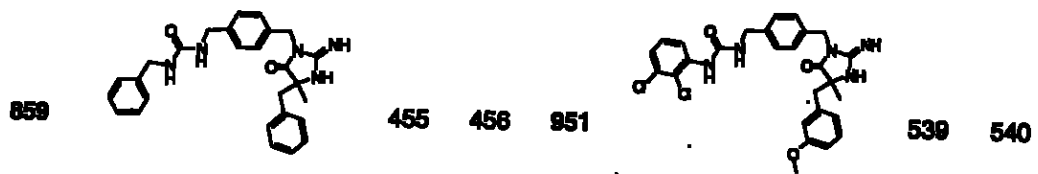
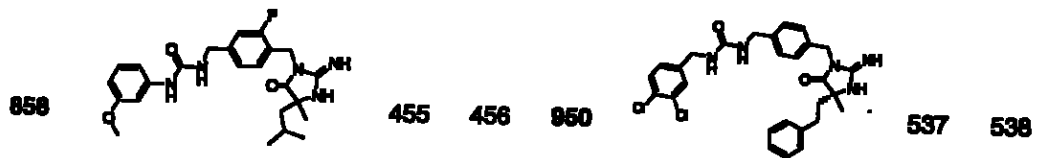


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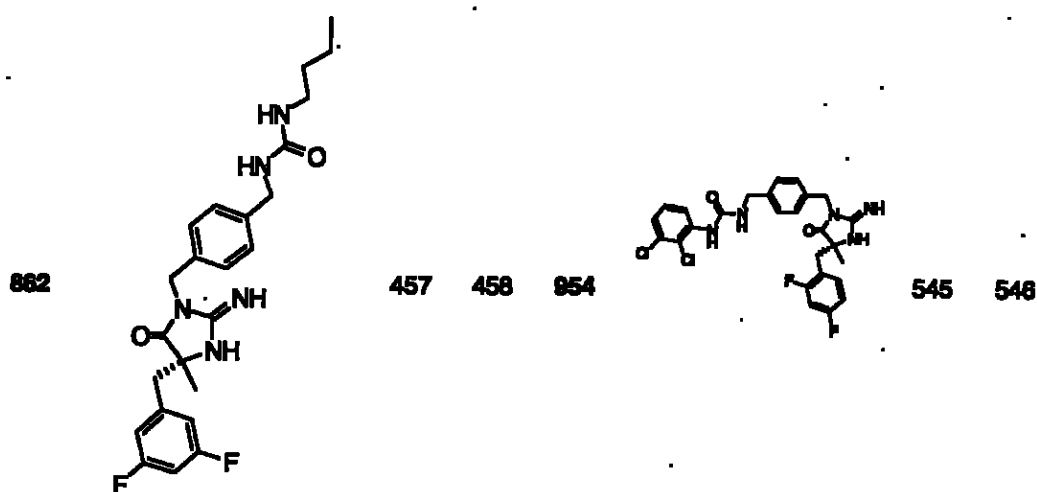
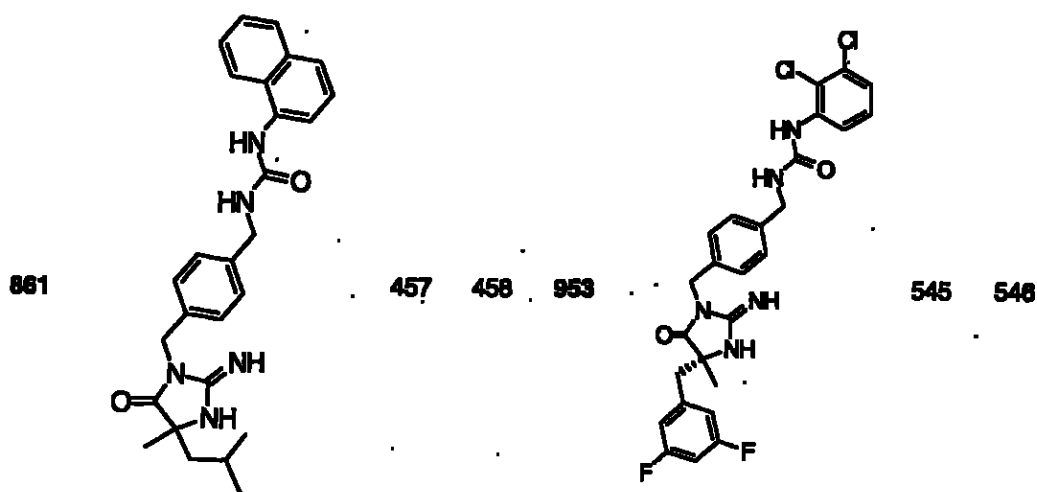
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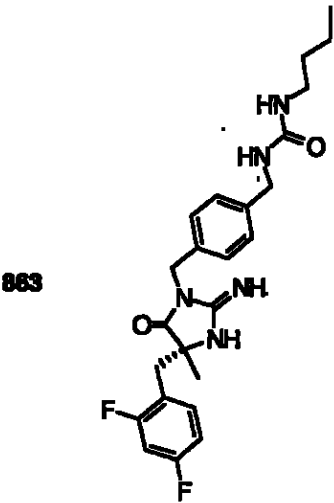


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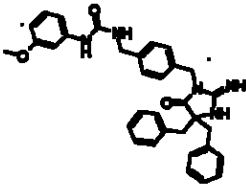
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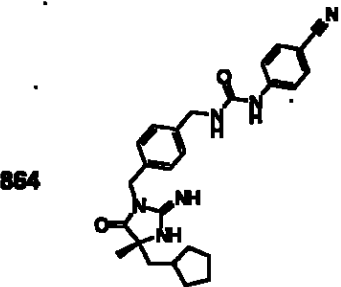
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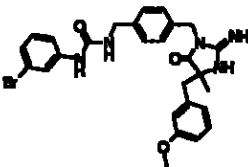
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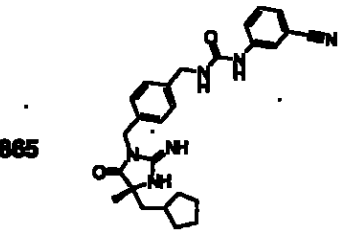
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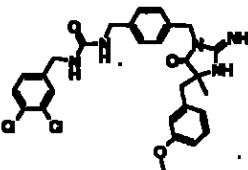
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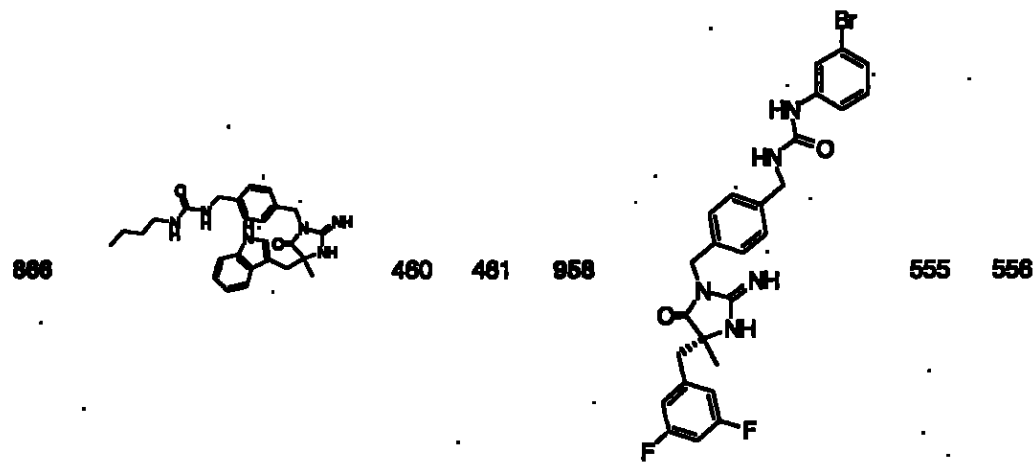


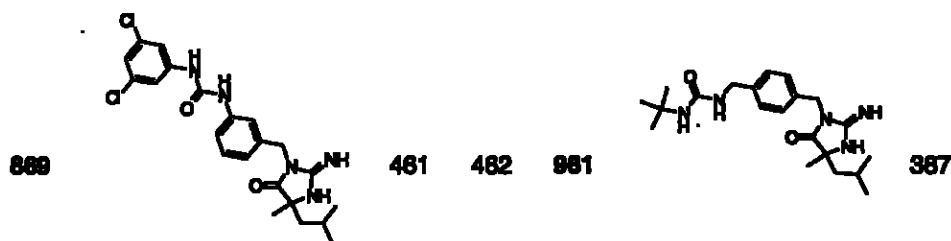
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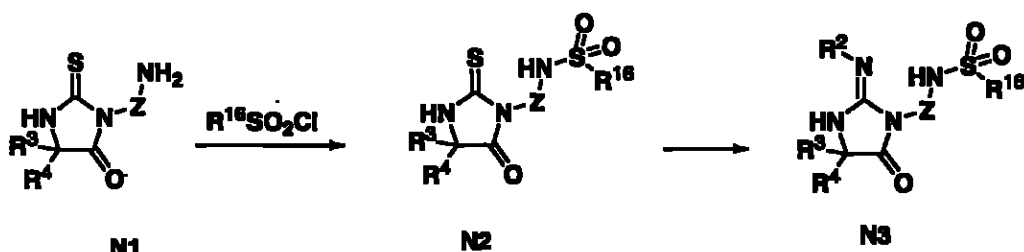
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Method N



- 5 (In the scheme, $-Z-NH-S(O)_2R^{16}$ is equivalent to R^1 substituted by R^{21} , or R^1 substituted by alkyl- R^{22} , wherein R^{21} and R^{22} are $-N(R^{16})-C(O)-NHR^{15}$ and R^{16} is H, and wherein Z is optionally substituted alkylene-arylene, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)
- 10

Method N, Step 1:

- Compound N2 ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para- $(CH_2)C_6H_4(CH_2)-$, $R^{16} = CH_2CH(CH_3)_2$) was prepared from N1 ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para- $(CH_2)C_6H_4(CH_2)-$) following the procedure described in Method K, Step 1.
- 15

Method N, Step 2:

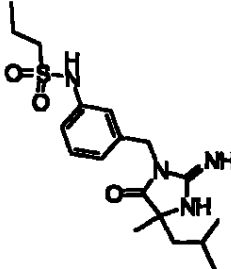
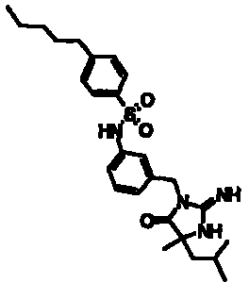
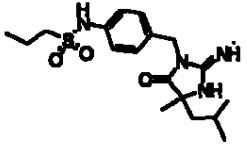
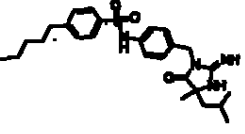
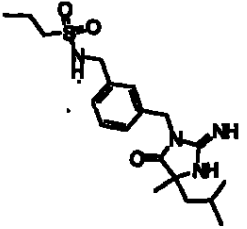
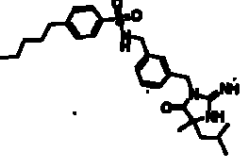
- Compound N3 ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para- $(CH_2)C_6H_4(CH_2)-$, $R^{16} = CH_2CH(CH_3)_2$) was prepared from N2 ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z =
- 20

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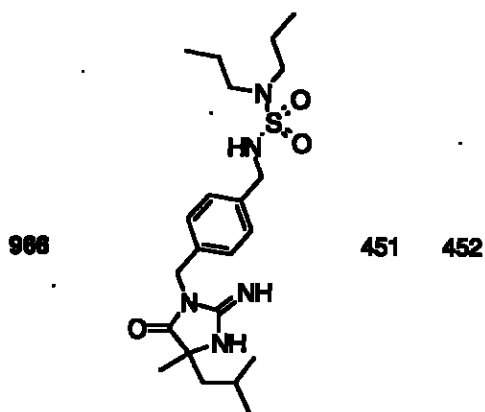
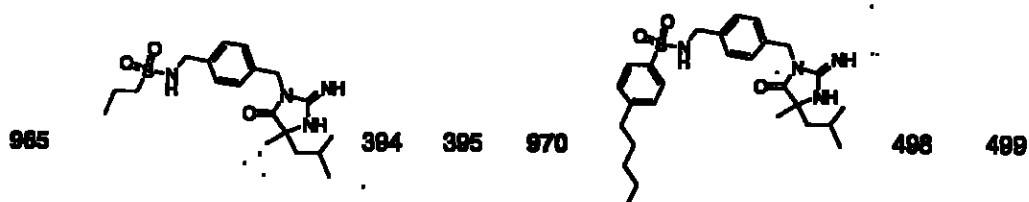
para-(CH₂)₆H₄(CH₂)-, R¹⁸ = CH₂CH(CH₃)₂) following the procedure described in Method A, Step 3.

The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
962		380	381	967		484	485
963		380	381	968		484	485
964		394	395	969		498	499

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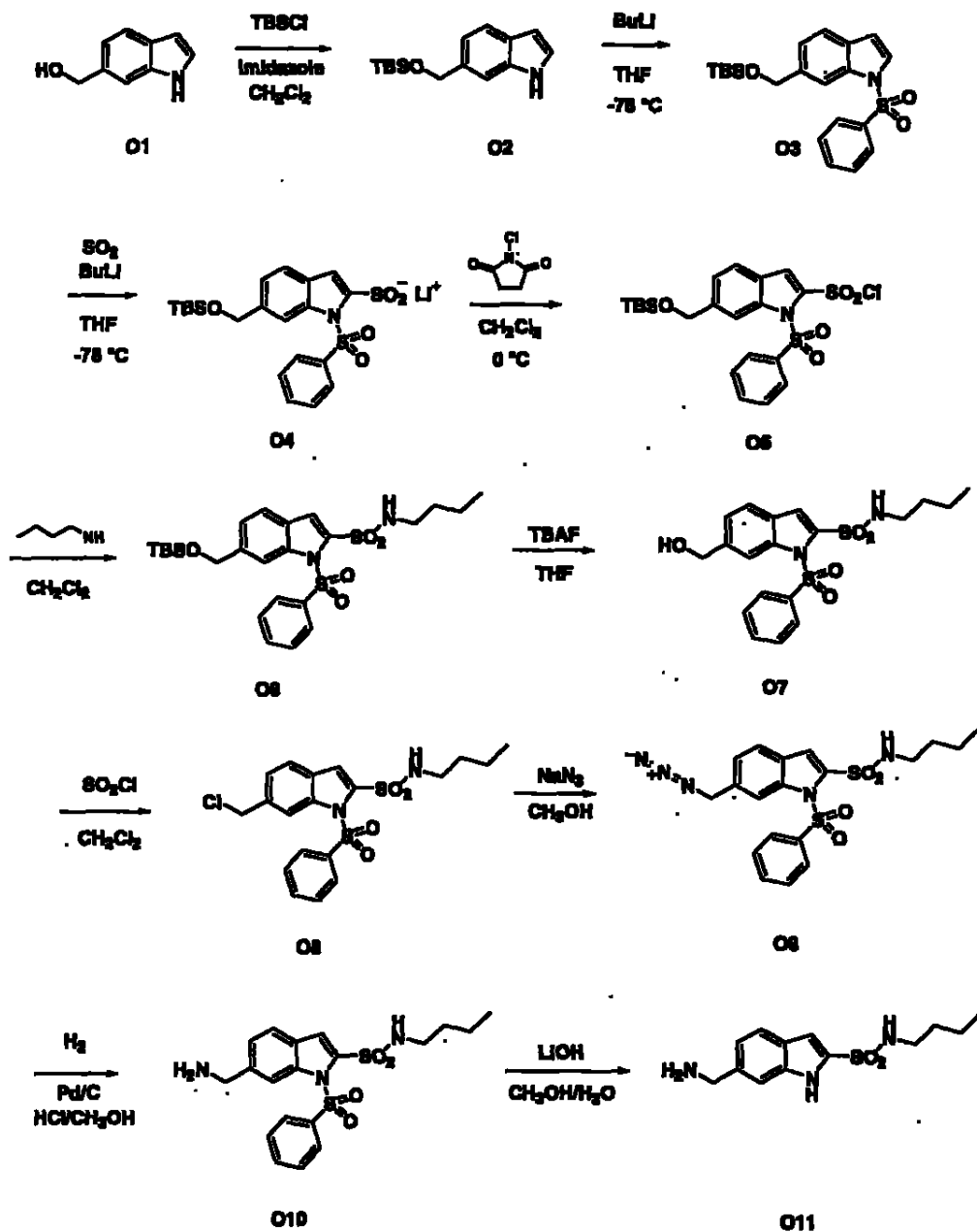
- 120 -



Method O

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**Method O, Step 1:**

5 A solution of indole-6-methanol (400 mg, 2.72 mmol), tert-butyldimethylsilyl chloride (816 mg, 5.41 mmol) and imidazole (740 mg, 10.9 mmol) in CH_2Cl_2 was stirred at rt. overnight before the solvent was evaporated and residue chromatographed using ethylacetate/hexane to give product **02**.

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- 122 -

Method O, Step 2:

To a solution of O2 (200 mg, 0.77 mmol) in THF (10 mL) at -78 °C was added butyl lithium (1.2 eq). The solution was stirred at -78 °C for 5 min and then warmed to rt. The reaction mixture was cooled to -78 °C and *p*-toluenesulfonyl chloride was added. The solution was warmed to rt and stirred overnight. The reaction was quenched with a saturated aqueous K₂CO₃ solution, extracted with ethyl acetate and CH₂Cl₂. The crude material was purified via flash chromatography using ethylacetate/hexane to afford 360 mg of O3.

10

Method O, Step 3:

A solution butyl lithium (1.2 eq) was added to a solution of O3 (340 mg, 0.829 mmol) in THF (20 mL). The reaction mixture was stirred for 15 min at -78 °C then sulfur dioxide was bubbled through the solution for 15 min. Hexane (100 mL) was added to the reaction mixture. The reaction mixture was evaporated to afford O4 which was used in the next step without further purification.

15

Method O, Step 4:

To a solution of O4 (0.829 mmol) in CH₂Cl₂ cooled to 0 °C was added N-chlorosuccinimide (220 mg, 1.66 mmol). After 2 h of stirring, the solution was filtered through a Celite plug. The filtrate was concentrated to afford O5.

20

Method O, Step 5:

To a solution of O5 in anhydrous pyridine (3 mL) was added butyl amine (100 µL). The reaction was agitated at rt for 4 d. The reaction mixture was partitioned between 1 N HCl and CH₂Cl₂. The organic layer was separated and washed with 1 N HCl (3x). The organic solution was dried over Na₂SO₄, filtered and concentrated. The crude material was purified via flash chromatography using ethylacetate/hexane to yield O6.

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Method O, Step 6:

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- 123 -

To a solution of O6 (70 mg) in THF was added TBAF. The reaction was stirred at rt. before the reaction mixture was chromatographed using ethylacetate/hexane to afforded 50 mg of O7 (95%).

5 **Method O, Step 7:**

To a solution of O7 (50 mg) in CH₂Cl₂ (5 mL) was added thionyl chloride (1 mL) the reaction was stirred for 5 min and then evaporated to afford O8.

Method O, Step 8:

10 To a solution of O8 in CH₃OH (5 mL) was added sodium azide (50 mg). The solution was stirred at rt overnight and solvent evaporated. The residue was chromatographed using ethylacetate/hexane to afforded O9 after purification.

Method O, Step 9:

15 To a suspension of O9 (70 mg) in CH₃OH was added 1 eq HCl (aq) and palladium on carbon. The reaction mixture was hydrogenated at 1 atm for 20 min to yield 90 mg of crude product O10.

Method O, Step 10:

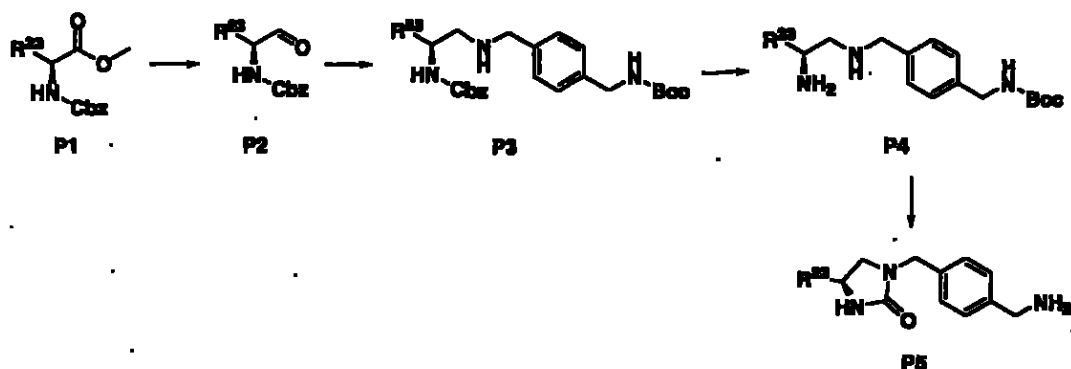
20 A solution of lithium hydroxide (30 mg) in H₂O was added to a solution of O10 (40 mg) in CH₃OH (3 mL). The reaction was stirred at rt for 2 h and an additional portion of LiOH (40 mg) was added and solution was stirred for 2 more hours. The solvent was evaporated and residue chromatographed using ethylacetate/hexane to afforded O11.

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Method P

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**Method P, Step 1:**

A 300 mL of THF solution of 100 g of P1 ($R^{23}=n\text{-Pr}$) was added to a suspension of 38 g of LAH in 2 L of anhydrous THF at 0 °C. The reaction mixture is stirred at r.t. for 1h before 30 ml of H_2O , 90 ml of 15% NaOH was added at 0 °C. The mixture was stirred at r.t. for one hour before Na_2SO_4 (anh) was added, the mixture was filtered, and the solution evaporated to give a product which was dried under vacuo overnight. This product was dissolved in 600 ml of DCM and the solution was added into a solution of oxalyl chloride (37.3 ml) and DMSO (60.8 ml) in 1.4 L of DCM at -78 °C over 40 min before Diisopropylethylamine (299 ml) was added at -78 °C. The reaction was allowed to reach -10 °C. The reaction was quenched with 1 L H_2O at -10 °C and the mixture was extracted with DCM. After removal of solvent, P2 ($R^{23}=Pr$, 106 g) was obtained. The crude material was used for next step without purification.

Method P, Step 2:

To a 1.5 L DCM solution of P2 ($R^{23}=Pr$, 106 g) was added p-Boc-aminomethylbenzylamine (1.1 eq) and sodium triacetoxyborohydride (1.1 eq) and the reaction was stirred at r.t. overnight. The reaction was quenched with H_2O and content extracted with DCM. After removal of solvents the residue was chromatographed using a silica gel column eluted with 3% MeOH in DCM to give 42.5 g of P3 ($R^{23}=Pr$).

Method P, Step 3:

A 10 ml MeOH solution of P3 ($R^{23}=Pr$, 110 mg) was hydrogenated using Pd/C (5%, 11 mg) at 1 atm of hydrogen to give product P4 ($R^{23}=Pr$) after removal of solvent and catalyst.

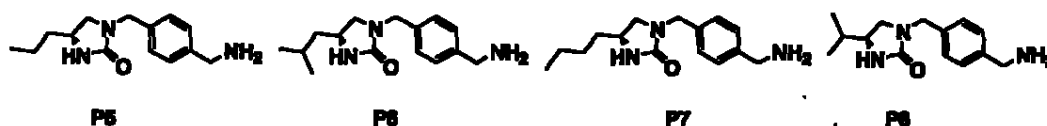
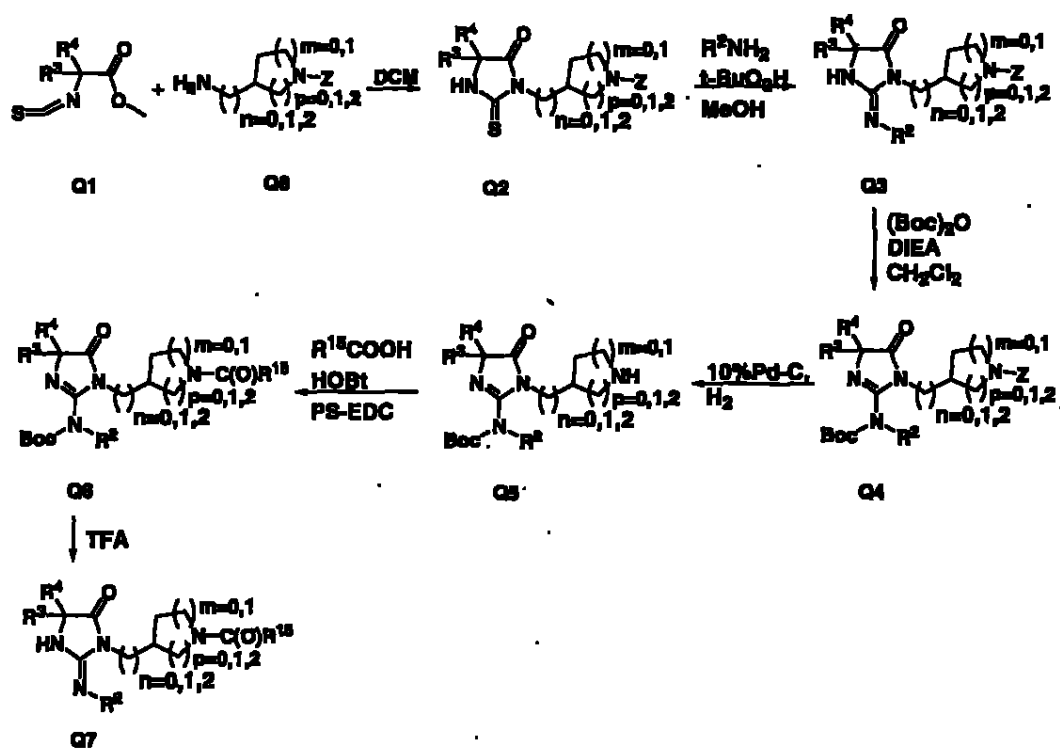
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Method P, Step 4:

To a 10 ml DCM solution of P4 at 0 °C ($R^{23}=Pr$) was added triphosgene (1.2 eq) and triethylamine (2.4 eq) and the solution was stirred at 0 °C for 2 h before the reaction was extracted with DCM/H₂O. After removal of the solvent, the residue was chromatographed using a silica gel column eluted with EtOAc/Hexane to give a white solid which was treated with 2N HCl in dioxane for 2 h. After removal of the solvent, compound P5 ($R^{23}=Pr$) as a white solid was obtained (80 mg).

The following compounds were synthesized using similar methods:

**Method Q**

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Method Q, Step 1

At room temperature, Q1 ($R^3=Me$; $R^4=iBu$) (1.00 g) and Q8 ($n=1$, $p=2$, $m=1$) (1.24 g) in dichloromethane (30 mL) were stirred for 42 h. This mixture was concentrated *in vacuo* to give an amber oil which was purified on a column of silica gel (200 mL) eluted with ethylacetate/hexane to give Q2 ($n=1$, $p=2$, $m=1$, $R^3=Me$; $R^4=iBu$), a colorless oil (1.59 g).

Method Q, Step 2

Compound Q3 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) was prepared from Q2 ($n=1$, $p=2$, $m=1$, $R^3=Me$; $R^4=iBu$) using method similar to method A step 3.

Method Q, Step 3

Compound Q3 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) (1.37 g) in anhydrous dichloromethane (25 mL) was treated with di-*tert*-butyl dicarbonate (0.66 g, 1.1 equiv.) and diisopropylethylamine (0.66 mL, 1.1 equiv.). The resulting solution was stirred at room temperature for 20 h before it was diluted with dichloromethane and washed with 1N hydrochloric acid. The dried dichloromethane solution was concentrated *in vacuo* to give a colorless film (1.32 g) which was purified on a column of silica gel (125 mL) and eluted with hexane : ethyl acetate to give compound Q4 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) as a white foam (0.74 g).

Method Q, Step 4

Compound Q4 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) (0.540 g) in absolute EtOH (20 mL) was hydrogenated with 10% Pd/C (0.400 g) at 1 atm for 2 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give Q5 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) as a colorless oil (0.35 g).

Method Q, Step 5

Compound Q5 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) (0.012 g) and HOBt (0.005 g) dissolved in acetonitrile (0.8 mL) and tetrahydrofuran (0.25 mL) was treated with EDC resin (0.080 g, 3 eq., 1.53 mmol/g) in a microtiter plate

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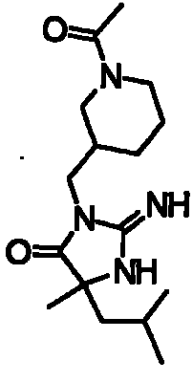
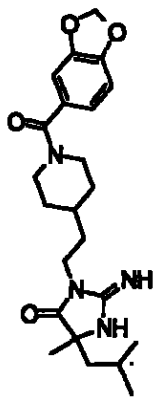
well followed by addition of a 1M dichloroethane solution of R^{15} -COOH (40 μ L, 1.25 eq.). After the well was capped and shaken for 18 h, the mixture was filtered and the resin washed with acetonitrile (0.5 mL). The combined solution was treated with Trisamine resin (0.050 g, 6 eq., 4.23 mmol/g) and Isocyanate resin (0.067 g, 3 eq., 1.53 mmol/g) for 18 h before the solution was filtered and the solvent was removed in vacuo to give **Q6** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$, $R^{15}=Me$).

Method Q, Step 6.

A dichloromethane solution (1.0 mL) of **Q6** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$, $R^{15}=Me$) was mixed with trifluoroacetic acid (1.0 mL) and the solution was shaken for 2 h before it was concentrated. Diethyl ether (0.5 mL) was added and then concentrated *in vacuo* to give a residue, which was purified on a Prep LCMS unit to give **Q7** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$, $R^{15}=Me$). NMR ($CDCl_3$): δ 8.38, br, 2H; δ 4.58, m, 1H; δ 3.79, m, 1H; δ 3.57, m, 2H; δ 2.99, m, 1H; δ 2.48, m, 1H; δ 2.04, s, 3H; δ 1.95, m, 1H; δ 1.5-1.8, m, 5H; δ 1.5, s, 3H; 1.25, m, 2H; δ 0.95, m, 3H; δ 0.85, m, 3H. ES_LCMS (m/e) 309.17.

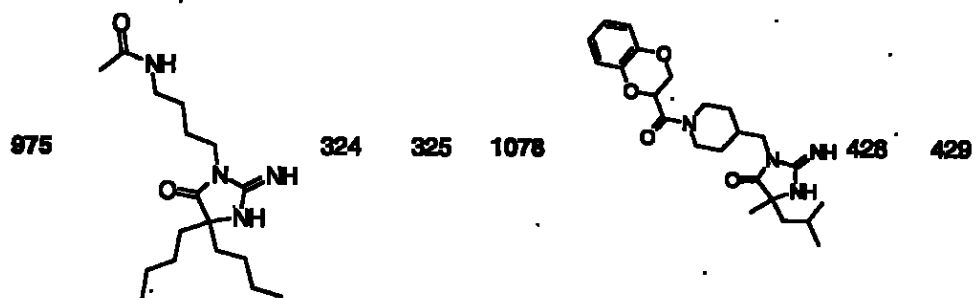
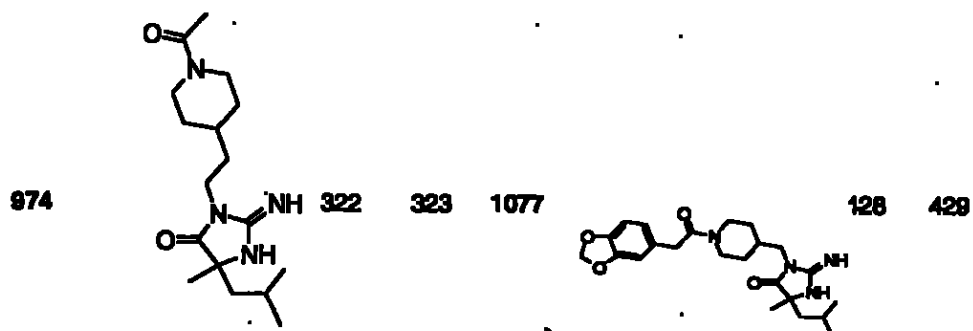
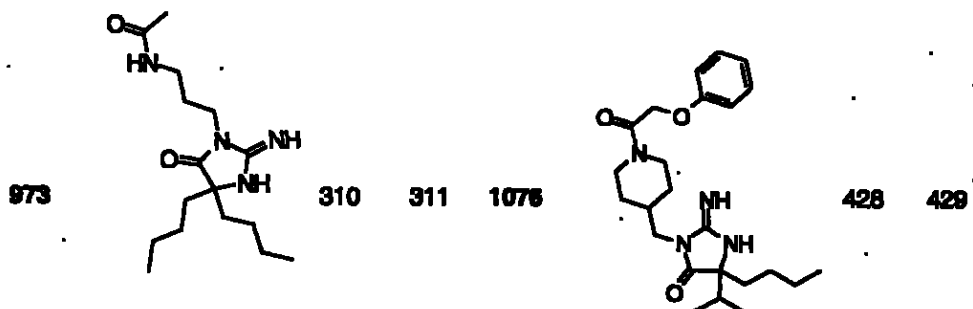
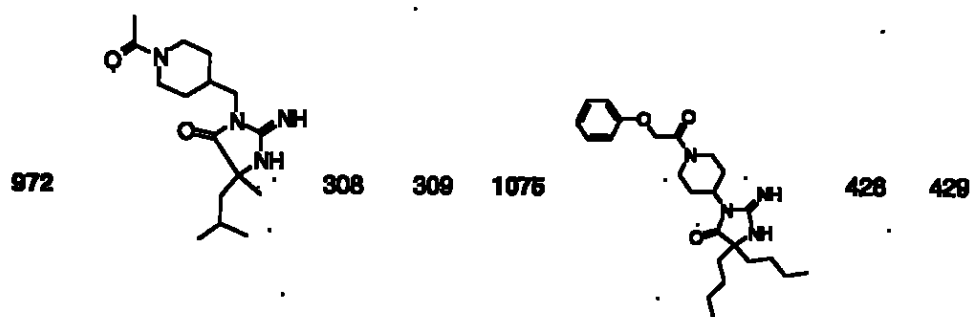
The following compounds were prepared using similar methods:

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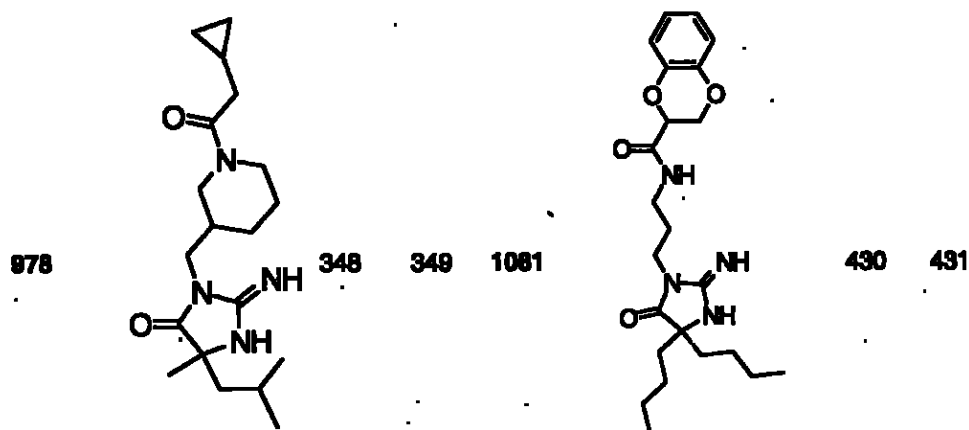
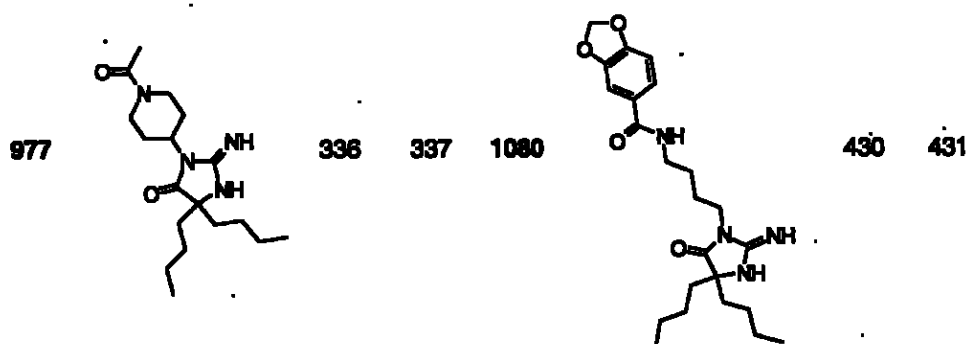
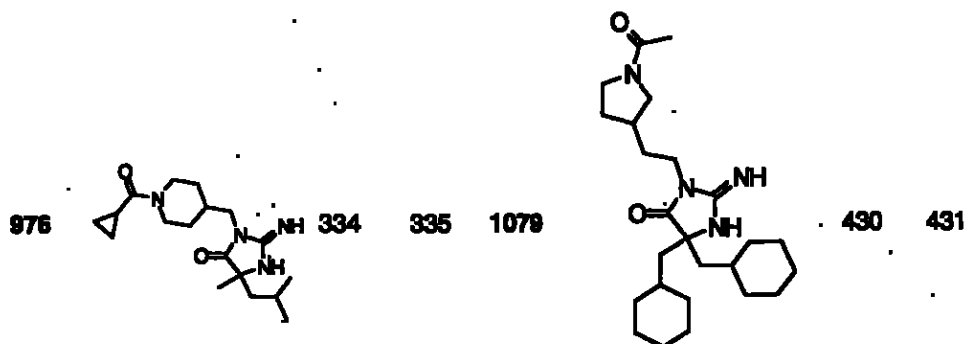
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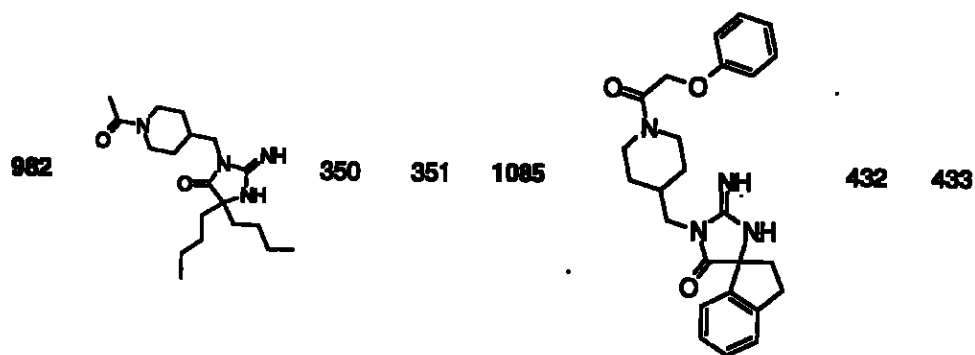
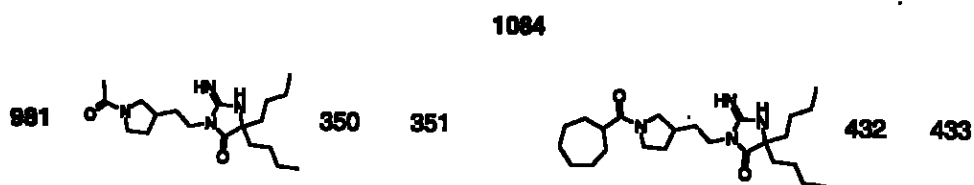
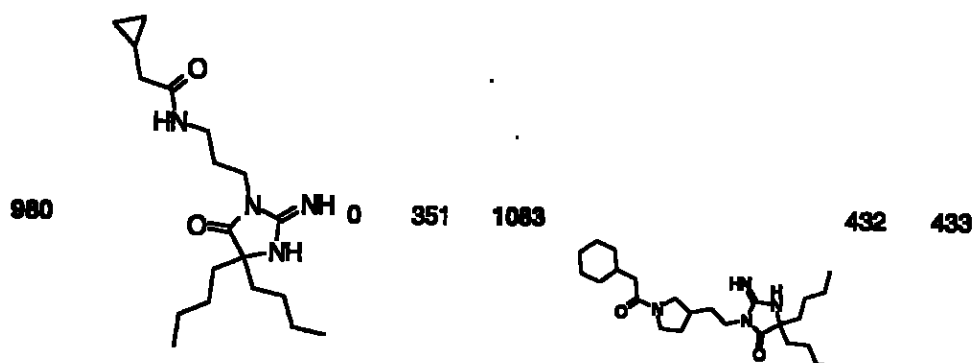
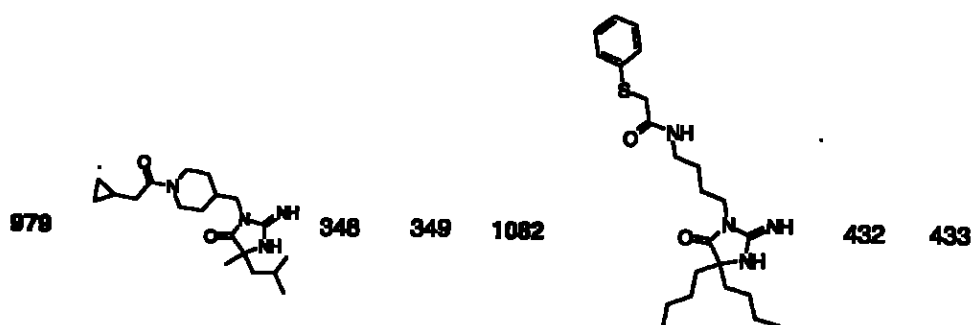
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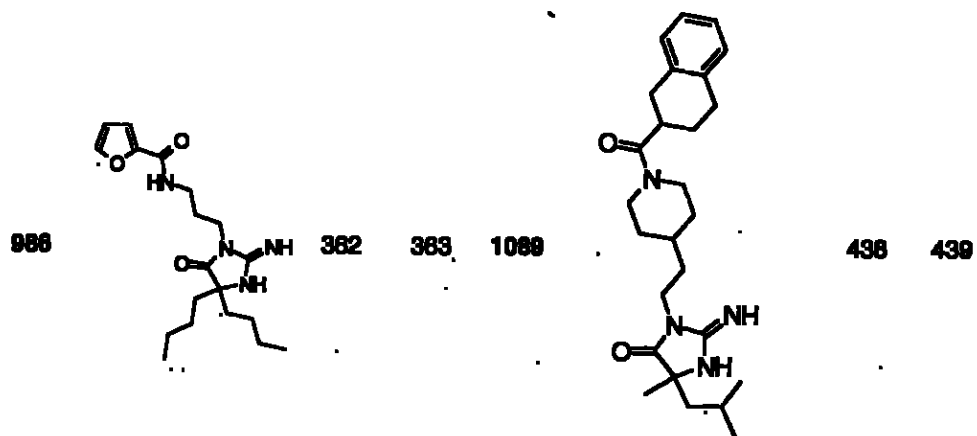
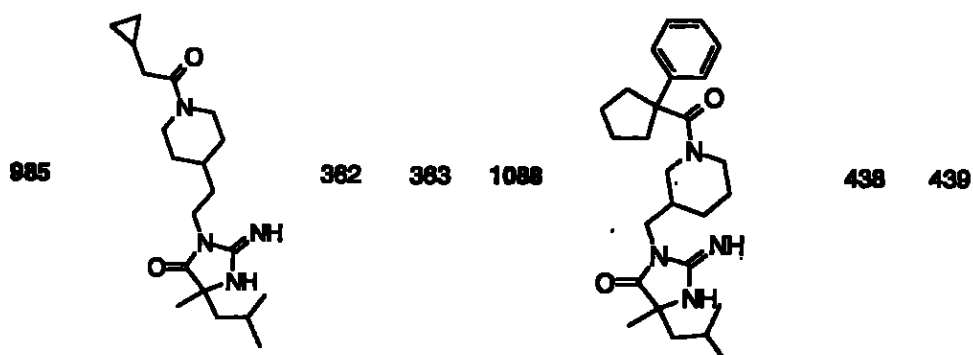
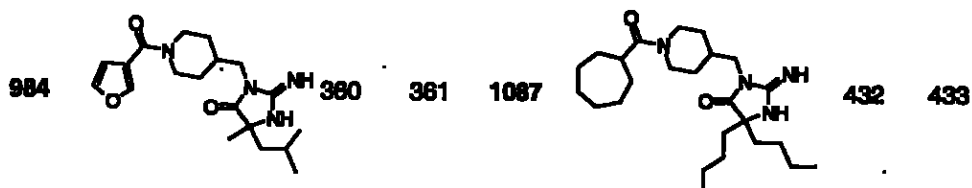
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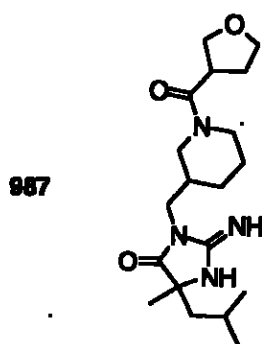
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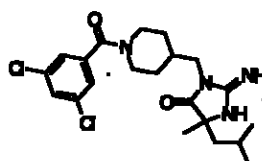
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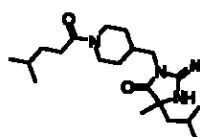
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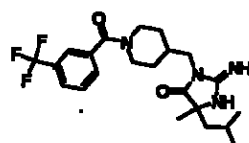
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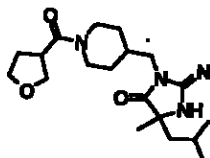
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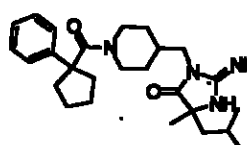
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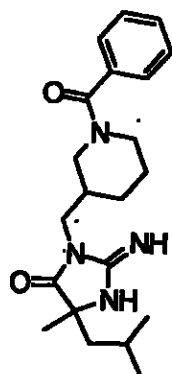
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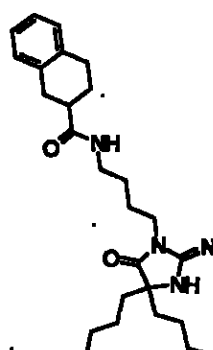
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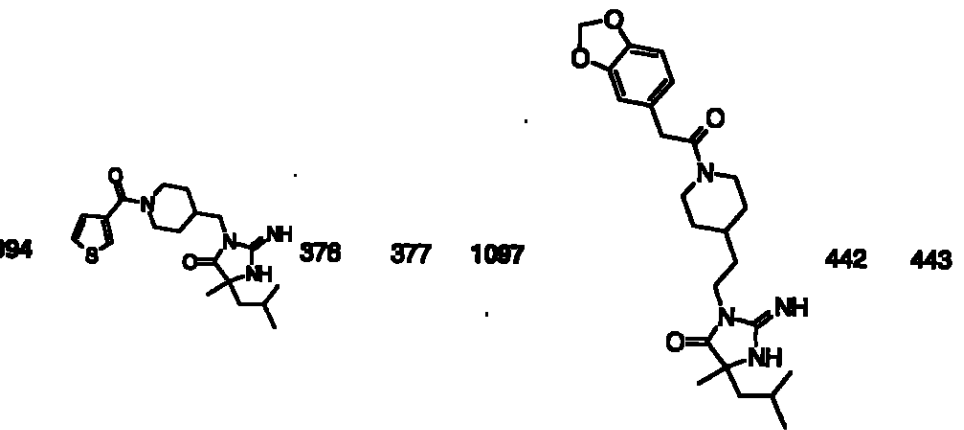
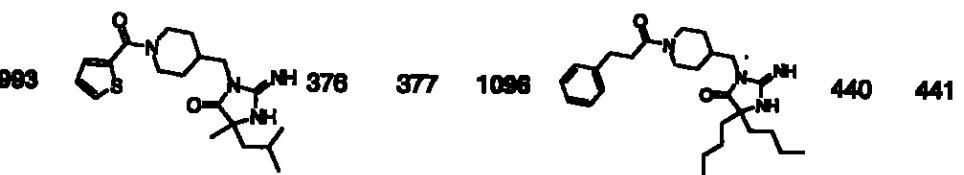
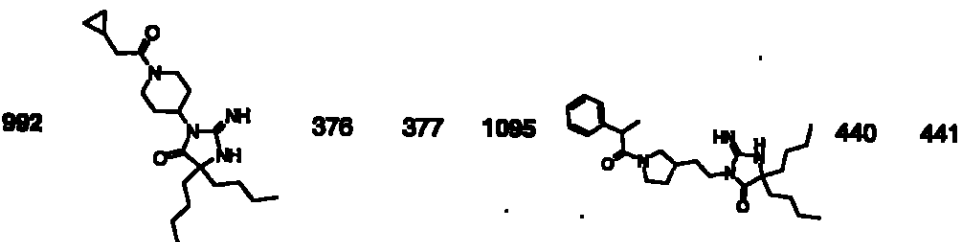
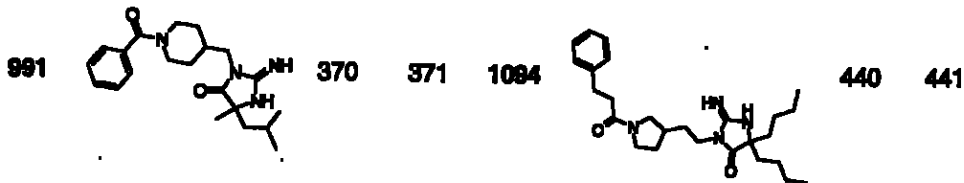
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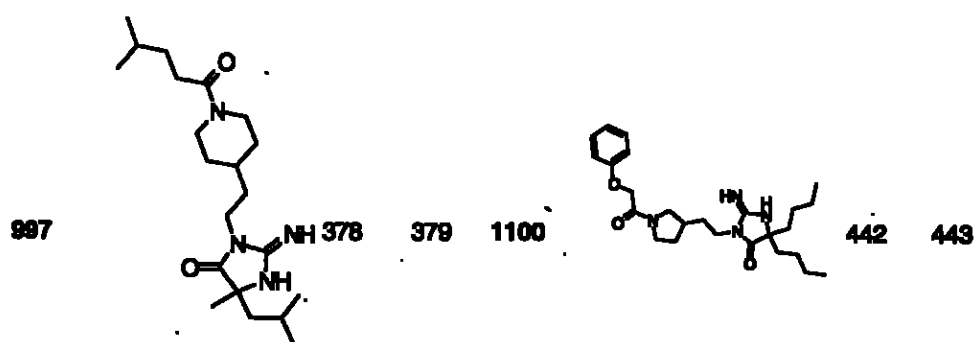
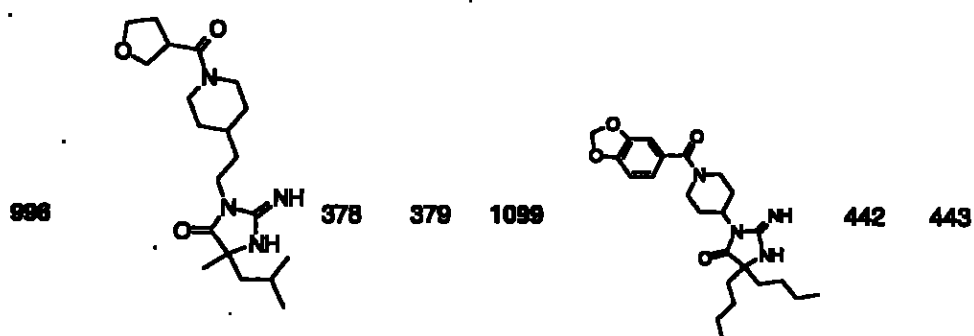
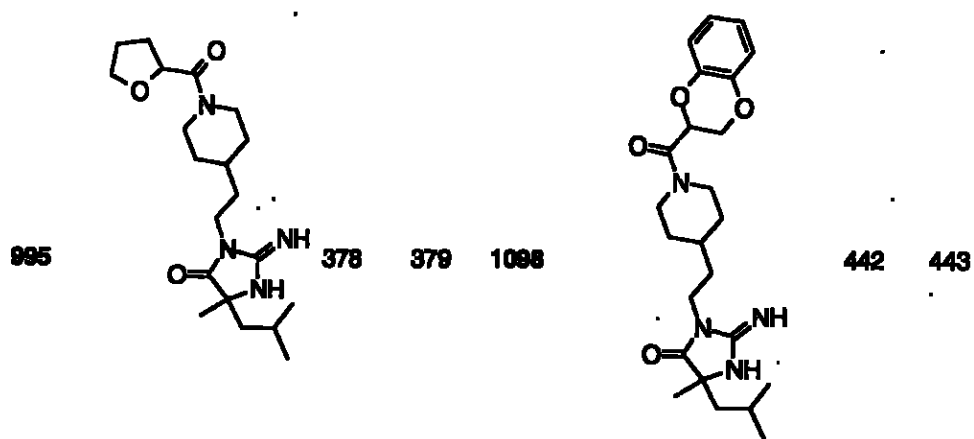


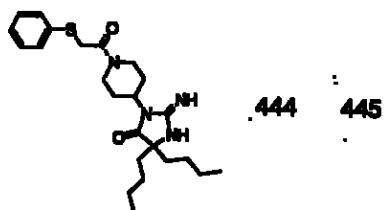
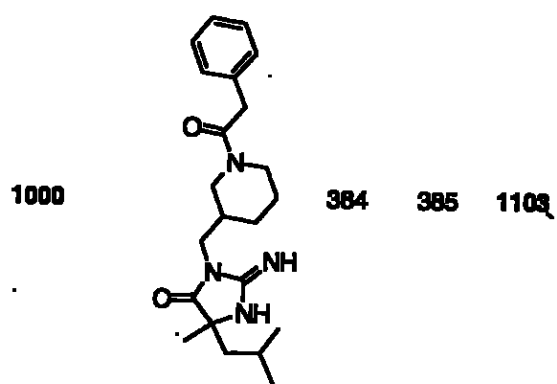
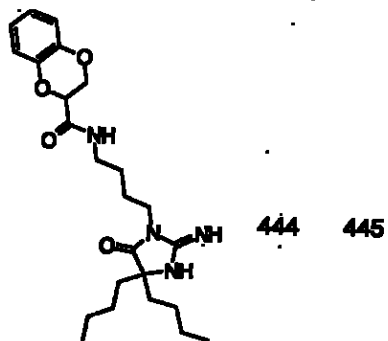
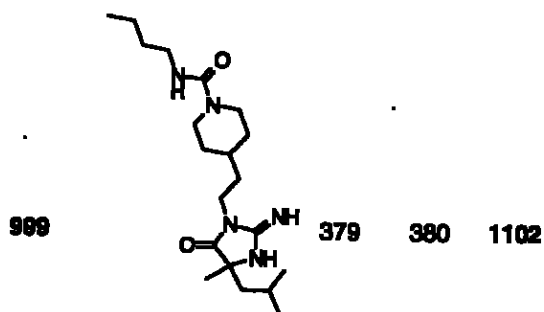
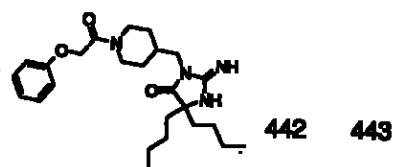
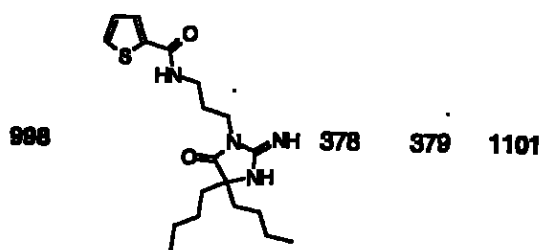
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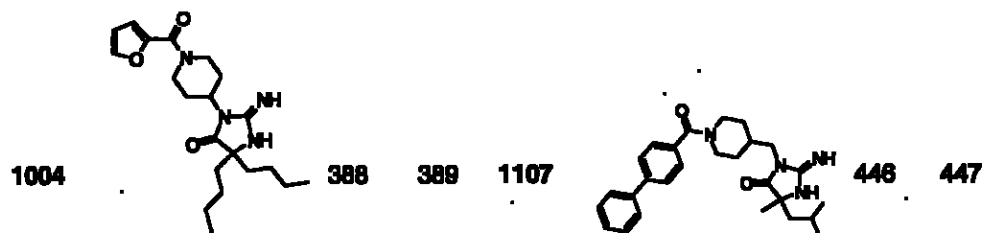
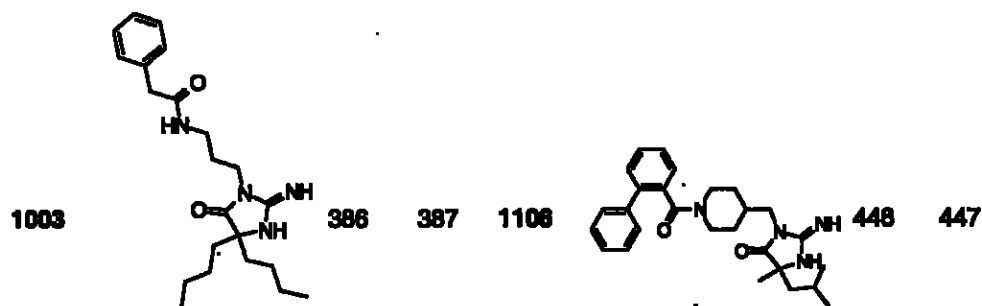
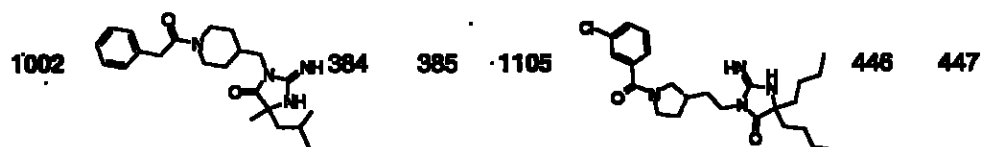
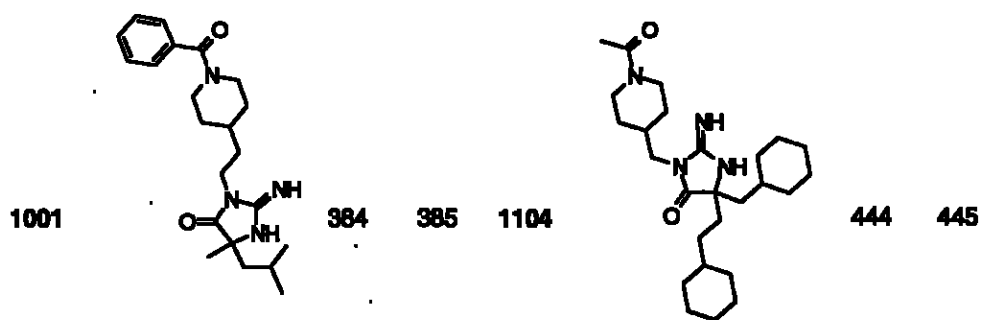




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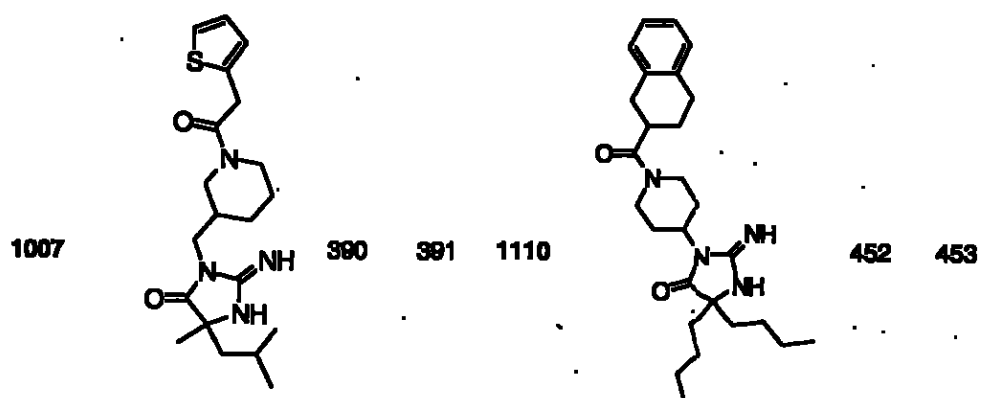
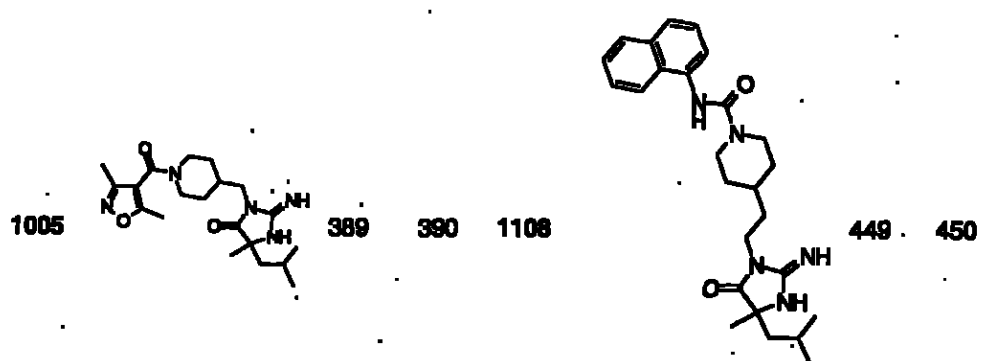
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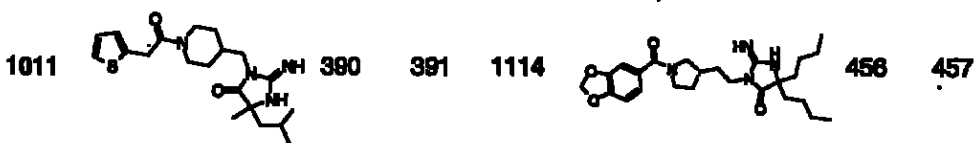
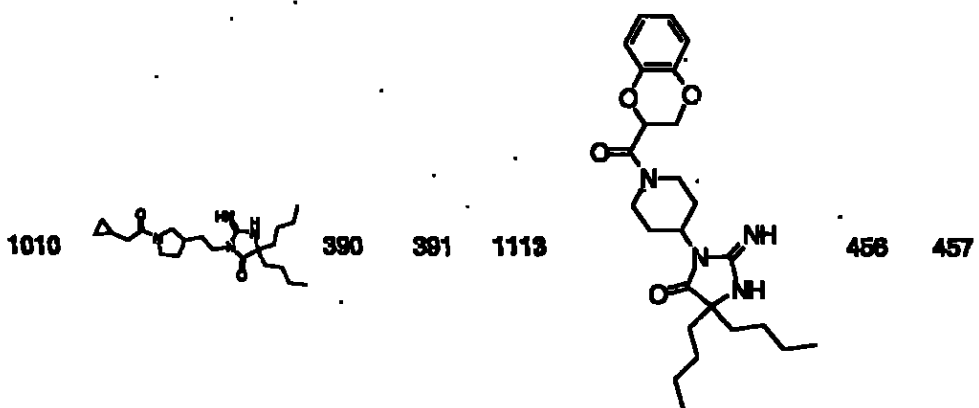
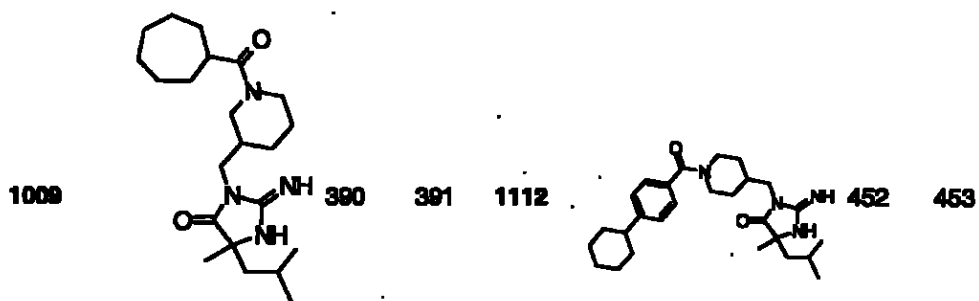
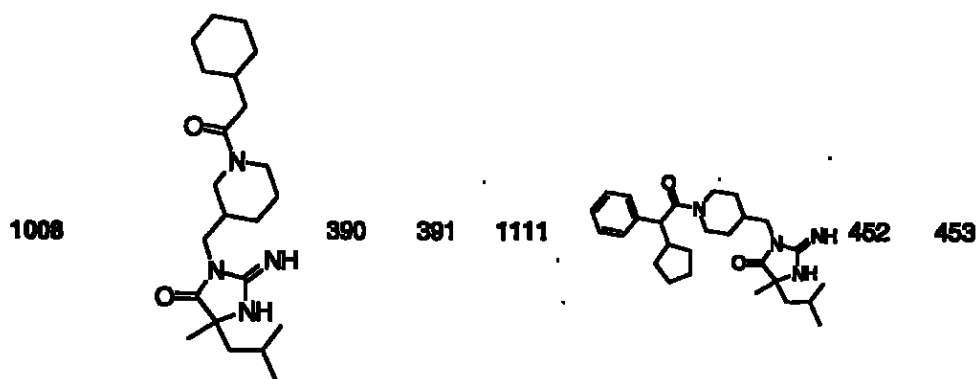
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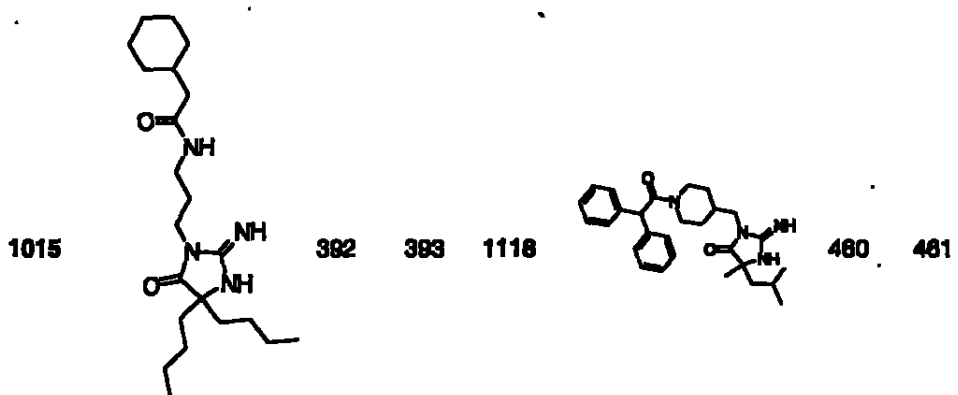
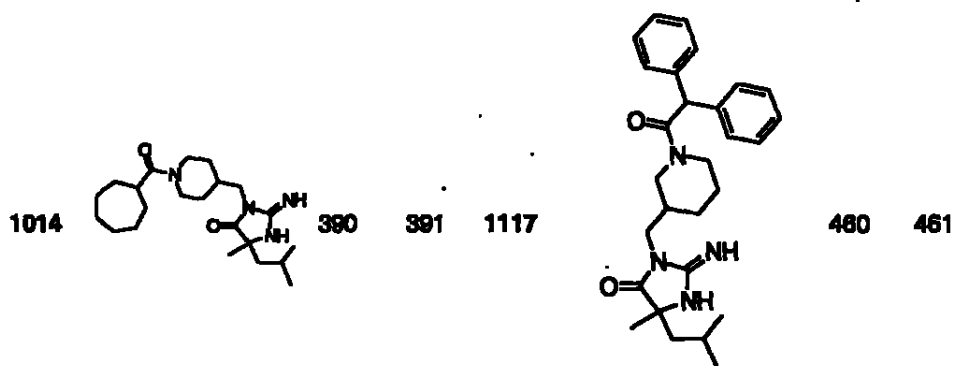
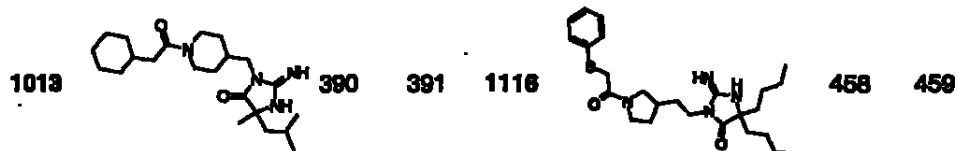
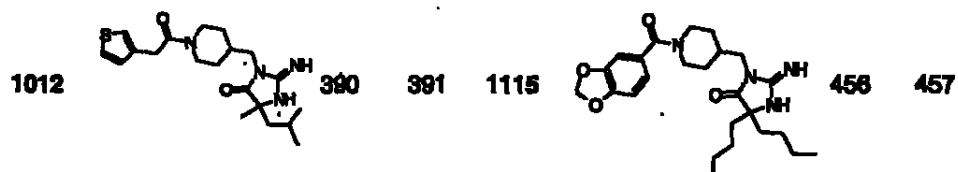
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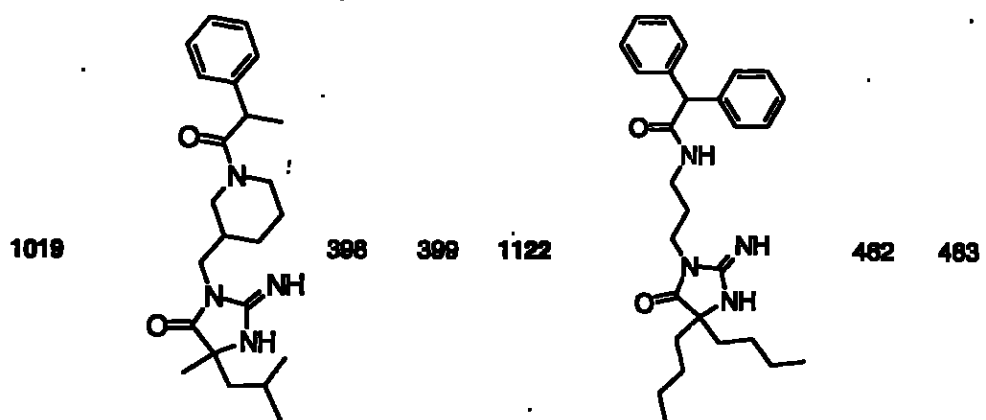
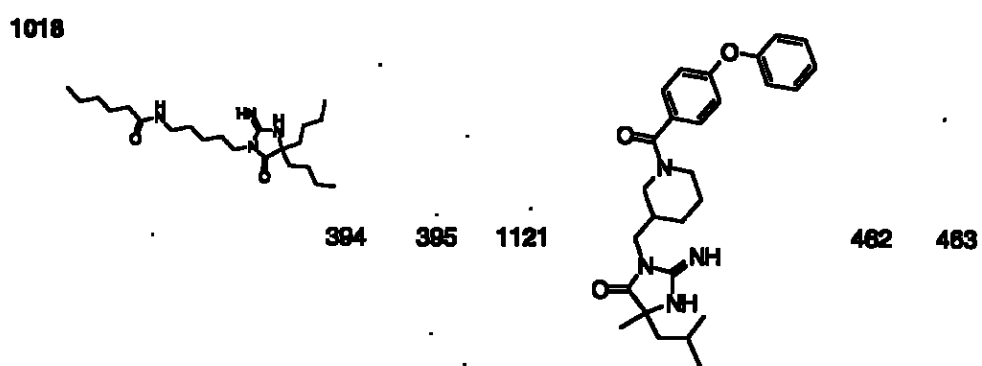
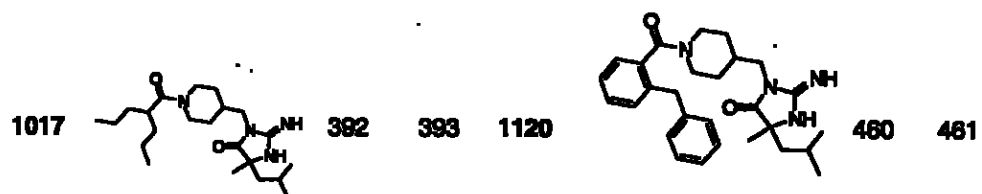
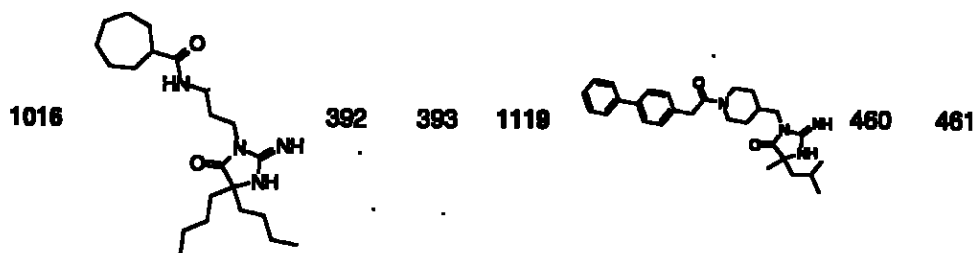
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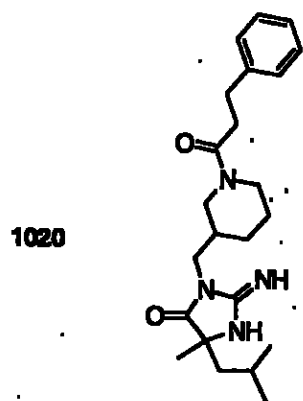
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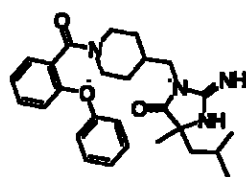
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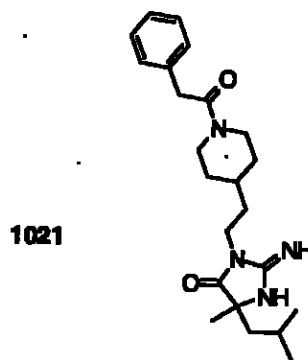
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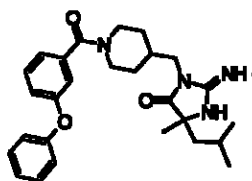
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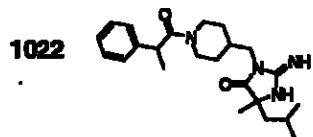
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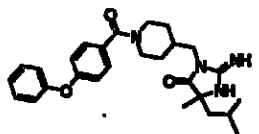
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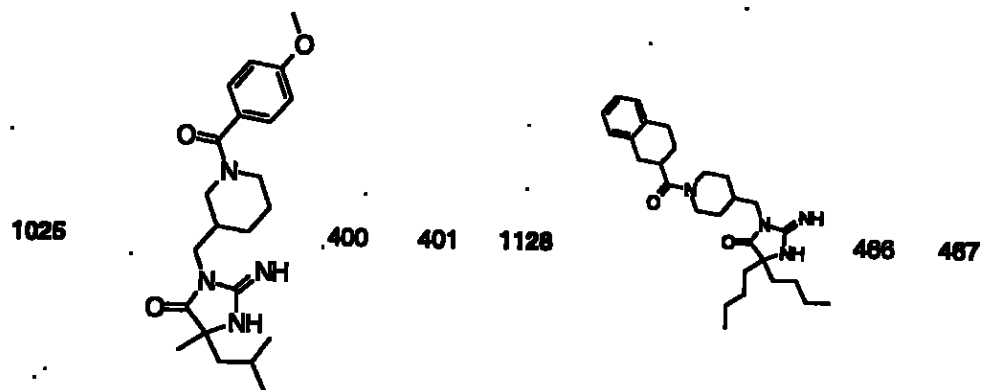
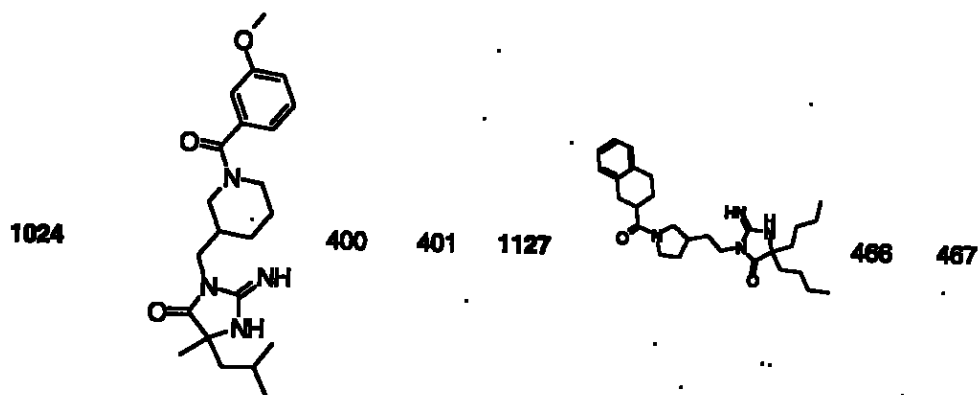
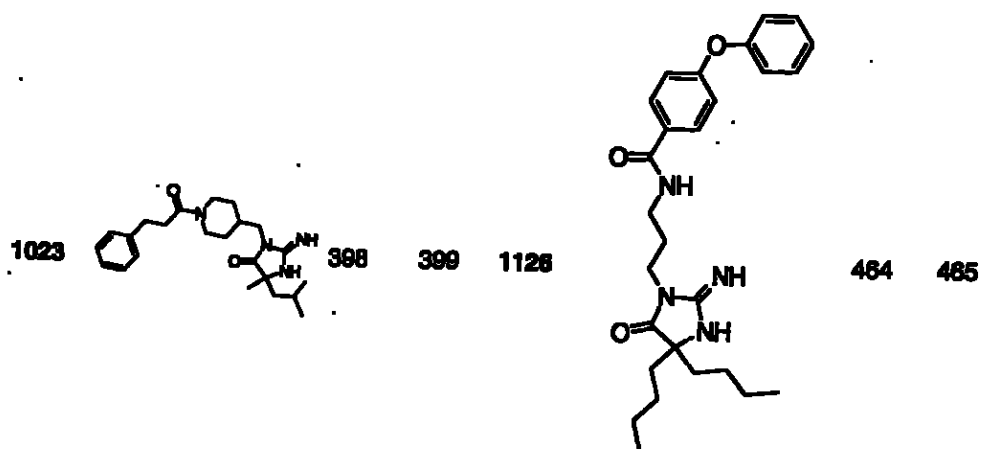
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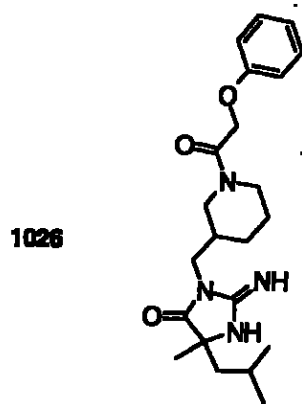
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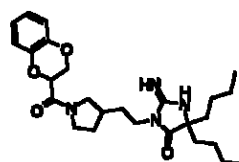
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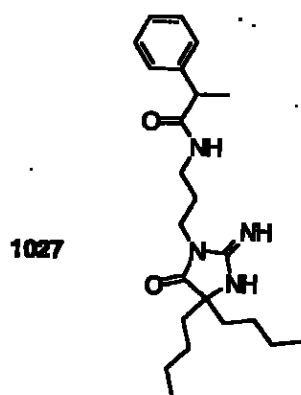
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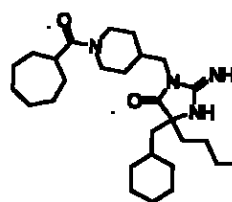
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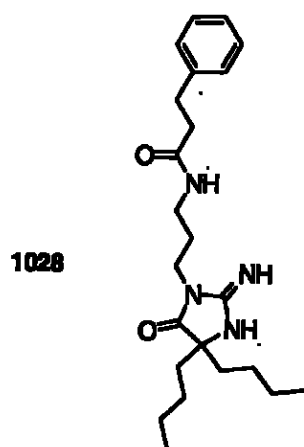
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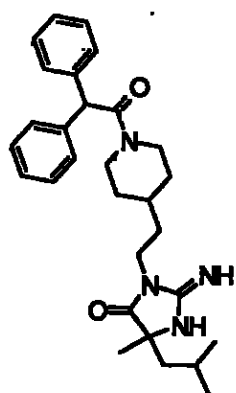
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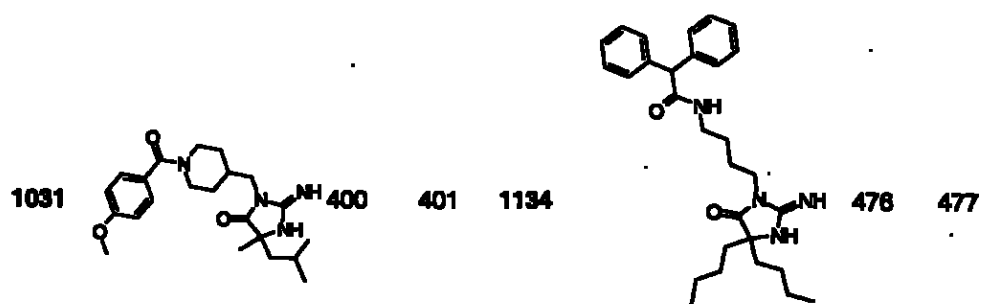
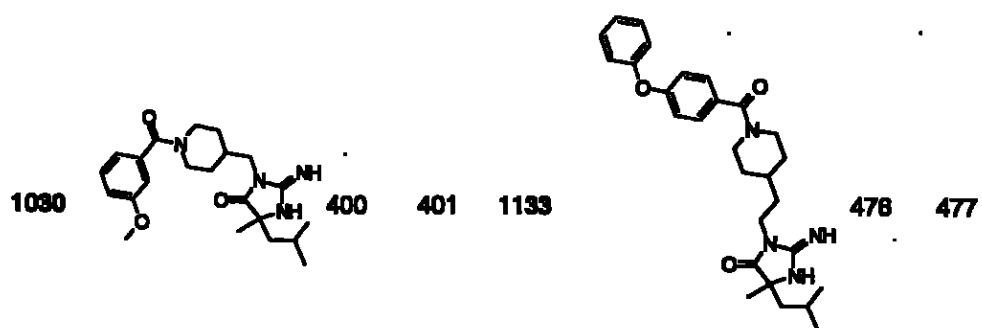
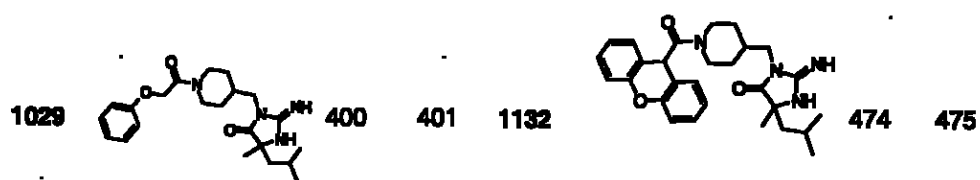
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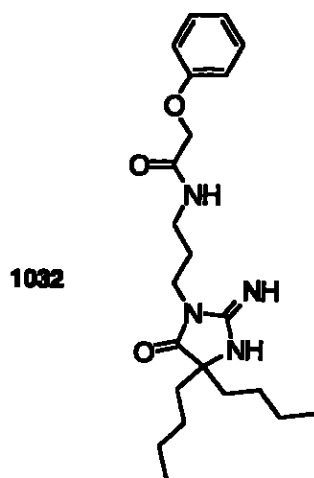
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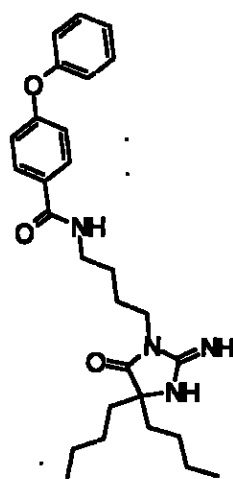
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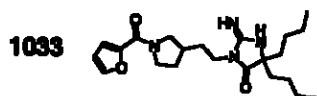
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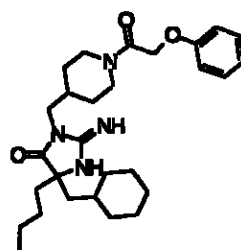
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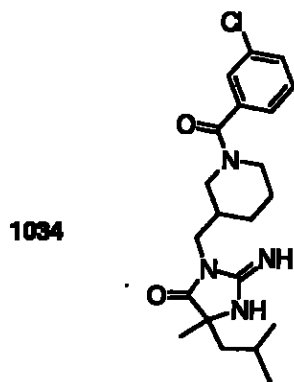
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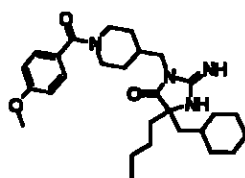
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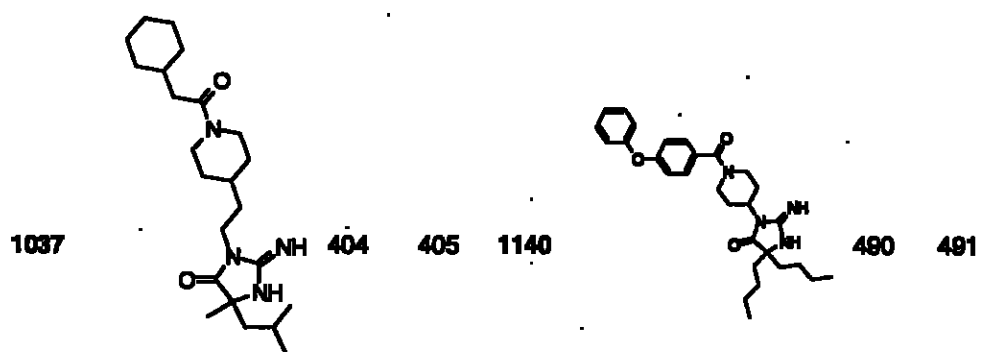
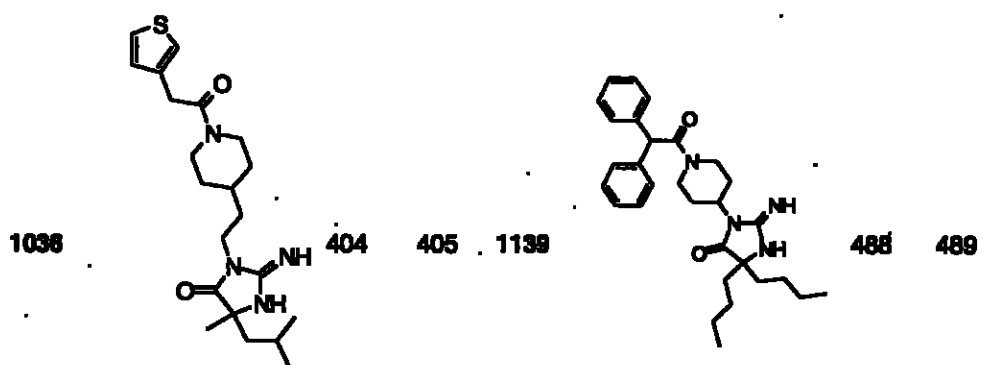
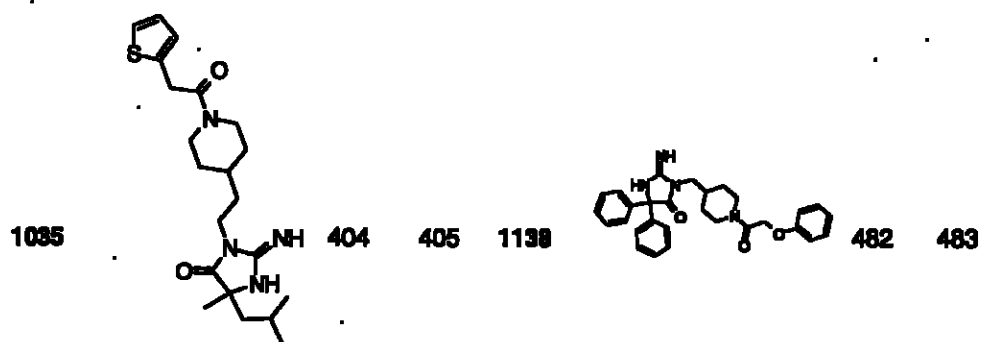
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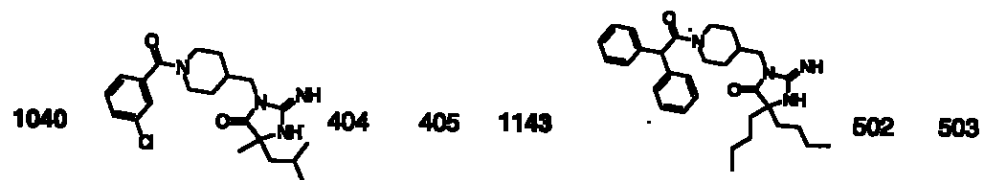
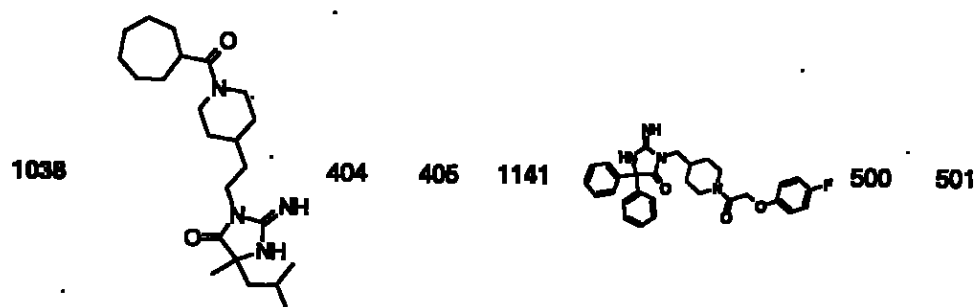
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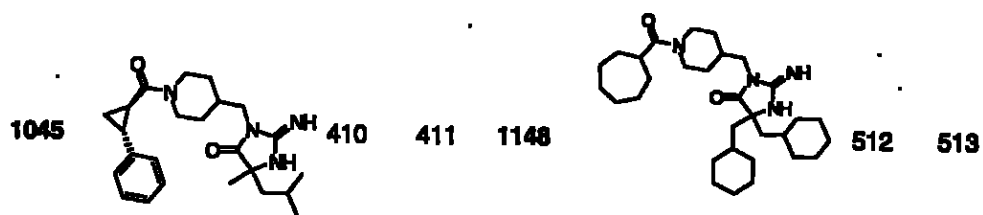
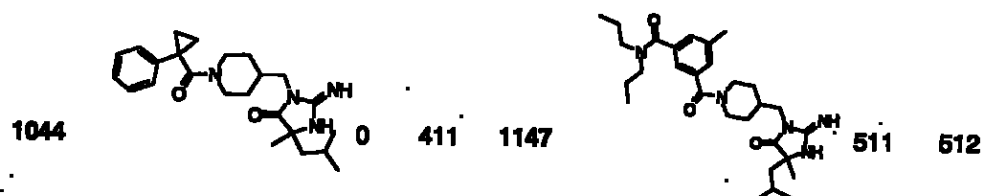
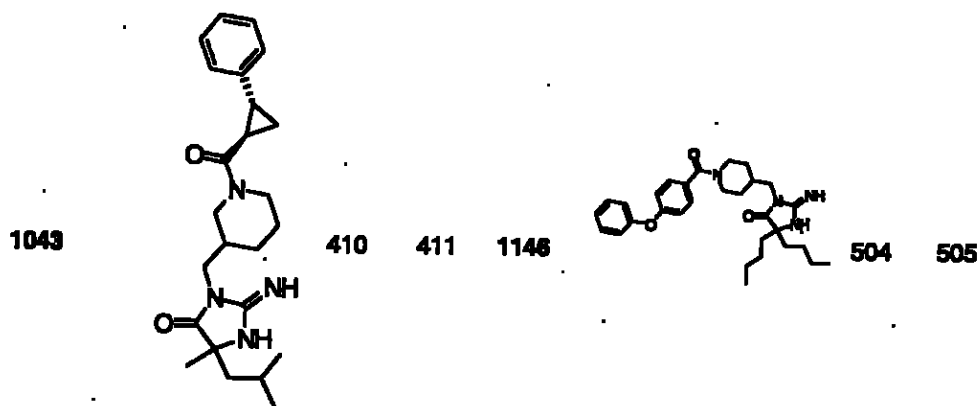
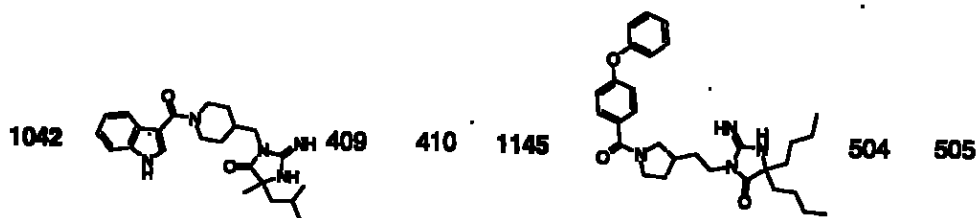
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- 146 -



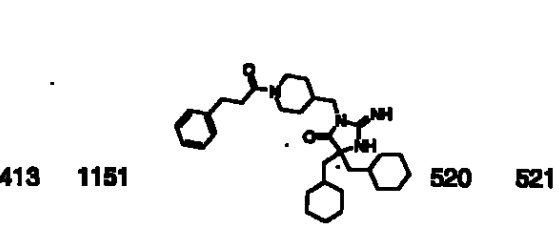
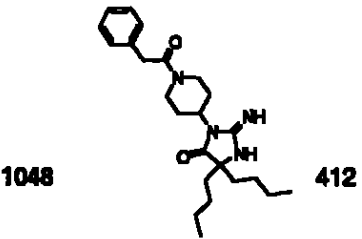
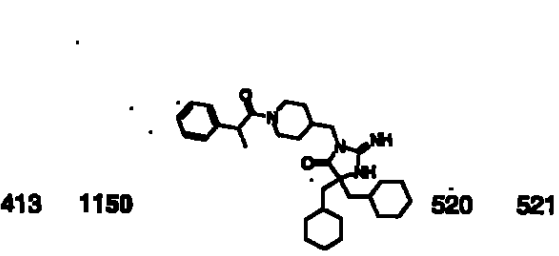
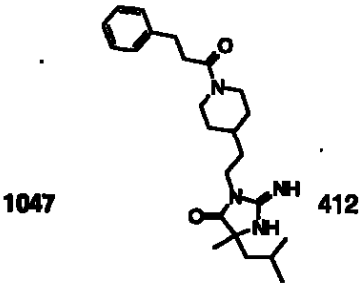
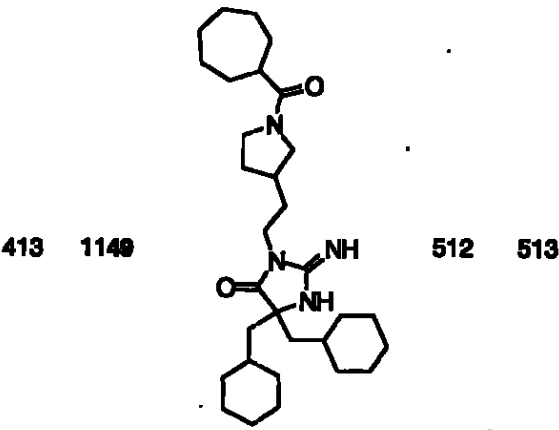
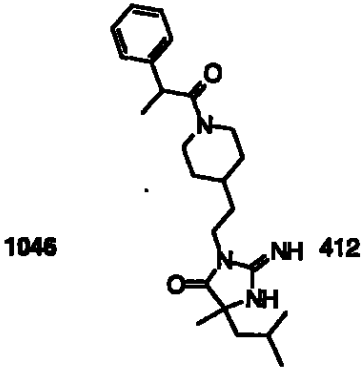




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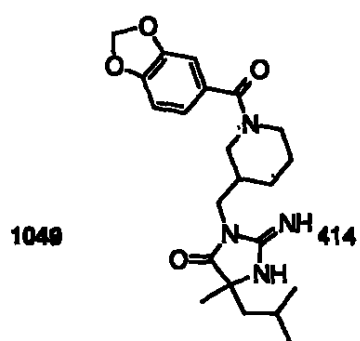
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- 149 -



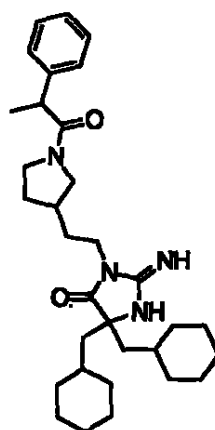
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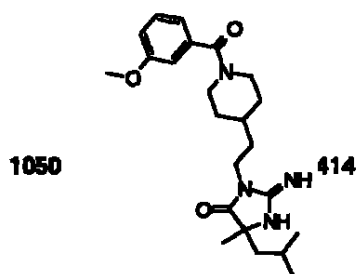


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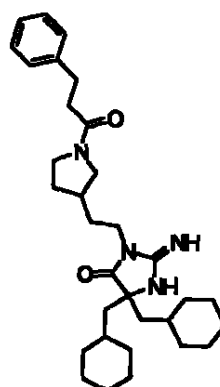


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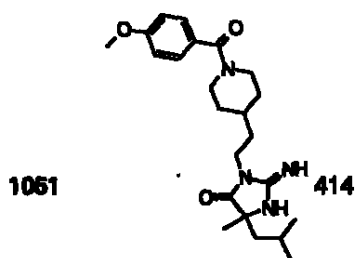


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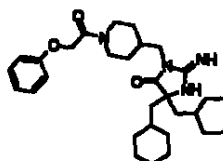


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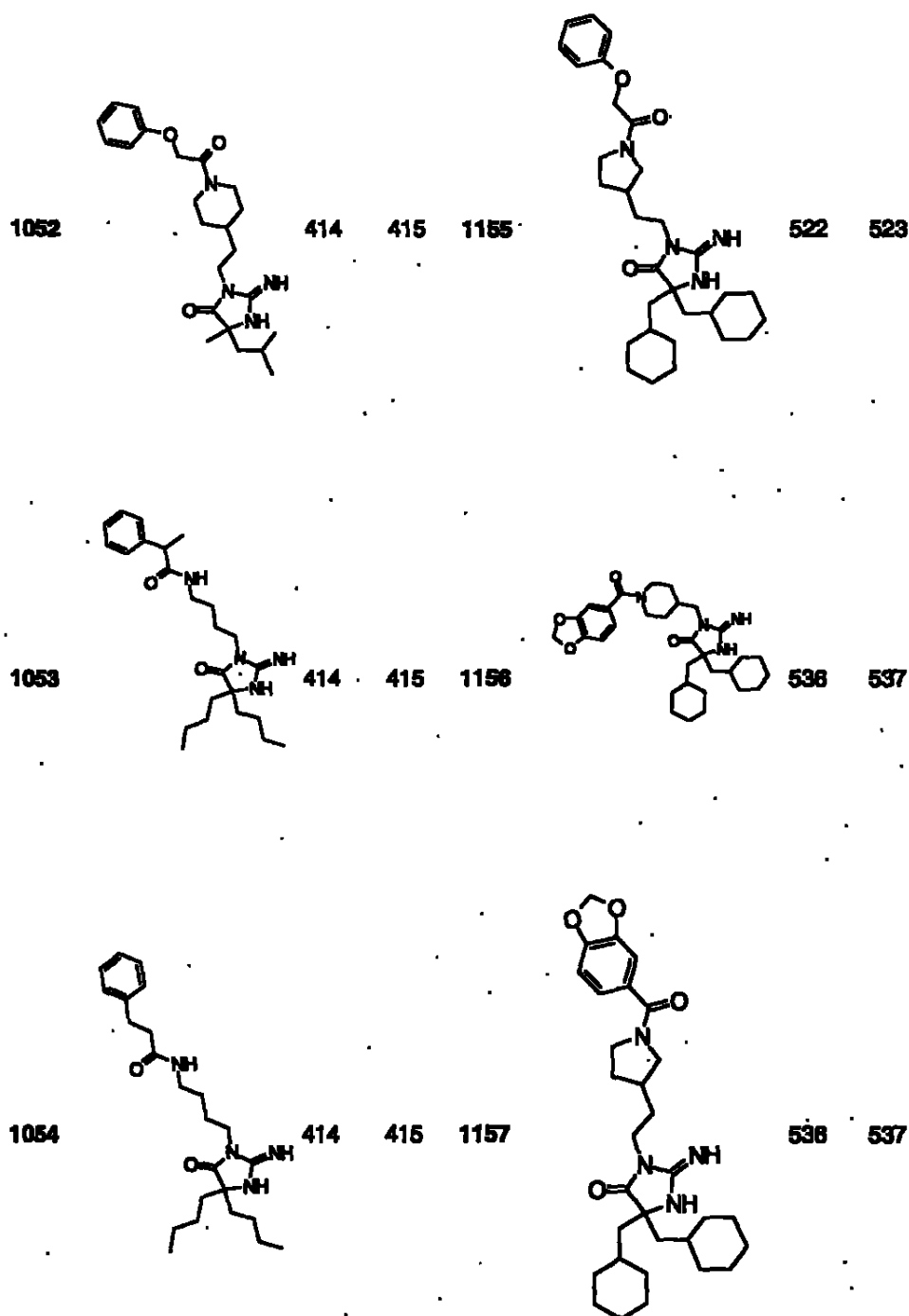
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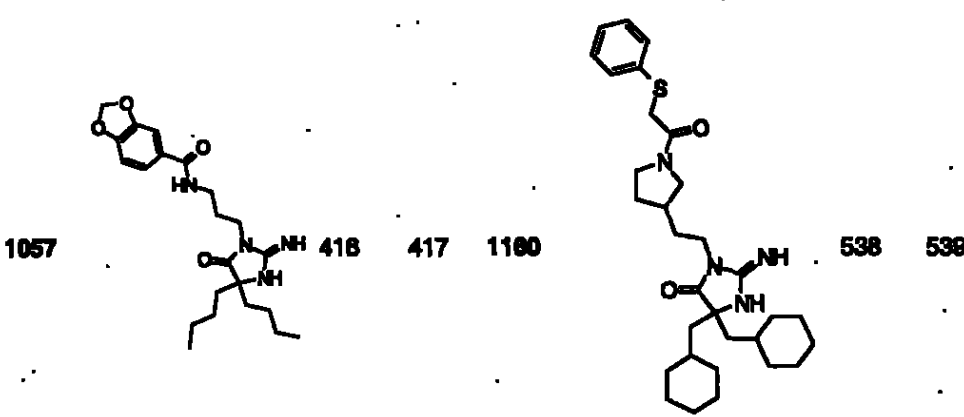
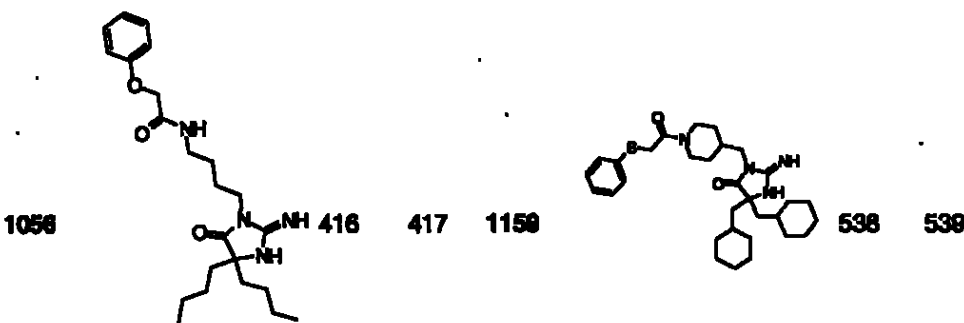
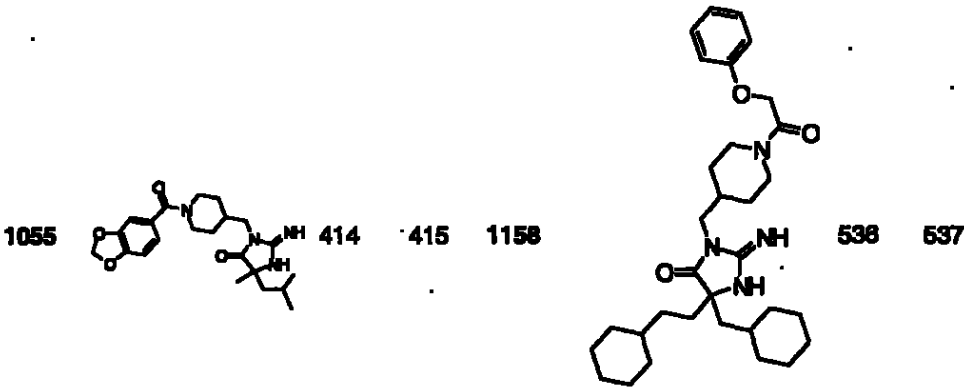


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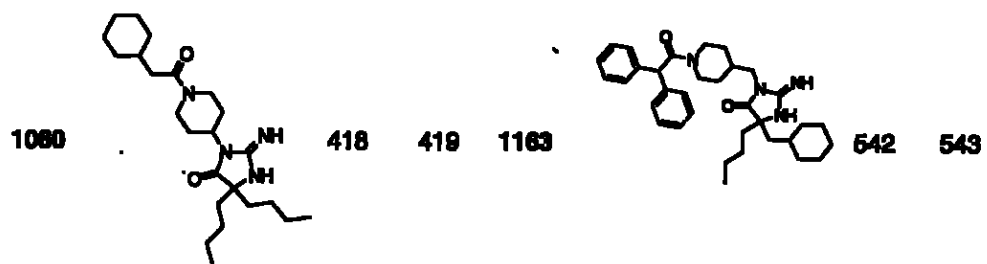
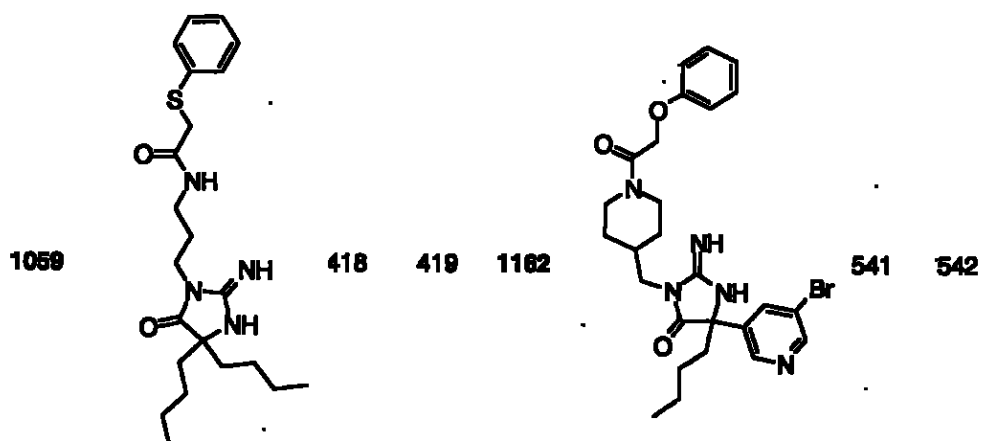
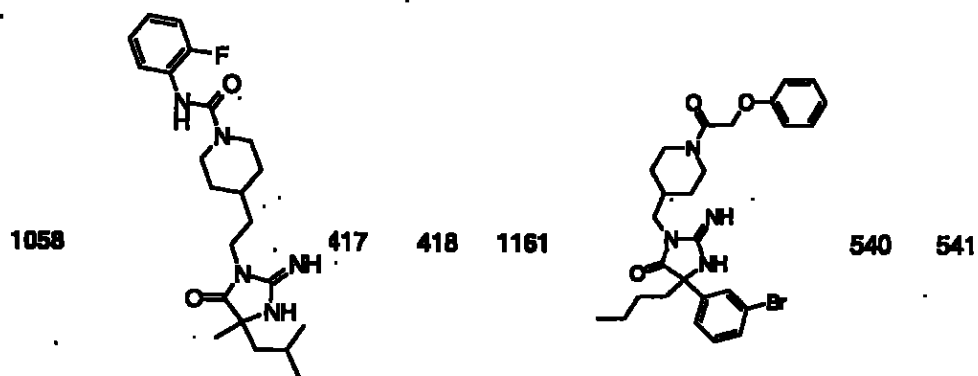


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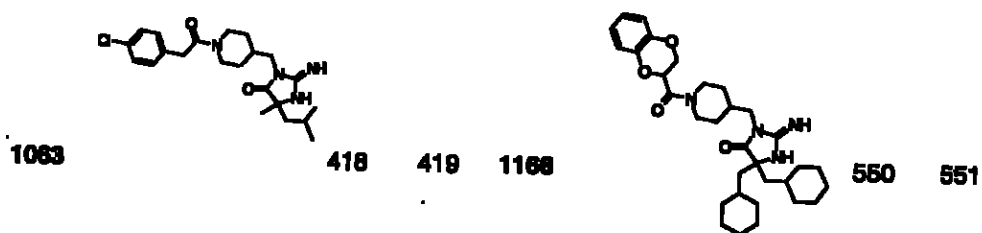
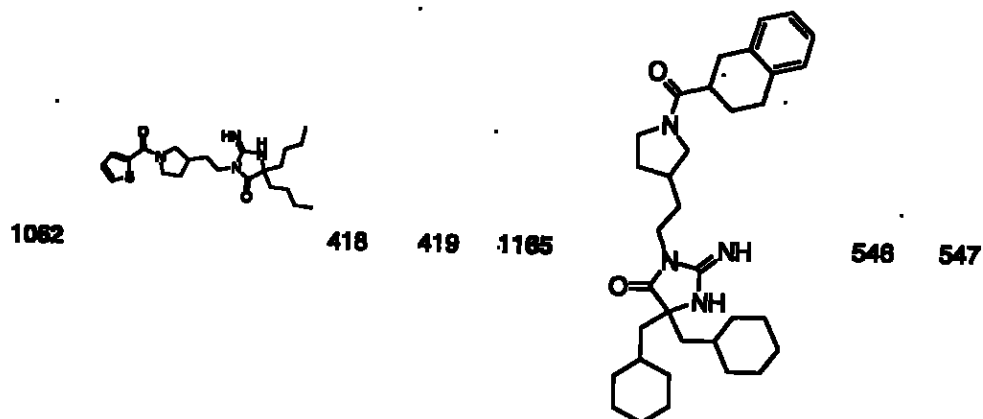
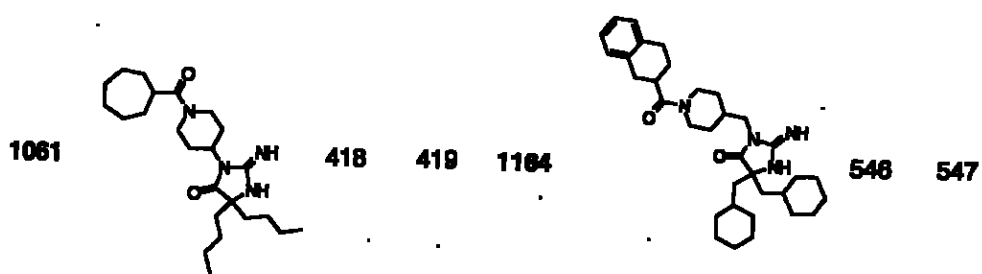
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- 153 -



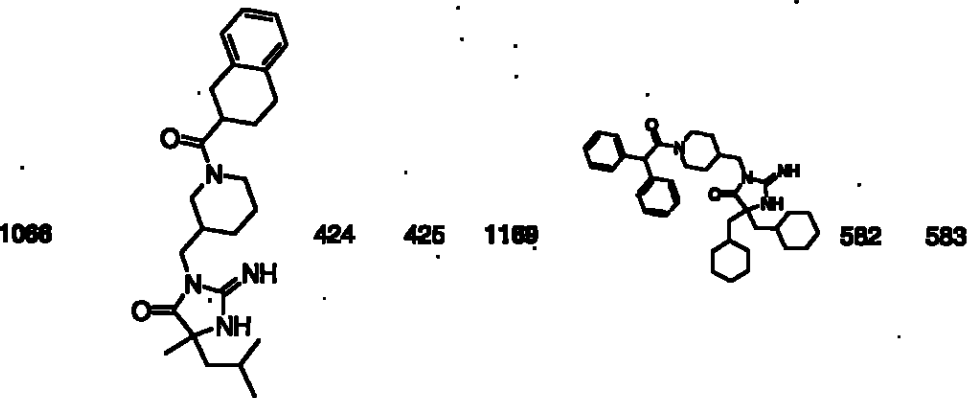
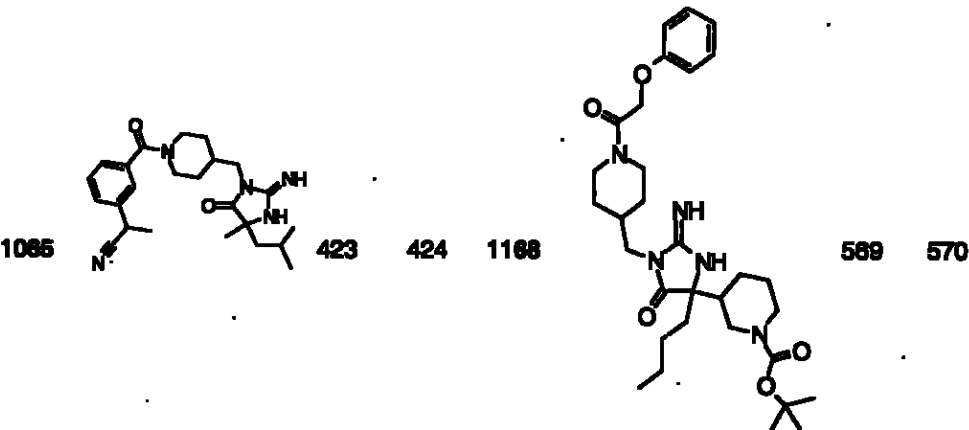
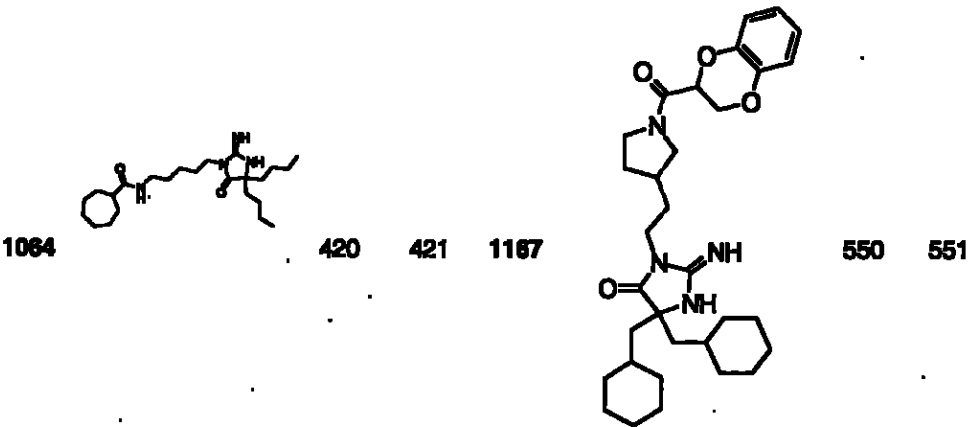
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- 154 -



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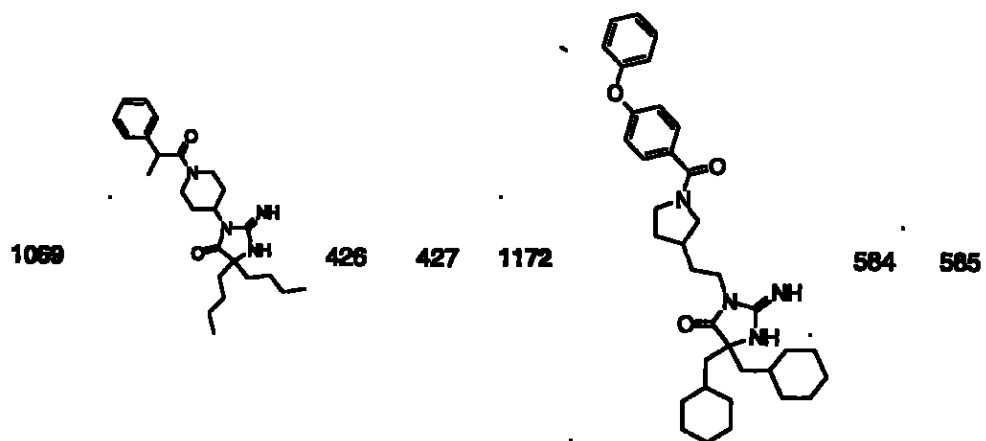
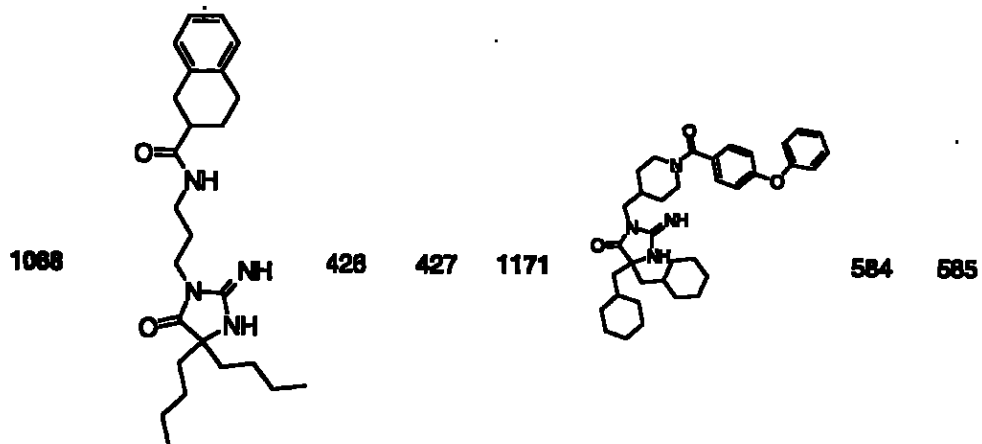
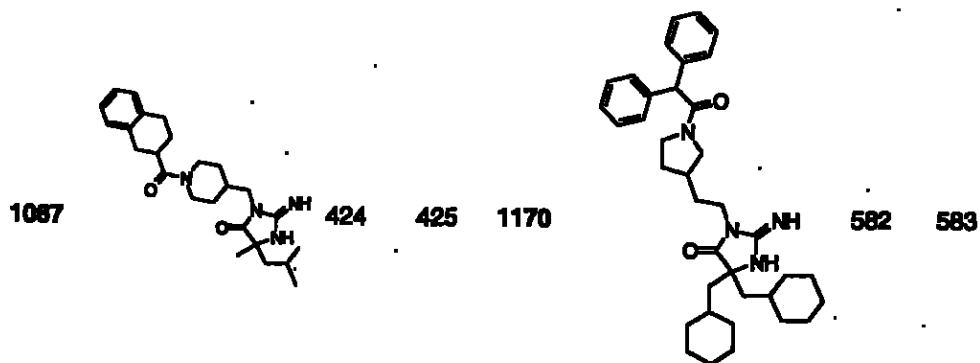
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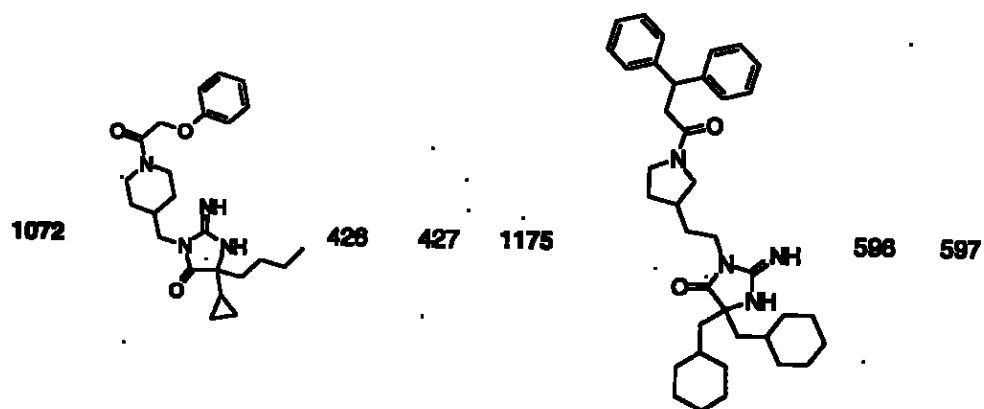
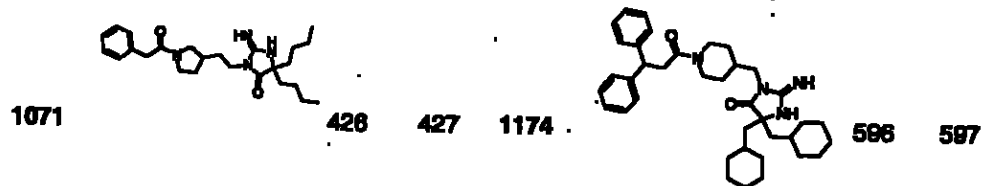
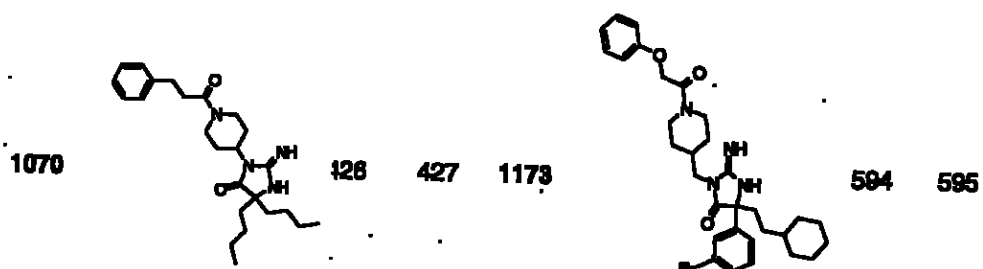
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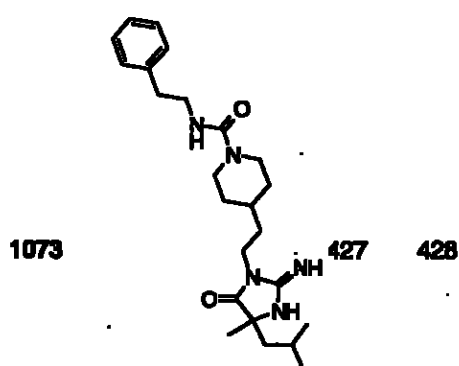
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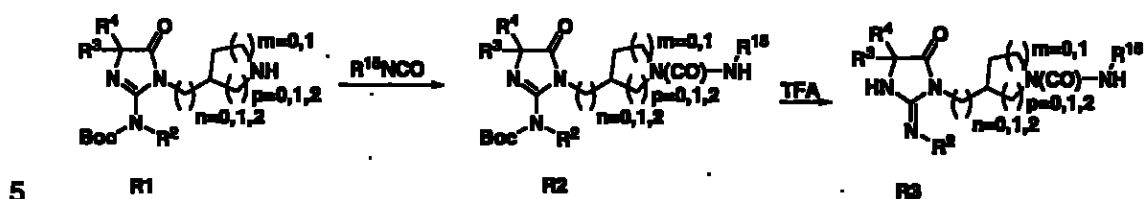
174

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Method R



Method R, Step 1.

A solution of R^1 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=^tBu$) (0.010 g) in acetonitrile (0.85 mL) and dichloroethane (0.15 mL) was put into a microtiter plate well followed by addition of 0.12 ml of 0.5M phenylisocyanate solution in dichloroethane. The well was sealed and the plate shaken for 20 h before the mixture was filtered and the solid washed with acetonitrile (0.5ml). The combined solution was treated with Trisamine resin (0.050 g, 6 eq., 4.23 mmol/g) and isocyanate resin (0.067 g, 3 eq., 1.53 mmol/g) and the mixture was shaken for 18 h. The mixture was filtered and the solution was evaporated to give R2 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=^tBu$ and $R^{15}=Ph$).

Method R, Step 2.

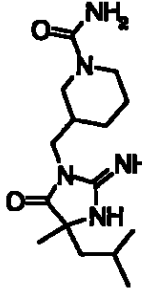
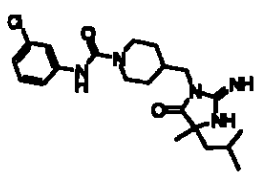
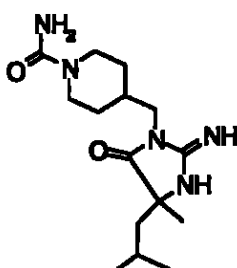
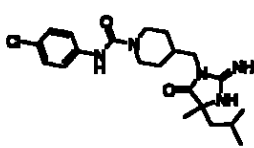
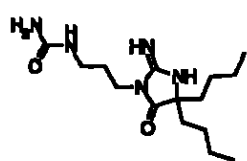
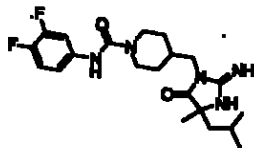
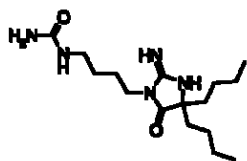
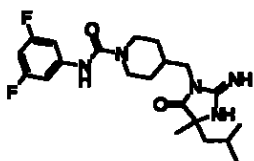
175

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Procedure similar to Method Q, step 6 was used for the transformation of R2 (n=1, p=2, m=1, R²=H, R³=Me; R⁴=^tBu and R¹⁵=Ph) to R3 (n=1, p=2, m=1, R²=H, R³=Me; R⁴=^tBu and R¹⁶=Ph).

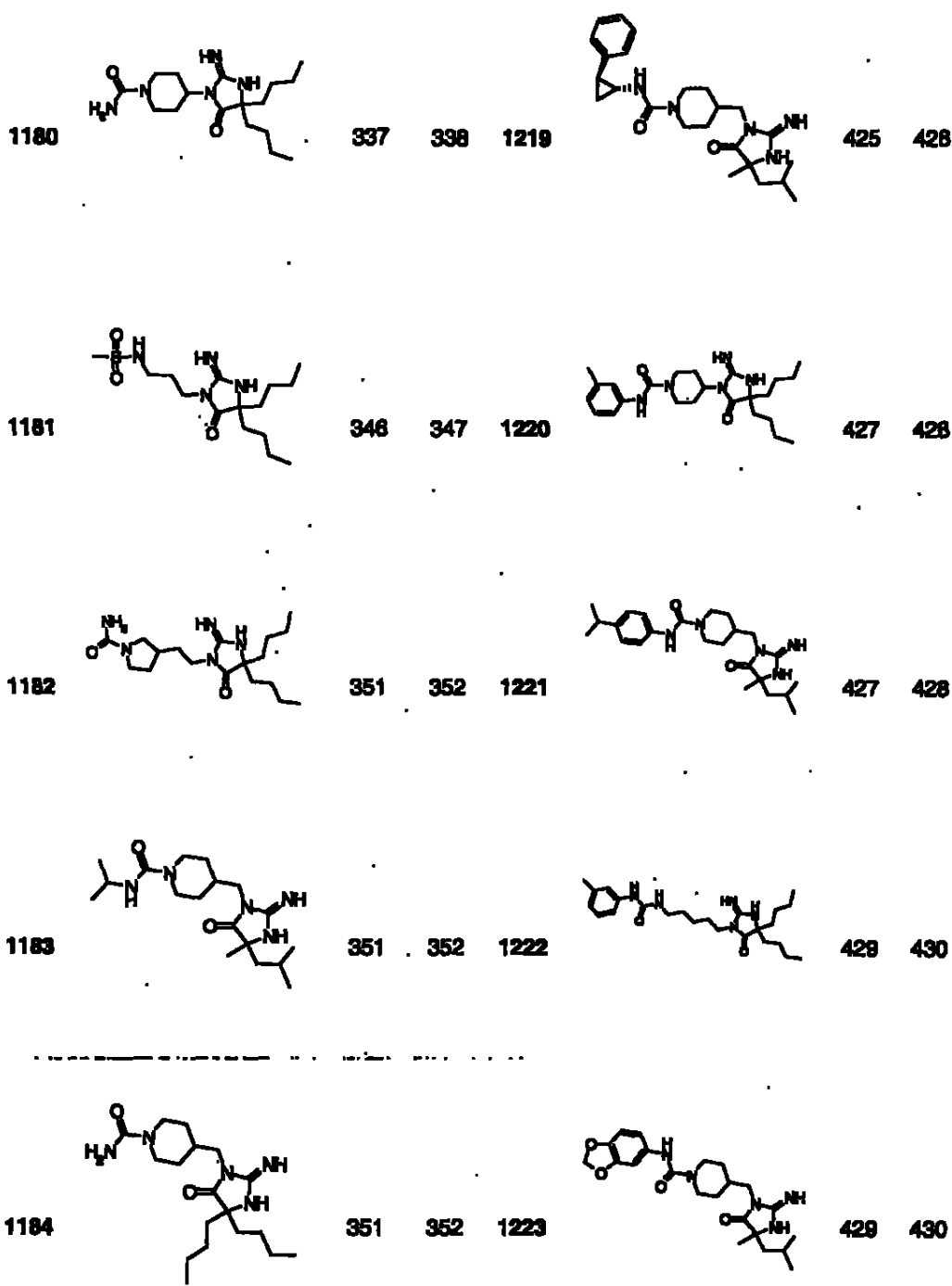
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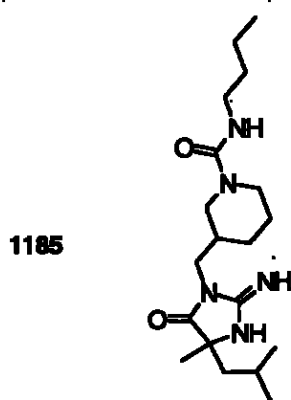
5 The following compounds were prepared using similar methods:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1176		309	310	1215		419	420
1177		309	310	1216		419	420
1178		311	312	1217		421	422
1179		325	326	1218		421	422

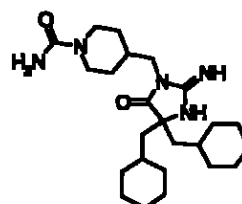
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175

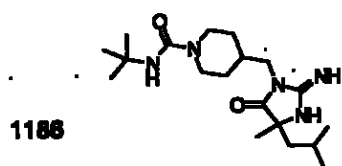




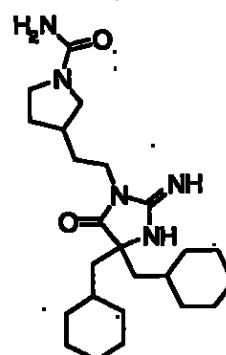
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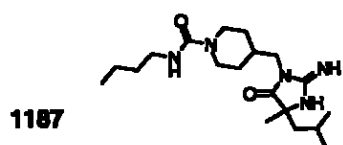
431 432



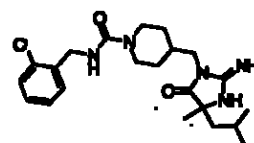
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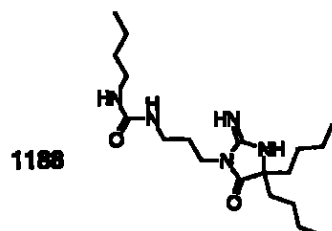
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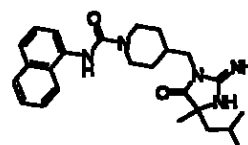
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433 434



367 368 1227

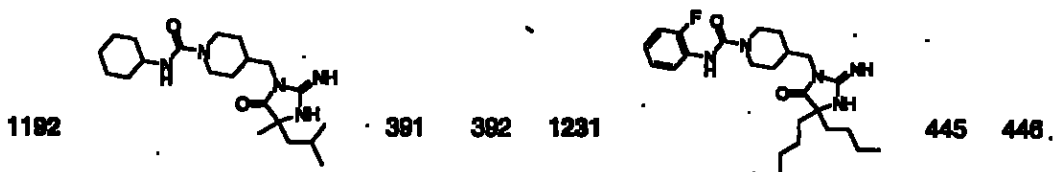
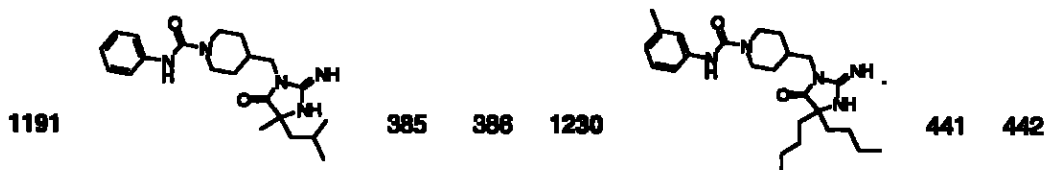
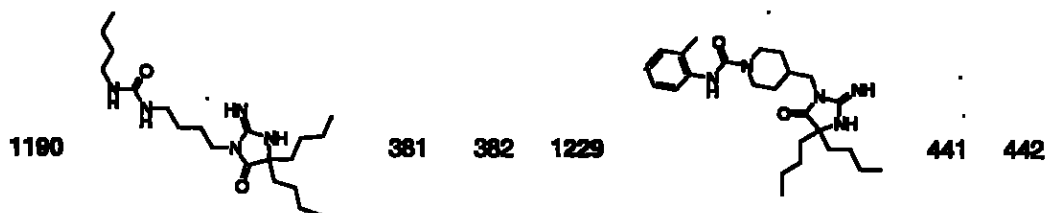
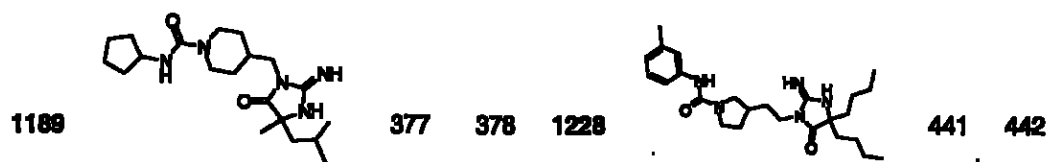


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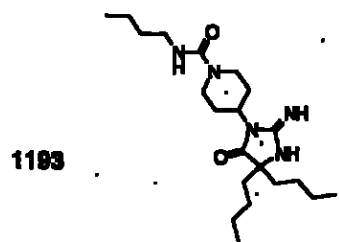
- 162 -

177



179

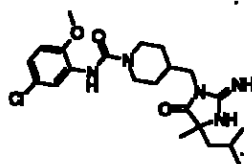
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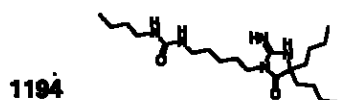
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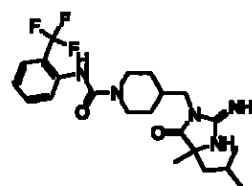
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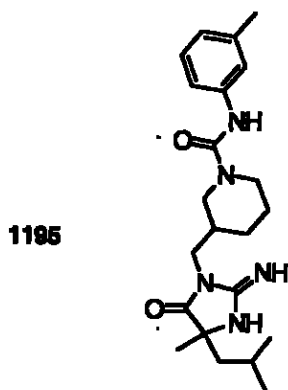
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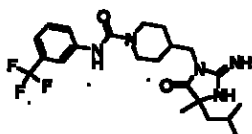
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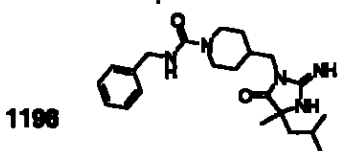
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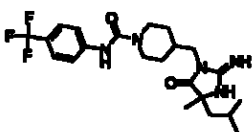
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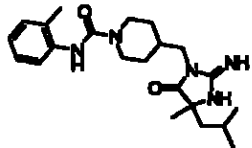
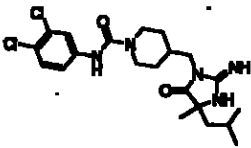
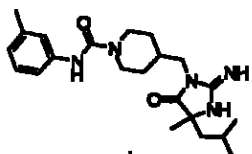
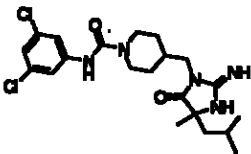
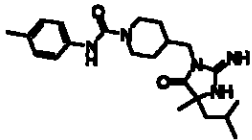
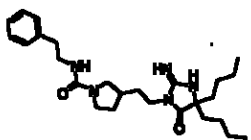
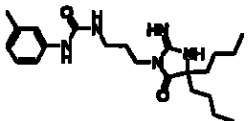
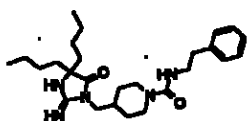
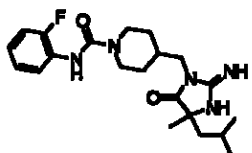
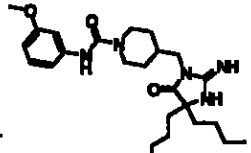
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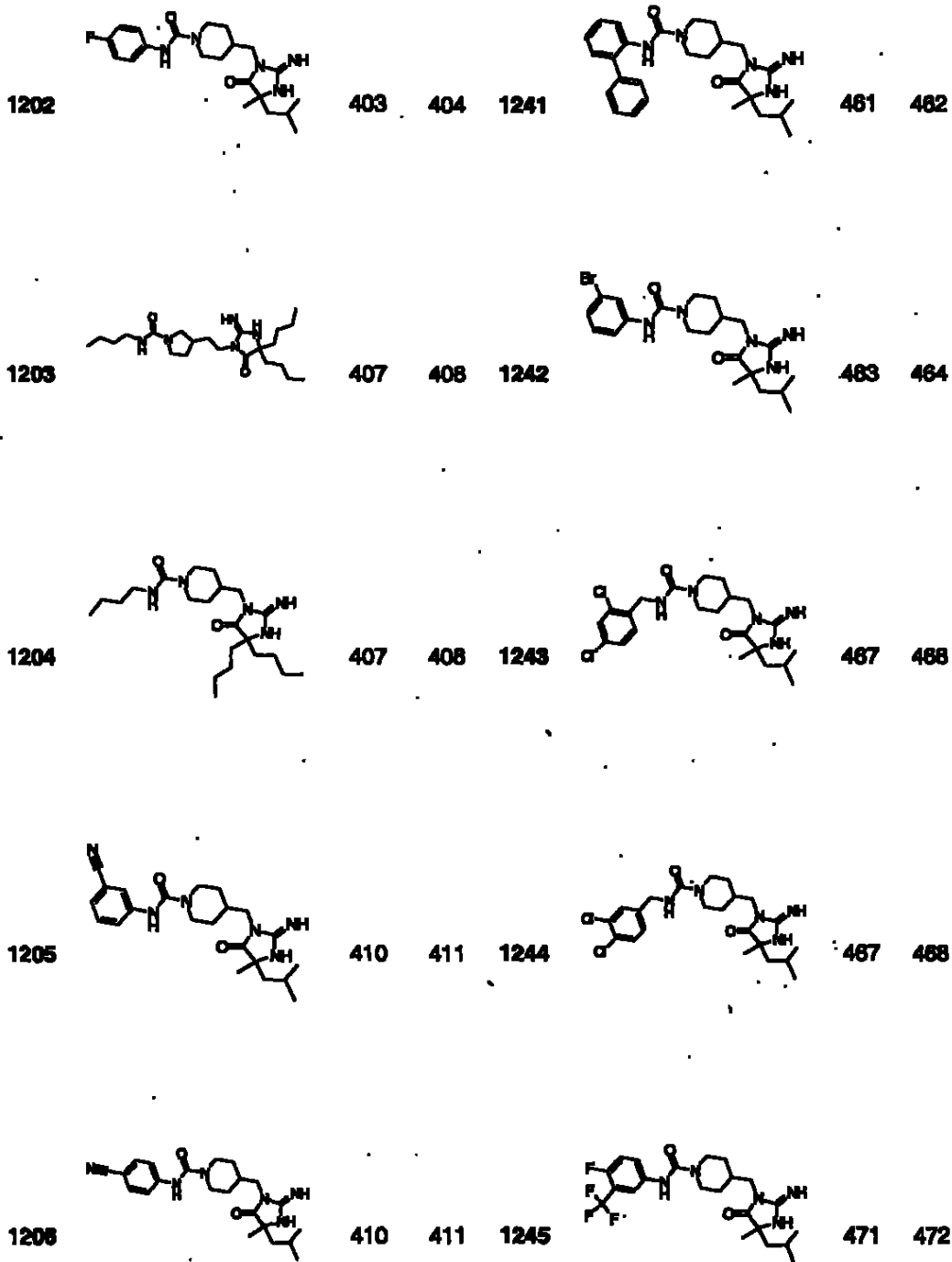
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181

180

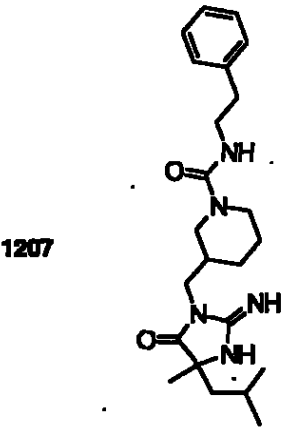
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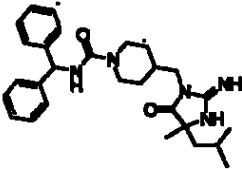
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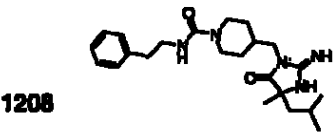
- 166 -



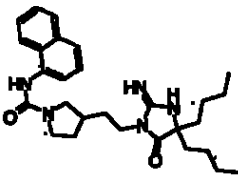
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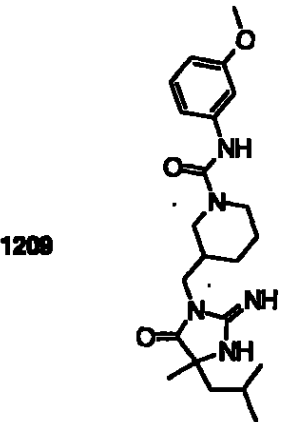
475 476



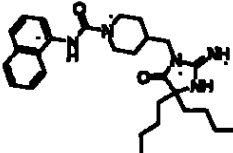
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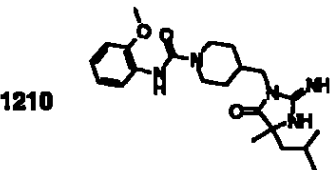
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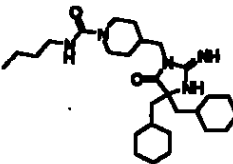
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477 478



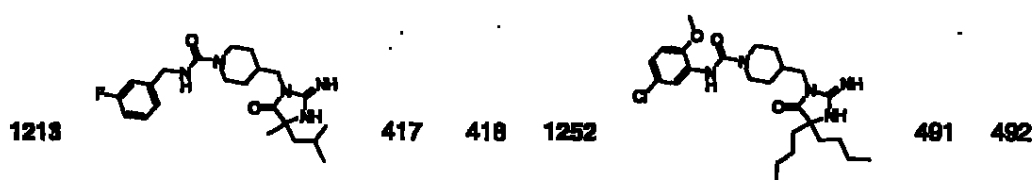
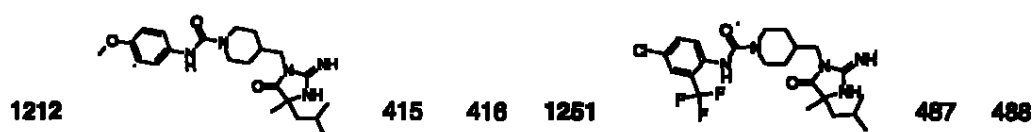
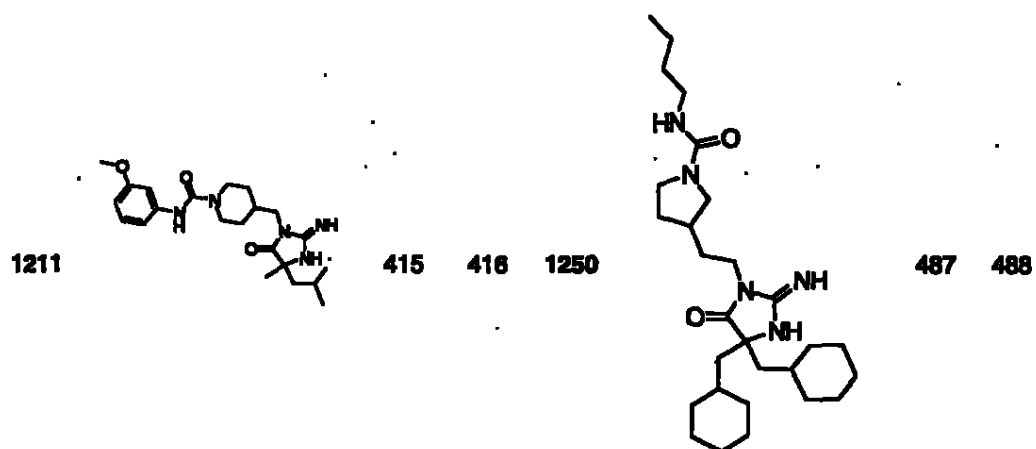
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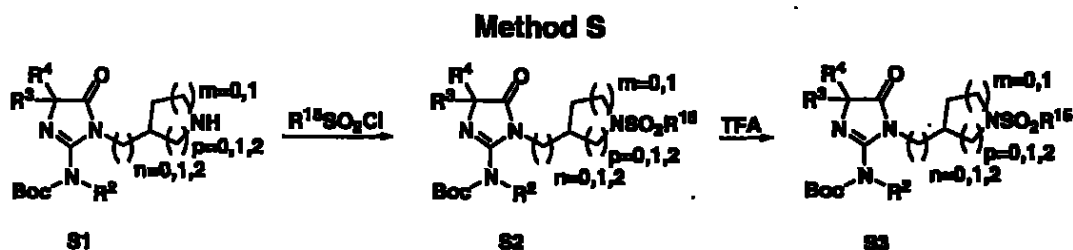
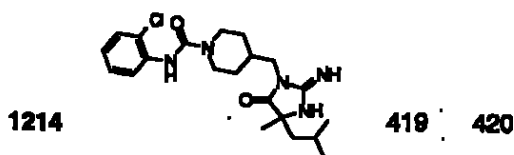
487 488

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5

Method S, Step 1.

A solution of **S1** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) (0.010 g) in acetonitrile (0.85 mL) and dichloroethane (0.15 mL) was put into a microtiter plate followed by addition of DIPEA-MP resin (0.030 g, 4 eq) and phenylsulfonyl chloride in dioxane (1M, 45 μ L, 0.045 mmol. The well was capped and shaken for 18 h before it was filtered and residue washed with acetonitrile (0.5 mL). The combined solution was treated with Trisamine resin (0.040 g, 6 eq., 4.23 mmol/g) and isocyanate resin (0.060 g, 3 equiv., 1.53 mmol/g) and shaken for 18 h before the mixture was filtered and the solvent removed to give **S2** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$ and $R^{15}=Ph$).

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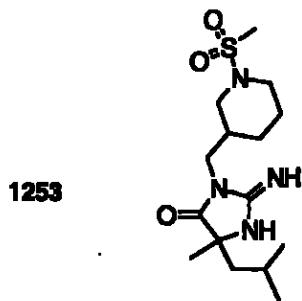
Method S, Step 2.

Procedure similar to Method Q, step 6 was used for the transformation of **S2** to **S3** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$ and $R^{15}=Ph$).

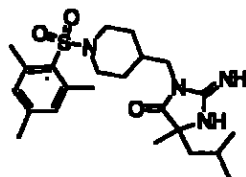
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The following compounds were prepared using similar methods:

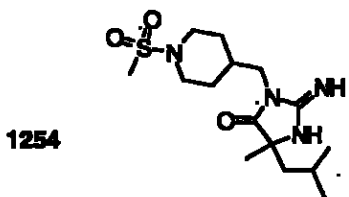
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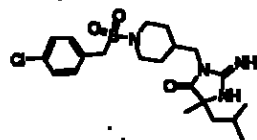
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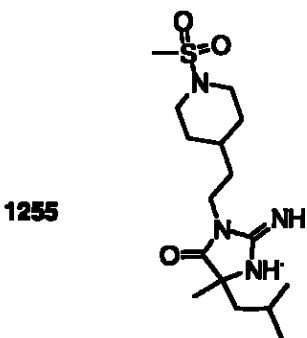
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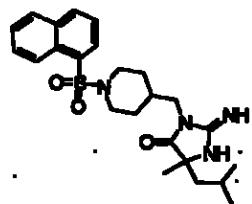
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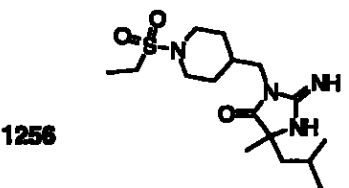
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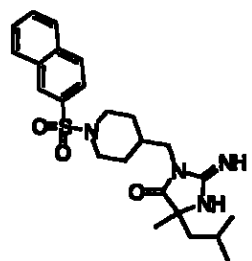
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456 457



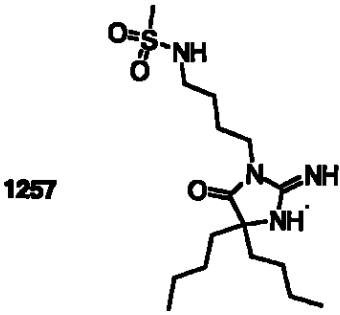
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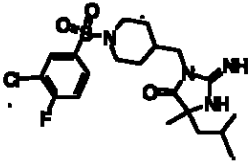
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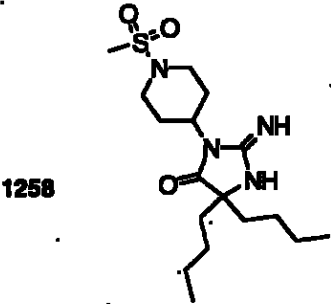
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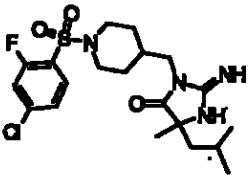
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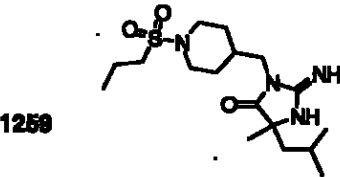
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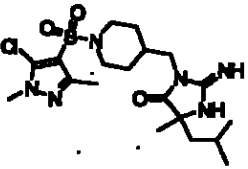
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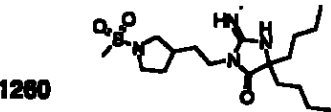
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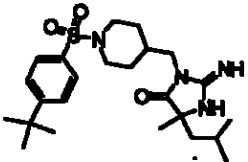
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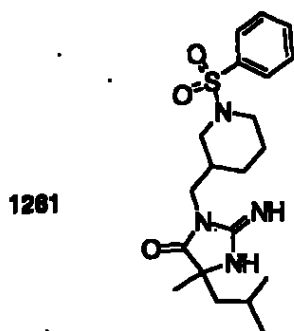


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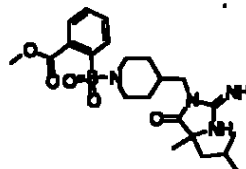


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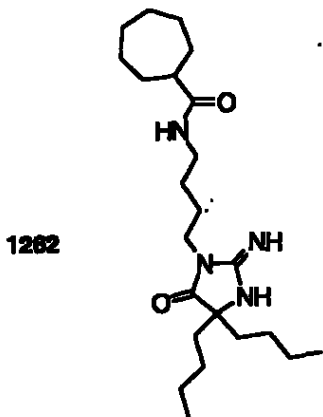
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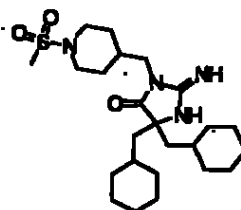
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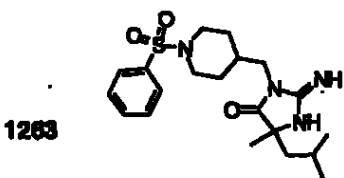
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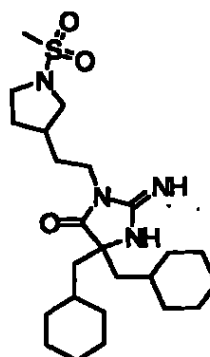
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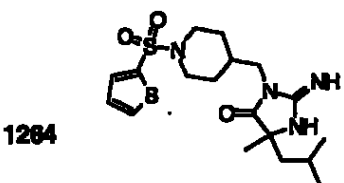
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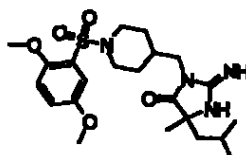
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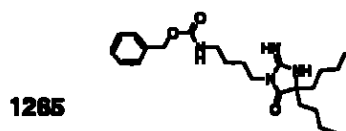


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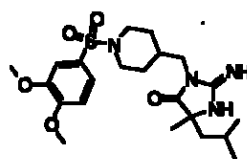


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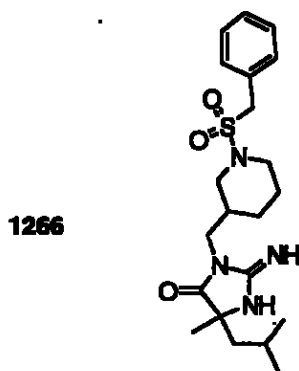
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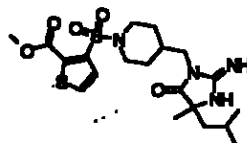
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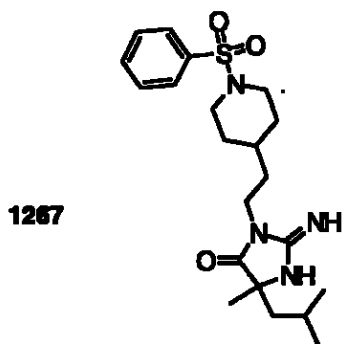
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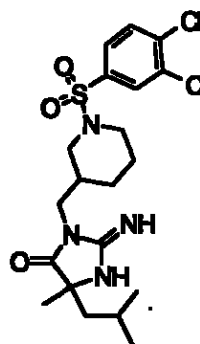
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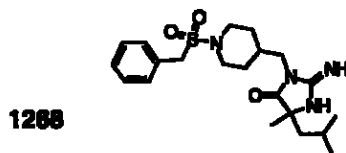
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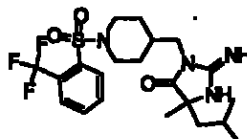
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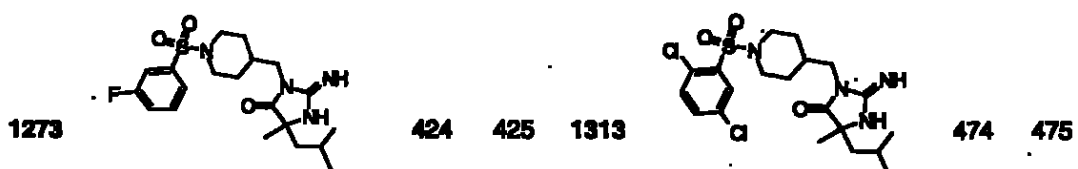
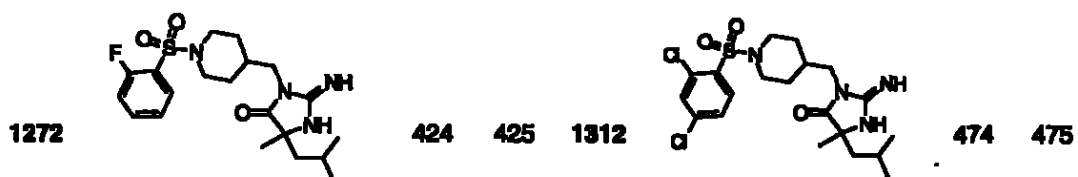
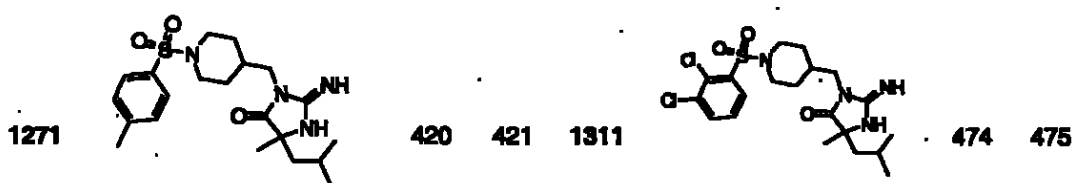
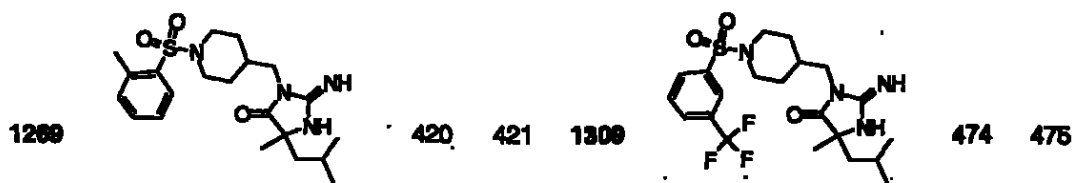
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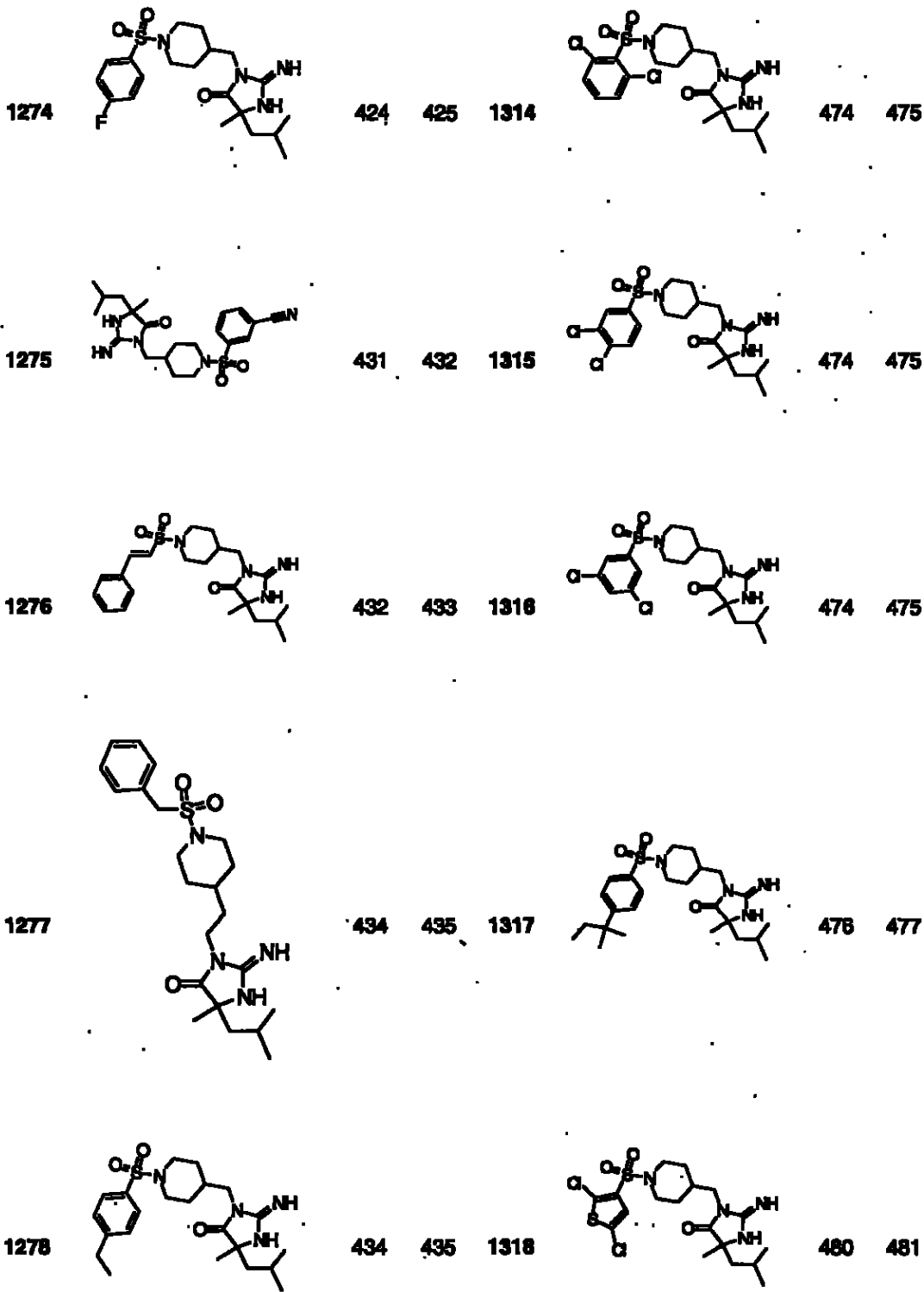
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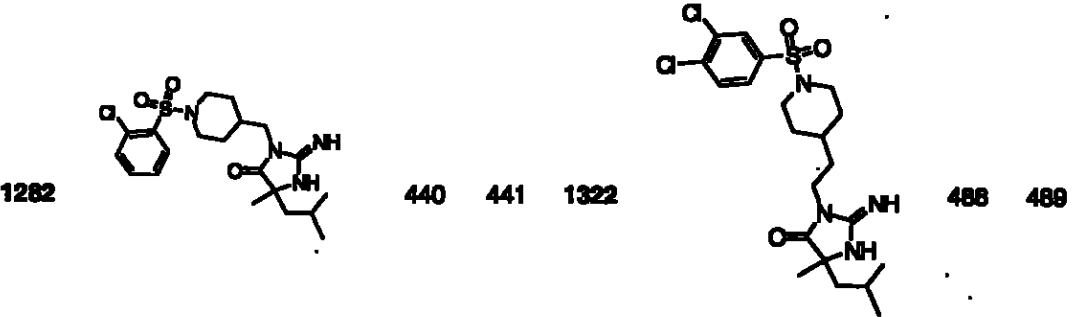
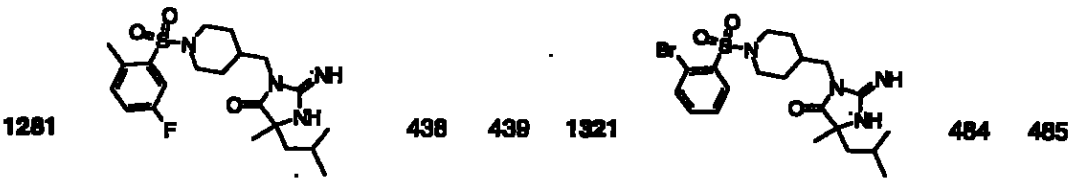
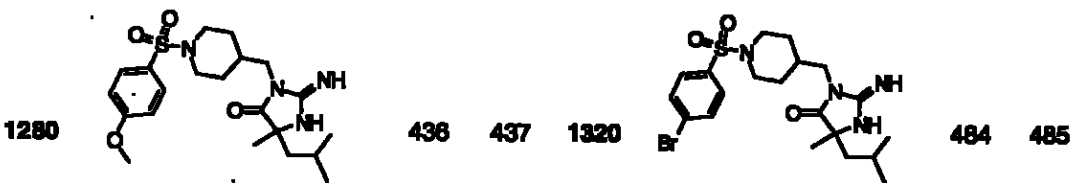
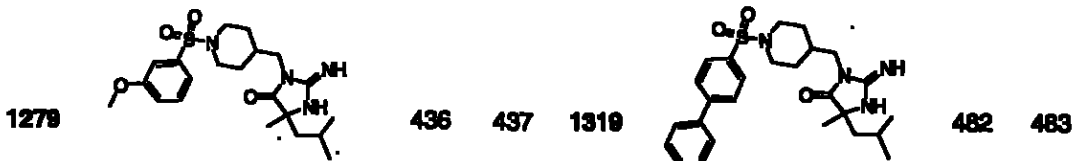
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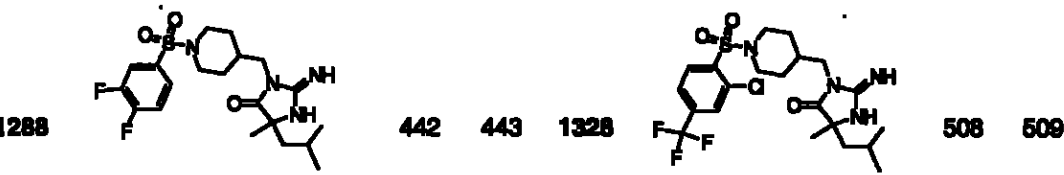
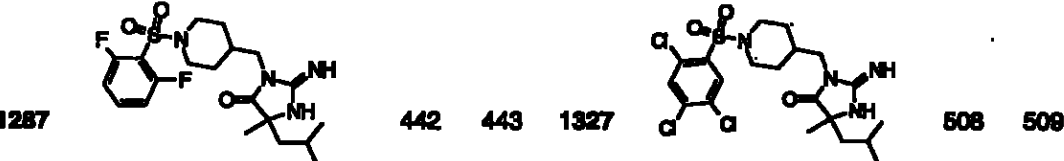
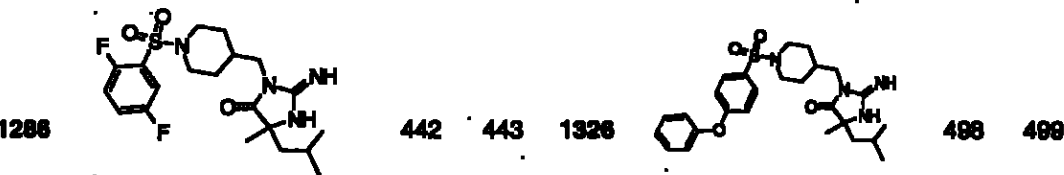
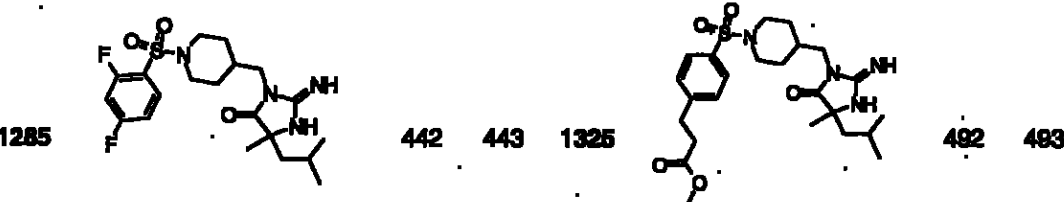
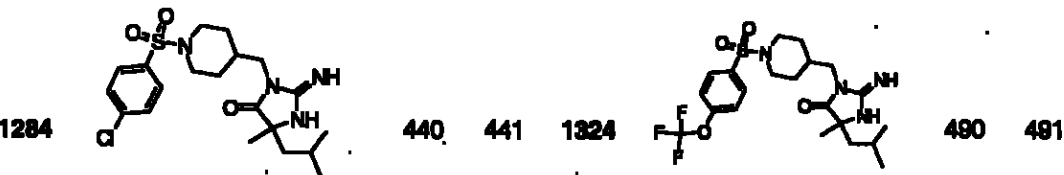


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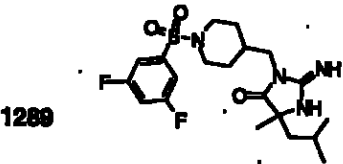


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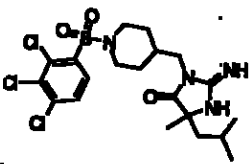
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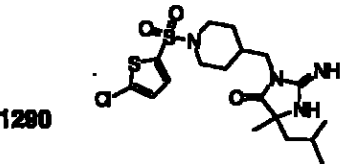
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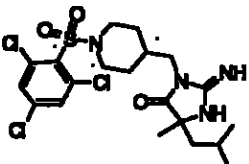
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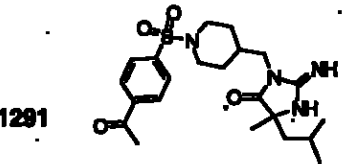
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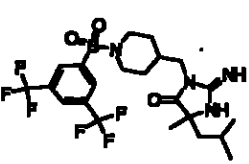
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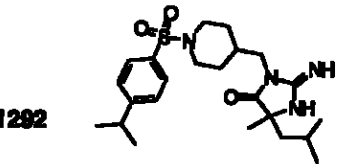
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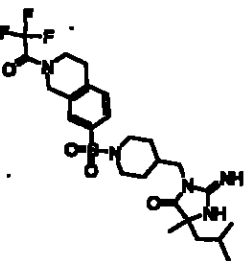
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542 543



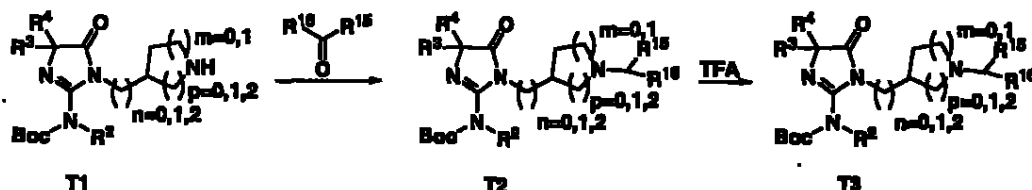
448 449 1332



557 558

Method T

- 178 -

**Method T, Step 1.**

To a microtiter plate well containing 1 ml solution of T1 ($n=1$, $p=2$, $m=1$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{Me}$; $\text{R}^4=\text{tBu}$) in DCM (0.010 g) and $\text{R}^{15}\text{C(O)R}^{16}$ (5 equiv, $\text{R}^{15}=\text{H}$, $\text{R}^{16}=\text{Ph}$) was added Sodium cyanoborohydride in dichloroethane (14.3 mg / mL, 2 equiv.). The well was capped and shaken for 20h before MP-TsOH Resin (100 mg, 1.29 mmol/g) was added to the well followed by additional MP-TsOH resin (50 mg) after 2 h. After the mixture was shaken for another 1 h, the mixture was filtered and the resin washed with dichloroethane (1 mL) (3 X), then MeOH (1 mL) (2 X). The resin was treated with 7N ammonia in MeOH (1 mL) for 30 min (2X) followed by filtration and evaporation of solvent to give T2 ($n=1$, $p=2$, $m=1$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{Me}$; $\text{R}^4=\text{tBu}$ and $\text{R}^{15}=\text{Ph}$ and $\text{R}^{16}=\text{H}$).

Method T, Step 2.

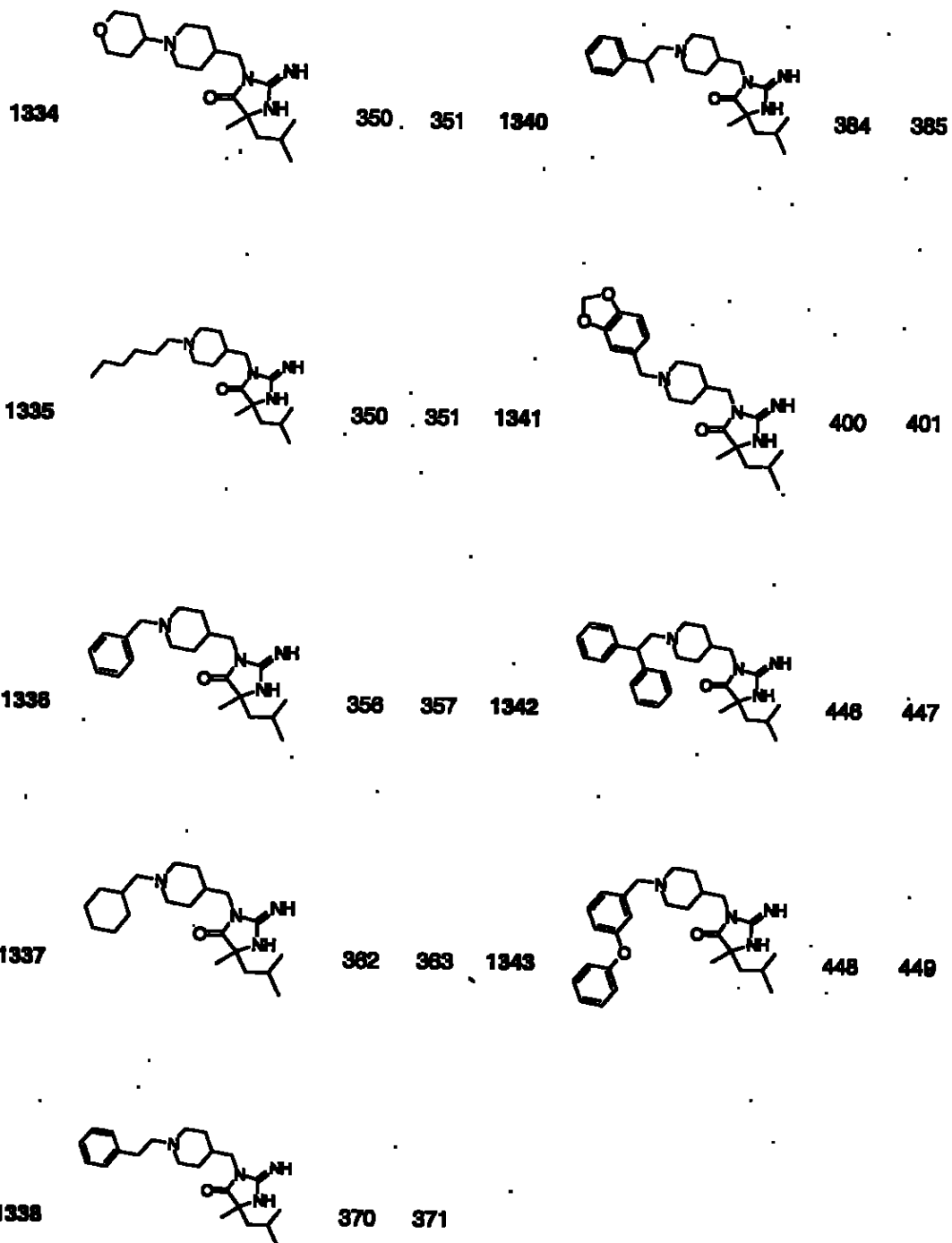
Procedure similar to Method Q, step 6 was used for the transformation of T2 ($n=1$, $p=2$, $m=1$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{Me}$; $\text{R}^4=\text{tBu}$ and $\text{R}^{15}=\text{Ph}$ and $\text{R}^{16}=\text{H}$) to T3 ($n=1$, $p=2$, $m=1$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{Me}$; $\text{R}^4=\text{tBu}$ and $\text{R}^{15}=\text{Ph}$ and $\text{R}^{16}=\text{H}$).

The following compounds were prepared using similar methods:

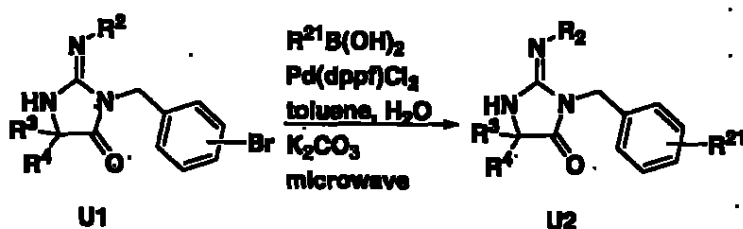
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195
194

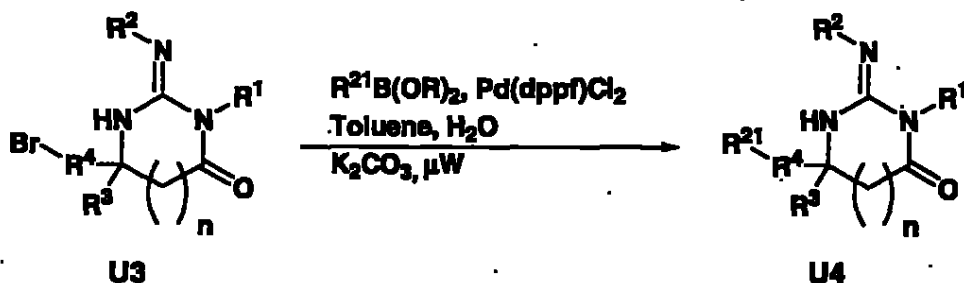
- 179 -



Method U

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195

Alternatively, similar synthetic method can be used for the generation of other types of compounds. I.e.

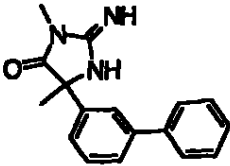
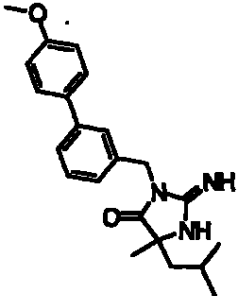
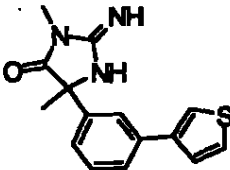
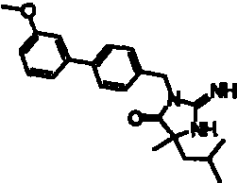
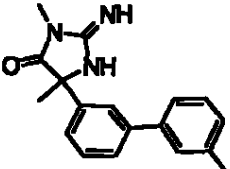
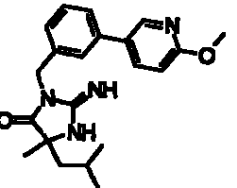
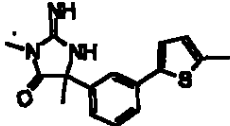
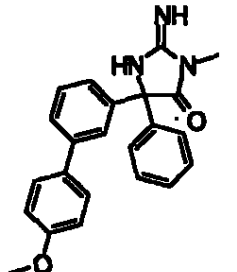


In a microwave vial was charged U1 ($\text{R}^2 = \text{H}$; $\text{R}^3 = \text{i-Bu}$, $\text{R}^4 = \text{Me}$) (0.025 g) in toluene (4 mL), potassium carbonate (0.035 g), Pd(dppf)Cl_2 (0.020 g), water (0.02 mL) and $\text{R}^{21}\text{B(OH)}_2$ ($\text{R}^{21} = \text{m-Methoxyphenyl}$) (3 eq.) were placed. The vial was placed in a microwave for 10 min. at 150°C . The reaction mixture was diluted with dichloromethane and extracted with 2.5N NaOH. The dried (MgSO_4) dichloromethane solution was concentrated *in vacuo* to give a brown residue which was purified via a RP Prep LCMS system to give product U2 ($\text{R}^2 = \text{H}$; $\text{R}^3 = \text{i-Bu}$; $\text{R}^4 = \text{Me}$; $\text{R}^{21} = \text{m-methoxyphenyl}$).

The following compounds were prepared using similar methods:

197
196

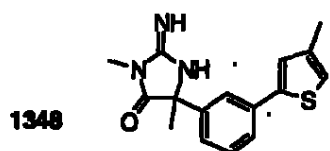
- 181 -

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
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1345		285	286	1382		365	366
1346		283	284	1383		366	367
1347		299	300	1384		371	372

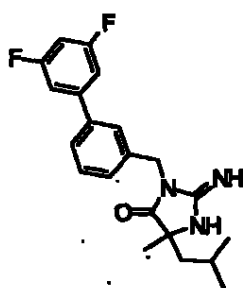
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197

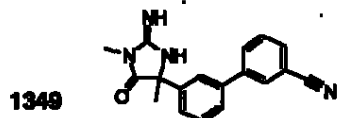
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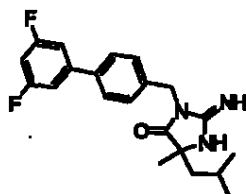
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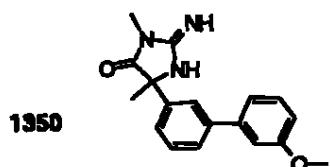
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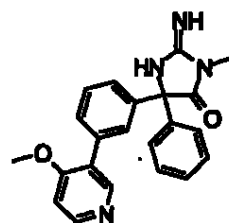
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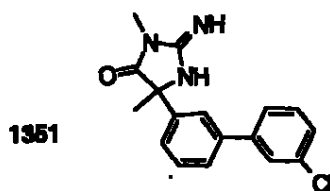
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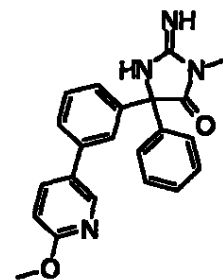
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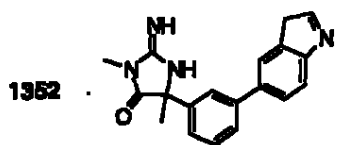
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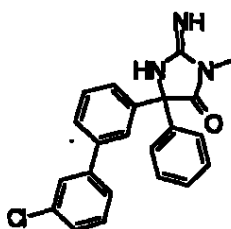
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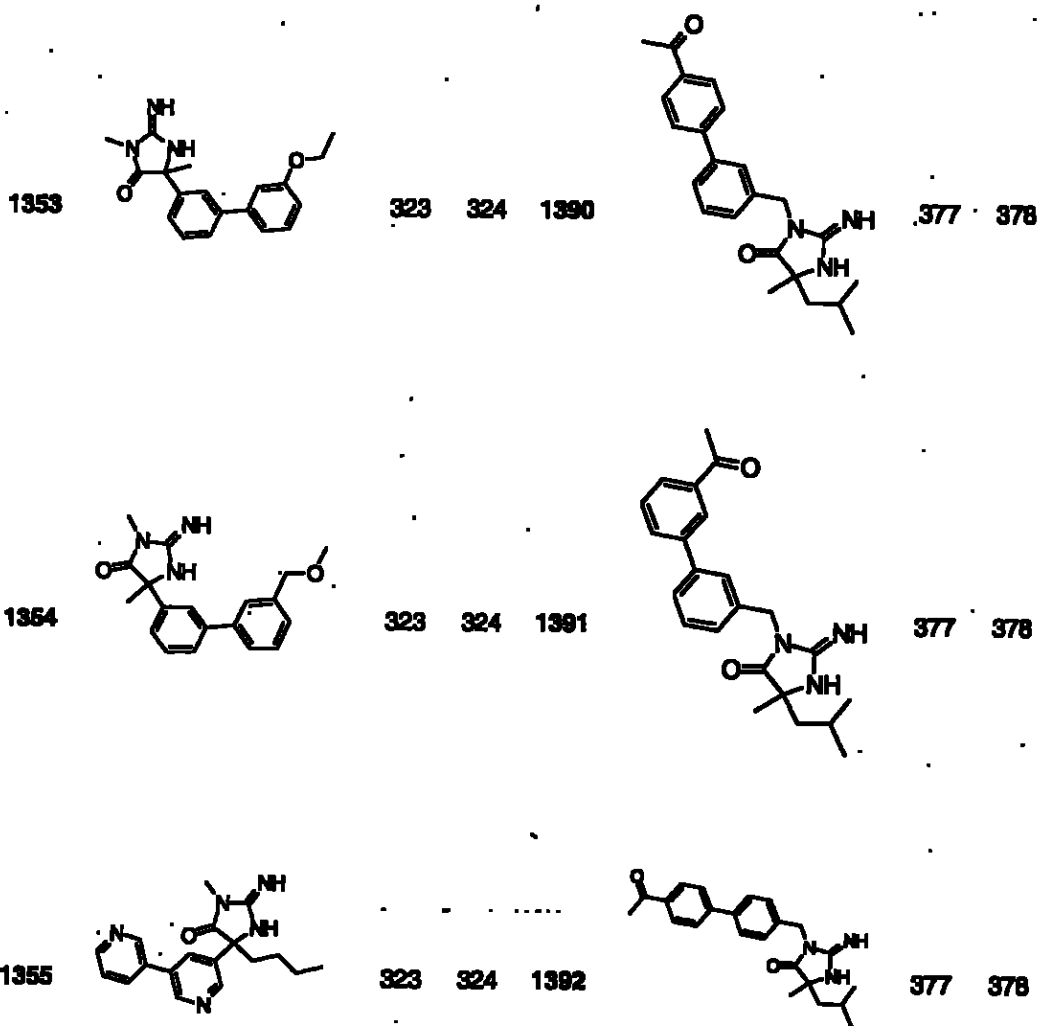
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318 319 1389



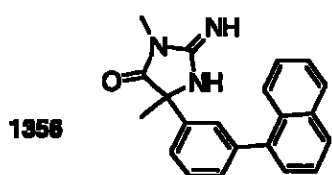
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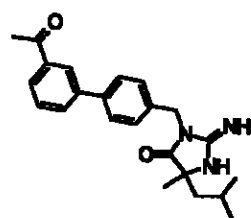
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199

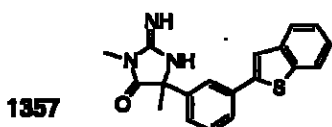
- 184 -



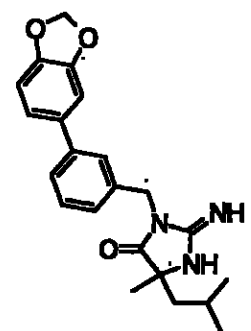
329 330 1383



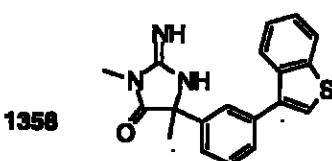
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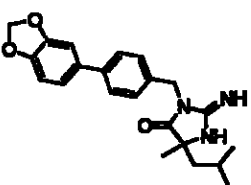
335 336 1384



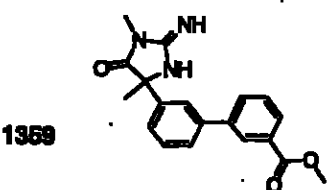
379 380



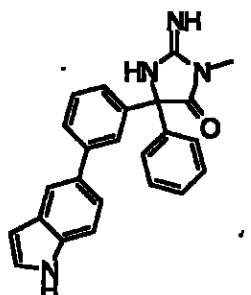
335 336 1385



379 380

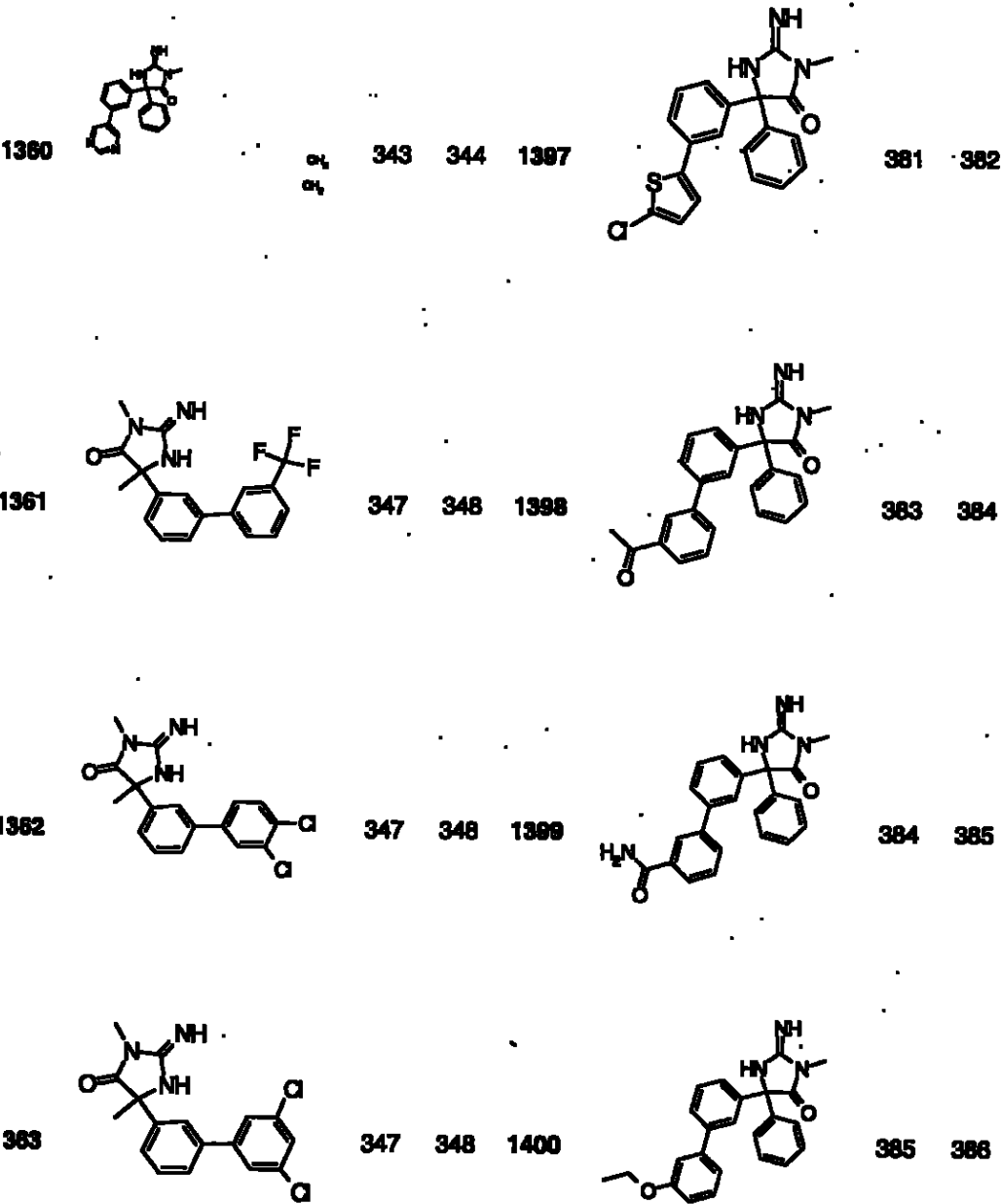


337 338 1386



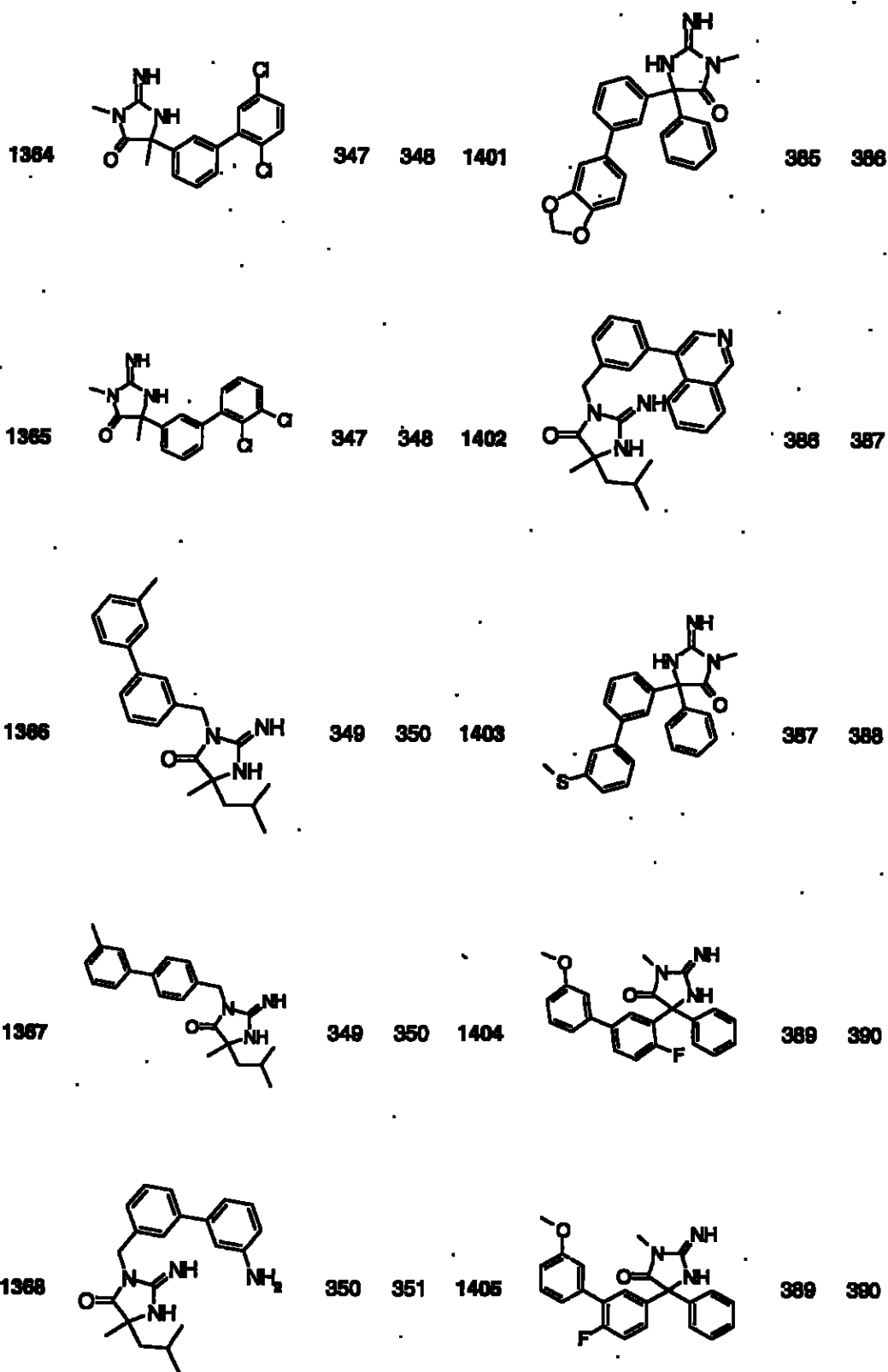
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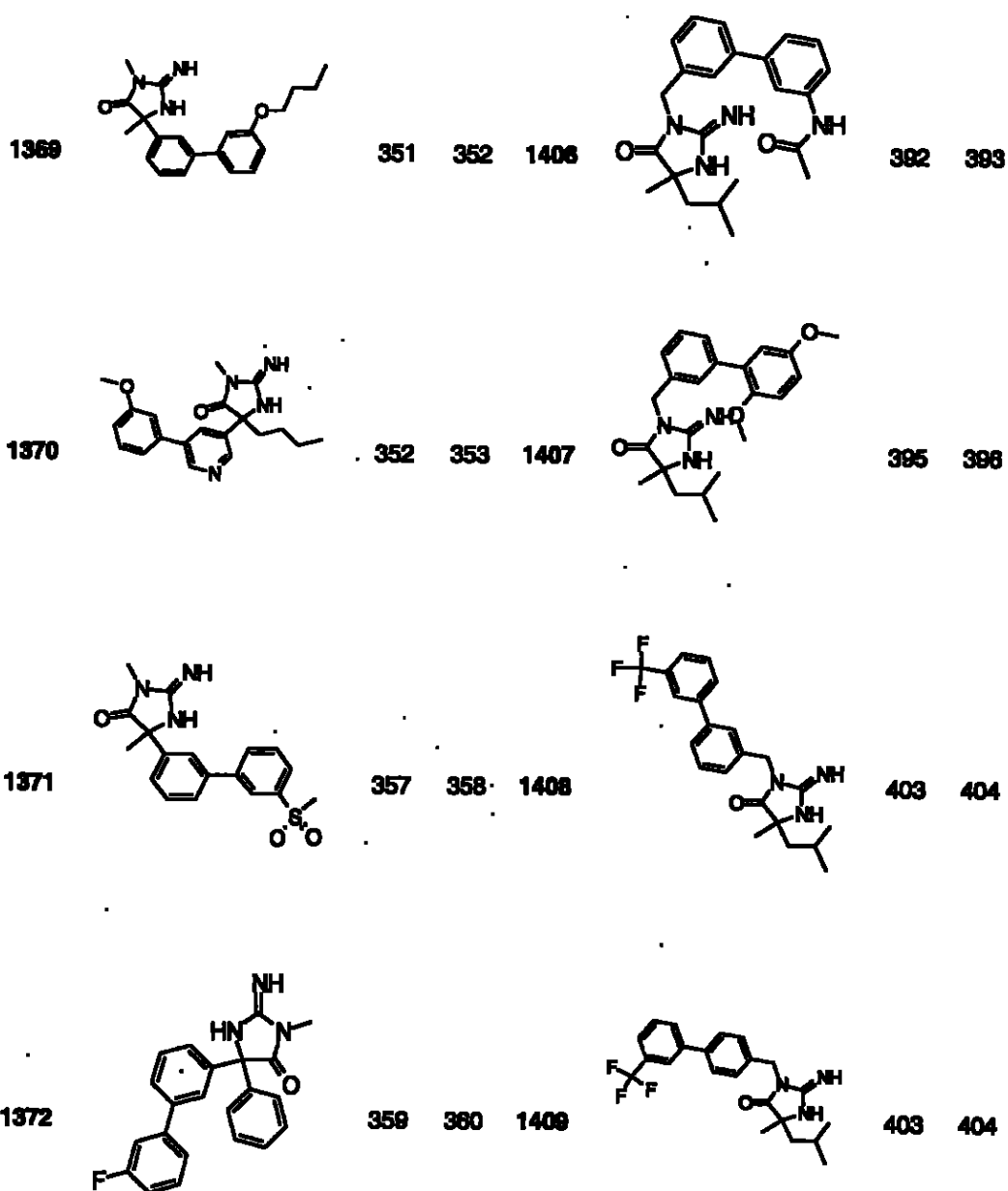
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~~200~~

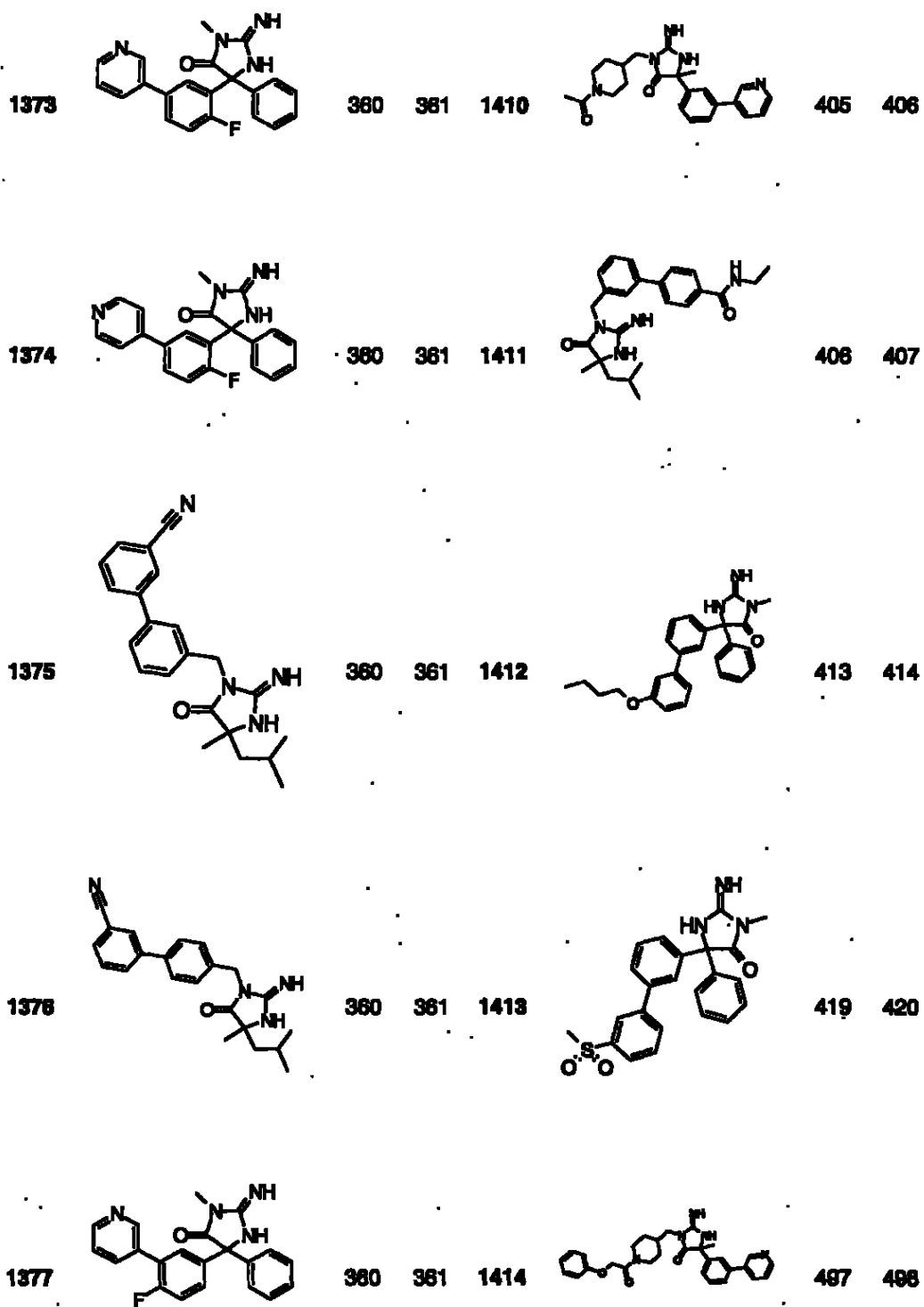


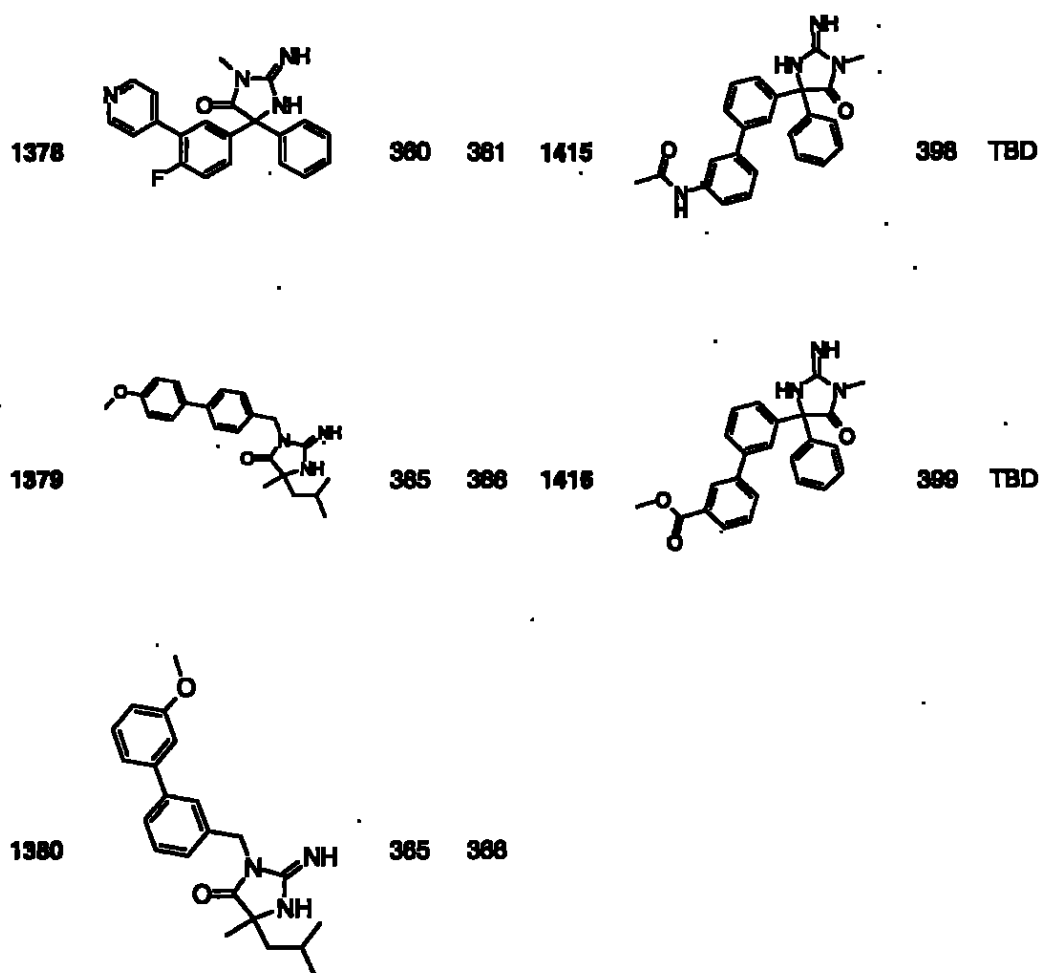
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- 186 -

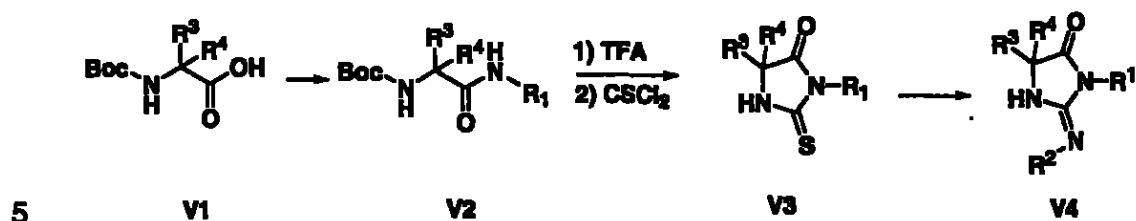








Method V



Method V, Step 1:

Compound V1 ($R^3 = R^4 = \text{Me}$) (14.76mmole), EDCI (14.76mmole), HOAt (14.76mmole), and DIEA (14.76mmole) were mixed with 36 ml DCM. This

mixture was stirred at RT for 15min before 3-chlorobenzylamine was added. After the reaction solution was stirred at RT overnight, it was washed with sodium carbonate (3X), water, 1N HCl (4 X), and aq sodium bicarbonate and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified on flash column to give the amide product V2 ($R^1 = 3$ -chlorobenzyl; $R^3 = R^4 = \text{Me}$).

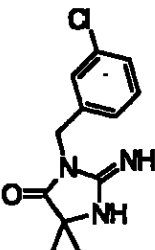
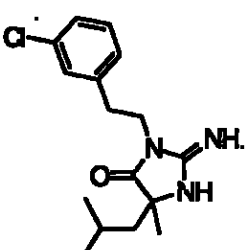
Method V, step 2

Compound V2 ($R^1 = 3$ -chlorobenzyl; $R^3 = R^4 = \text{Me}$) (8.33mmole) was dissolved in 35 ml anhydrous DCM, and cooled to 0-5°C. Thiophosgene (9.16mmole) in 10ml DCM was added dropwise under N_2 followed by addition of DIEA (11.96mmole). The solution was stirred in ice bath for 0.5 h before the reaction mixture was washed with saturated sodium bicarbonate (3 X), brine, and dried over anhydrous sodium sulfate. The solvent was evaporated and residue purified on flash column using ethylacetate/hexane to give the thiohydantoin V3 ($R^1 = 3$ -chlorobenzyl; $R^3 = R^4 = \text{Me}$).

Method V, step 3:

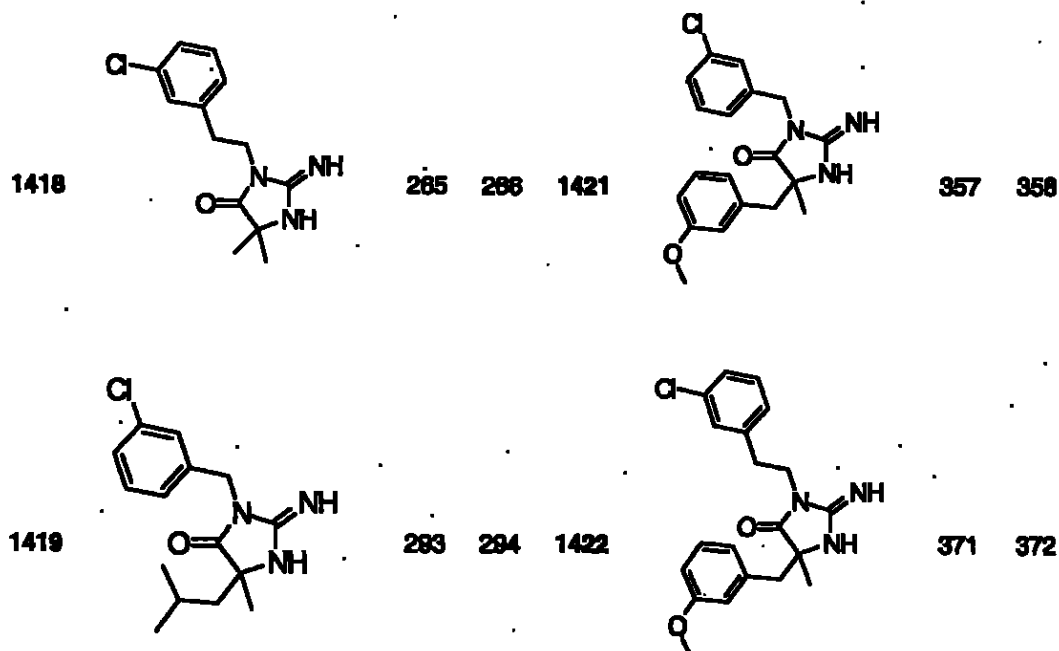
The thiohydantoin V3 ($R^1 = 3$ -chlorobenzyl; $R^3 = R^4 = \text{Me}$) was treated with t-butyl hydroperoxide and ammonium hydroxide in MeOH at RT for 48 h to give compound V4 ($R^1 = 3$ -chlorobenzyl; $R^2 = \text{H}$; $R^3 = R^4 = \text{Me}$).

The following compounds were prepared using similar method.

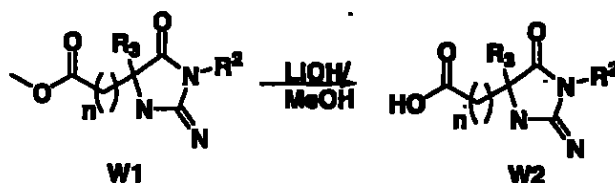
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1417		251	252	1420		307	308

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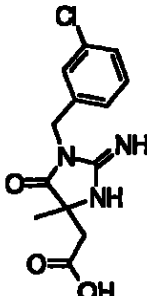
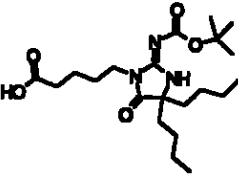


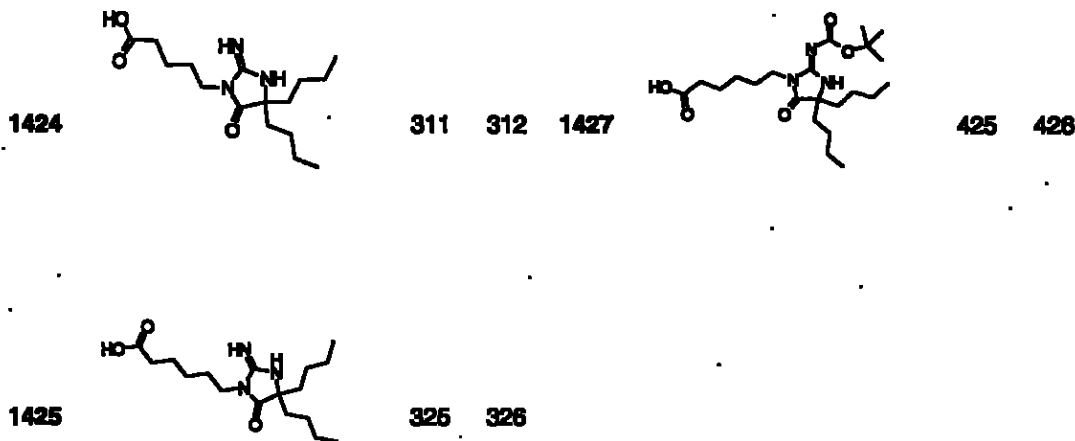
Method W



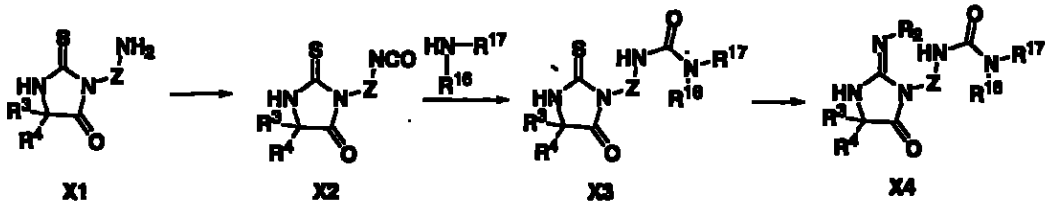
Compound W1 obtained using method A ($n=1$, $R^2=m\text{-Cl-Bn}$, $R^3=\text{Me}$) was hydrolyzed to W2 ($n=1$, $R^2=m\text{-Cl-Bn}$, $R^3=\text{Me}$) using two equivalent of LiOH in MeOH.

The following compounds were synthesized in similar fashion:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
1423		285	296	1426		411	412



Method X



5

(In the scheme, -Z-NH-C(O)-N(R¹⁶)(R¹⁷) - is equivalent to R¹ substituted by R²¹, or R¹ Substituted by alkyl-R²², wherein R²¹ and R²² are -NH-C(O)-N(R¹⁶)(R¹⁷) and R¹⁵ is H, and wherein Z is optionally substituted alkylene-arylene, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

10

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Method X, Step1:

To a mixture of the amine X1 obtained using method L ($R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) (10 mg) in DCM and sat. NaHCO_3 (1:1 by volume) was added triphosgene (0.33 eq) at r.t. The solution was stirred vigorously for 40 minutes before the organic layer was separated and dried over anhydrous Na_2SO_4 . The organic solution was evaporated to give compound X2 ($R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$).

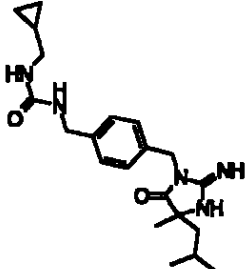
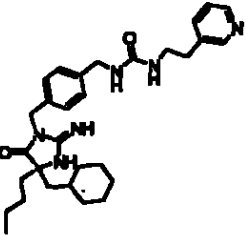
Method X, Step2:

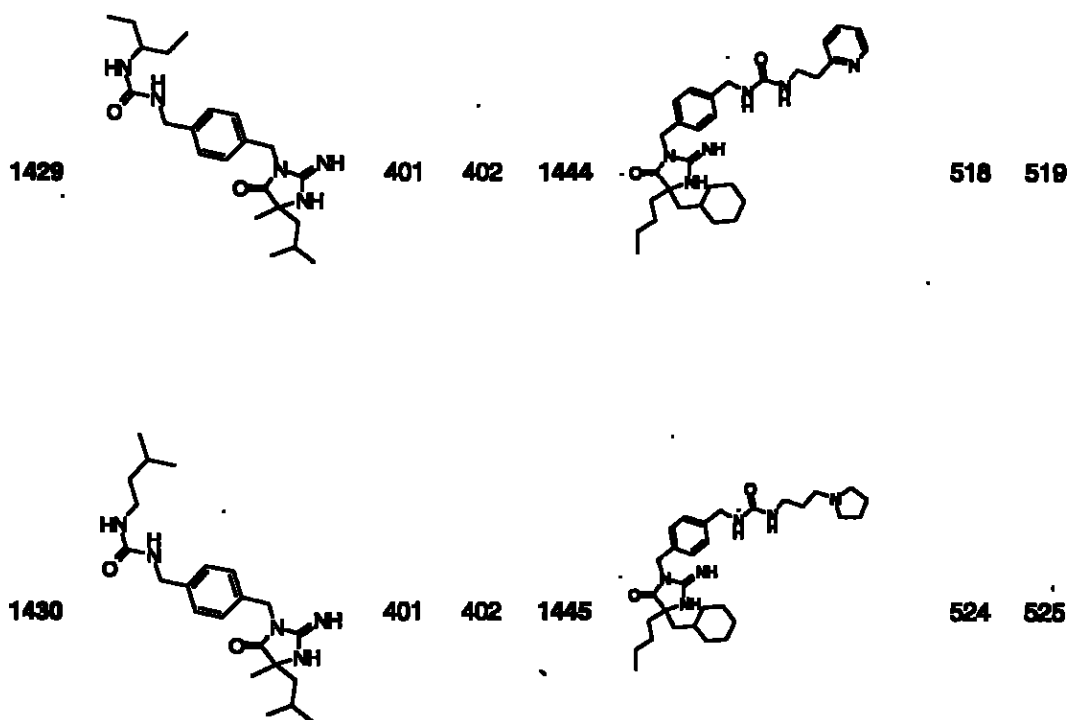
Compound X3 ($R^{16} = \text{H}$; $R^{17} = \text{cyclopropylmethyl}$; $R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) was prepared from X2 ($R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) using method similar to method M, step 1.

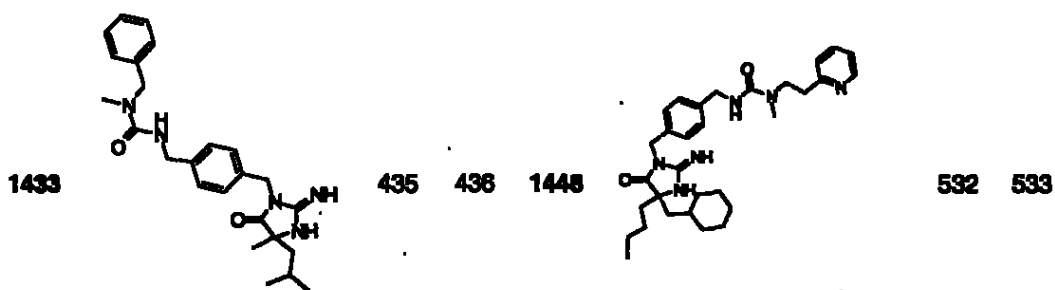
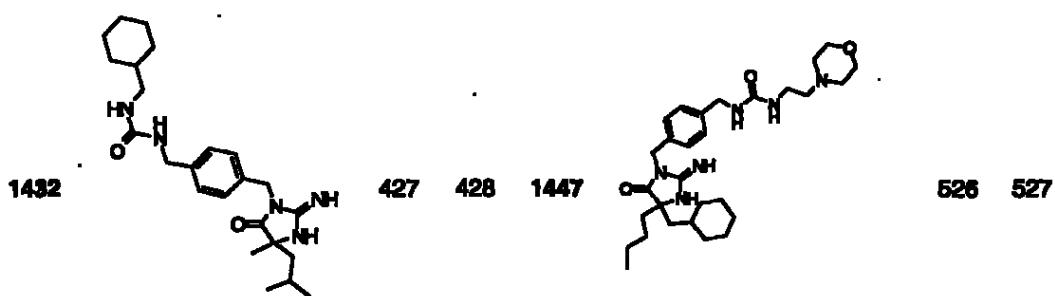
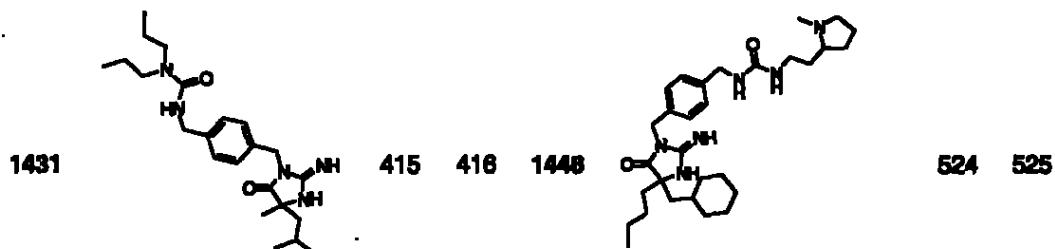
Method X, Step3:

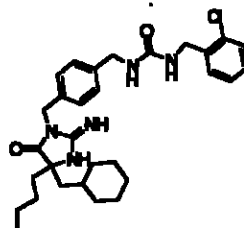
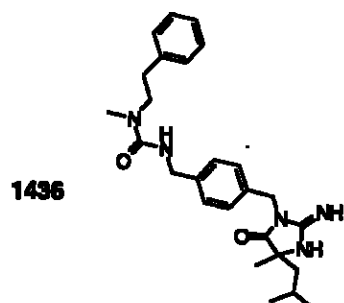
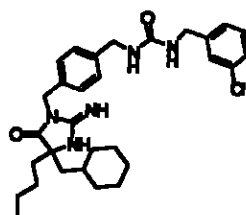
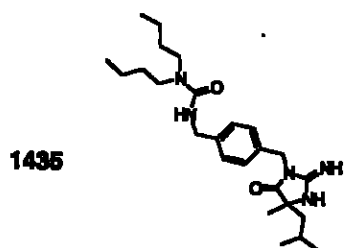
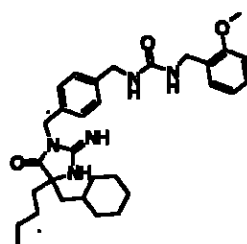
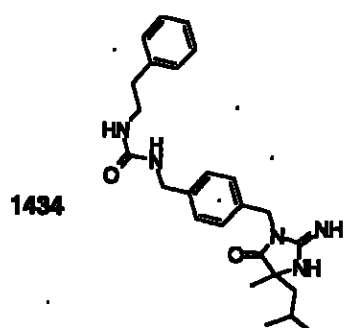
Compound X4 ($R^{16} = \text{H}$; $R^{17} = \text{cyclopropylmethyl}$; $R^2 = \text{H}$; $R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) was prepared from X3 ($R^{16} = \text{H}$; $R^{17} = \text{cyclopropylmethyl}$; $R^2 = \text{H}$; $R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) using method similar to method A Step 3. NMR (CD_3OD): δ 7.25, s, 4H; δ 4.8, m, 2H; δ 4.25, s, 2H; δ 2.9, m, 2H; δ 1.68, m, 2H; δ 1.44, m, 1H; δ 1.36, s, 3H; δ 0.9, m, 1H; δ 0.82, m, 3H; δ 0.66, m, 3H; δ 0.4, m, 2H; δ 0.12, m, 2H. ES_LCMS (m/e) 386.1.

The following compounds were prepared using a similar method.

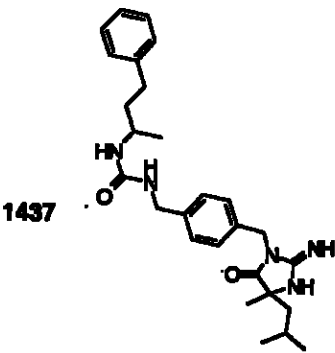
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1428		385	388	1443		518	519



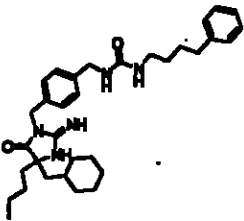




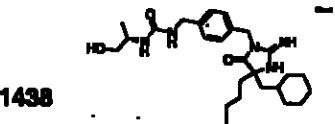
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213



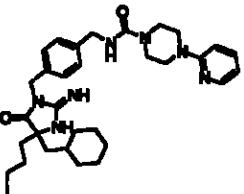
463 464 1452



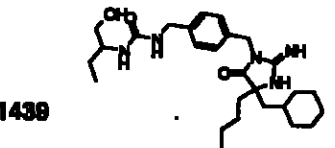
545 546



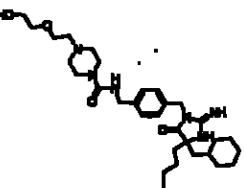
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559 560



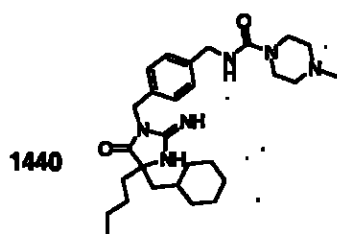
485 486 1454



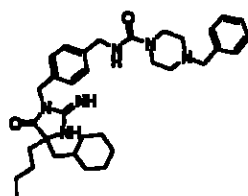
570 571

21A

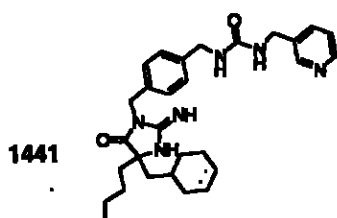
- 198 -



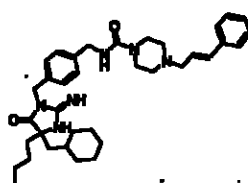
496 497 1455



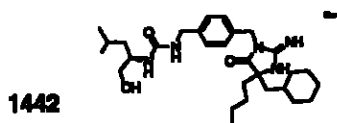
572 573



504 505 1456

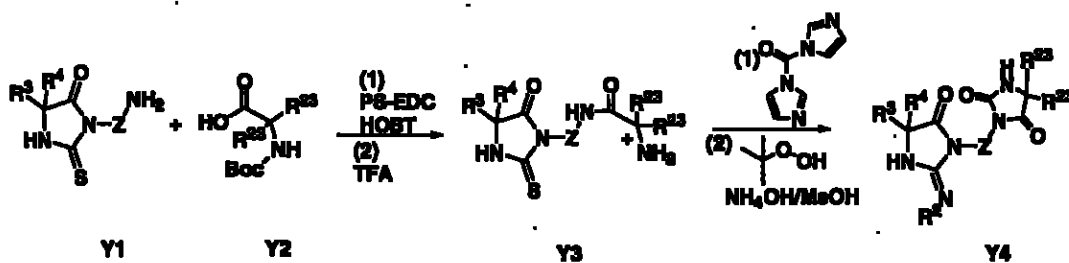


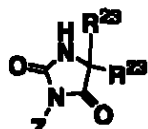
598 599



513 514

Method Y





(In the scheme, Z - is equivalent to R^1 substituted by R^{21} , or R^1 substituted by alkyl- R^{22} , wherein R^{21} and R^{22} are $-\text{N}(\text{R}^{16})-\text{C}(\text{O})-\text{N}(\text{R}^{16})(\text{R}^{17})$ and R^{16} and R^{17} form a ring as defined above, and wherein Z is optionally substituted alkylene-arylene, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

Method Y, Step 1:

The reaction mixture of compound Y1 obtained from Method L ($\text{R}^3 = \text{Me}$; $\text{R}^4 = \text{i-Bu}$; $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) (0.1639mmole), Y2 ($\text{R}^{23} = \text{H}$; $\text{R}^{23} = \text{Pr}$) (0.1967mmole), PS-EDC resin (0.4917mmole) and HOBT (0.2459mmole) in 3.5 ml of mixture of THF, MeCN and DMF (1:1:0.3) was shaken overnight at RT before 6 eq of PS-trisamine resin 3 eq of PS-isocyanate resin were added. After 6hrs the reaction mixture was filtered and the resin was washed with THF, DCM and MeOH. The combined filtrate was evaporated and the crude was treated with 40% TFA in DCM for 40 min before the solvent was evaporated and residue purified on RP HPLC system to give product Y3 ($\text{R}^3 = \text{Me}$; $\text{R}^4 = \text{i-Bu}$; $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $\text{R}^{23} = \text{H}$; $\text{R}^{23} = \text{Pr}$).

Method Y, Step 2:

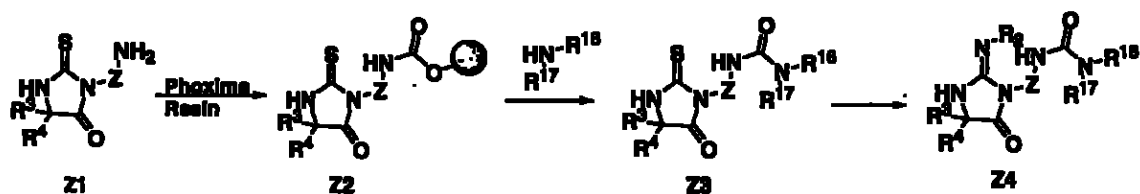
The reaction solution of Y3 ($\text{R}^3 = \text{Me}$; $\text{R}^4 = \text{i-Bu}$; $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $\text{R}^{23} = \text{H}$; $\text{R}^{23} = \text{Pr}$) (0.030mmole), carbonyl diimidazole (0.032mmole), and DIEA (0.09mmole) in 0.5 ml DCM was shaken overweekend at RT. The crude was then purified on reverse column to give the thiohydantoin product which was converted into Y4 ($\text{R}^2 = \text{H}$; $\text{R}^3 = \text{Me}$; $\text{R}^4 = \text{i-Bu}$; $\text{Z} = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $\text{R}^{23} = \text{H}$; $\text{R}^{23} = \text{Pr}$).

The following compounds were prepared using similar method.

#	Structure	M W	Obs. m/e	#	Structure	MW	Obs. m/e
1457		413	414	1458		427	428
1459		413	414	1458		413	414

5

Method Z



27

- 201 -

(In the scheme, $-Z-NH-C(O)-N(R^{16})(R^{17})$ - is equivalent to R^1 substituted by R^{21} , or R^1 Substituted by alkyl- R^{22} , wherein R^{21} and R^{22} are $-N(R^{15})-C(O)-N(R^{16})(R^{17})$ and R^{15} is H, and wherein Z is optionally substituted alkylene-arylene, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

Method Z, Step 1:

To the solution of the Phoxime™ resin (1.23 mmol/g) in DCM was added the amine Z1 obtained from method L ($R^3 = Me$; $R^4 = ^iBu$; Z = para-(CH₂)C₆H₄(CH₂)-) (2 eq). The mixture was shaken overnight before the resin was filtered and washed with DCM, MeOH, THF (3 cycles), then DCM (x2), dried in vacuum to get resin Z2 ($R^3 = Me$; $R^4 = ^iBu$; Z = para-(CH₂)C₆H₄(CH₂)-).

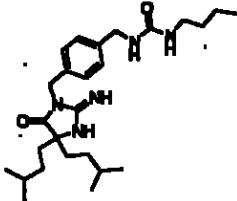
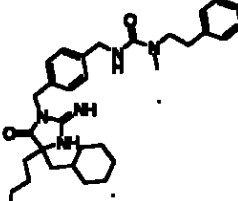
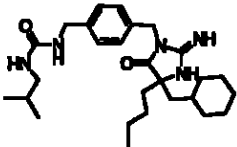
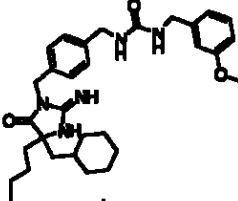
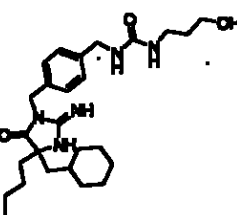
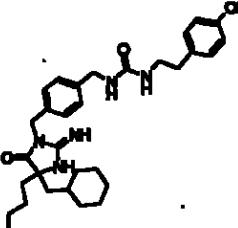
Method Z, Step 2:

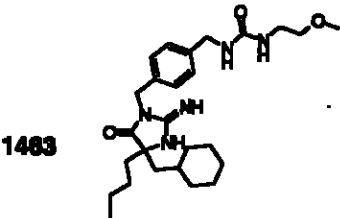
To the resin Z2 ($R^3 = Me$; $R^4 = ^iBu$; Z = para-(CH₂)C₆H₄(CH₂)-), swelled in DCM, in toluene was added N-methylbenzylamine (4 eq). The mixture was heated at 80-90°C overnight before MP-TSOH resin (1.3 mmol/g, 12 eq) was added. The mixture was shaken for 1.5 hours, the solution was filtered and the resin washed with DCM and MeOH. The combined organic solution was concentrated in vacuo to get Z3 ($R^3 = Me$; $R^4 = ^iBu$; Z = para-(CH₂)C₆H₄(CH₂)-; $R^{16} = Me$; $R^{17} = Bn$).

Method Z, Step 3:

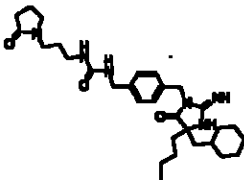
Compound Z4 ($R^3 = Me$; $R^4 = ^iBu$; Z = para-(CH₂)C₆H₄(CH₂)-; $R^{16} = Me$; $R^{17} = Bn$) was generated from Z3 ($R^3 = Me$; $R^4 = ^iBu$; Z = para-(CH₂)C₆H₄(CH₂)-; $R^{16} = Me$; $R^{17} = Bn$) using method similar to Method A step 3.

The following compounds were prepared using similar method.

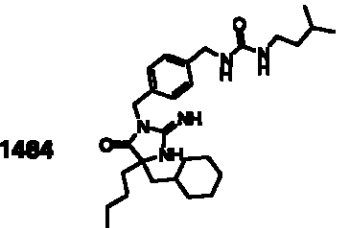
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1461		469	470	1475		533	534
1462		471	472	1476		533	534



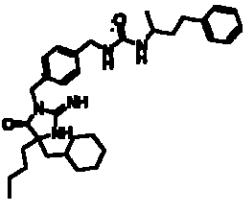
471 472 1477



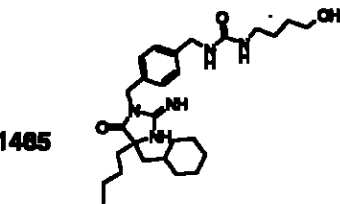
538 539



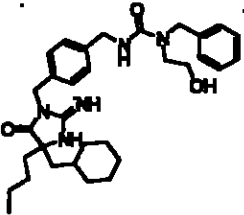
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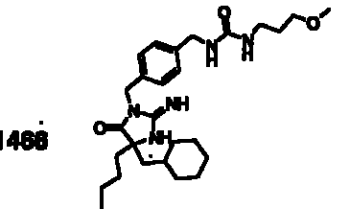
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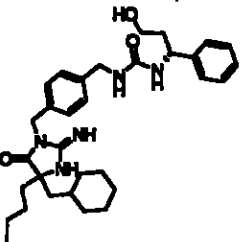
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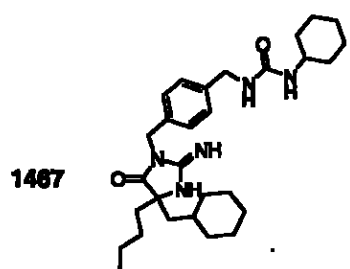


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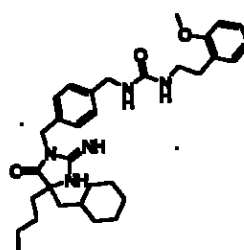


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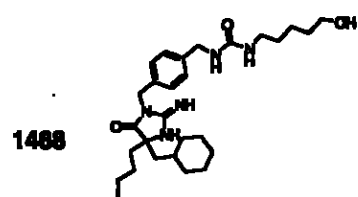
- 204 -



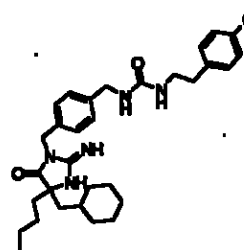
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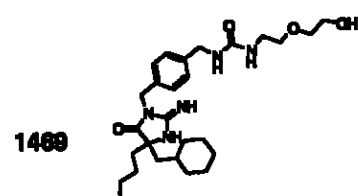
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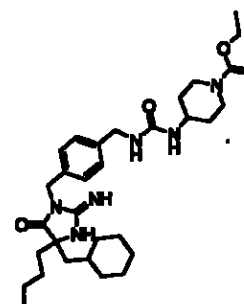
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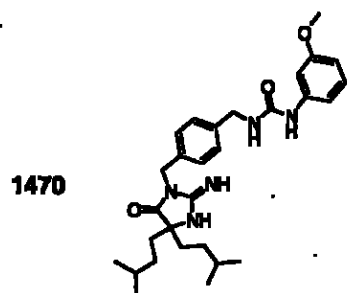
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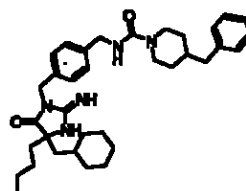
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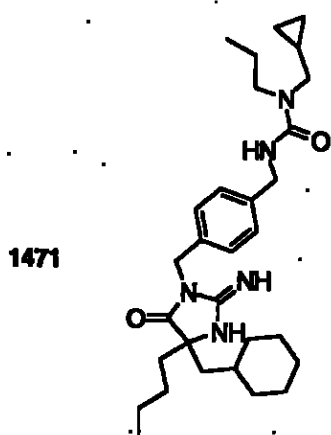
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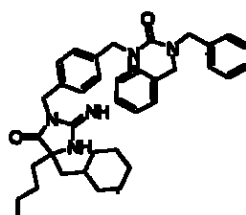
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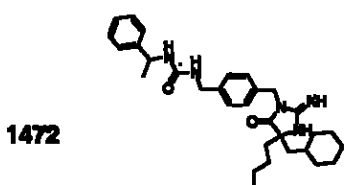
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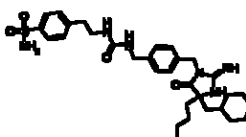
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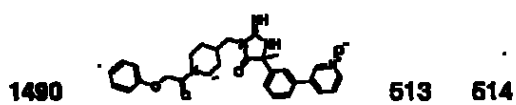
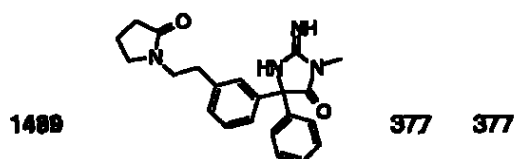
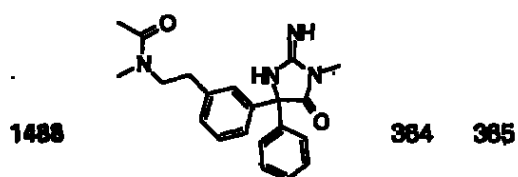
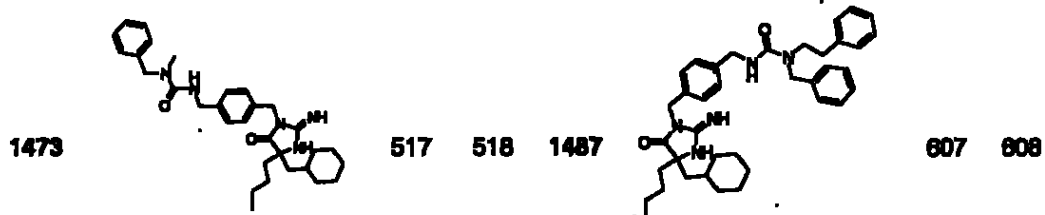
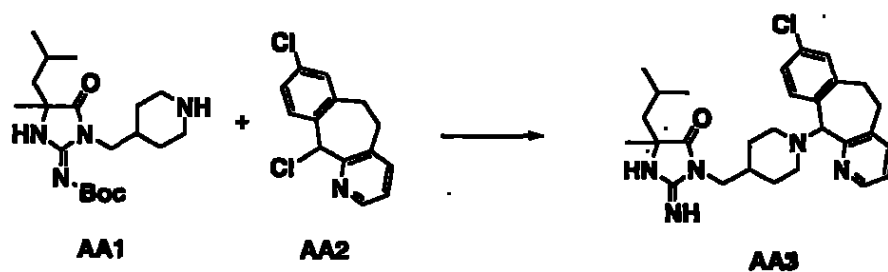
593 594



517 518 1486



596 597

**Method AA**

223

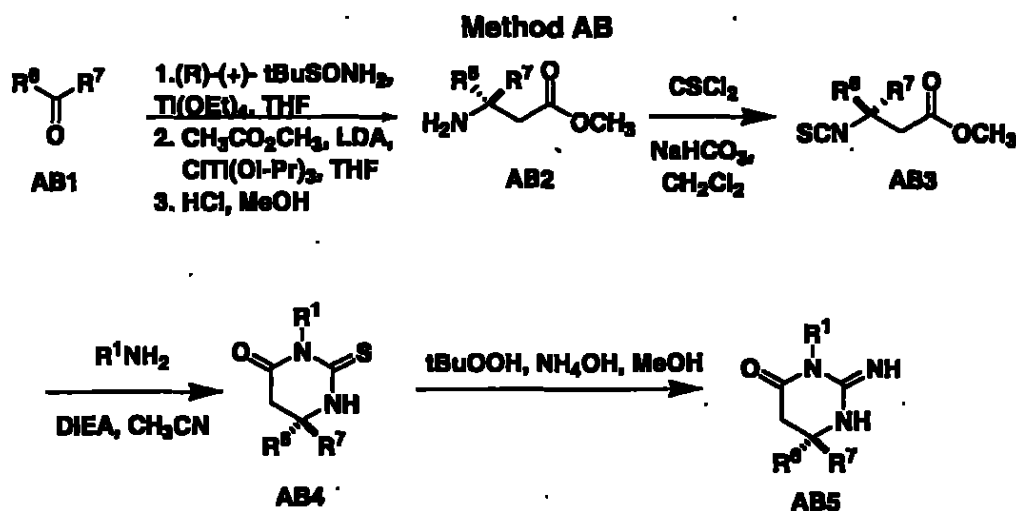
- 207 -

8,11-Dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (AA2) (18 mg) was reacted with AA1, obtained from method Q, and diisopropylethylamine (14 μ L) in acetonitrile (2.5 mL). The resulting mixture was heated at 85 °C for 18 h. The reaction mixture was placed on a preparative silica gel plate and eluted with hexane : ethyl acetate 3:1 to give the desired product which was treated with 40% TFA. Evaporation of the solvent followed by purification afforded compound AA3.

The following compounds were prepared by similar methods:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
187		491	492	188		493	494

10



Method AB, Step 1:

To a solution of (R)-(+)-2-methyl-2-propane sulfinamide (1.0 g, 8.3 mmol, 1 eq) and AB1 (R^6 =Ph, R^7 =n-Bu) (3 mL, 9.1 mmol, 1.1eq) in anhydrous THF

22A

- 208 -

(30 mL) at room temperature was added $\text{Ti}(\text{OEt})_4$ (7 mL, 17 mmol, 2 eq). The mixture was heated at 70 °C for 24 h. After cooling to room temperature, the mixture was poured into 30 mL of brine under vigorous stirring. The resulting suspension was filtered through a pad of Celite and the solid was washed with EtOAc (2 x 20 mL). The filtrate was washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica by eluting with hexane/ Et_2O (5:1) to give 1.9 g (85%) of (R)-2-methyl-N-(1-phenylpentylidene)propane-2-sulfonamide. ^1H NMR (CDCl_3 , 300 MHz): δ 7.91 (m, 2H), 7.52-7.37 (m, 3H), 3.27 (m, 1H), 3.15 (m, 1H), 1.73-1.61 (m, 2H), 1.47-1.38 (m, 2H), 1.31 (s, 9H), 0.95 (m, 3H). MS(ESI): $\text{MH}^+ = 265.9$. HPLC $t_R = 7.24, 7.58$ min (E/Z = 5.5:1).

To a solution of methyl acetate (0.6 mL, 6.9 mmol, 2 eq) in THF (5 mL), LDA (2M in heptane/THF, 3.4 mL, 6.9 mmol, 2 eq) was added dropwise via a syringe at -78 °C. After stirring at -78 °C for 30 min, a solution of $\text{ClTi}(\text{O}i\text{-Pr})_3$ (1.8 mL, 7.6 mmol, 2.2 eq) in THF (5 mL) was added dropwise. After stirring for another 30 min, a solution of (R)-2-methyl-N-(1-phenylpentylidene)propane-2-sulfonamide (0.9 g, 3.4 mmol, 1 eq) in THF (2 mL) was added dropwise via a syringe. The mixture was stirred at -78 °C for 3 h and TLC showed no starting material left. A saturated aqueous solution of NH_4Cl (10 eq) was added and the suspension was warmed to room temperature. The mixture was diluted with H_2O (50 mL) and stirred for 10 min. The mixture was then partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried (MgSO_4) and concentrated to give 1.1 g of a brown oil. Chromatography on silica gel using 50% EtOAc/hexanes as eluent gave 0.8 g (76%) of methyl 3-((R)-2-methylpropan-2-ylsulfonamido)-3-phenylheptanoate as a yellow oil. ^1H NMR (CDCl_3 , 300 MHz): δ 7.15-7.07 (m, 5H), 3.35 (s, 1H), 3.19 (dd, $J=16, 5.6\text{Hz}$, 1H), 3.01 (dd, $J=15.8, 5.5\text{Hz}$, 1H), 2.07 (m, 2H), 1.71 (m, 2H), 1.35-1.26 (m, 4H), 1.17 (s, 9H), 0.89 (m, 3H). MS(ESI): $\text{MH}^+ = 339.9$. HPLC $t_R = 7.50, 7.6$ min (E/Z = 1.5:1).

To a solution of methyl 3-((R)-2-methylpropan-2-ylsulfonamido)-3-phenylheptanoate (0.4 g, 1.1 mmol) in 12 mL of MeOH was added 16 mL of 4N HCl/dioxane. After stirring for 30 min, the volatiles were removed in vacuo. The

residue was re-dissolved in MeOH (6 mL), stirred for 5 min, and evaporated again to afford 0.30 g (97%) of AB2 ($R^6=Ph$, $R^7=n-Bu$) as a yellow solid.

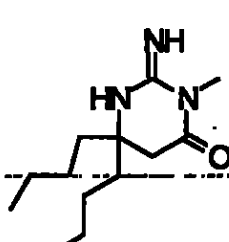
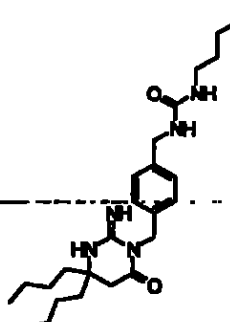
^1H NMR ($CDCl_3$, 300 MHz): δ 9.01 (br s, 2H), 7.37-7.12 (m, 5H), 3.64 (m, 1H), 3.54 (s, 3H), 3.31 (m, 1H), 2.09 (m, 2H), 1.8 (m, 2H), 1.1 (m, 4H), 1.07 (s, 9H),

5 0.7 (m, 3H). MS(ESI): $MH^+ = 235.9$. HPLC $t_R = 4.72$ min.

Method AB, Step 2:

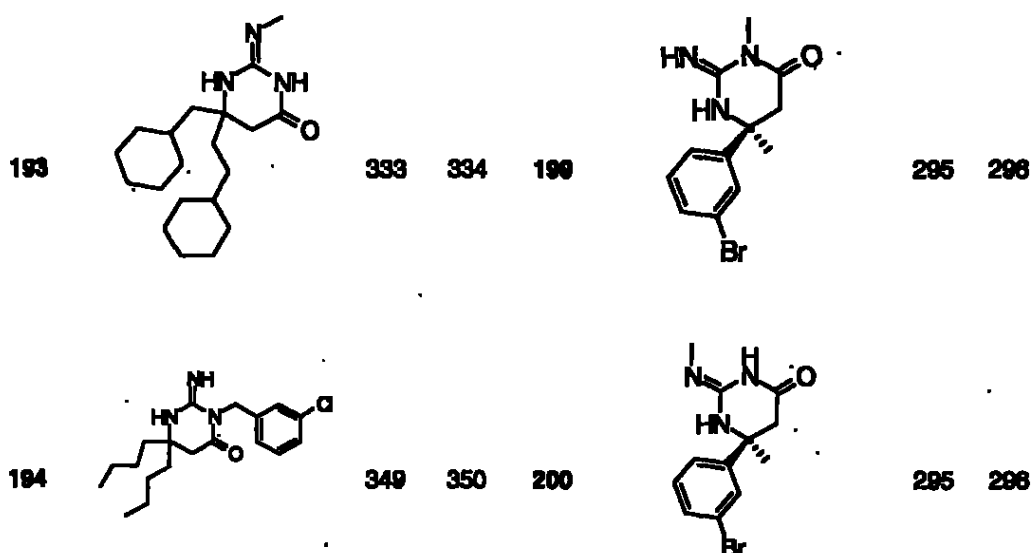
Treatment of compound AB2 ($R^6=Ph$, $R^7=n-butyl$) with thiophosgene in CH_2Cl_2 in the presence of aqueous $NaHCO_3$ at 0 °C generates Isothiocyanate
 10 AB3 ($R^6=Ph$, $R^7=n-butyl$) which was converted into final product using method similar to Method A Step 2 and Method A Step 3 to give product AB5 ($R^6=Ph$, $R^7=n-butyl$, $R^1=Me$). ^1H NMR ($CDCl_3$, 300 MHz): δ 10.4 (br s, 1H), 7.25-7.11 (m, 5H), 3.23 (dd, $J = 16, 5.6$ Hz, 1H), 3.03 (s, 3H), 2.8 (dd, $J = 15.8, 5.5$ Hz, 1H), 2.49 (s, 1H), 1.78 (m, 2H), 1.1-1.0 (m, 4H), 0.99 (m, 3H). MS(ESI): $MH^+ = 260.2$.
 15 HPLC $t_R = 5.09$ min.

The following compounds were synthesized using similar methods:

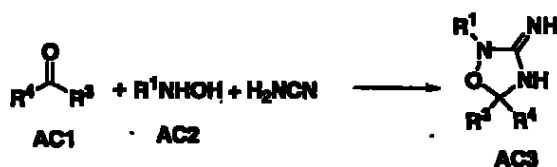
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
189		239	240	195		443	444

227

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Method AC

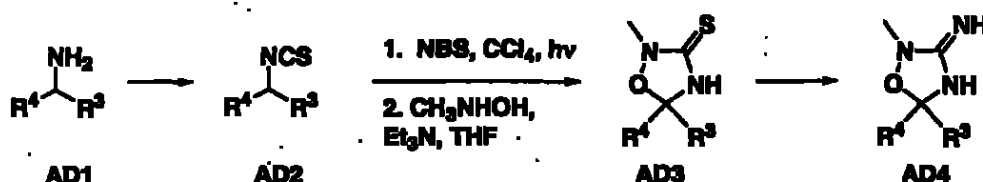


- 5 The synthesis was adapted from a procedure by Hull, R. *et al*, *J. Chem. Soc.* 1963, 6028-6033. Thus, to a solution of AC2 (R¹=Benzyl) (0.72 g, 5.9 mmol) in AC1 (R⁴=Me, R³=Me) (1.4 mL) was added a 50% aqueous solution of cyanamide (0.31 mL, 8.0 mmol). The reaction was heated with stirring at reflux (~40 °C) for 0.5 h, then cooled to 25 °C and stirred for an additional 16 h.
- 10 The volatiles were removed *in vacuo* and the residue was partitioned between ether and H₂O. The organic layer was dried over Na₂SO₄, filtered and the volatiles were removed *in vacuo*. The residue was purified by column chromatography using 5-10% CH₃OH/CH₂Cl₂ as eluent followed by reverse phase preparative HPLC to give 0.15 g (8.0%) of AC3 (R¹=benzyl, R⁴=Me and R³=Me) as a white solid.
- 15 ¹H NMR (CH₃OH, 300 MHz): δ 7.35-7.33 (m, 5H), 4.71 (s, 2H), 1.46 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 157.8, 135.6, 129.1, 128.5, 127.9, 104.2, 59.6, 28.8. MS (ESI) *m/e* 206.1 (M+H)⁺.

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#	Structure	MW	Obs. m/e
201		205	208

Method AD



5

Method AD, Step 1:

AD2 ($R^3 = \text{Ph}$, $R^4 = \text{tert-Butyl}$) was prepared from AD1 using method similar to Method AB, step 2.

10

Method AD, Step 2:

The synthesis was adapted from a procedure by Hussein, A. Q. *et al*, *Chem. Ber.* 1979, 112, 1948-1955. Thus, to a mixture of AD2 ($R^3 = \text{Ph}$, $R^4 = \text{tert-Butyl}$) (0.56 g, 2.7 mmol) and boiling chips in CCl_4 (25 mL) was added *N*-bromosuccinimide (0.49 g, 2.7 mmol). The mixture was irradiated with a 200 watt light source for 1 h. The reaction was cooled, the solid filtered off and the volatiles were removed *in vacuo*. Chromatography on silica gel by eluting with 5% EtOAc/hexane gave 0.57 g (73%) of 1-(1-bromo-1-isothiocyanato-2,2-dimethylpropyl)benzene as a beige powder. ^1H NMR (CDCl_3 , 300 MHz): δ 7.63-7.61 (m, 2H), 7.37-7.26 (m, 3H), 1.17 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 139.1, 129.0, 128.9, 128.6, 127.5, 91.2, 45.6, 26.6. MS (ESI) m/e 284.9 ($\text{M} + \text{H}$) $^+$.

To a solution of 1-(1-bromo-1-isothiocyanato-2,2-dimethylpropyl)benzene (0.13 g, 0.47 mmol) and the hydrochloride salt of *N*-methylhydroxylamine (0.047 g, 0.57 mmol) in THF (3 mL) was added triethylamine (0.18 mL, 1.32 mmol). The mixture was stirred at 25 °C for 16 h, filtered and the volatiles were removed *in vacuo*. The residue was purified by column chromatography using $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ as eluent to give 0.050 g (42%) of AD3 ($R^3 = \text{Ph}$, $R^4 = \text{tert-Butyl}$) as

25

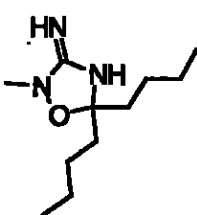
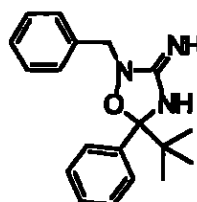
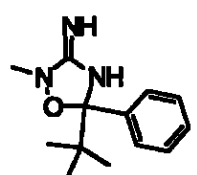
- 213 -

a glassy solid. ^1H NMR (CDCl_3 , 300 MHz): δ 7.35-7.26 (m, 5H), 3.38 (s, 3H), 1.0 (s, 9H); MS (ESI) m/e 251.1 ($\text{M}+\text{H}$) $^+$.

Method AD, Step 3:

- 5 To a solution of AD3 ($\text{R}^3=\text{Ph}$, $\text{R}^4=\text{tert-Butyl}$) (0.065 g, 0.26 mmol) in CH_3OH (5 mL) at 0 $^\circ\text{C}$ was added a solution of aqueous ammonia (2 mL) followed by a 70% aqueous solution of *t*-butylhydroperoxide (2 mL). The reaction was allowed to warm to 25 $^\circ\text{C}$ and stirred for 16 h. The volatiles were removed and the residue was purified by reverse phase HPLC to give 2.0 mg (2.2%) of
- 10 AD4 ($\text{R}^3=\text{Ph}$, $\text{R}^4=\text{tert-Butyl}$) as a colorless oil. ^1H NMR (CDCl_3 , 300 MHz) δ 7.47-7.43 (m, 2H), 7.39-7.35 (m, 3H), 3.23 (s, 3H), 1.0 (s, 9H); MS (ESI) m/e 234.2 ($\text{M}+\text{H}$) $^+$.

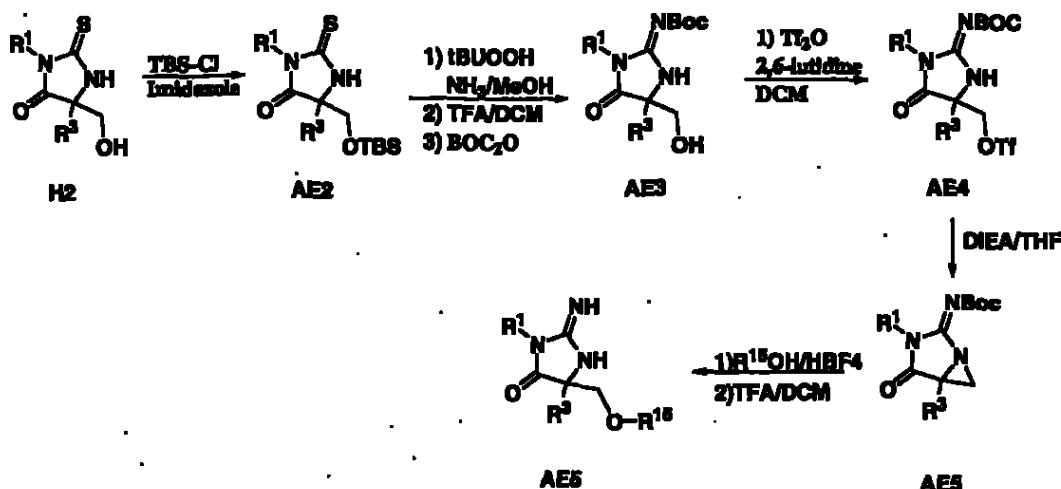
The following compounds were synthesized using similar methods:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
202		213	214	204		309	310
203		233	234				

15

Method AE

230

**Method AE, Step 1:**

5 **TBDMs-Cl** (5.3g, 35.19mmole) and **Imidazole** (2.4g, 35.19mmole) were added to a suspension of **H2** (**R¹**=Me, **R³**=cyclohexylmethyl) (8.2g, 31.99mmole) in 220 ml **DCM**. The reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered, and the filtrate was diluted with 1200ml **EtOAc**. The organic phase was washed with saturated **NaHCO₃** 3X and brine 3X, and dried over anhydrous **Na₂SO₄** to give 12g of **AE2** (**R¹**=Me, **R³**=cyclohexylmethyl), which was used for next step without further purification.

10

Method AE, Step 2:

15 **AE2** (**R¹**=Me, **R³**=cyclohexylmethyl; 12 grams crude) was converted to Iminohydantoin using conditions similar to Method A Step 3, which was subsequently treated with 75% **TFA** in **DCM** at room temperature for 24 hrs. The solvent was evaporated *in vacuo* to give 13.6g of a product that was reacted with **Boc anhydride** to give 5.8g **AE3** (**R¹**=Me, **R³**=cyclohexylmethyl) after column purification.

20 **Method AE, Step 3:**

AE4 (**R¹**=Me, **R³**=cyclohexylmethyl) (8.2 g) was obtained from **AE3** (5.8g) according to the step 4 of the method H.

25 **Method AE, Step 4:**

To a solution of **AE4** (**R¹**=Me, **R³**=cyclohexylmethyl) (3.95 g, 8.38 mmol) in anhydrous **THF** (98 mL) was added diisopropylethylamine (7 mL, 40 mmol).

231

The reaction was stirred under N₂ (gas) at room temperature. After 5.5 h, the reaction was concentrated and the crude material was purified via flash chromatography eluting with a gradient of 0 to 75% ethyl acetate in hexane to afford AE5 (R¹=Me, R³=cyclohexylmethyl) (2.48 g, 92%).

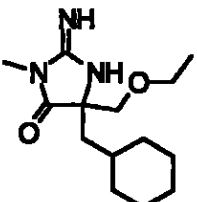
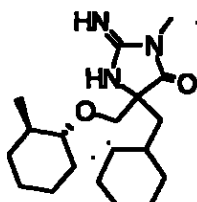
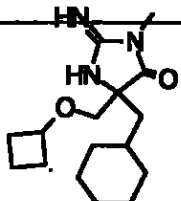
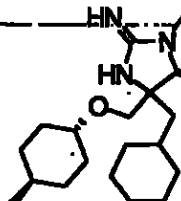
5

Method AE, Step 4:

To a solution of R¹⁵OH (R¹⁵=cyclobutyl) (10 μ l) and HBF₄ (1 equiv) in anhydrous methylene chloride (0.5 mL) was added a solution of AE5 (R¹=Me, R³=cyclohexylmethyl) (20 mg; 0.062 mmol) in methylene chloride (0.5 mL). The reaction was agitated overnight at rt. Trifluoroacetic acid (1 mL) was added to the reaction mixture and the solution was agitated for 1 h at rt. The reaction was concentrated and the crude material was purified via reverse phase preparative HPLC/MS eluting with a 7 min gradient of 5 to 95% CH₃CN in H₂O with 0.1% formic acid to afford AE5 (R¹=Me, R³=cyclohexylmethyl, R¹⁵=cyclobutyl).

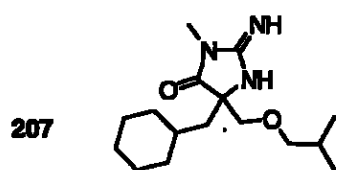
15

The following compounds were synthesized using similar method:

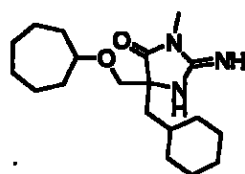
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206		283	284	227		335	336

232

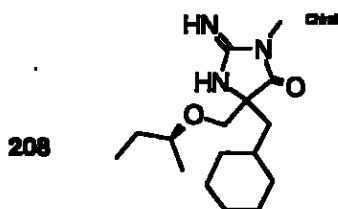
- 216 -



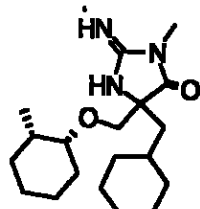
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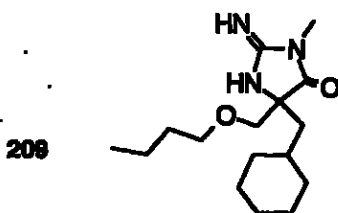
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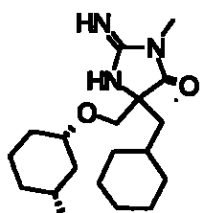
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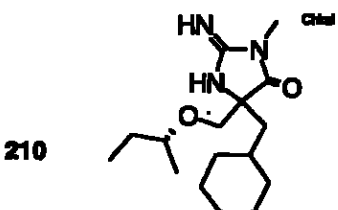
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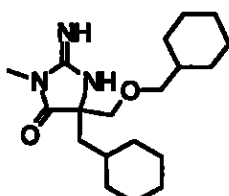
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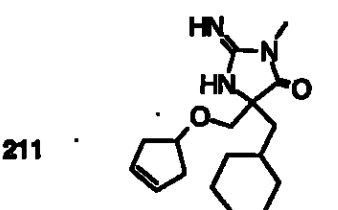
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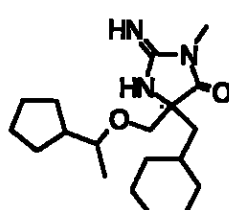
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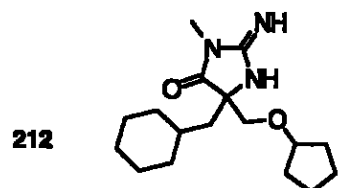
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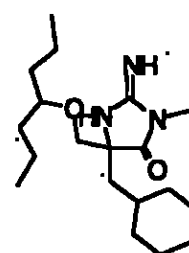
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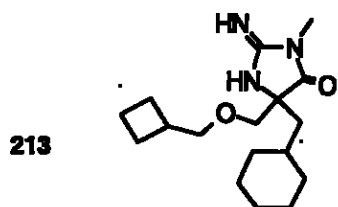
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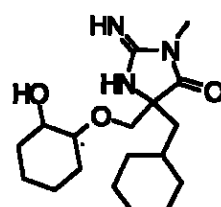
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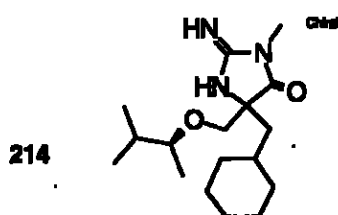
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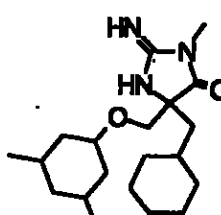
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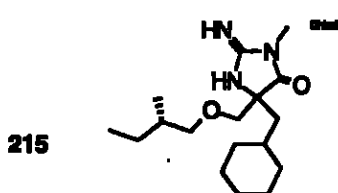
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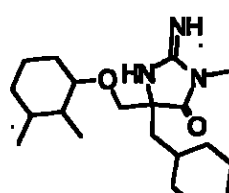
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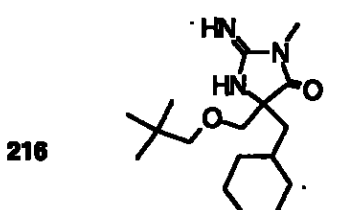
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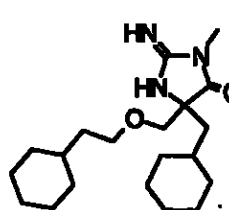
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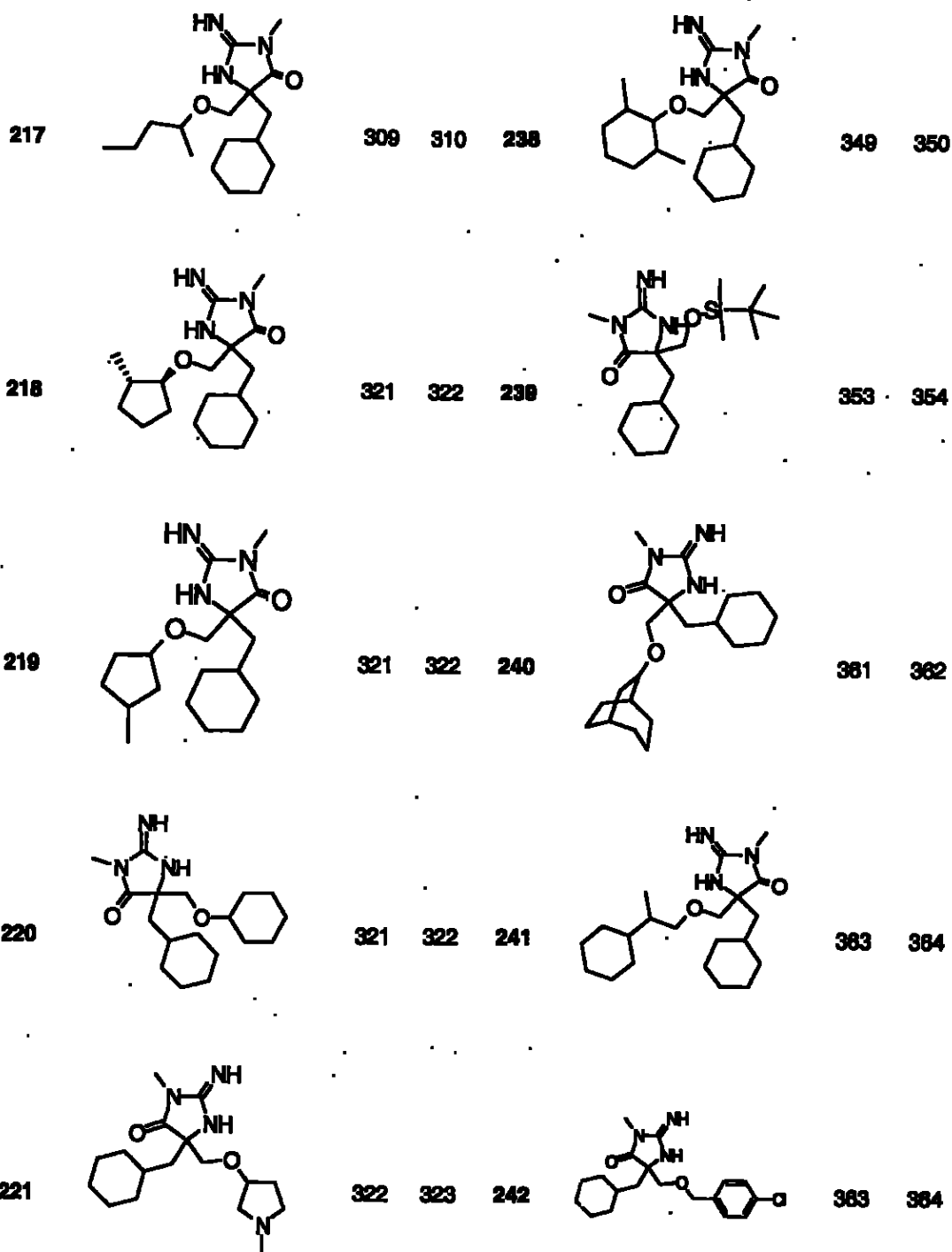
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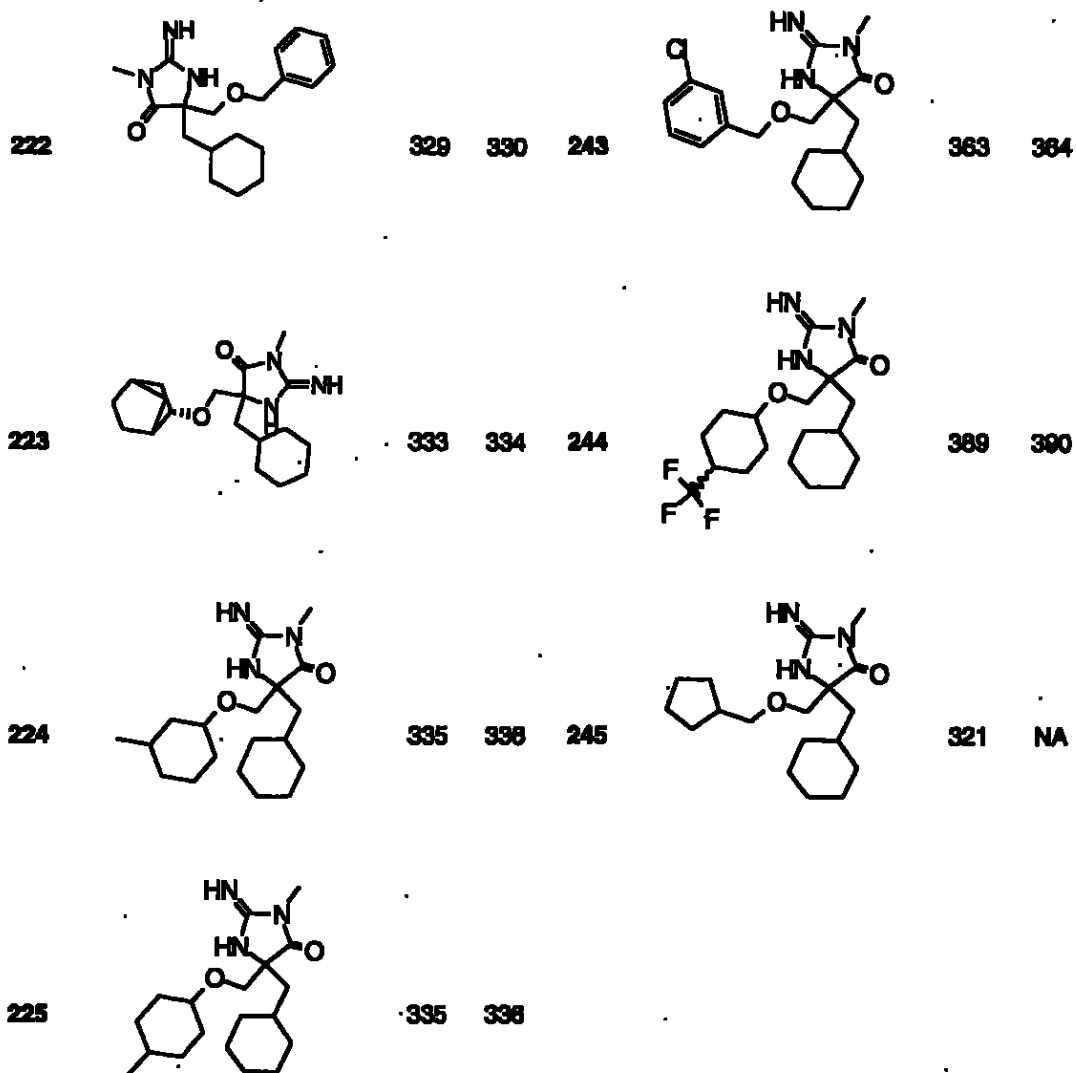
23A

- 218 -

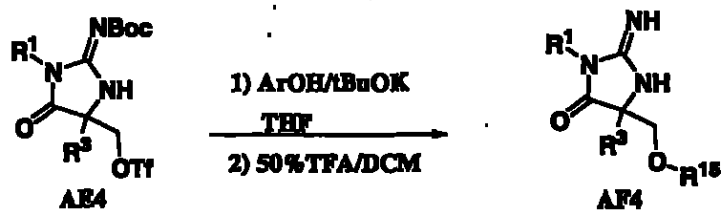


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Method AF



5

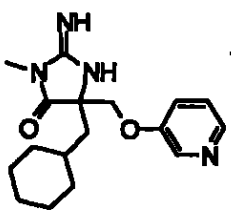
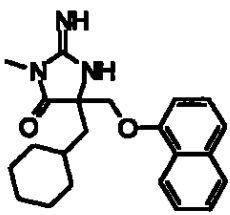
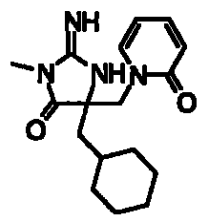
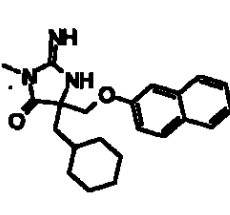
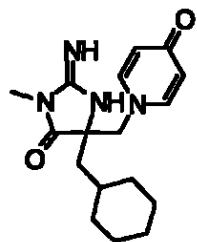
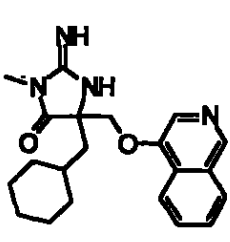
To a solution of tBuOK (9.5mg, 0.0848mmole) in 0.5ml anhydrous THF was added ArOH (Ar=m-Chlorophenyl)(13μl, 0.1273mmole) in 0.5ml anhydrous

236

- 220 -

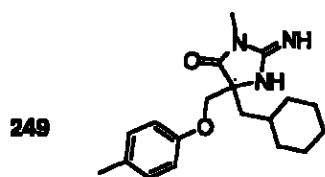
THF followed by addition of AE4 ($R^1=Me$, $R^3=cyclohexylmethyl$) (20mg, 0.0424mmole) in 0.5ml anhydrous THF. The reaction mixture was stirred at room temperature for 2 days before it was diluted with 1ml MeCN, treated with 100mg MP-TsOH resin and 100mg Amberlyst A26 resin. The resin was removed by filtration and the filtrate was evaporated down to give a product that was treated with 50% TFA for 1 hr. After evaporation of TFA *in vacuo*, the residue was dissolved in 2ml MeCN, and treated with 100mg MP-TsOH resin. The resin was washed thoroughly with THF, MeCN and MeOH, and then treated with 2M NH_3 in MeOH to give AF2 ($R^1=Me$, $R^3=cyclohexylmethyl$ and $R^{16}=3$ -chlorophenyl).

The following compounds were synthesized using similar method:

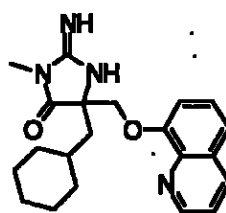
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237

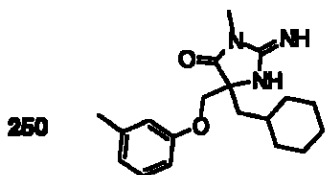
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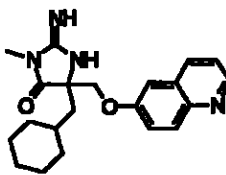
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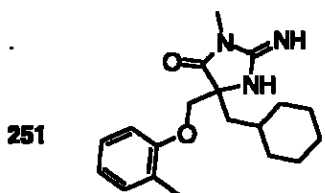
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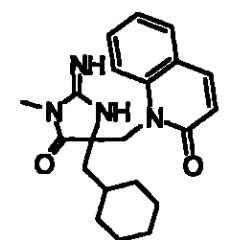
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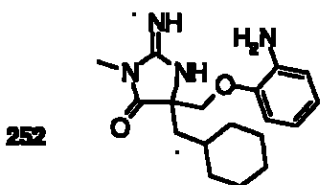
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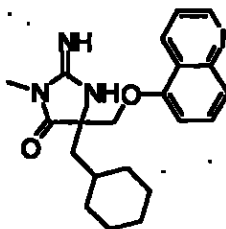
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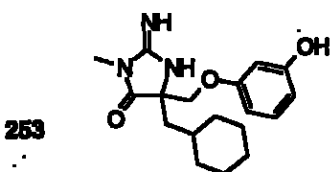
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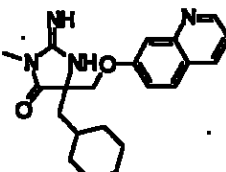
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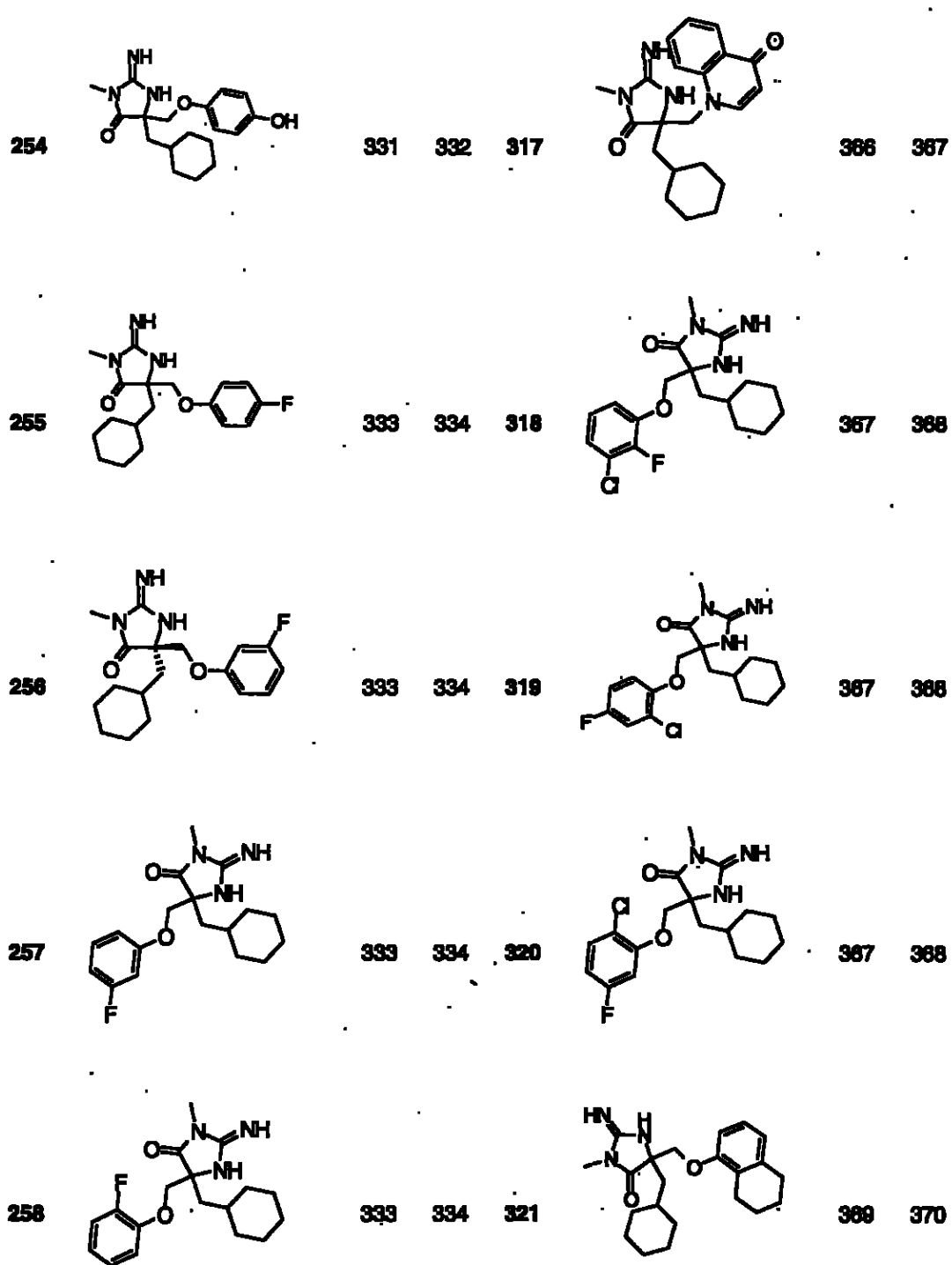


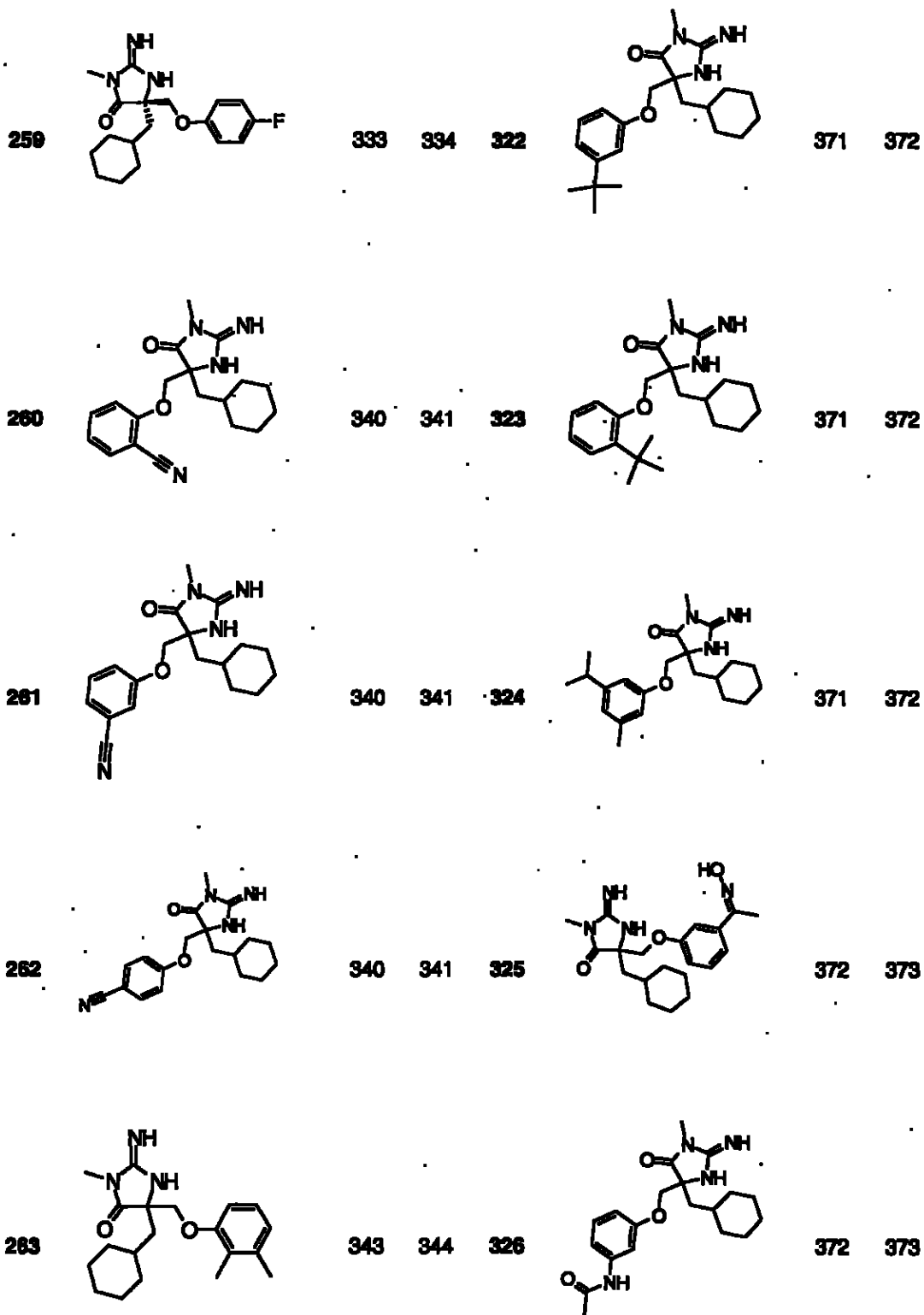
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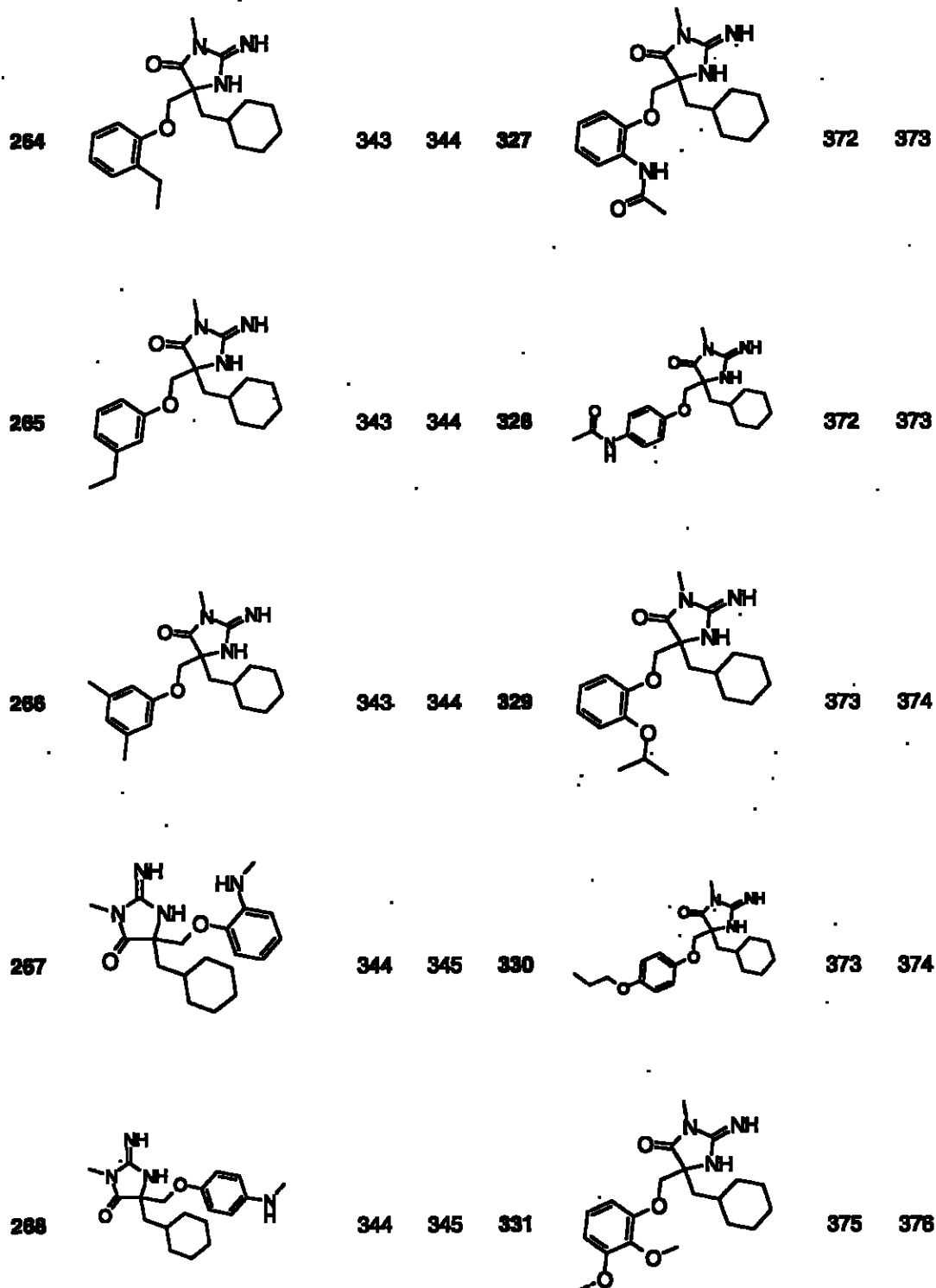
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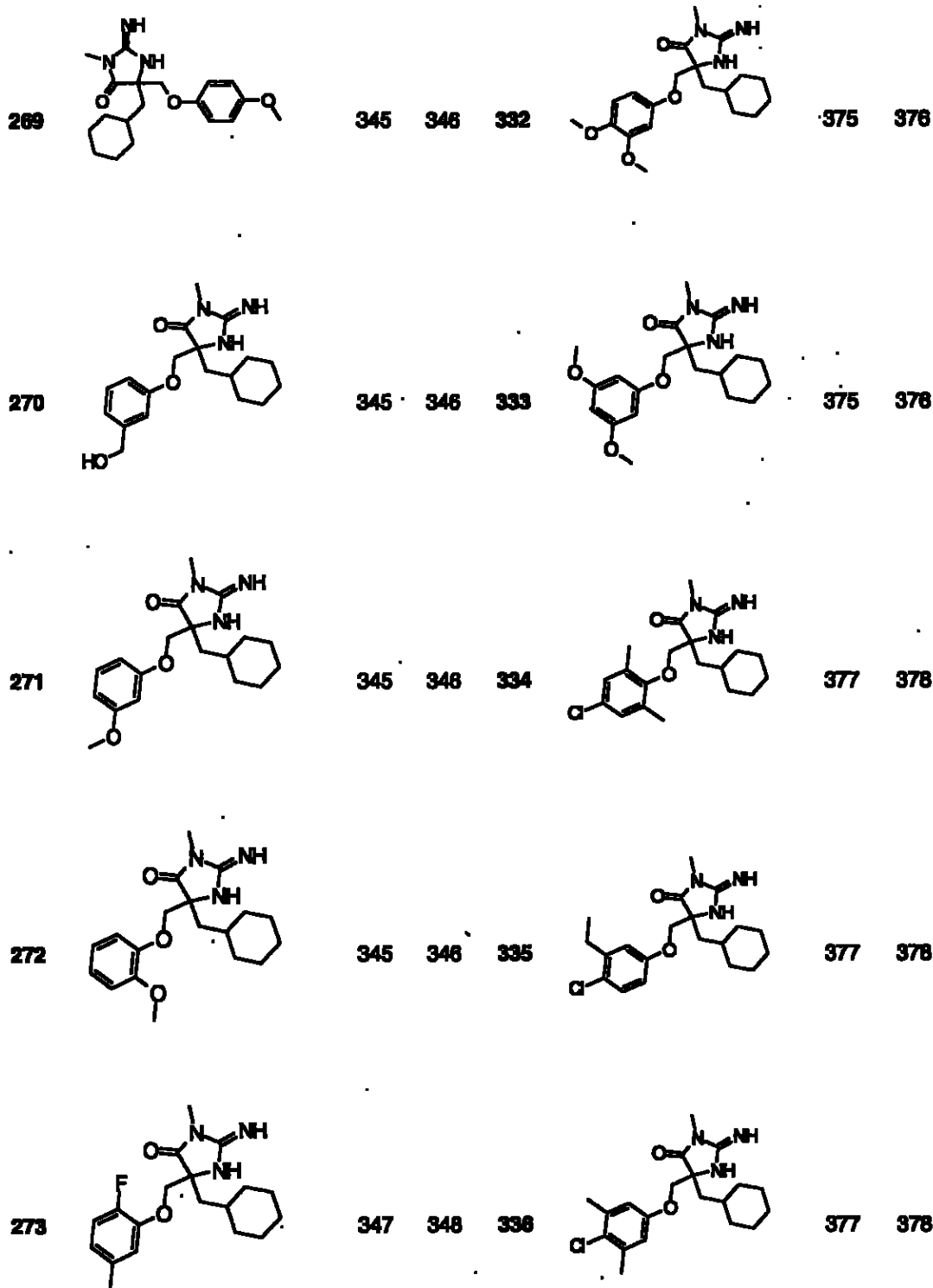


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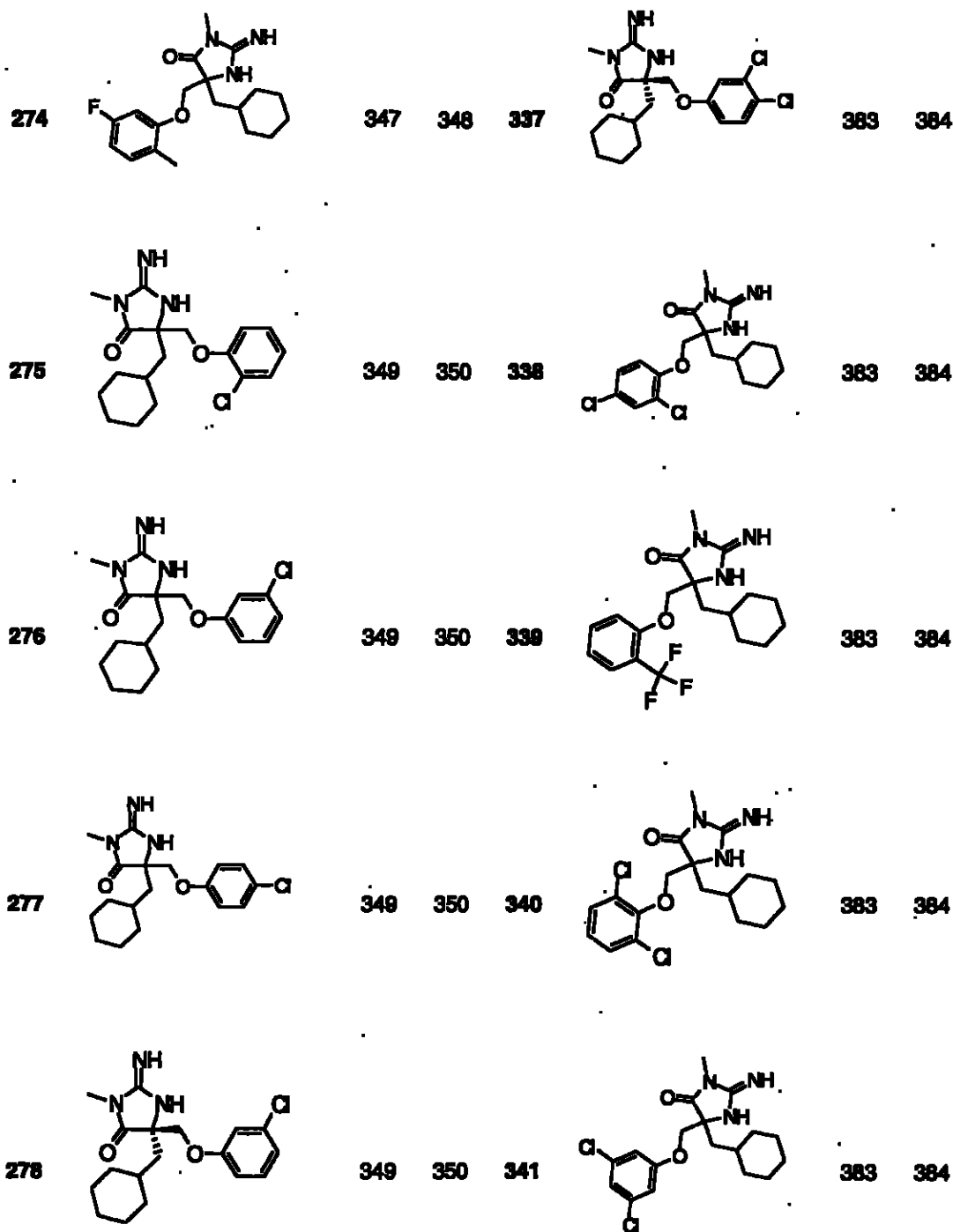
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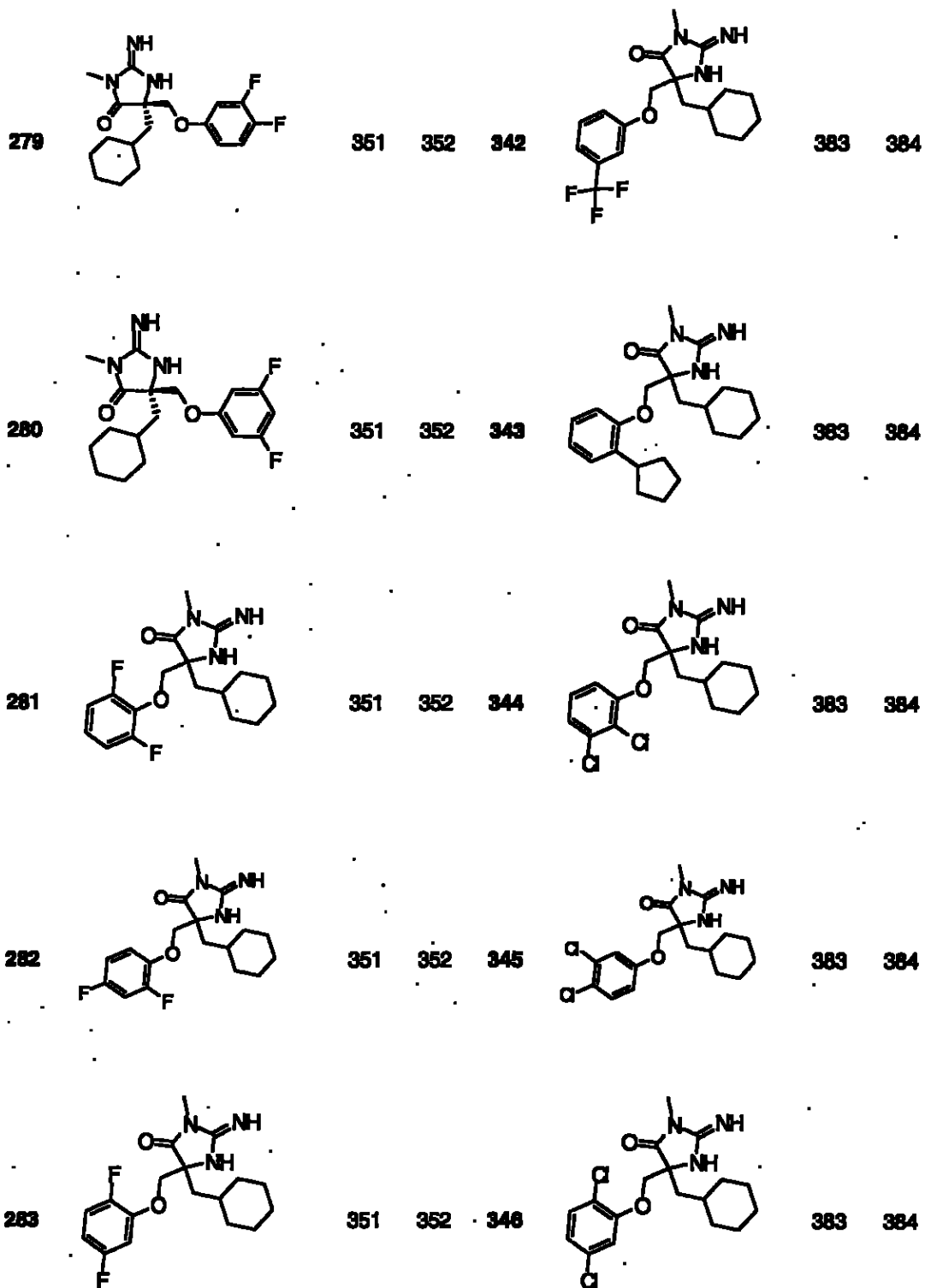


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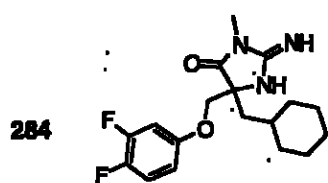
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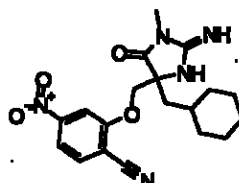
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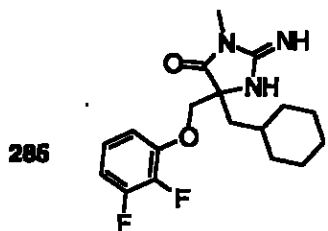
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347



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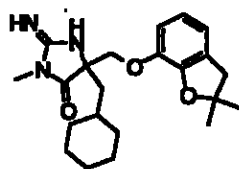
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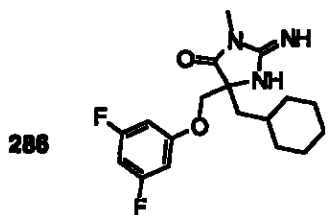
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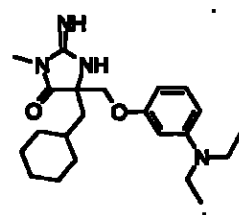
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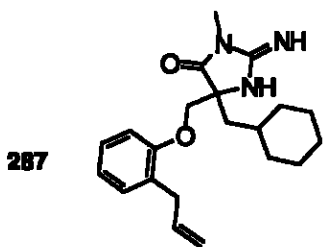
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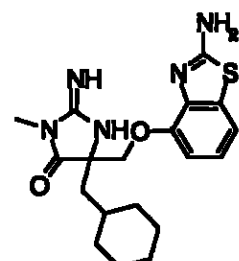
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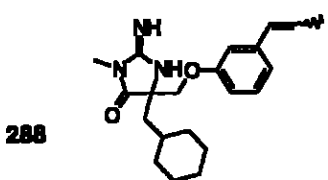
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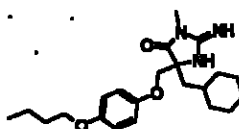
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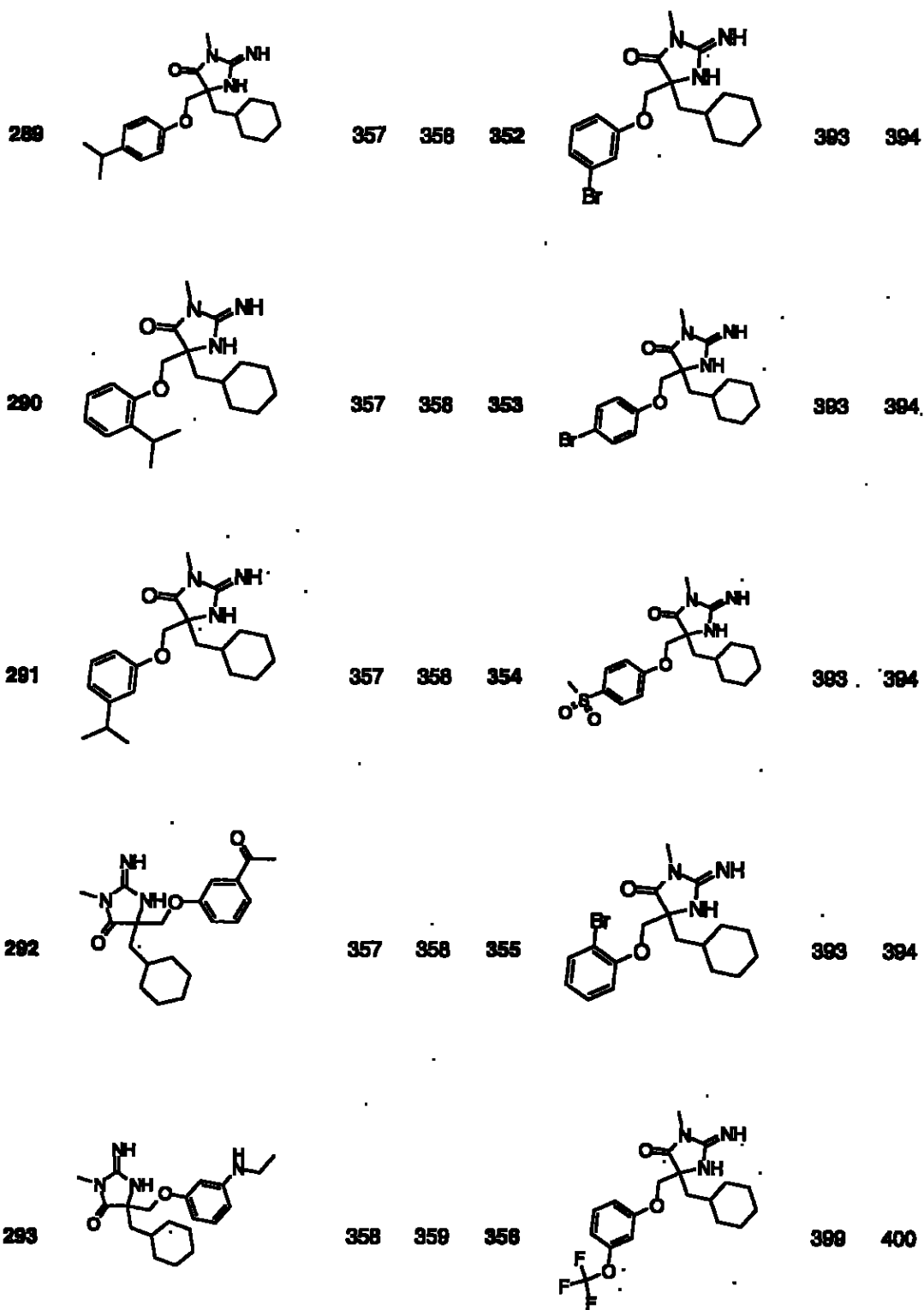


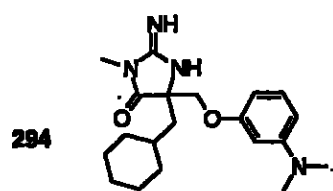
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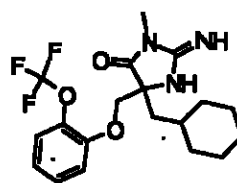
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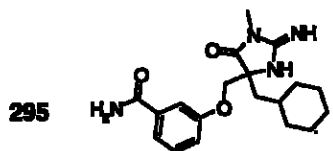




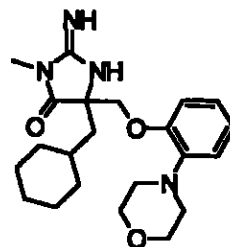
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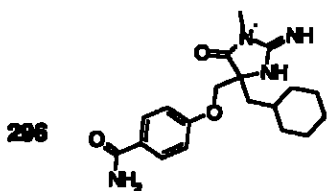
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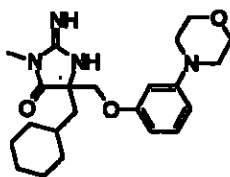
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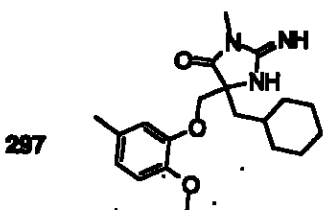
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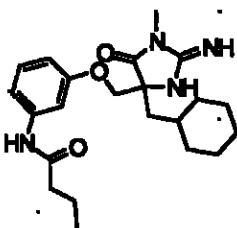
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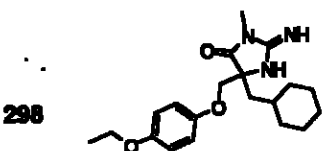
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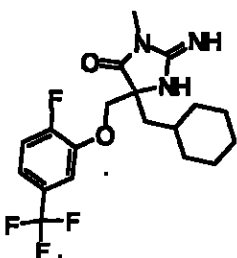
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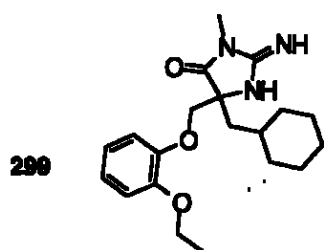
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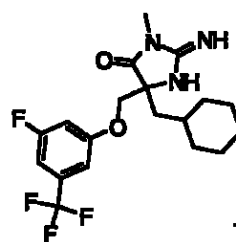
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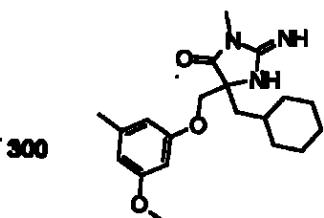
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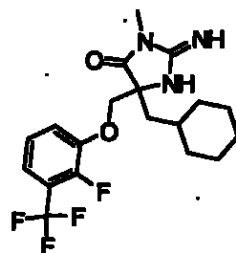
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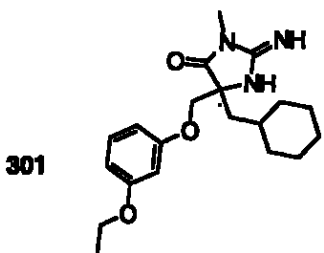
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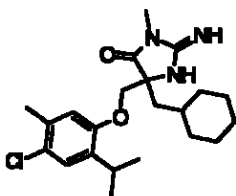
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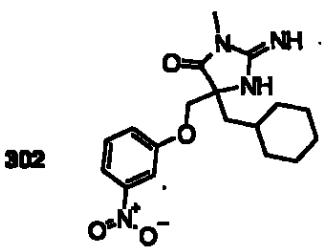
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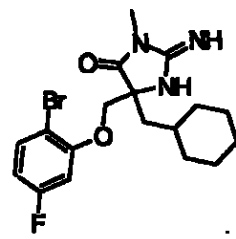
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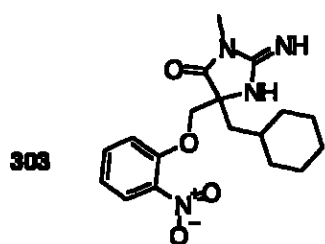


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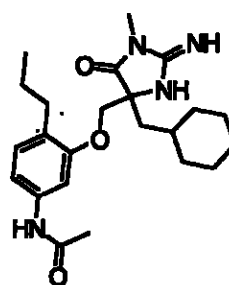


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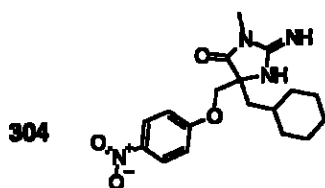
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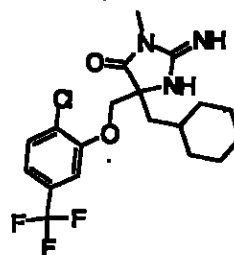
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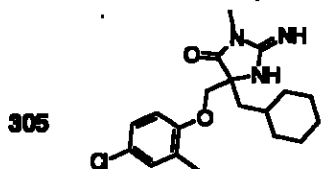
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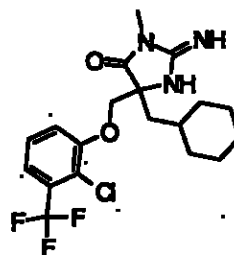
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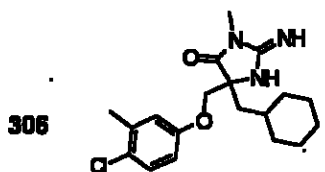
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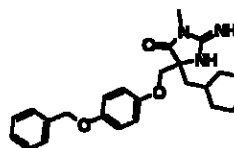
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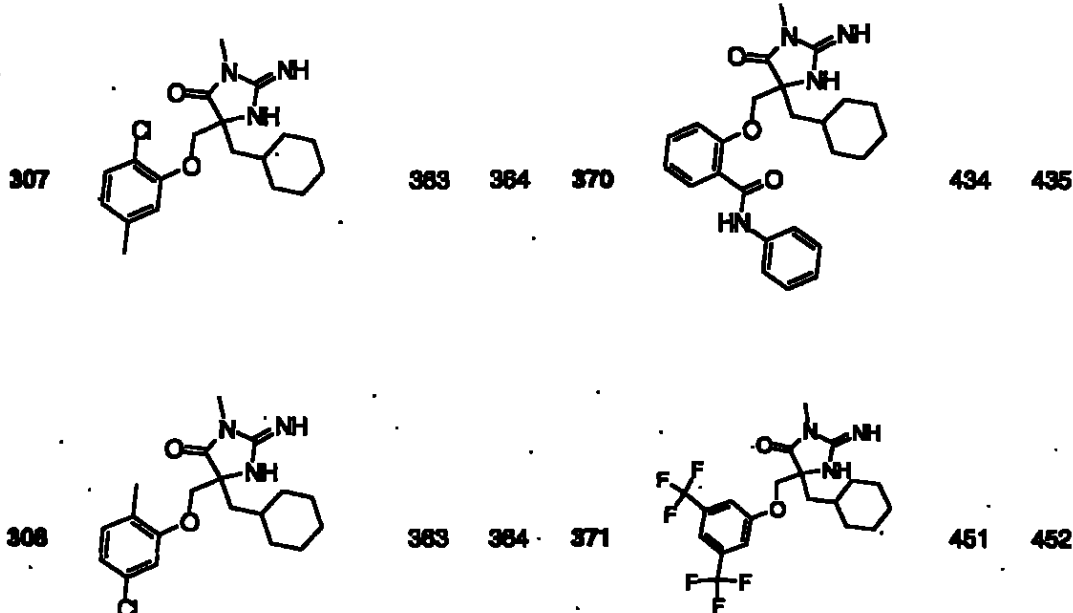
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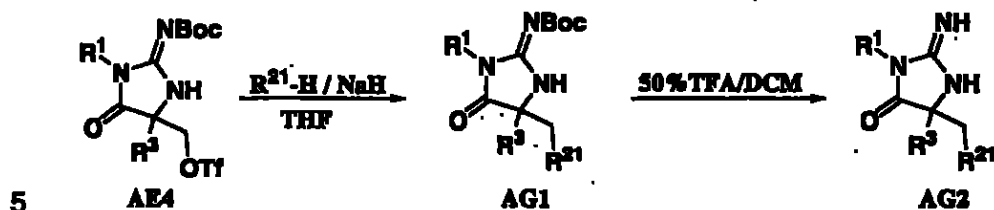
363 364 369



421 422

249
249

Method AG



Method AG, Step 1:

- $\text{R}^{21}\text{-H}$ ($\text{R}^{21} = \text{PhS-}$) (33 μl , 0.318 mmole) was treated with NaH (10.2 mg, 60% in mineral oil) in 0.5 ml anhydrous THF. A solution of AE4 ($\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{Cyclohexylmethyl}$) (20 mg, 0.0424 mmol) in 0.5 ml anhydrous THF was added.
- 10 The reaction mixture was stirred at room temperature overnight before it was partitioned between ether and saturated NaHCO_3 water solution. The aqueous phase was extracted with ether 2 times. The combined organic phase was washed with brine 2 times, and dried over anhydrous NaSO_4 . The crude was purified on flash column with EtOAc / hexane to give 9 mg of AG1 ($\text{R}^{21} = \text{PhS-}$, $\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{cyclohexylmethyl}$) (49.2 % yield).
- 15

Method AG, Step 2:

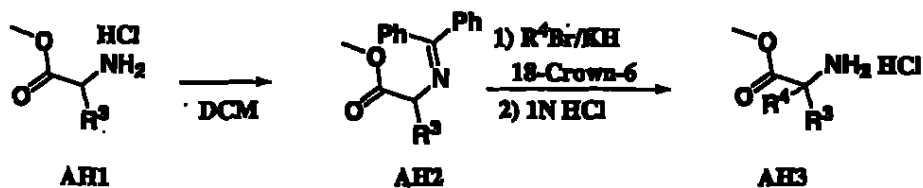
AG1 ($R^{21}=\text{PhS-}$, $R^1=\text{Me}$, $R^3=\text{cyclohexylmethyl}$) was treated with 50% TFA according to the Step 6 of the method H to give AG2 ($R^{21}=\text{PhS-}$, $R^1=\text{Me}$, $R^3=\text{cyclohexylmethyl}$).

The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
372		315	316	374		337	338
373		331	332				

Method AH

10

**Method AH, Step 1:**

Benzophenone imine (3.27g, 18.04mmole) was added to a suspension of AH1 ($R^3=\text{cyclohexylmethyl}$) (4g, 18.04mmole) in 65ml DCM. The reaction mixture was stirred at room temperature overnight under N_2 before the solid was filtered, and the solvent was evaporated. The residue was dissolved in 100 ml ether, washed with water 2X and dried over anhydrous MgSO_4 . The crude was

251

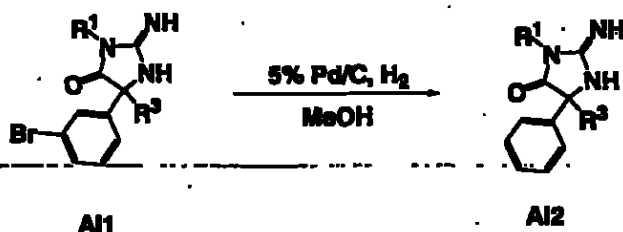
- 235 -

purified on flash column to give 5.08 g (80.57% yield) of AH2 (R^3 =cyclohexylmethyl).

Method AH, Step 2:

5 A solution of AH2 (R^3 =cyclohexylmethyl) (1g, 2.86mmole) in 12 ml anhydrous THF was added to a suspension of 18-crown-6 (0.76g, 2.86mmole) and 30% KH in mineral oil (1.16g, 8.58mmole) in 4ml anhydrous THF under N₂. The mixture was cooled in ice-bath and R^4 Br (R^4 =3-pyridylmethyl, as a hydrobromide salt) was then added. The reaction mixture was stirred in ice-bath
10 for 30min and at room temperature for 2 more hrs before the reaction was quenched with 2ml of HOAc/THF/H₂O (0.25:0.75:1). The mixture was diluted with 40ml EtOAc/H₂O (1:1). The aqueous phase was extracted with EtOAc 3 times. The combined organic phase was washed with brine 3 times and dried over anhydrous MgSO₄. The crude was purified on flash column to give 0.44g
15 (35.14% yield) of product which was treated with 1N HCl (2.2ml, 2.22mmole) in 3ml ether in ice-bath followed by stirred at r.t. overnight. The aqueous phase was evaporated and purified on C-18 reverse phase column to give 0.22g (66% yield) of AH3 (R^4 =3-pyridylmethyl; R^3 =cyclohexylmethyl).

20

Method AI

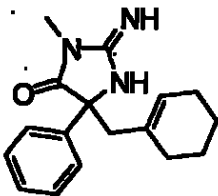
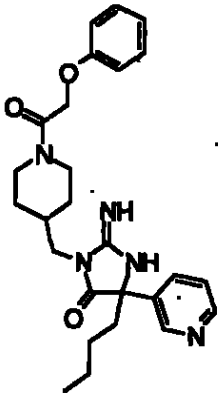
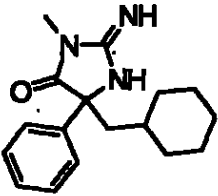
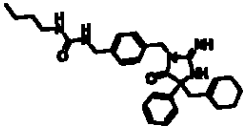
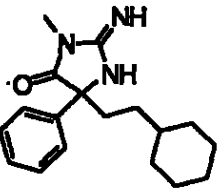
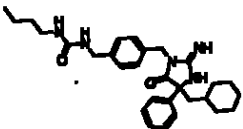
25 To a solution of compound AI1 (R^1 =Me, R^3 =n-Bu) (34mg, 0.105mmol) in methanol (1ml) was added 10% Pd/C (5mg). The mixture was kept under an H₂ balloon for 1 hr. After filtration of the catalyst, the filtrate was concentrated to get crude product. This residue was purified by RP HPLC to get compound AI2 (R^1 =Me, R^3 =n-Bu) (25mg, 100%). Observed MW (M+H) 246.1; exact mass

252

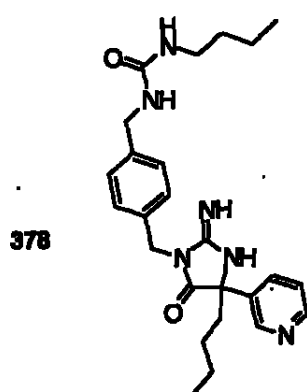
- 236 -

245.15. ^1H NMR (400 MHz, CD_3OD): δ = 7.59 (m, 2H), 7.36 (m, 3H), 3.17 (s, 3H), 2.17 (m, 2H), 1.27 (m, 4H), 0.86 (t, 3H, $J=7.2\text{Hz}$).

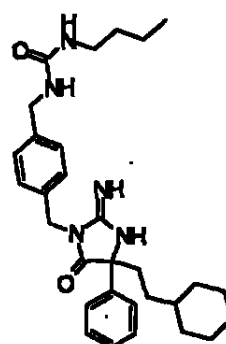
The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
375		283	284	380		483	484
376		285	286	381		487	488
377		289	300	382		489	490

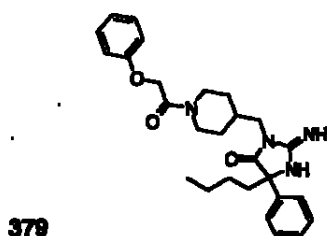
- 237 -



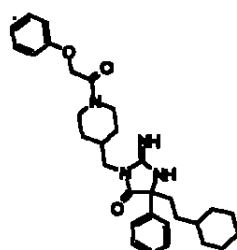
450 451 383



503 504

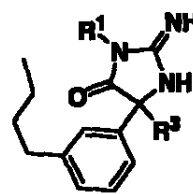
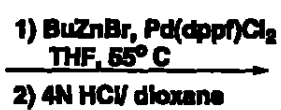
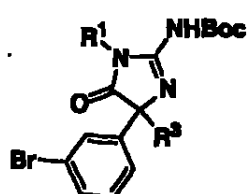


462 463 384



516 517

Method AJ



5

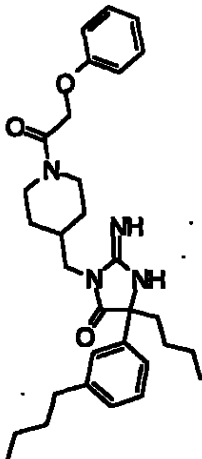
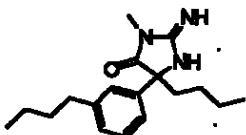
To a mixture of compound AJ1 (R¹=Me, R³=n-Bu) (70mg, 0.165mmol) and butylzincbromide (1.32ml, 0.6mmol) was added Pd(dppf)Cl₂. The mixture

234

- 238 -

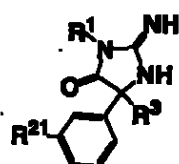
was degassed, sealed and heated at 55 °C for 1 day. The mixture was diluted with CH₂Cl₂ and NH₃/H₂O. The organic layer was separated, dried, concentrated, and purified by RP HPLC to get product which was then treated with 4N HCl/dioxane for 30min to give compound AJ2 (R¹=Me, R³=n-Bu) (12mg, 25%). Observed MW (M+H) 302.1; ¹H NMR (400 MHz, CD₃OD): δ = 7.32 (m, 3H), 7.22 (m, 1H), 3.19 (s, 3H), 2.65 (m, 2H), 2.20 (m, 2H), 1.60 (m, 2H), 1.38 (m, 4H); 1.24 (m, 2H), 0.92 (m, 6H).

The following compound was synthesized in a similar fashion:

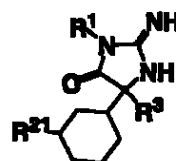
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
386		518	519	385		301	302

10

Method AK



AK1



AK2

To a solution of AK1 (R¹=Me, R³=n-Butyl, R²¹=n-Bu) (9mg, 0.03mmol) in methanol (1ml) was added 5% Pt/C (5mg), Rh/C (5mg) and conc. HCl (0.05ml). The mixture was kept under H₂ (50 psi) for 2 days. After the filtration of the catalyst, the filtrate was concentrated to get compound AK2 (R¹=Me, R³=n-butyl,

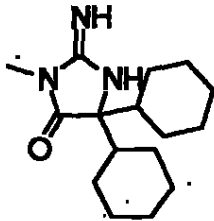
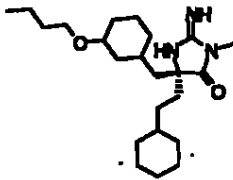
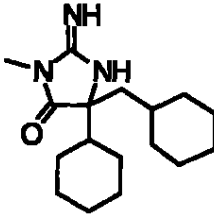
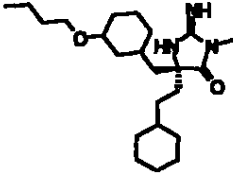
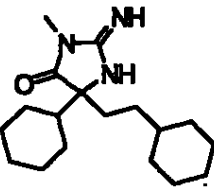
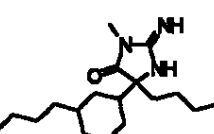
15

255

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$R^{21}=n\text{-Bu}$) Observed MW (M+H) 308.1. ^1H NMR (CD_3OD): δ = 3.16 (s, 3H), 1.80 (m, 6H), 1.26 (m, 16H), 0.88 (m, 6H).

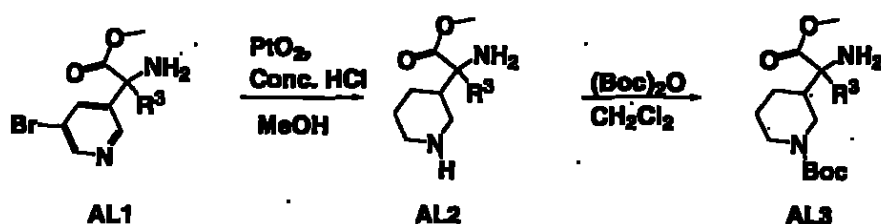
The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
387		277	278	381		381	382
388		291	292	382		391	392
389		305	308				
390		307	308				

256

- 240 -

Method AL



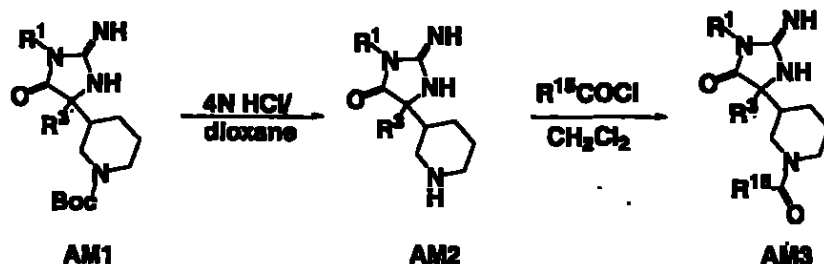
5 Method AL, Step 1:

To a solution of compound AL1 ($R^3=n\text{-Bu}$) (418mg, 1.39mmol) in methanol (8ml) was added PtO_2 (40mg) and conc. HCl (0.4ml). The mixture was hydrogenated (50psi) for 1 day. After filtration of the catalyst, the filtrate was concentrated. The crude residue was basified to pH=11-12 by 1N NaOH. This mixture was extracted with ethyl acetate. The organic layer was separated, dried and concentrated to get compound AL2 ($R^3=n\text{-Bu}$) (316mg, 100%).

Method AL, Step 2:

To a solution of compound AL2 ($R^3=n\text{-Bu}$) (300mg, 1.32mmol) in dichloromethane (6ml) was added $(\text{BOC})_2\text{O}$ (316mg, 1.45mmol). The mixture was stirred at RT for 1.5hr. It was diluted with water and dichloromethane. The organic layer was separated, dried and concentrated to get compound AL3 ($R^3=n\text{-Bu}$) (464mg, 100%).

Method AM



20

Method AM, Step 1:

Compound AM1 ($R^1=\text{Me}$, $R^3=n\text{-Butyl}$) was treated with 4N HCl in dioxane for 2 hr. The mixture was concentrated to get compound AM2 as an HCl salt ($R^1=\text{Me}$, $R^3=n\text{-Butyl}$). Observed MW ($M+H$) 470.1; ^1H NMR (CD_3OD): $\delta = 7.28$

25

257

- 241 -

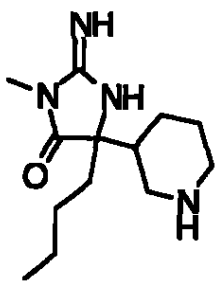
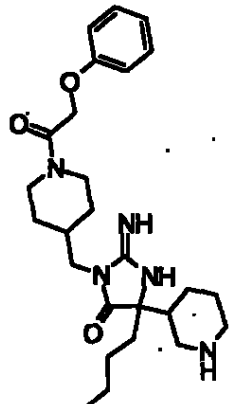
(m, 2H), 6.96 (m, 3H), 4.80 (m, 2H), 4.56 (m, 1H), 4.00 (m, 1H), 3.64 (m, 4H), 3.37 (m, 2H), 3.12 (m, 1H), 3.00 (m, 1H), 2.90 (m, 1H), 2.72 (m, 1H), 2.38 (m, 1H), 2.12-1.62 (m, 8H), 1.35 (m, 6H), 1.12 (m, 1H), 0.91 (m, 3H).

5 Method AM, Step 2:

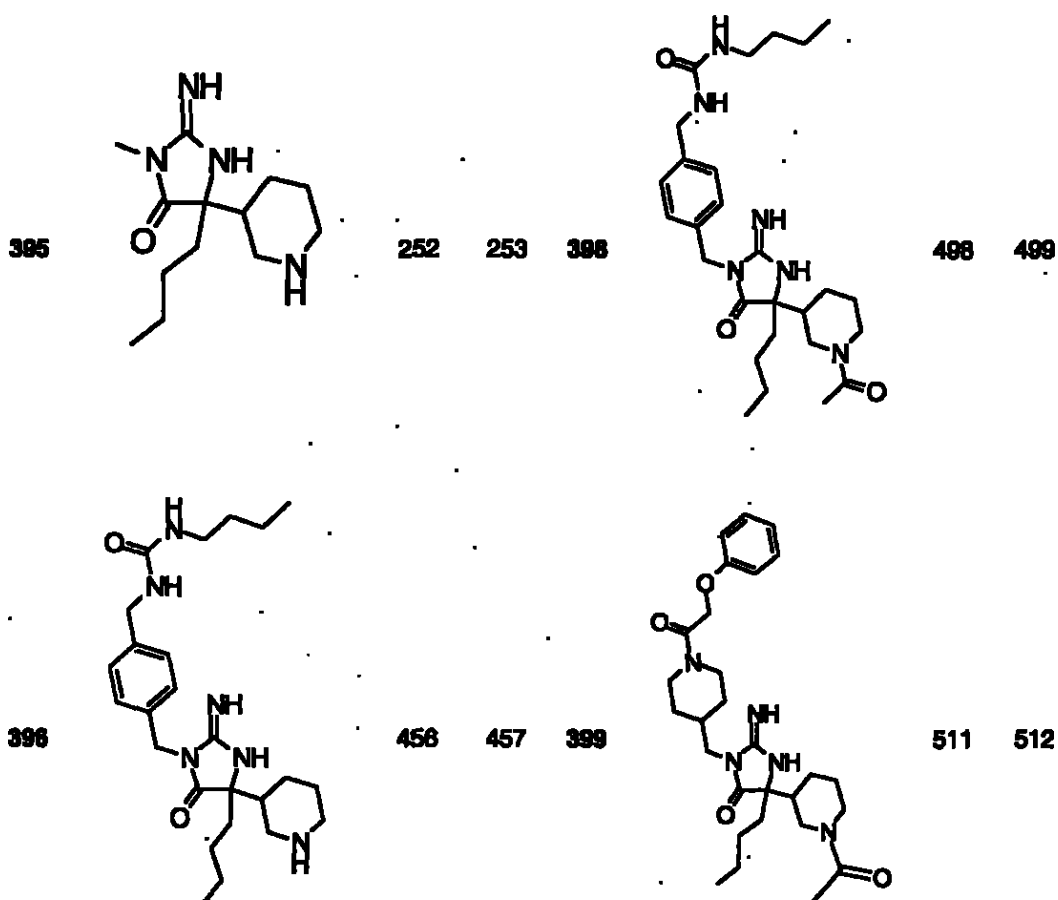
To a solution of compound AM2 ($R^1=Me$, $R^3=n\text{-Butyl}$) ($3\frac{1}{2}$: 0.068mmol) in dichloromethane (1ml) was added acetyl chloride (5ul, 0.072mmol). The mixture was stirred for 2 hr. It was then diluted with CH_2Cl_2 and water. The organic layer was separated, dried, concentrated and purified by RP HPLC to get compound AM3 ($R^1=Me$, $R^3=n\text{-Butyl}$ and $R^{18}=Me$) Observed MW (M+H) 512.3; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27 (m, 2H), 6.98 (m, 1H), 6.92 (m, 2H), 4.65 (s, 2H), 4.50 (m, 2H), 3.98 (m, 1H), 3.70 (m, 1H), 3.41 (m, 2H), 2.98 (m, 2H), 2.62 (m, 1H), 2.50 (m, 1H), 2.47 (m, 1H), 2.02 (m, 5H), 1.75 (m, 6H), 1.26 (m, 7H), 0.84 (m, 3H).

15

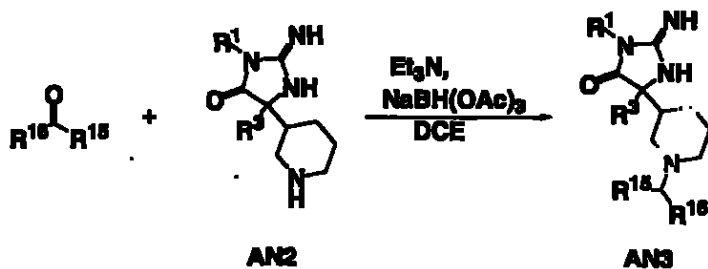
The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
394		252	253	397		469	470

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Method AN



To a solution of compound AN2 ($R^1=4\text{-N-(}\alpha\text{-phenoxyacetyl) piperidinylmethyl}$, $R^3=n\text{-Butyl}$) (28mg, 0.06mmol) in dichloroethane (2ml) was added butyraldehyde (5.3ul, 0.06mmol), triethylamine

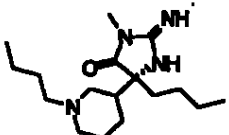
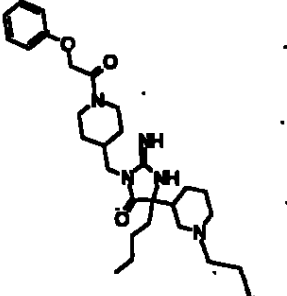
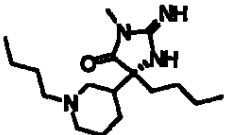
- 243 -

(8.4ul, 0.06mmol) and NaBH(OAc)₃ (18mg, 0.084mmol). The mixture was stirred overnight. It was then diluted with dichloromethane and water. The organic layer was separated, dried, concentrated and purified by RP HPLC to get AN2 (R¹=4-N-(a-phenoxyacetyl)piperidinylmethyl, R³=n-Butyl, R¹⁵=propyl and R¹⁶=H)

5 (5.4mg, 17%). Observed MW (M+H) 526.1; exact mass 525.37. ¹H NMR (CD₃OD): δ = 7.28 (m, 2H), 6.96 (m, 3H), 4.76 (m, 2H), 4.55 (m, 1H), 4.05 (m, 1H), 3.77 (m, 1H), 3.61 (m, 3H), 3.50 (m, 1H), 3.11 (m, 4H), 2.85 (m, 1H), 2.68 (m, 1H), 2.38 (m, 1H), 2.05 (m, 2H), 1.95 (m, 2H), 1.73 (m, 5H), 1.39 (m, 8H), 1.10 (m, 1H), 0.99 (m, 3H), 0.92 (m, 3H).

10

The following compound was synthesized using similar method:

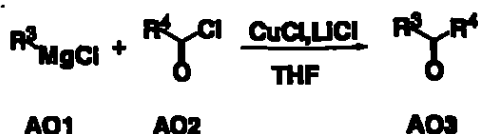
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
400		308	309	402		525	526
401		308	309				

Method AO

15

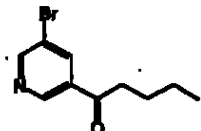
260

- 244 -



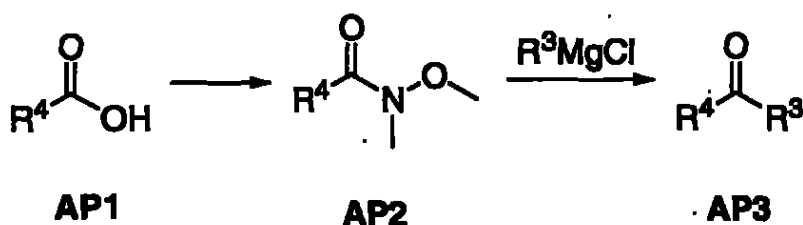
A mixture of copper chloride (2.06g, 20.8mmol) and lithium chloride (1.76g, 41.6mmol) in 100ml of THF was cooled down to -78 °C. To this mixture, a 2.0M solution of AO1 (R³=n-butyl) (10ml, 20mmol) was added gradually. The reaction was warmed up to -60 °C, and AO2 (R⁴=m-Br-Ph) (2.9ml, 22mmol) was injected. The mixture was stirred at -60 °C for 15 minutes and then quickly warmed up to RT by removing the dry-ice bath. The reaction was quenched with water and sat. NaHCO₃. After addition of diethyl ether, a lot of precipitate formed and was filtered. From the biphasic filtrate, the organic layer was separated, dried, concentrated and purified by silica gel chromatography (10% EtOAc/hexane) to get ketone AO3 (R⁴=m-BrPh, R³=n-Bu) (3.93g, 82%). Observed MW (M+H) 241.1; exact mass 240.01. ¹H NMR (400 MHz, CDCl₃): δ = 8.07 (m, 1H), 7.88 (m, 1H), 7.64 (m, 1H), 7.34 (m, 1H), 2.94 (t, 3H, J=7.2Hz), 1.71 (m, 2H), 1.40 (m, 2H), 0.95 (t, 3H, J=7.6Hz).

The following ketones were made according to Method 9:

Structure	Observed MW (M+H)	Exact mass
	242.1	241.01

20

Method AP



267

- 245 -

Method AP, Step 1:

To a solution of AP1 ($R^4=3$ -Bromophenyl) (5g, 25mmol) in
5 dichloromethane (10ml) were added N,O-dimethylhydroxylamine hydrochloride
(2.58g, 26.25mmol) and 4-methylmorpholine (2.95ml, 26.25mmol). EDCI (5.04g,
26.25mmol) was then added portionwise. The reaction mixture was stirred at RT
overnight and was then quenched with 1N HCl (60ml). The mixture was
extracted with dichloromethane. The organic layer was washed with 1N HCl and
10 brine, dried over Na_2SO_4 , and concentrated to give the Weinreb amide AP2
($R^4=m$ -BromoPhenyl) (5.96g, 98%). Observed MW (M+H) 244.1; exact mass
243.99. ^1H NMR ($CDCl_3$): δ = 7.78 (m, 1H), 7.58 (m, 2H), 7.24 (m, 1H), 3.51 (s,
3H), 3.32 (s, 3H). This material was used in the next step without purification.

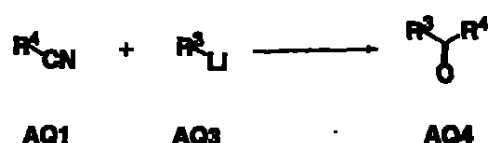
Method AP, Step 2:

15 To a suspension of magnesium turnings (1.19g, 48.8mmol) in 30ml of
THF was added dropwise a solution of R^3Br ($R^3=cyclohexylethyl$) (5.73ml,
36.6mmol) in 24ml of THF. After addition of half of the solution of bromide,
several crystals of iodine were added to initiate the reaction. The mixture
became cloudy and heat evolved. The rest of the solution of bromide was added
20 dropwise. The mixture was stirred at RT for 30 minutes and then was cooled to 0
 $^{\circ}C$, and the AP2 ($R^4=m$ -BromoPhenyl) (5.96g, 24.4mmol) was added. The
mixture was stirred at RT for 3 hr and then quenched with 1N HCl until no
residual Mg(0) was left. The phases were separated, and the water layer was
extracted with ether. The combined organic layers were washed with brine,
25 dried, and concentrated. The crude was purified by silica chromatography (15%
EtOAc/hexane) to get ketone AP3 ($R^4=m$ -BromoPhenyl, $R^3=Cyclohexylethyl$)
(8.06g, 100%). Observed MW (M+H) 295.2; exact mass 294.06. ^1H NMR (400
MHz, $CDCl_3$): δ = 8.18 (m, 1H), 7.85 (m, 1H), 7.64 (m, 1H), 7.33 (m, 1H), 2.94 (t,
3H, $J=7.2Hz$), 1.70 (m, 9H), 1.63 (m, 4H).

10

Method AQ

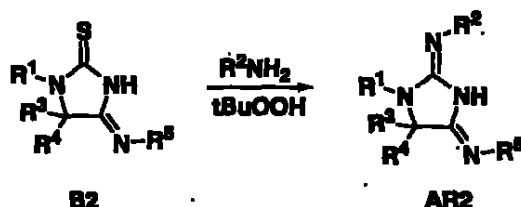
- 246 -



To a -78 °C solution of AQ1 (R⁴ = cyclopropyl) (2.55 g, 38.0 mmol) in diethyl ether (100 ml) was added AQ3 (R³ = *n*-Bu) (38 ml, 1.5 M in hexanes, 57 mmol). After 45 min, the cooling bath was removed. After 3h at RT, the reaction was quenched by dropwise addition of water and then diluted further with EtOAc and water. The phases were separated and the aqueous layer was extracted with EtOAc (2X). The organic portions were combined, washed with brine, dried over MgSO₄, and concentrated. This crude residue was subjected to column chromatography (silica gel, 0% → 100% CH₂Cl₂/hexanes) to provide the desired ketone AQ4 (R⁴ = cyclopropyl, R³ = *n*-Butyl) (2.57 g, 20.4 mmol, 54%). ¹H NMR (CDCl₃) δ 2.52 (t, *J* = 7.2 Hz, 2 H), 1.90 (m, 1 H), 1.57 (m, 2 H), 1.30 (m, 2 H), 0.98 (m, 2 H), 0.89 (t, *J* = 7.6 Hz, 3 H), 0.83 (m, 2 H).

15

Method AR



Method AR:

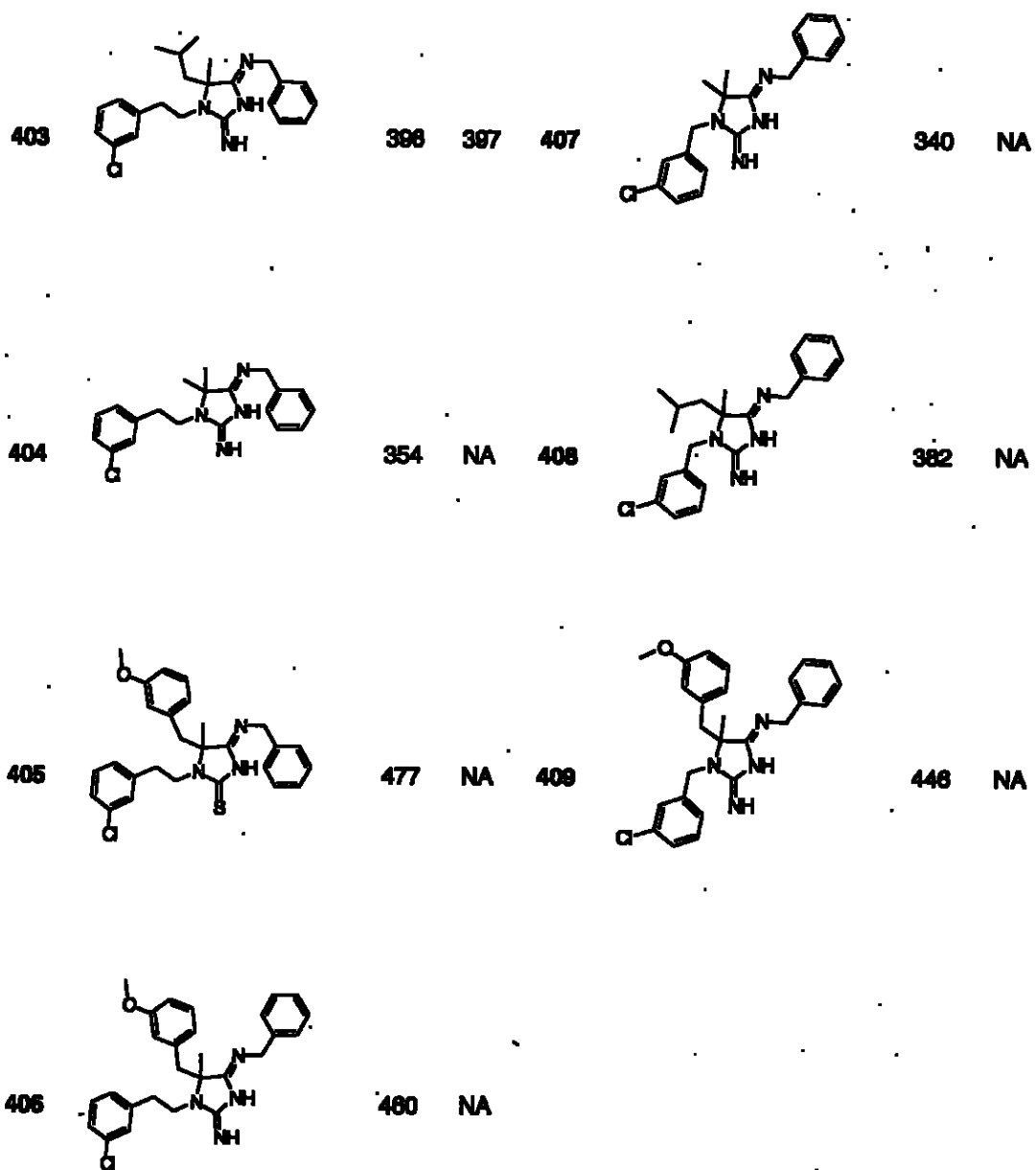
Compound B2 (R¹ = *m*-Cl-Phenethyl, R³ = Me, R⁴ = *i*-butyl and R⁵ = benzyl) was converted into AR2 (R¹ = *m*-Cl-Phenethyl, R³ = Me, R⁴ = *i*-butyl and R⁵ = benzyl) using method A step 3.

The following compounds were synthesized using similar methods:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
---	-----------	----	-------------	---	-----------	----	-------------

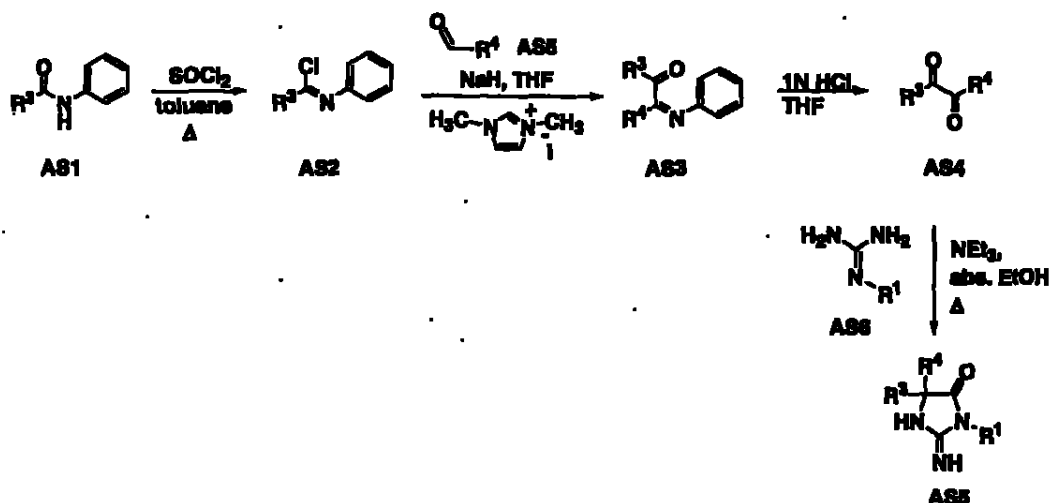
263
263

- 247 -



Method AS

- 248 -

**Method AS, Step 1:**

To a mixture of AS1 ($R^3=Ph$) (3.94 g) in toluene (10 ml) was added thionyl chloride (1.61 ml) and the resulting mixture was heated under reflux for 6 h (until HCl evolution ceased). The reaction mixture was kept overnight at rt before it was concentrated *in vacuo*. Toluene (10 ml) was added and the mixture was concentrated *in vacuo* again. The reaction mixture was dissolved in CH_2Cl_2 , solid sodium bicarbonate added, filtered and then the CH_2Cl_2 solution was concentrated *in vacuo* to give AS2 ($R^3=Ph$).

Method AS, Step 2:

To AS2 ($R^3=Ph$) (0.645 g) and AS5 ($R^4=4$ -chlorophenyl) (0.464 g), and 1,3-dimethylimidazolium iodide (0.225 g) in anhydrous THF (20 ml) was added 60% sodium hydride in oil (0.132 g). The resulting mixture was stirred at rt for 18 h. The reaction mixture was concentrated and partitioned between H_2O and Et_2O . The dried Et_2O solution was concentrated *in vacuo* to give a yellow residue which was placed on preparative silica gel plates and eluted with CH_2Cl_2 to give AS3 ($R^3=Ph$, $R^4=p$ -ClPh). (Miyashita, A., Matsuda, H., Hagiaskino, T., Chem. Pharm. Bull., 1992, 40 (10), 2627-2631).

Method AS, Step 3:

Hydrochloric acid (1N, 1.5 ml) was added to AS3 ($R^3=Ph$, $R^4=p$ -ClPh) in THF (10 ml) and the resulting solution was stirred at rt for 20 h. The reaction mixture was concentrated *in vacuo* and then partitioned between CH_2Cl_2 and H_2O . The dried CH_2Cl_2 was concentrated *in vacuo* to give a residue which was

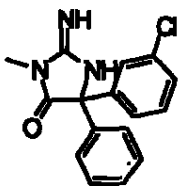
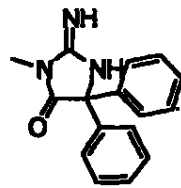
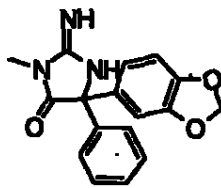
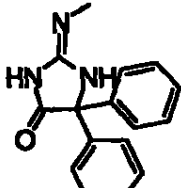
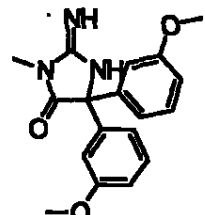
- 249 -

placed on preparative silica gel plates and eluted with CH₂Cl₂:hexane 1:1 to afford AS4 (R³=Ph, R⁴=p-ClPh).

Method AS, Step 4:

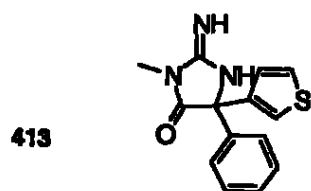
- 5 AS4 (R³=Ph, R⁴=p-ClPh) (0.12 g) and methylguanidine, HCl (AS8, R¹=Me) (0.055 g) were mixed in absolute EtOH (5 ml) with triethylamine (0.2 ml) and then heated under reflux for 20 h. The resulting mixture was concentrated and then partitioned between CH₂Cl₂ and H₂O. The dried CH₂Cl₂ was concentrated *in vacuo* to give a residue which was placed on preparative silica
- 10 gel plates and eluted with CH₂Cl₂:MeOH 9:1 to afford AS5 (R³=Ph, R⁴=p-ClPh and R¹=Me).

The following compounds were synthesized using similar methods:

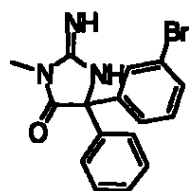
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
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411		285	286	420		309	310
412		285	286	421		325	326

266

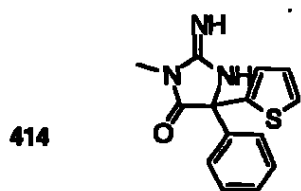
- 250 -



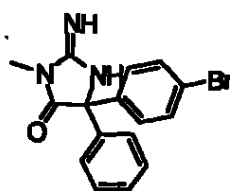
271 272 422



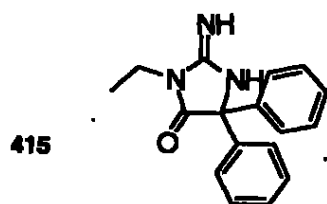
343 344



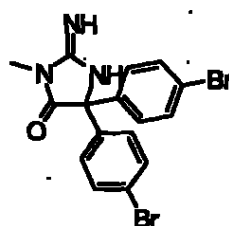
271 272 423



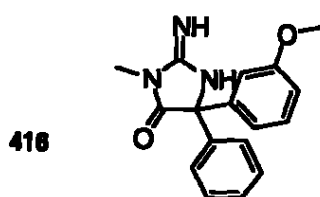
343 344



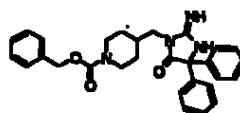
279 280 424



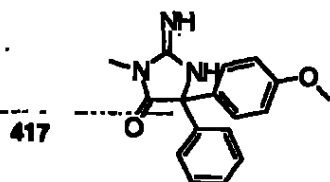
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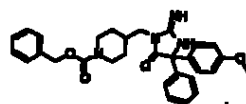
295 296 425



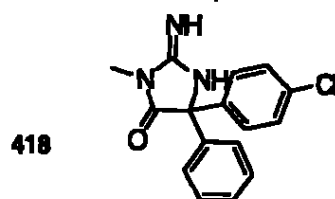
482 483



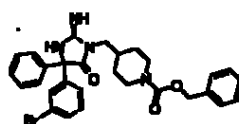
295 296 426



512 513



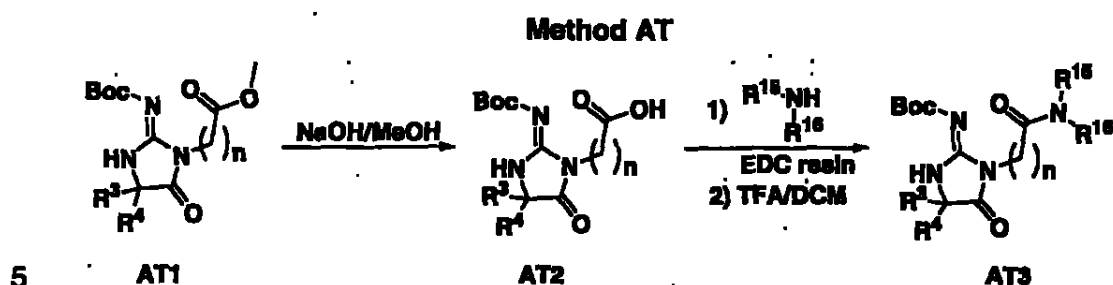
299 300 427



580 581

267

- 251 -

**Method AT, Step1:**

AT1, prepared using a method similar to Method H, Step1,2 and 3, ($n=4$, $R^3=R^4=n\text{-Bu}$) (0.146 g) in MeOH (3 ml) and 1N NaOH (0.727 ml) were stirred
 10 overnight at rt. The mixture was concentrated and then partitioned in water (pH ~3, adjusted using conc. HCl) and EtOAc. The dried EtOAc layer was concentrated *in vacuo* to afford AT2 ($n=4$, $R^3=R^4=n\text{-Bu}$).

Method AT, Step 2:

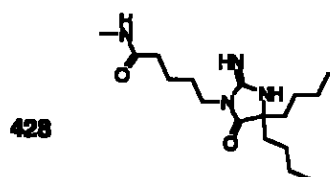
15 Compound AT2 ($n=4$, $R^3=R^4=n\text{-Bu}$) (0.012 g) in MeCN (1 ml) was treated with EDC resin (0.12 g, 1.44 mmol/g), HOBT (0.004 g) in THF (1 ml), and *n*-butylamine ($R^{15}=H$, $R^{16}=n\text{-butyl}$) (0.007 ml). The reaction was carried out overnight at rt. before Argonaut PS-NCO resin (0.150 g), PS-polyamine resin (0.120g) and THF (2 ml) were added and the mixture shaken for 4 h. The
 20 reaction mixture was filtered and resin washed with THF (2 ml). The combined organic phase was concentrated *in vacuo* before the residue was treated with 1N HCl in MeOH (1ml) for 4 h followed by evaporation of solvent to give AT3 ($n=4$, $R^3=R^4=n\text{-Bu}$, $R^{15}=H$ and $R^{16}=n\text{-Butyl}$).

25 The following compounds were synthesized using similar method:

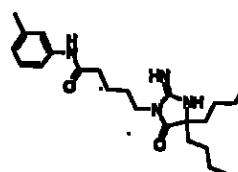
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268

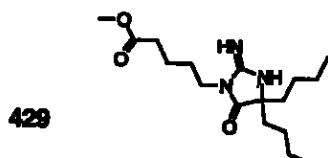
- 252 -



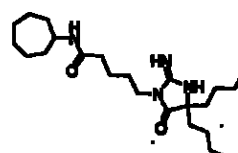
324 325 436



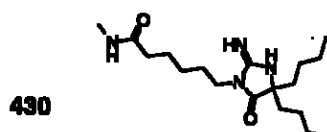
400 401



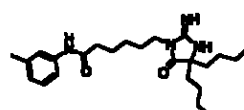
325 326 437



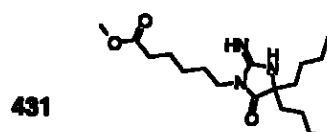
406 407



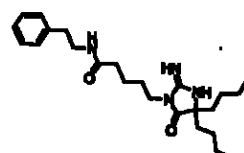
338 339 438



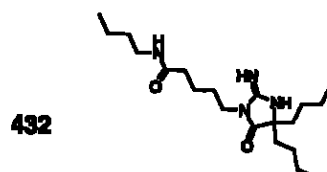
414 415



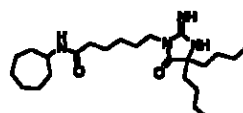
339 340 439



414 415



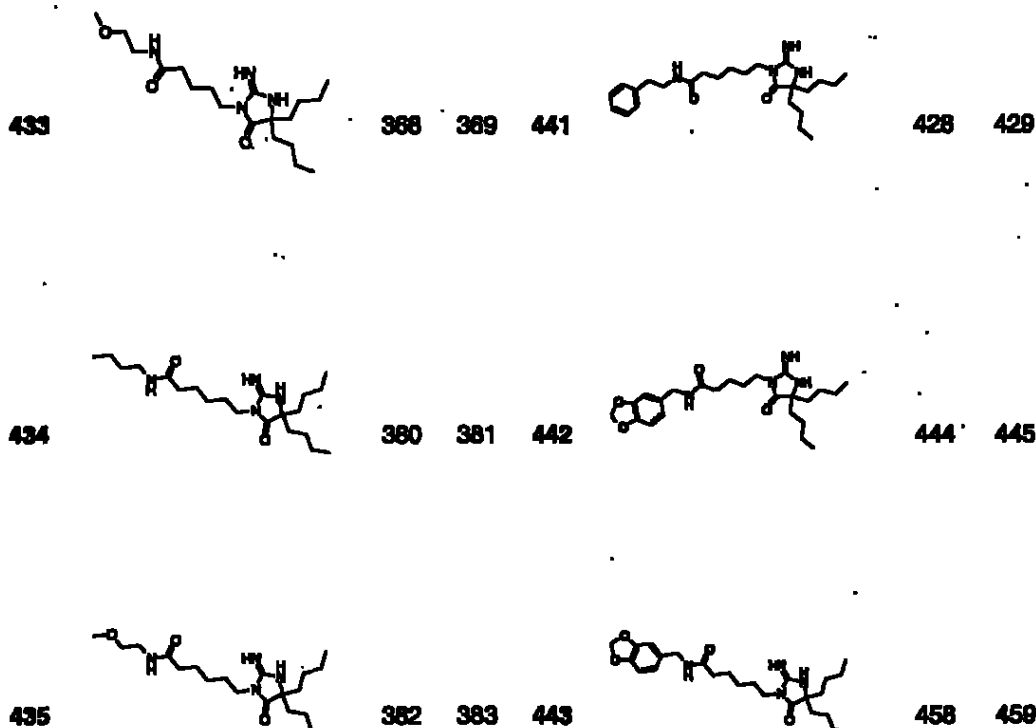
366 367 440



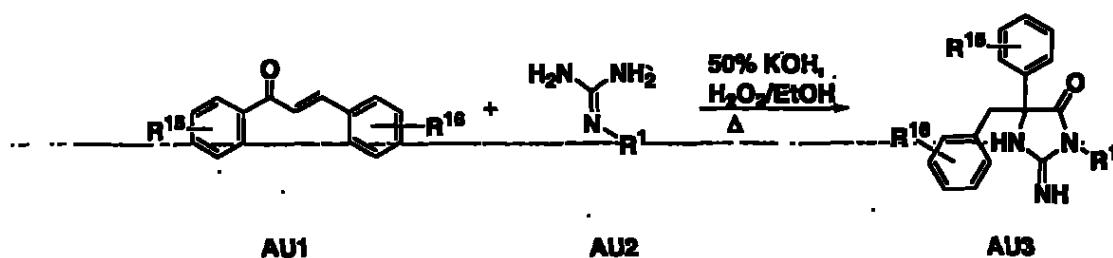
420 421

269

- 253 -



Method AU



5

A published procedure was adapted (Varga, I.; Nagy, T.; Kovcsdi, I.; Benet-Buchholz, J.; Dornab, G.; Urge, L.; Darvas, F. *Tetrahedron*, 2003, (59) 655-662).

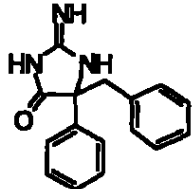
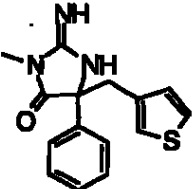
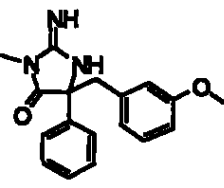
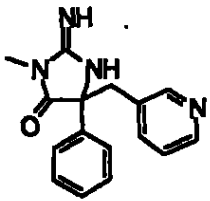
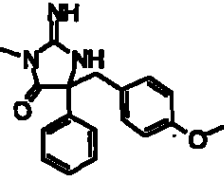
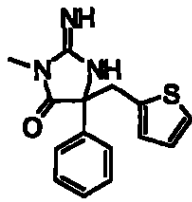
AU1 ($R^{15}=H$, $R^{16}=H$) (0.300 g), prepared according to procedure described by Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R.,

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(Vogel's Textbook of Practical Organic Chemistry, 5th ed. Longman: new York, 1989; pp1034-1035), AU2 (HCl salt, R¹=Me) (0.237 g), 50% KOH (0.305 ml), 30% H₂O₂ (0.115 ml) and EtOH (4.6 ml) were heated in a sealed tube for 2 h. Reaction mixture was concentrated and extracted with CH₂Cl₂. The dried organic solution was concentrated *in vacuo* to give a residue which was placed on preparative silica gel plates eluting with CH₂Cl₂:MeOH 9:1 to afford AU3 (R¹⁵=H, R¹⁶=H, R¹= Me).

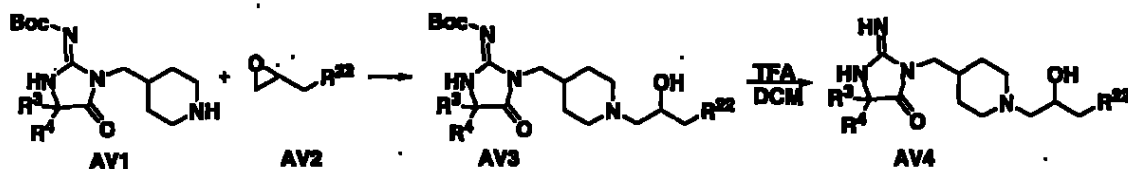
The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
444		285	286	448		285	286
				449		309	310
446		280	281	450		309	310
447		285	286				

271

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Method AV



5

Method AV, Step 1:

In a microwave tube, AV1 ($R^3=Me$, $R^4=i-Bu$) (0.0012 g) and AV2 ($R^{22}=OPh$) (0.0059 ml) in isopropanol (2 ml) was placed in a microwave at 125°C for 5 min. The reaction mixture was concentrated *in vacuo* to give AV3 ($R^3=Me$, $R^4=i-Bu$, $R^{22}=OPh$).

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Method AV, Step 2:

AV3 ($R^3=Me$, $R^4=i-Bu$, $R^{22}=OPh$) in CH_2Cl_2 (1 ml) and TFA (1 ml) was shaken for 2h and the concentrated *in vacuo* and purified on Prep LCMS to afford AV4 ($R^3=Me$, $R^4=i-Bu$, $R^{22}=OPh$).

15

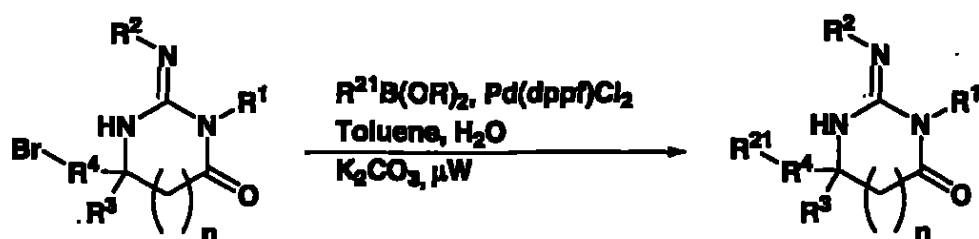
The following compounds were synthesized in a similar fashion.

#	Structure	M W	Obs. m/e	#	Structure	M W	Obs. m/e
451		378	379 · 453	416 · 417		416	417
452		396	387				

272

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Method AW

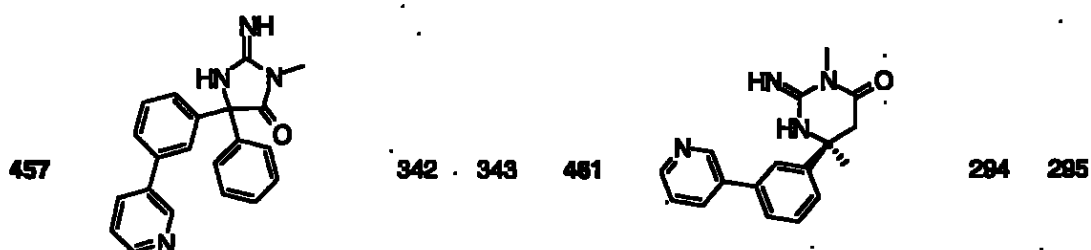


Method similar to Method U was used for this transformation. The following compounds were generated using similar methods.

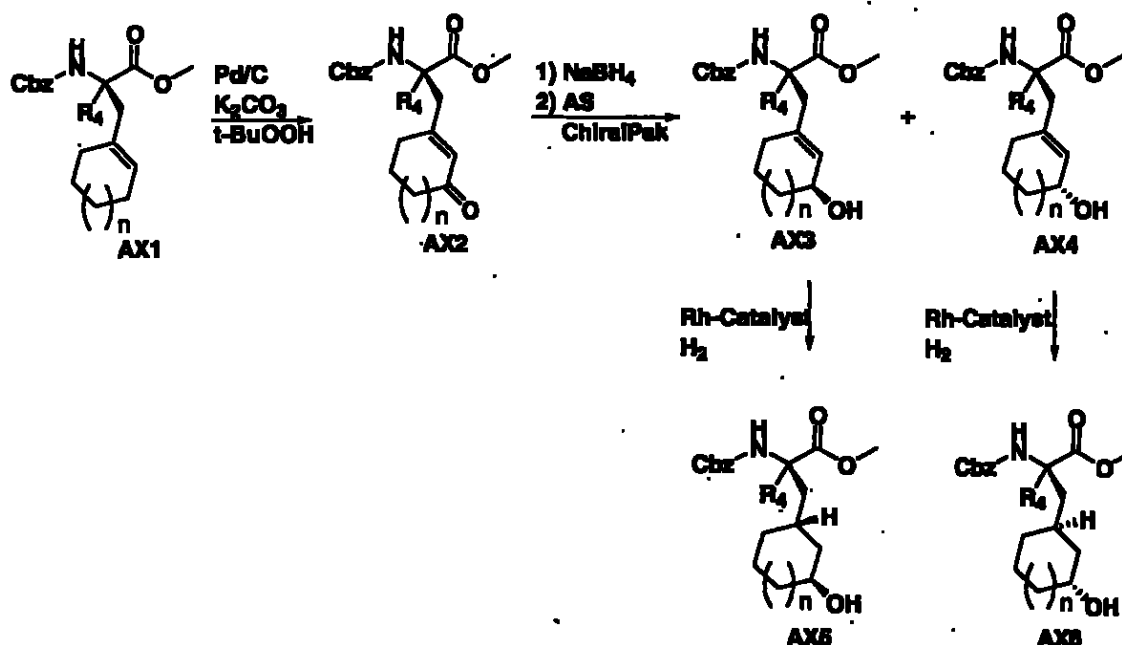
The following compounds were synthesized in a similar fashion:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
454		341	342	458		347	348
455		341	342	459		359	380
456		342	343	460		323	324

- 257 -



Method AX



5

Method AX, Step 1.

A literature procedure was adapted. (J-Q Yu and E.J. Corey, *Organic Letters*, 2002, 4, 2727-2730).

To a 400 ml DCM solution of AX1 ($n=1$, R^4 =phenethyl) (52 grams) in a ice bath was added 5 g of Pd/C (5% w/w), 50 g of potassium carbonate and 100 ml of anhydrous t-BuOOH. The mixture was stirred in air for overnight before it was diluted with DCM and washed with water. The residue after removal of organic solvent and drying was chromatographed using ethylacetate/hexane to give 25 g of AX2 ($n=1$, R^4 =phenethyl).

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279

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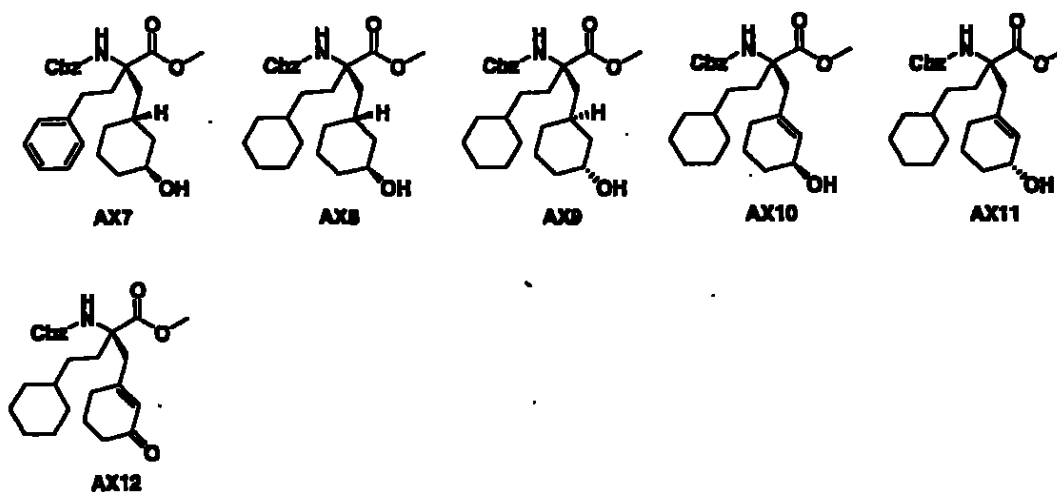
Method AX, Step 2.

A solution of AX2 (4.5 g, $n=1$, R^4 =phenethyl) in MeOH (50 ml) was treated with 0.4 g of Sodium borohydride and the reaction was stirred for 30 min before the solvent was removed and residue chromatographed to give a mixture of AX3 ($n=1$, R^4 =phenethyl) and AX4 ($n=1$, R^4 =phenethyl) which was separated using an AS chiralpak column eluted with 8% IPA in Hexane (0.05% DEA) to give 2.1 g of AX3 ($n=1$, R^4 =phenethyl) as the first fraction and 2.2 g of AX4 ($n=1$, R^4 =phenethyl) as the second fraction.

Method AX, Step 3.

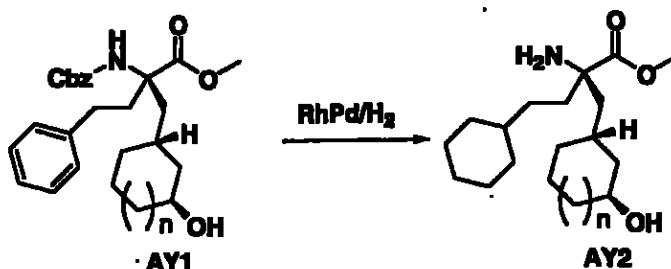
A 100 ml methanolic solution of AX4 ($n=1$, R^4 =phenethyl) (2.2 g) and 1,1'-bis(di-*i*-propylphosphino)ferrocene (1,5-cyclooctadiene)rhodium (I) tetrafluoroborate (0.4 g, 0.57 mmol) was hydrogenated at 55 psi overnight. The reaction was concentrated, and the brown oil was purified by silica gel chromatography to yield AX6 ($n=1$, R^4 =phenethyl) (1.7g).

The following compounds were generated using similar method.

**Method AY**

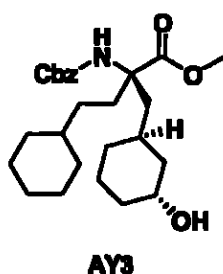
275

- 259 -



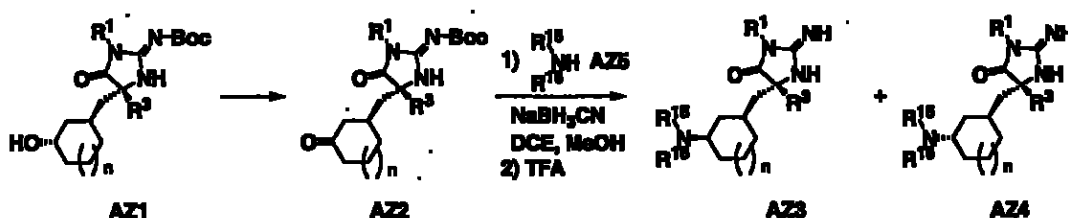
A solution of AY1 ($n = 1$; 1.5g, 3.4 mmol), 5% Rh/C (1.5g), 5% Pd/C (0.5g) in AcOH (30 mL) was shaken in a Parr apparatus at 55 psi for 18 hours. The vessel was flushed with N_2 , and the reaction was filtered through a pad of celite. After concentration AY2 was obtained which was carried on without purification. MS m/e : 312.0 ($\text{M}+\text{H}$).

AY3 was generated using similar method.



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Method AZ



Method AZ, Step 1

To a solution of AZ1 ($n=1$, $\text{R}^1=\text{Me}$, $\text{R}^3=2\text{-cyclohexylethyl}$) (0.441 g, 1.01 mmol), generated from AY2 using Method C and Method H Step 3, in DCM was added Dess-Martin Periodinane (0.880 g, 2.07 mmol). The reaction was stirred for 3 hours at room temperature. The reaction was quenched with H_2O and diluted with EtOAc. After removal of the organic phase, the aqueous layer was extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), filtered,

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276

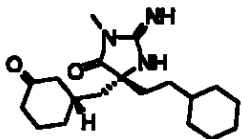
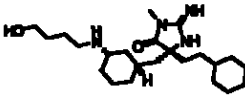
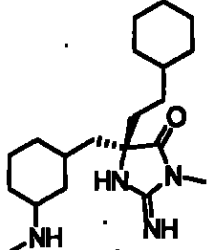
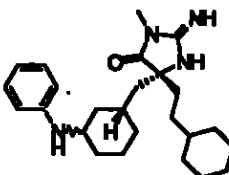
- 260 -

and concentrated. The residue was purified by silica gel chromatography (0-100% EtOAc/hexanes) to yield **AZ2** ($n=1$, $R^1=Me$, $R^3=2$ -cyclohexylethyl) (0.408 g, 0.94 mmol, 93% yield). MS m/e : 434.1 ($M+H$).

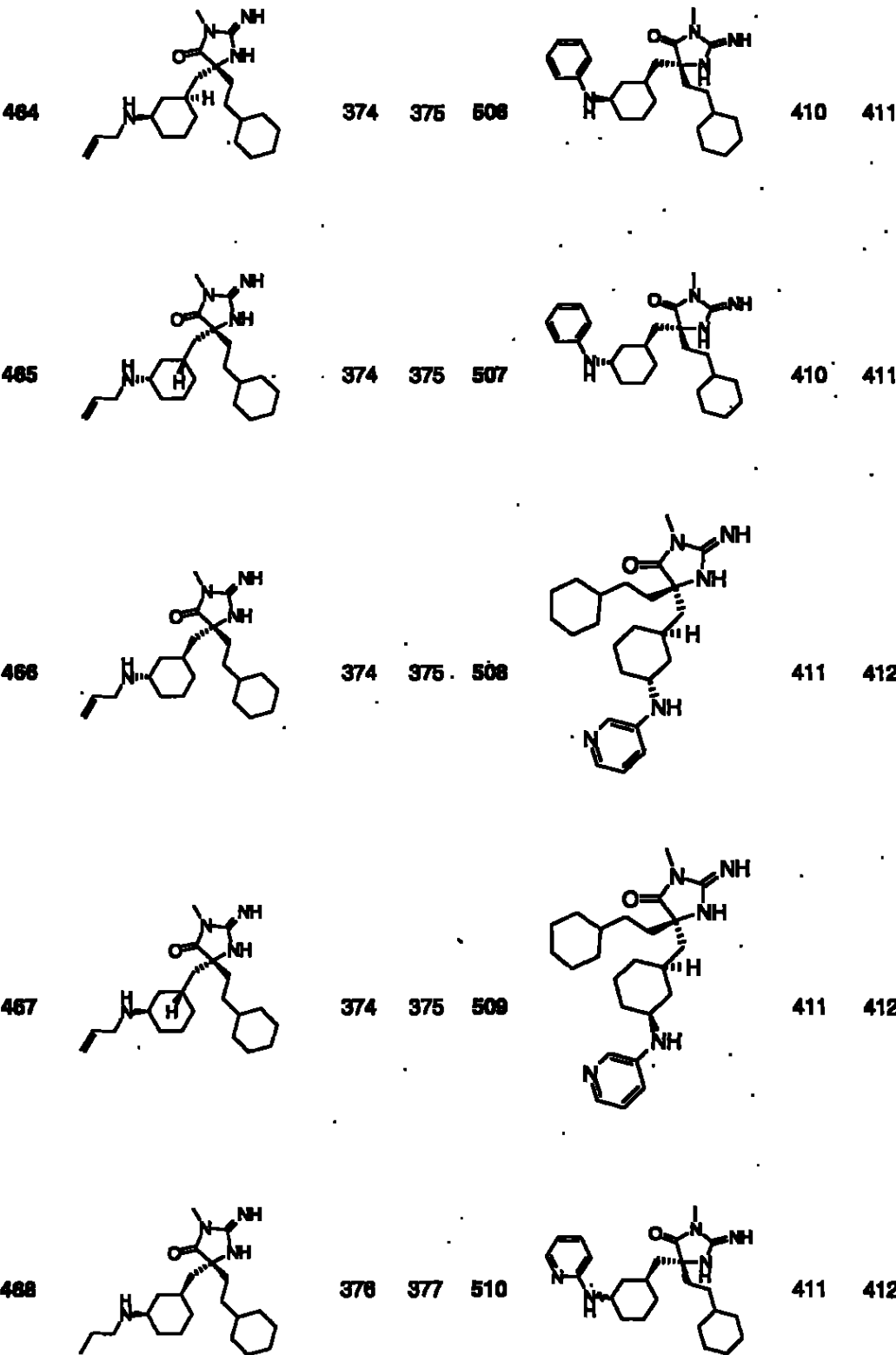
Method AZ Step 2:

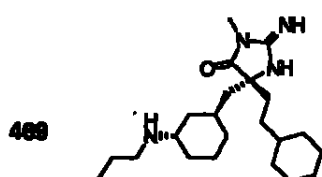
- 5 To a solution of **AZ2** ($n=1$, $R^1=Me$, $R^3=2$ -cyclohexylethyl) (0.011 g, 0.025 mmol) and **AZ5** ($R^{15}=H$ and $R^{16}=m$ -pyridylmethyl) (0.0067 mL, 0.066 mmol) in DCE (1.8 mL) and MeOH (0.2 mL) was added AcOH (4 drops) and MP-cycanoborohydride resin (0.95 g, 2.42 mmol/g). The reaction was agitated for 40 hours at room temperature. The reaction was treated with 7N NH_3 /MeOH, and solution was filtered. After concentration, the residue was purified by silica gel HPLC (0-4% [(5% 7N NH_3 /MeOH)/MeOH]/(50%DCM/hexanes) to furnish fraction 1 and fraction 2 which, after removal of solvent, were treated with 20% TFA in DCM for 3h at r.t. to give **AZ4** ($n=1$, $R^1=Me$, $R^3=2$ -cyclohexylethyl, $R^{15}=H$ and $R^{16}=m$ -pyridylmethyl) (0.005 g, 0.009 mmol) and the **AZ3** ($n=1$, $R^1=Me$, $R^3=2$ -cyclohexylethyl, $R^{15}=H$ and $R^{16}=m$ -pyridylmethyl) (0.012 g, 0.022 mmol) respectively.
- 10
- 15

The following compounds were generated using similar methods:

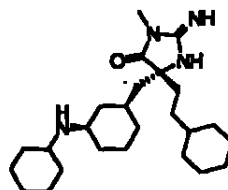
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463		348	349	505		410	411

277

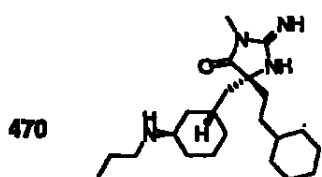




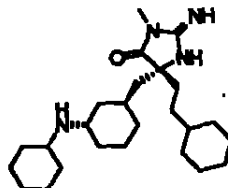
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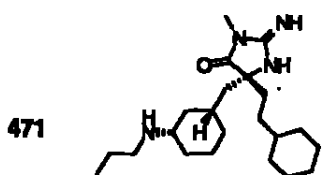
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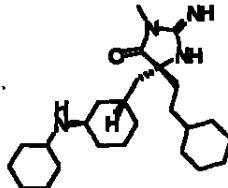
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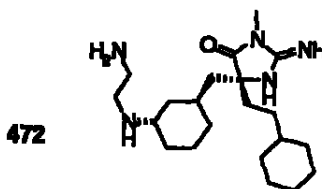
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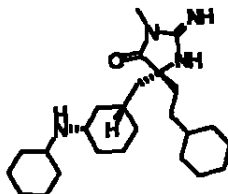
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418 417



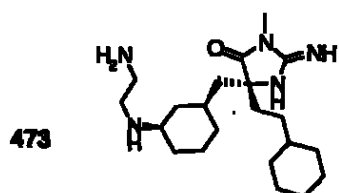
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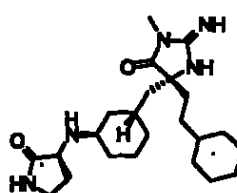
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279

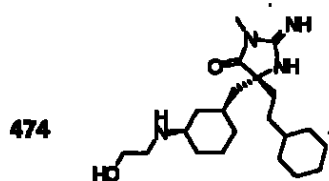
- 263 -



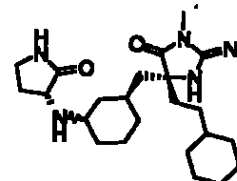
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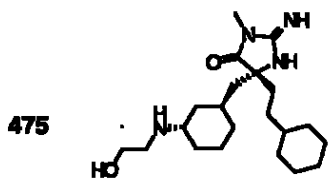
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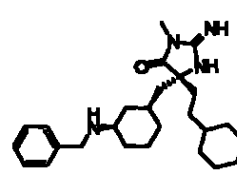
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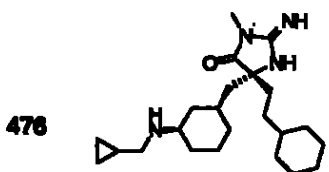
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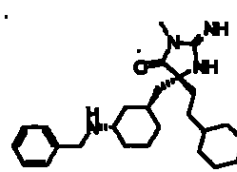
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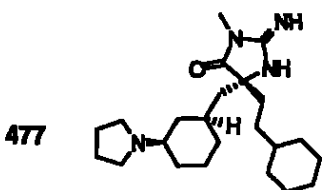
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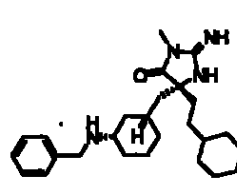
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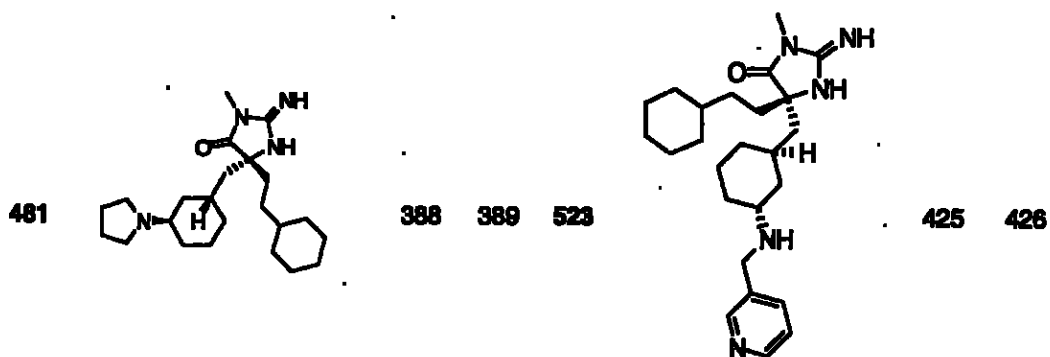
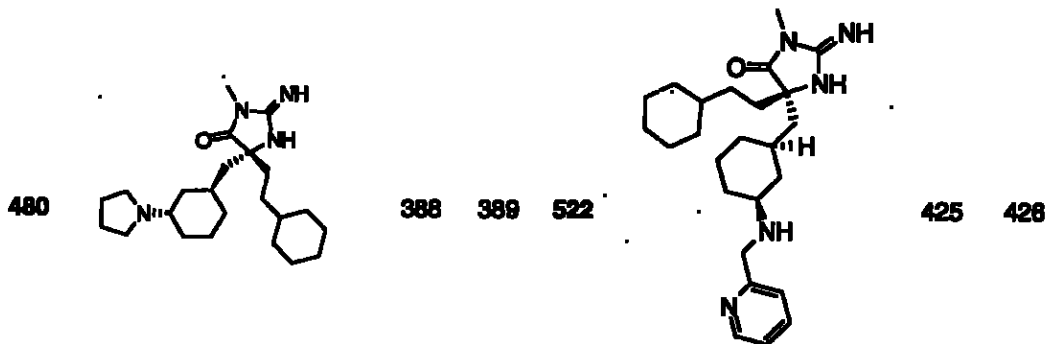
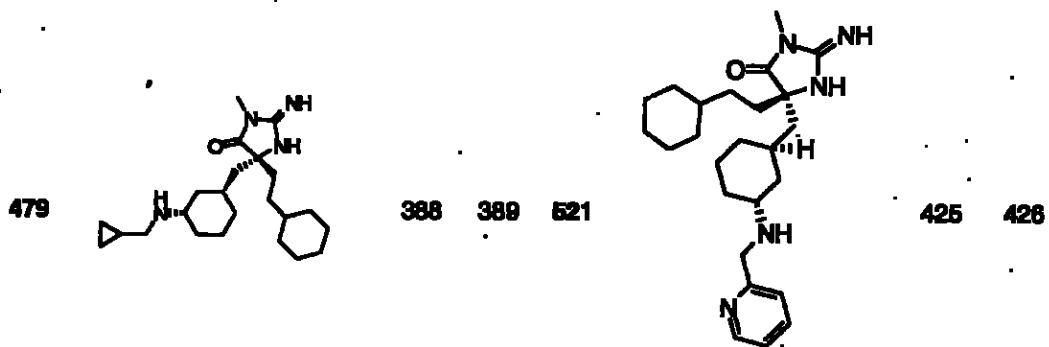
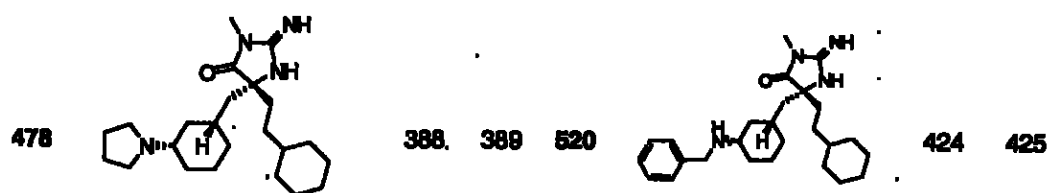


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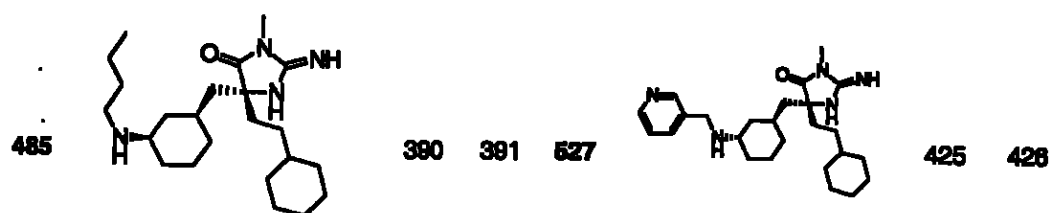
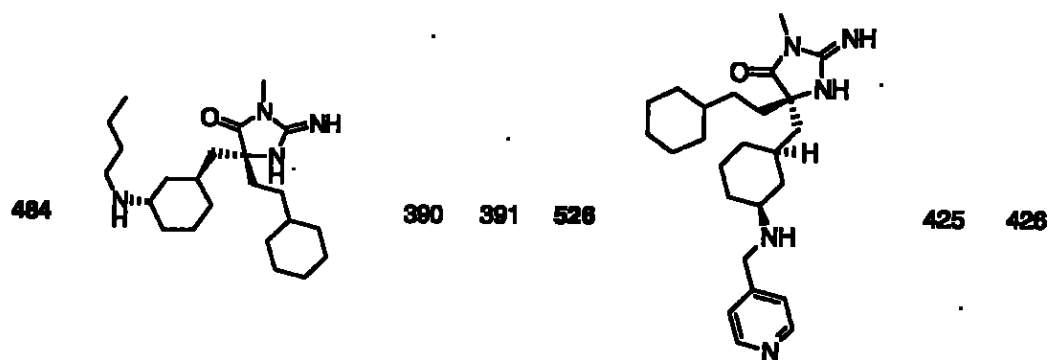
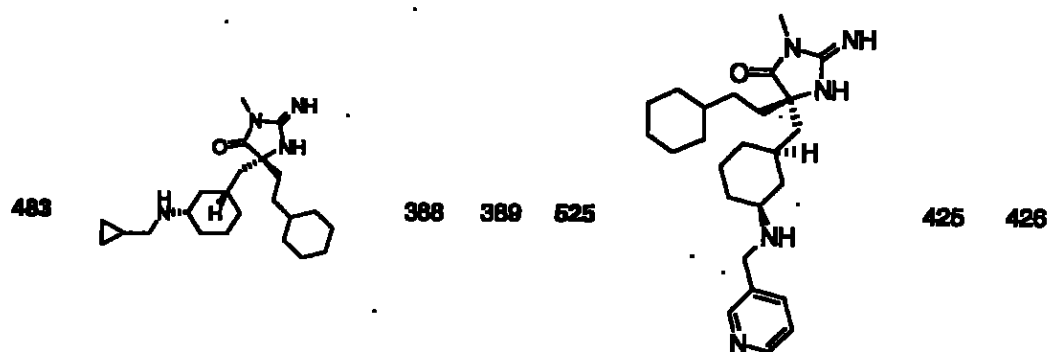
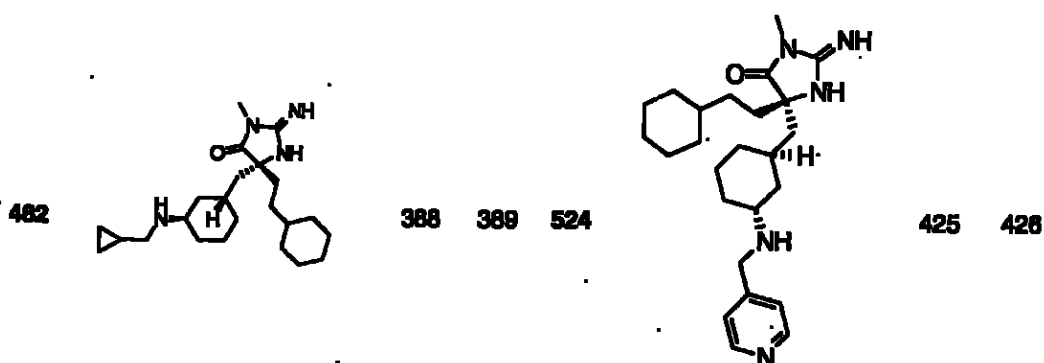


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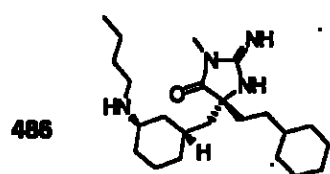
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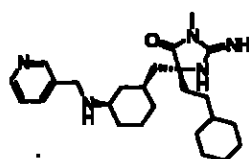
- 265 -



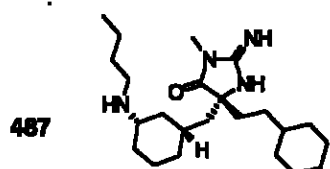
- 266 -



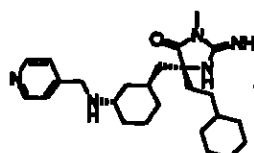
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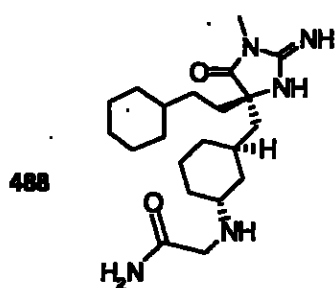
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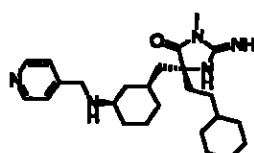
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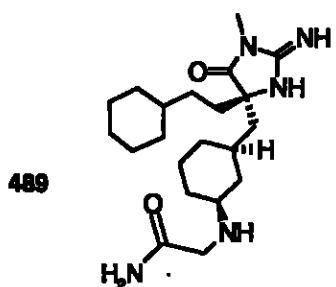
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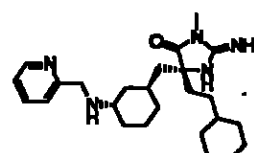
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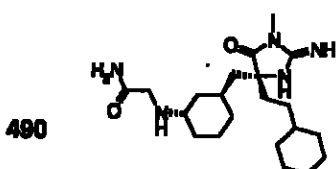
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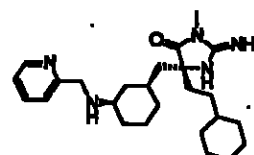
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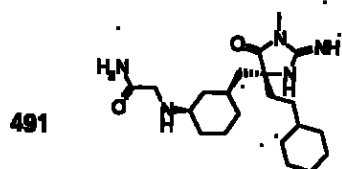


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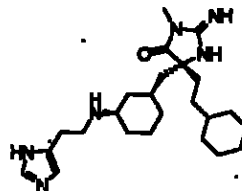


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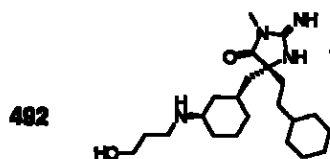
- 267 -



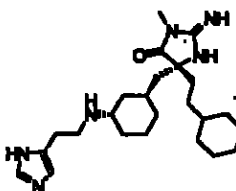
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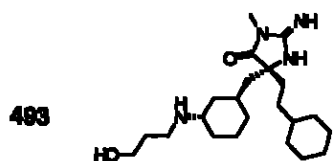
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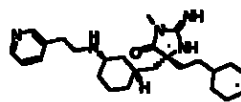
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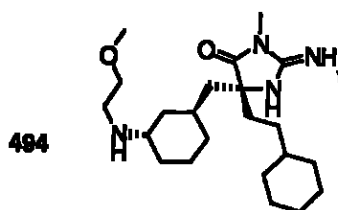
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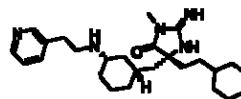
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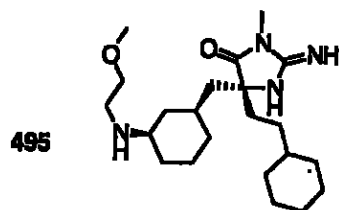
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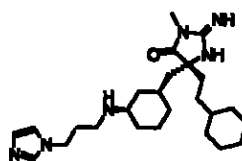
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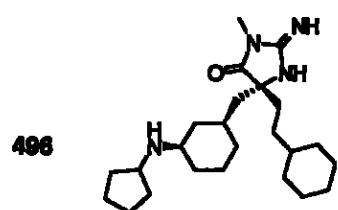


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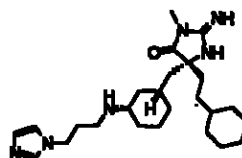


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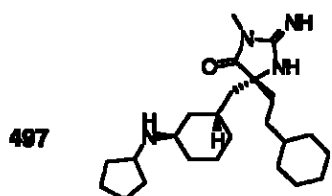
- 268 -



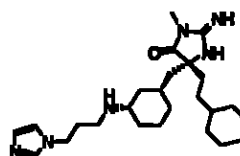
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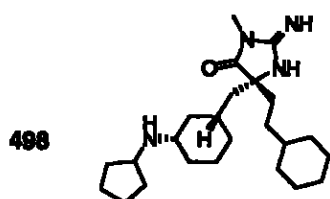
442 443



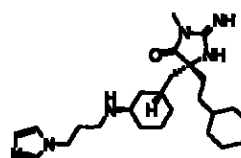
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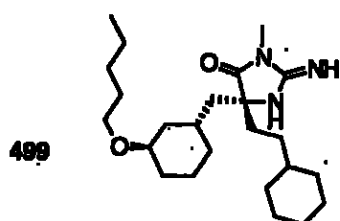
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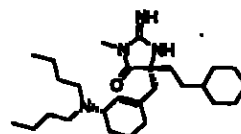
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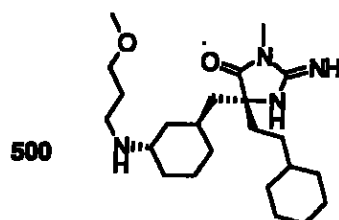
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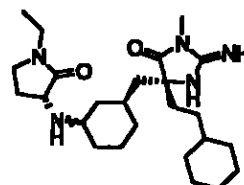
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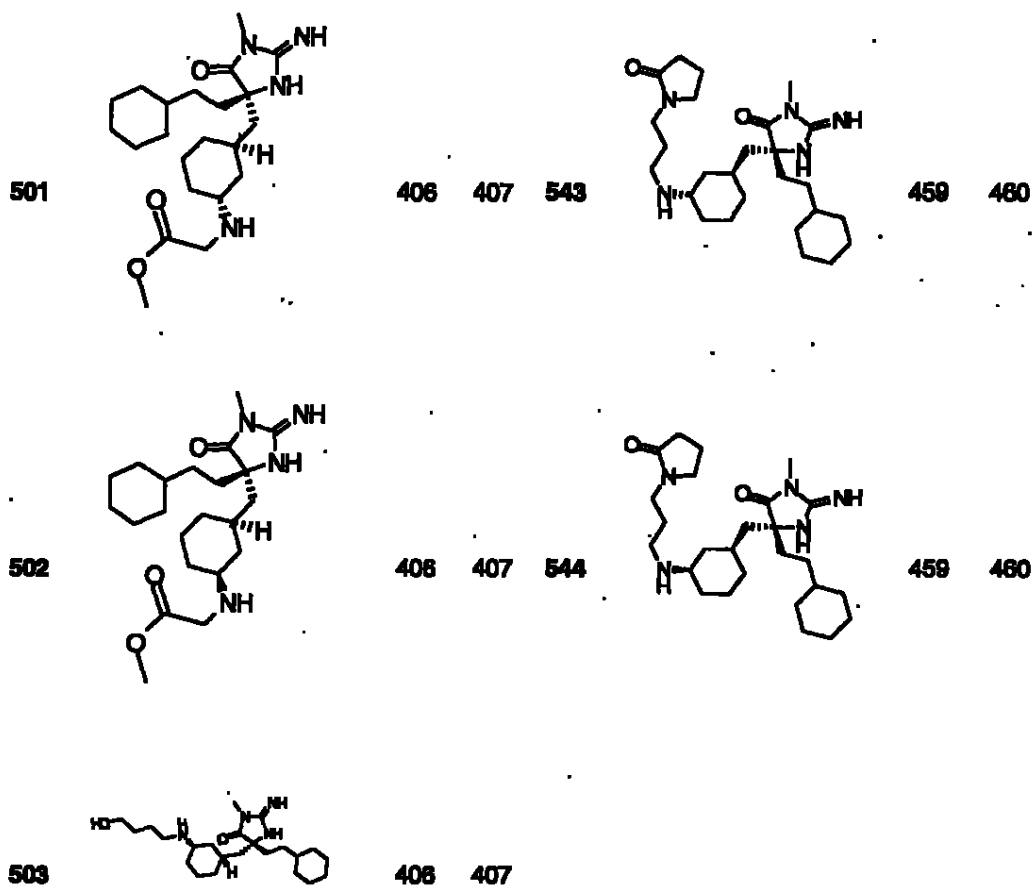


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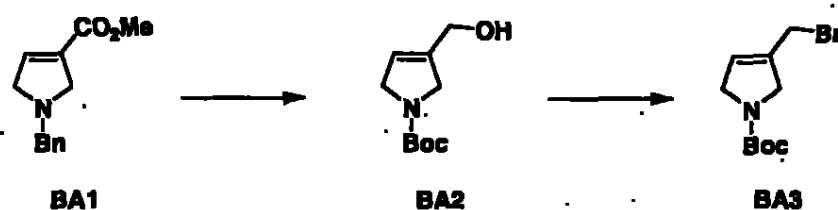


445 446

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Method BA



5

Method BA, Step 1:

BA1, prepared according to a literature procedure (Terao, Y; Kotaki, H; Imai, N and Achiwa K. Chemical and Pharmaceutical Bulletin, 33 (7), 1985, 2762-2766) was converted to BA2 using a procedure described by Coldham, I;

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- 270 -

Crapnell, K.M; Fernandez, J-C; Moseley J.D. and Rabot, R. (*Journal of Organic Chemistry*, 67 (17), 2002, 6185-6187).

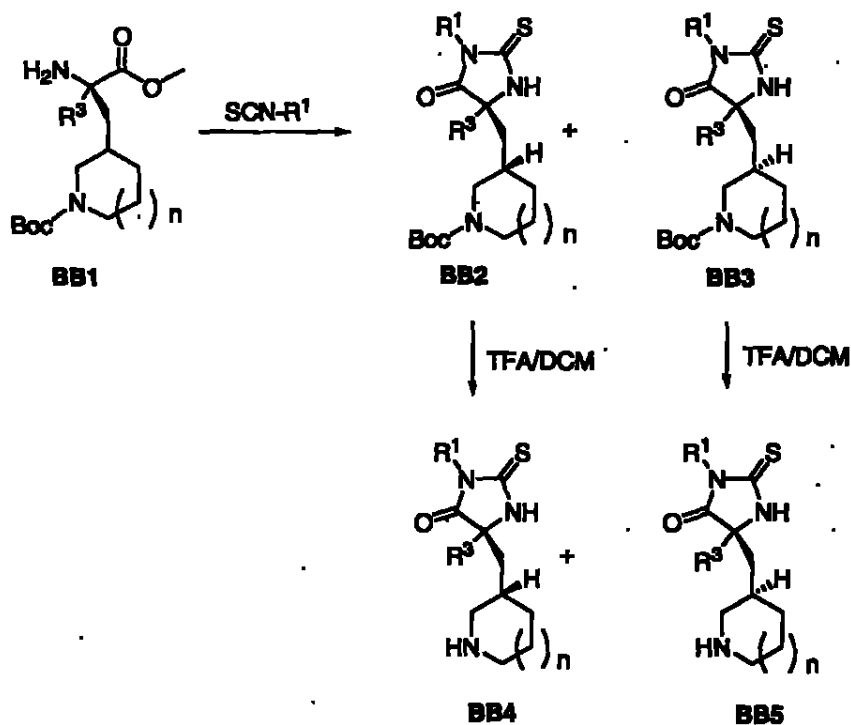
^1H NMR(CDCl_3) for BA2: 1.42 (s, 9H), 4.06 (d, 4H), 4.09 (s, 1H), 4.18 (s, 2H), 5.62 (d, 1H).

5 **Method BA, Step 2:**

BA3 was generated from BA2 using a literature procedure described by Winkler J. D.; Axten J.; Hammach A. H.; Kwak, Y-S; Lengweiler, U.; Lucero, M. J.; Houk, K. N. (*Tetrahedron*, 54 1998, 7045-7056). Analytical data for compound BA3: MS m/e: 262.1, 264.1 ($\text{M}+\text{H}$). ^1H NMR(CDCl_3) 1.43 (s, 9H), 3.98 (s, 2H), 4.11 (d, 4H), 5.78 (d, 1H).

10

Method BB



Method BB, Step 1;

15 Compound BB1 ($n=1$, $\text{R}^1=\text{Me}$, $\text{R}^3=\text{cyclohexylethyl}$) was converted to BB2 ($n=1$, $\text{R}^1=\text{Me}$, $\text{R}^3=\text{cyclohexylethyl}$) and BB3 ($n=1$, $\text{R}^1=\text{Me}$, $\text{R}^3=\text{cyclohexylethyl}$) which were separated via a silica gel column eluted with EtOAc in Hexane (0-15%).

287

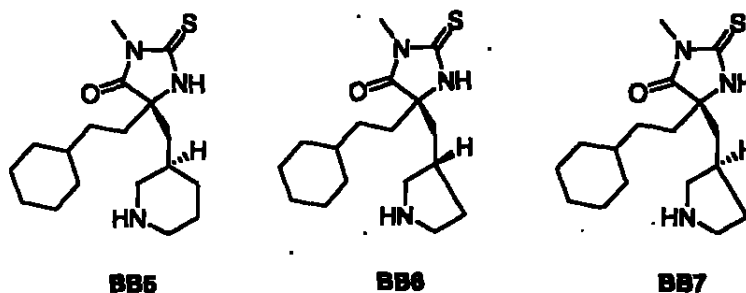
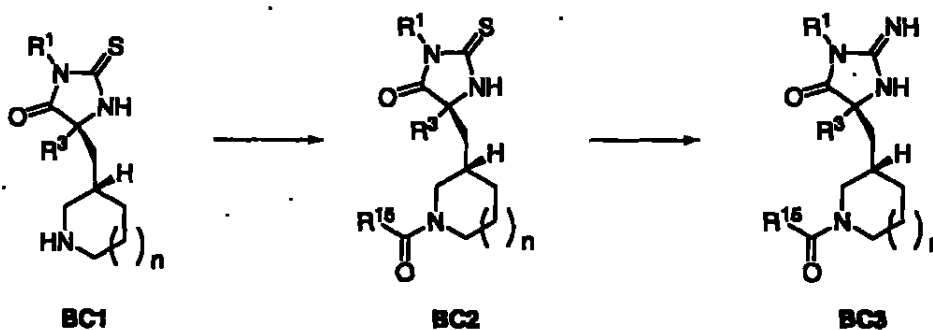
- 271 -

Method BB, Step 2;

Compound **BB4** ($n=1$, $R^1=\text{Me}$, $R^3=\text{cyclohexylethyl}$) was generated from **BB2** ($n=1$, $R^1=\text{Me}$, $R^3=\text{cyclohexylethyl}$) using 20% TFA in DCM.

The following compounds were generated using similar method:

5

**Method BC**

10

Method BC, Step 1;

Compound **BC2** ($n=1$, $R^1=\text{Me}$, $R^3=\text{cyclohexylethyl}$ and $R^{15}=\text{m-Pyridyl}$) was obtained from **BC1** ($n=1$, $R^2=\text{Me}$, $R^3=\text{cyclohexylethyl}$) using method L step 2.

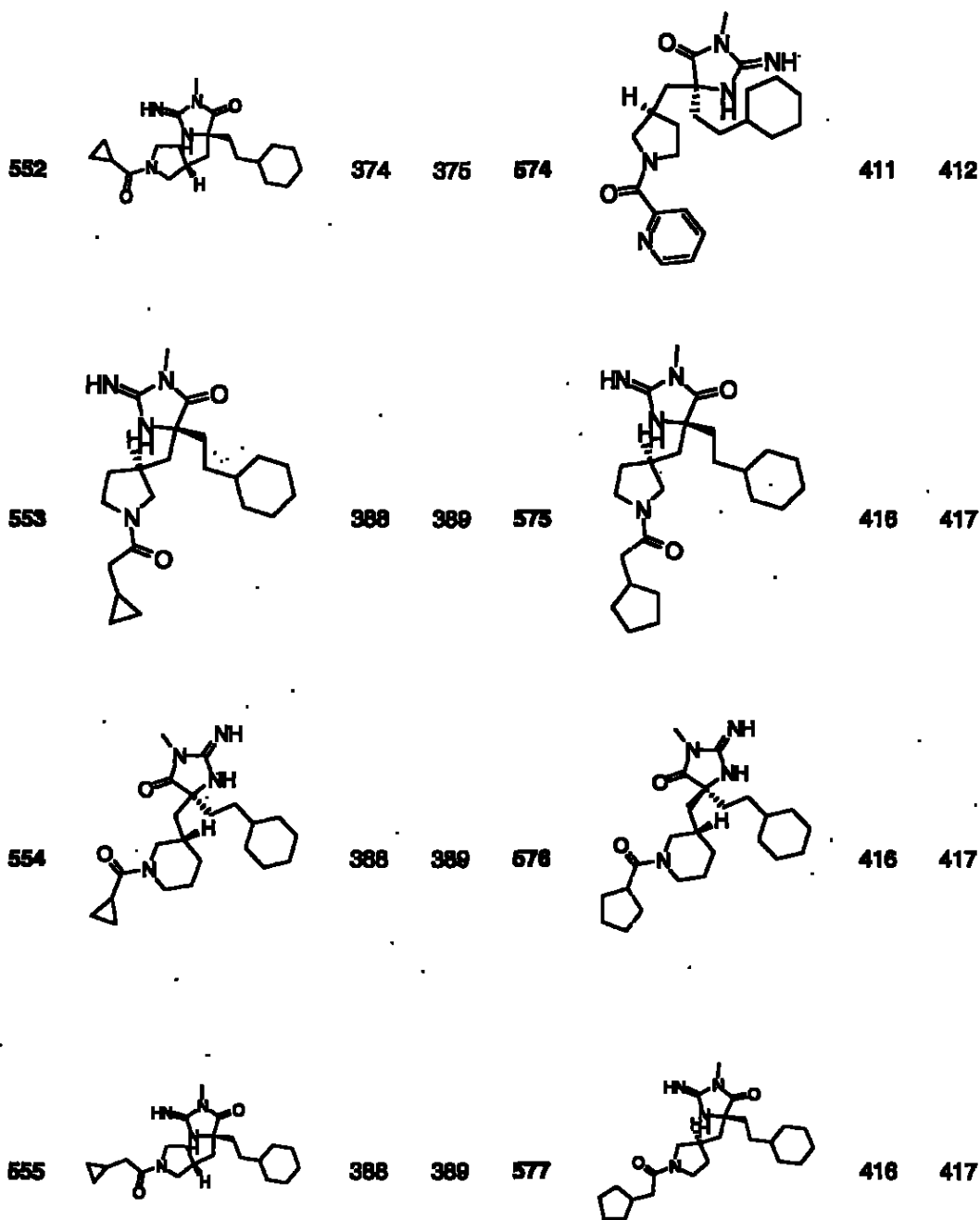
Method BC, Step 2;

5 Compound **BC3** ($n=1$, $R^1=\text{Me}$, $R^3=\text{cyclohexylethyl}$ and $R^{15}=\text{m-Pyridyl}$) was obtained from **BC2** ($n=1$, $R^1=\text{Me}$, $R^3=\text{cyclohexylethyl}$ and $R^{15}=\text{m-Pyridyl}$) using method L step 3.

The following compounds were generated using a similar method:

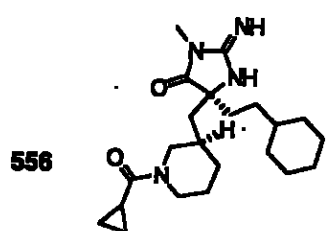
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
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- 272 -



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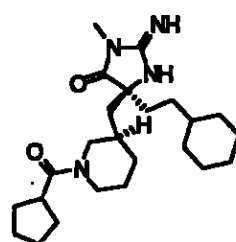
- 273 -



388

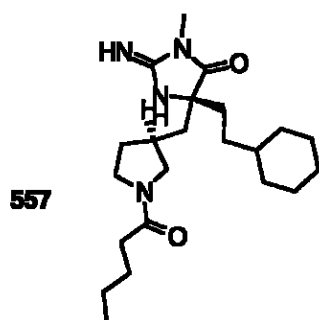
389

578



416

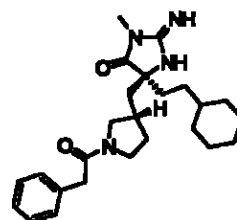
417



390

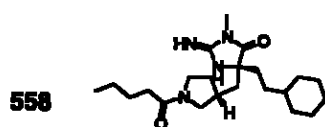
391

579



424

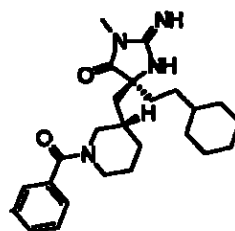
425



390

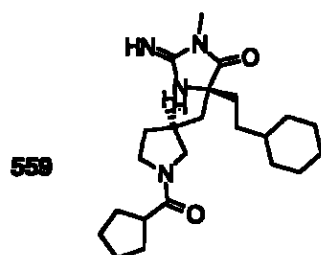
391

580



424

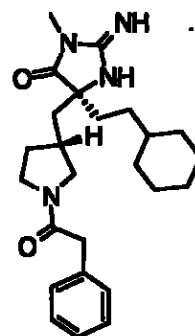
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402

403

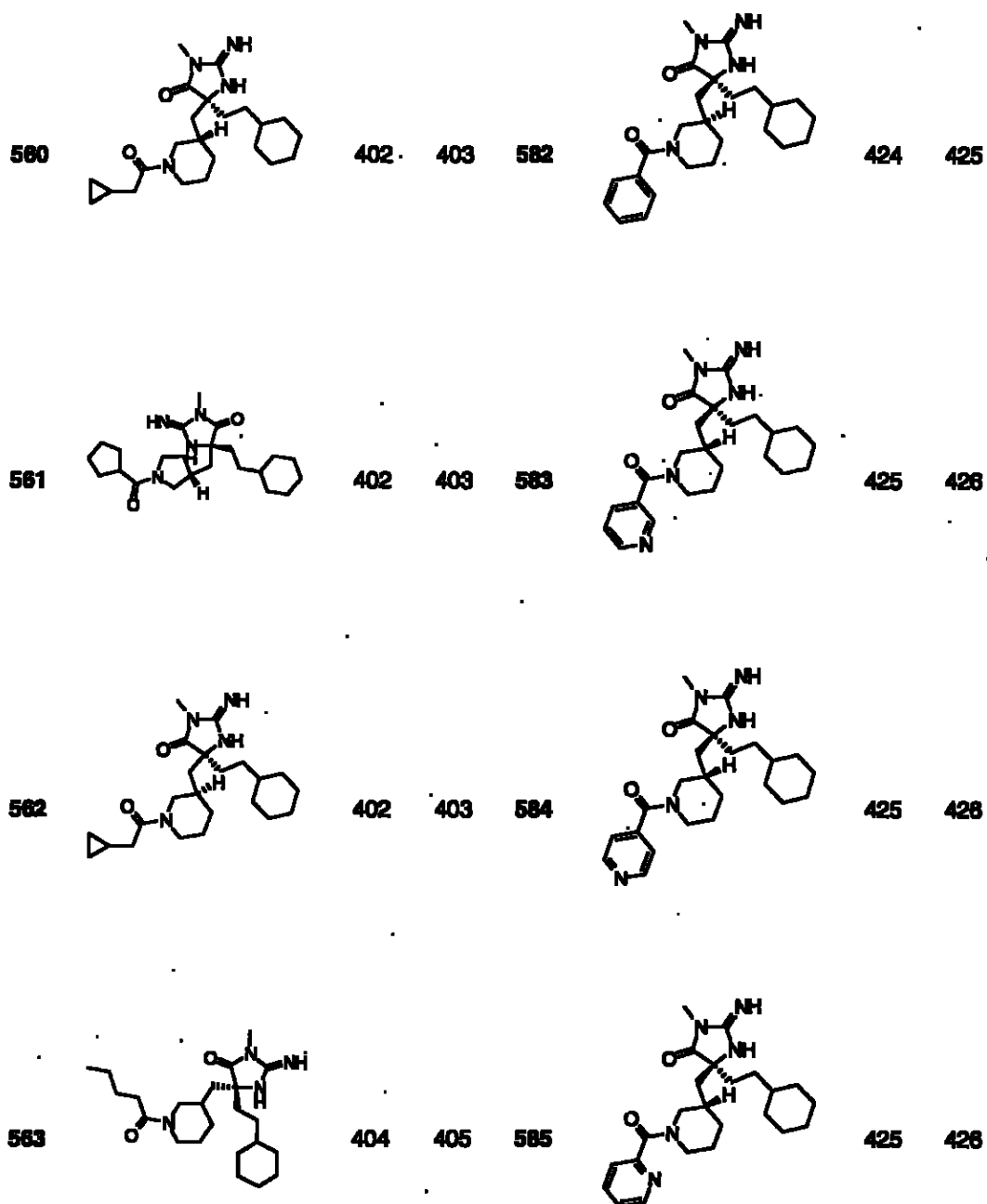
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424

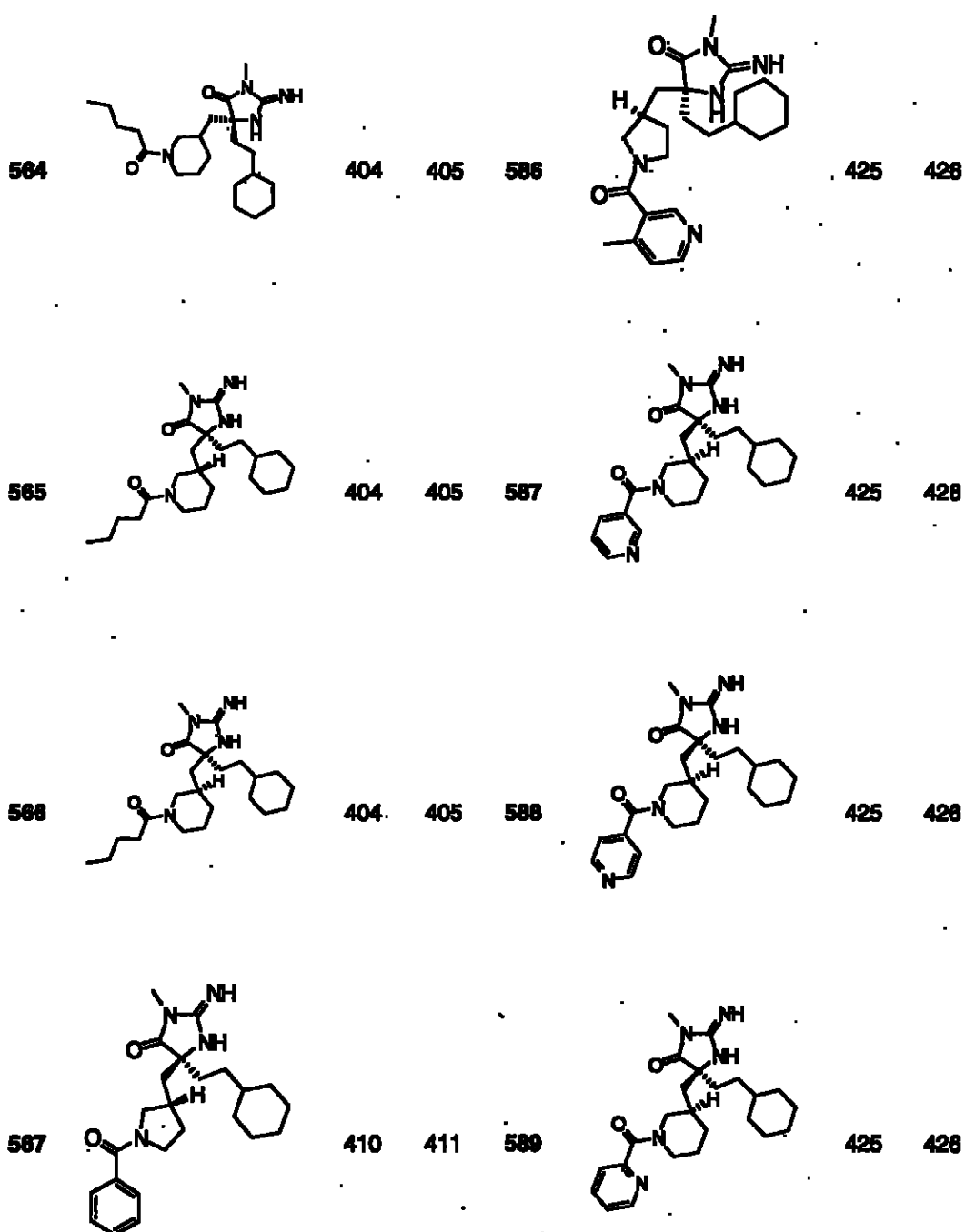
425

- 274 -

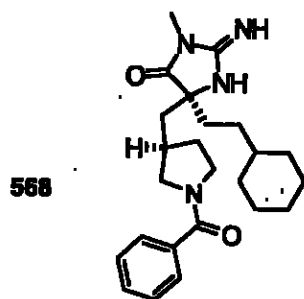


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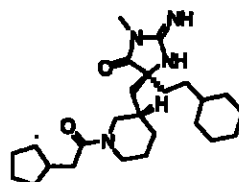
- 275 -



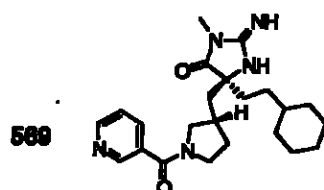
- 276 -



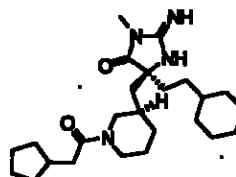
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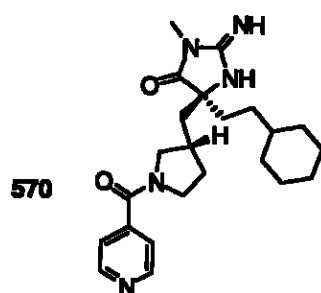
430 431



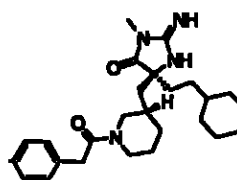
411 412 591



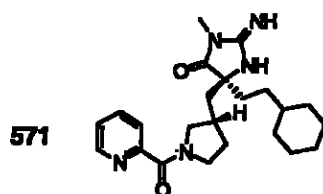
430 431



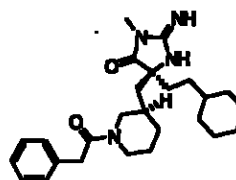
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438 439



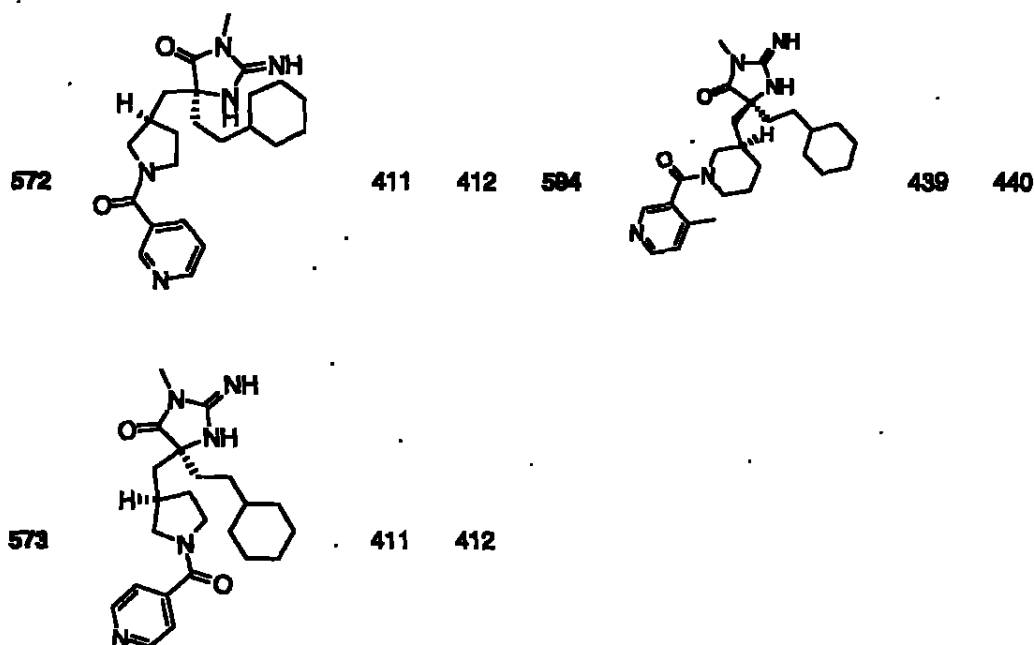
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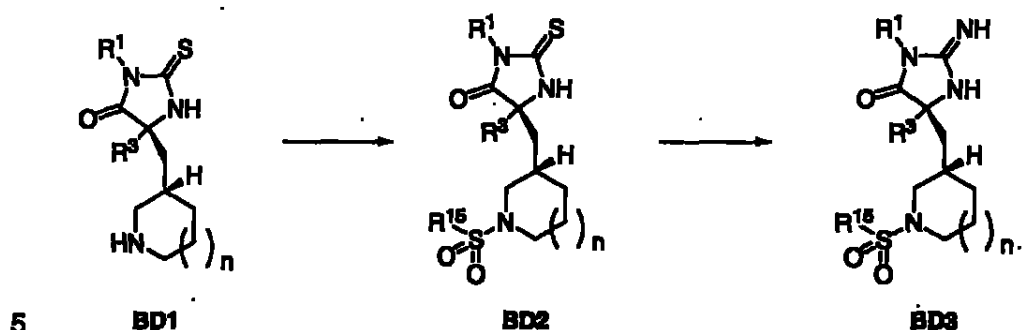
438 439

293

- 277 -



Method BD



Method BD, Step 1;

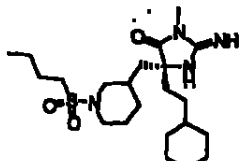
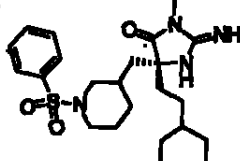
Compound BD2 ($n=1$, $R^1=Me$, $R^3=cyclohexylethyl$ and $R^{15}=Ph$) was obtained from BD1 ($n=1$, $R^2=Me$, $R^3=cyclohexylethyl$) using Method N, Step 1.

Method BD, Step 2;

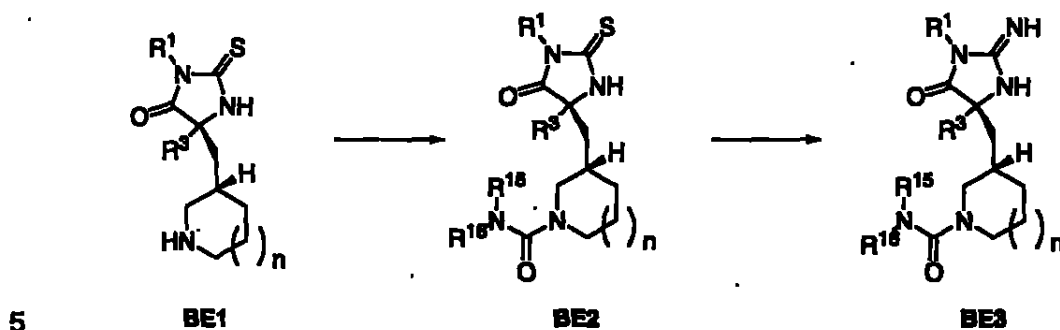
10 Compound BD3 ($n=1$, $R^1=Me$, $R^3=cyclohexylethyl$ and $R^{15}=Ph$) was obtained from BD2 ($n=1$, $R^1=Me$, $R^3=cyclohexylethyl$ and $R^{15}=m-Pyridyl$) using Method N, Step 2.

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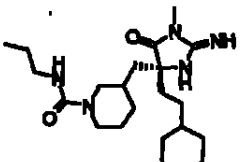
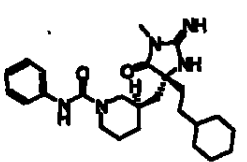
The following compounds were generated using a similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
585		440	441	586		460	461

Method BE



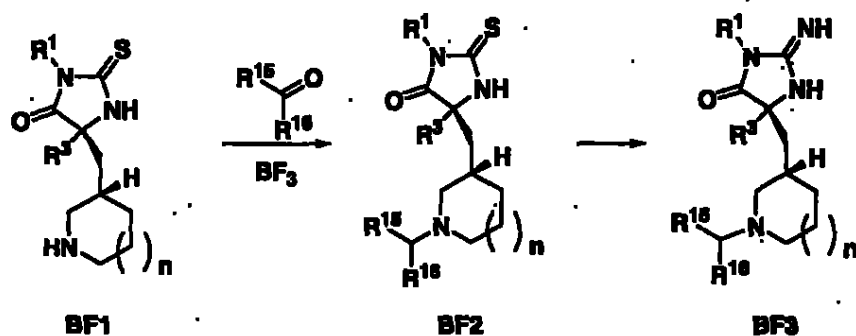
Method similar to Method M was adapted for these transformations. The following compounds were generated similar methods.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
587		405	406	588		439	440

0

Method BF

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**Method BF, Step 1:**

Method similar to Method T, Step 1 was used for the synthesis of BF2 ($n=1$, $\text{R}^1=\text{Me}$ and $\text{R}^3=\text{phenethyl}$, $\text{R}^{15}=\text{H}$ and $\text{R}^{16}=\text{n-propyl}$).

5

Method BF, Step 2:

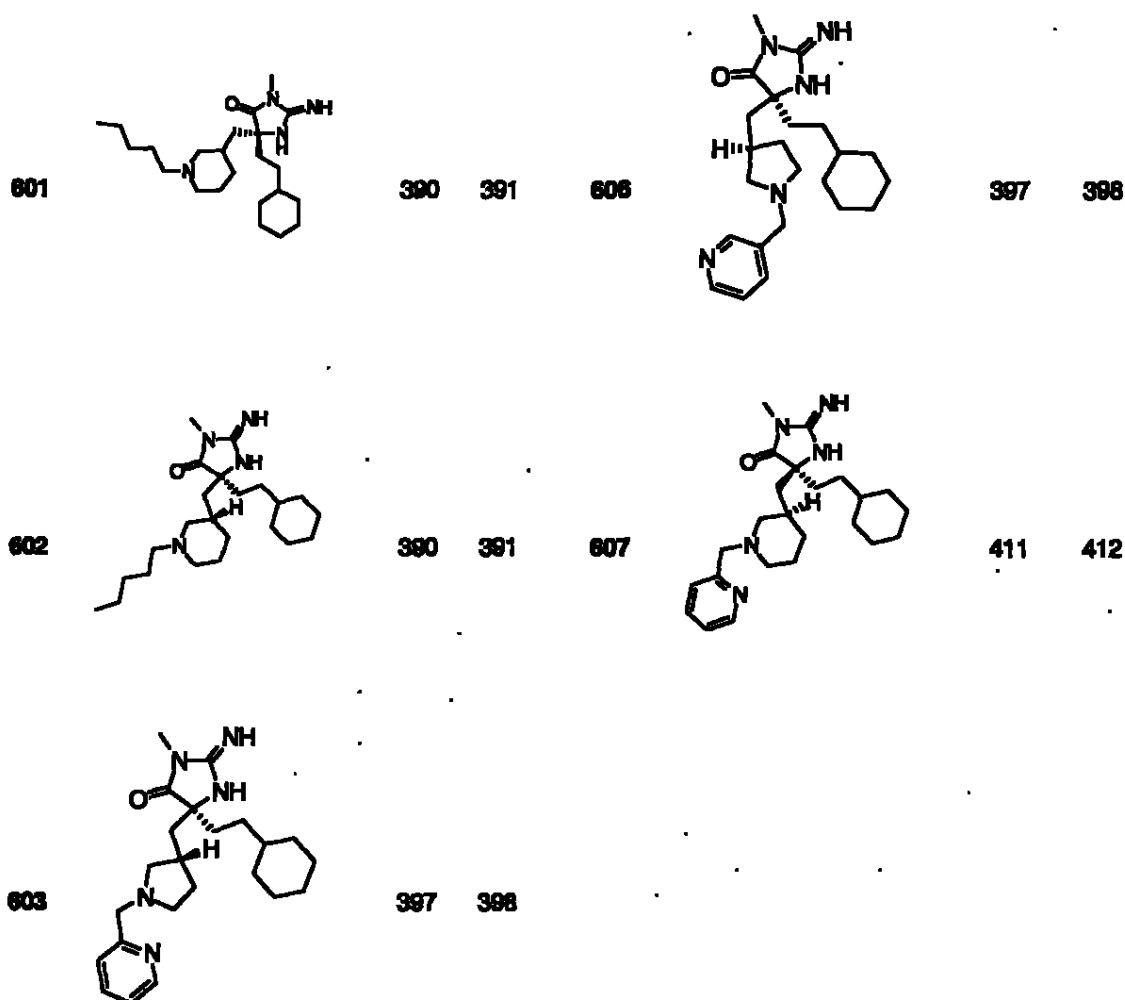
Method similar to method L Step 3 was adapted for this transformation.

The following compounds were generated using similar methods.

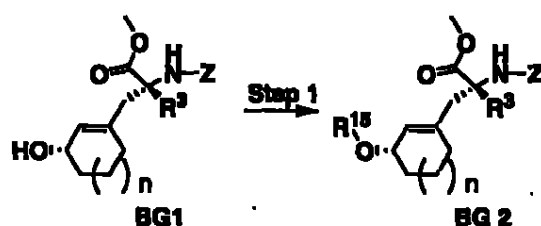
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
588		376	377	604		397	398
600		380	381	605		397	398

29.6

- 280 -



Method BG



Method BG:

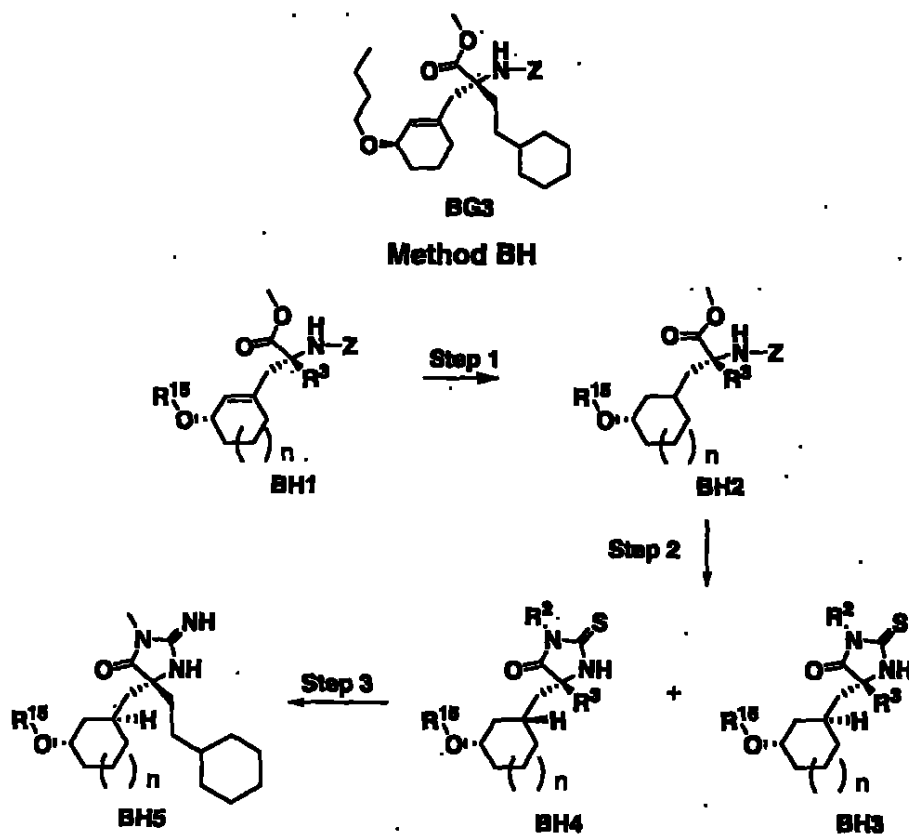
- 5 To a solution of BG1 ($n=1$, R^3 =cyclohexylethyl) (0.136 g, 0.31 mmol) in CH_2Cl_2 was added 2,6-lutidine, AgOTf, and butyl iodide. The reaction was stirred at room temperature for 96 hours. The reaction was filtered through a

297

- 281 -

pad of Celite, and the solution was concentrated. The residue was purified by silica chromatography (0-100% EtOAc/hexanes) to furnish **BG2** ($n=1$, R^3 =cyclohexylethyl, R^{16} =n-butyl) (0.124 g, 0.25 mmol, 80% yield). MS m/e : 426.1 (M-OBu).

5 The following compound was prepared using similar method:



0 Method BH, Step 1.

Compound **BH1** ($n=1$, R^3 =cyclohexylethyl and R^{16} =n-butyl) (0.060 g, 0.12 mmol) and 5% Pd(OH)₂/C (0.040 g) in EtOAc (1 mL)/MeOH (0.2 mL) was stirred under an atmosphere of H₂ for 20 hours at room temperature. The reaction was filtered through a pad of Celite, and the solution was concentrated. The crude product mixture **BH2** ($n=1$, R^3 =cyclohexylethyl and R^{16} =n-butyl) was carried on to the next step without purification.

Method BH, Step 2.

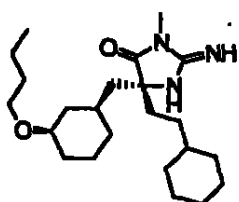
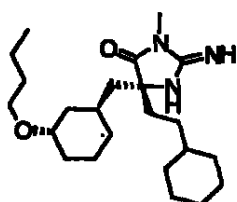
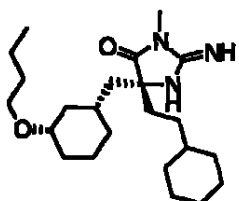
- 282 -

A solution of BH2 ($n=1$, R^3 =cyclohexylethyl and R^{15} =n-butyl) was converted to a product mixture of BH4 and BH3 using a method similar to Method C Step 1. The mixture was purified by silica gel chromatography using EtOAc/hexanes to yield BH4 ($n=1$, R^2 =Me, R^3 =cyclohexylethyl and R^{15} =n-butyl) (0.032 g, 0.078 mmol, 56% yield) and BH3 ($n=1$, R^2 =Me, R^3 =cyclohexylethyl and R^{15} =n-butyl) (0.008 g, 0.020 mmol, 14% yield). For BH4 ($n=1$, R^2 =Me, R^3 =cyclohexylethyl and R^{15} =n-butyl), MS m/e : 409.1 ($M+H$). For BH3 ($n=1$, R^2 =Me, R^3 =cyclohexylethyl and R^{15} =n-butyl), MS m/e : 409.1 ($M+H$).

10 Method BH, Step 3.

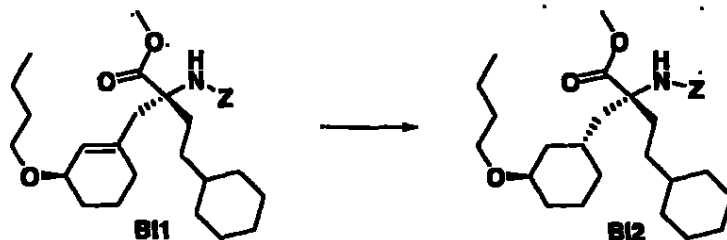
Compound BH4 ($n=1$, R^2 =Me, R^3 =cyclohexylethyl and R^{15} =n-butyl) (0.032 g, 0.078 mmol) was converted to BH5 ($n=1$, R^2 =Me, R^3 =cyclohexylethyl and R^{15} =n-butyl) (0.016 g, 0.043 mmol, 57% yield) using a method similar to Method A, step 3. MS m/e : 392.1 ($M+H$).

15 The following compound was generated using a similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
608		391	392	610		391	392
609		391	392				

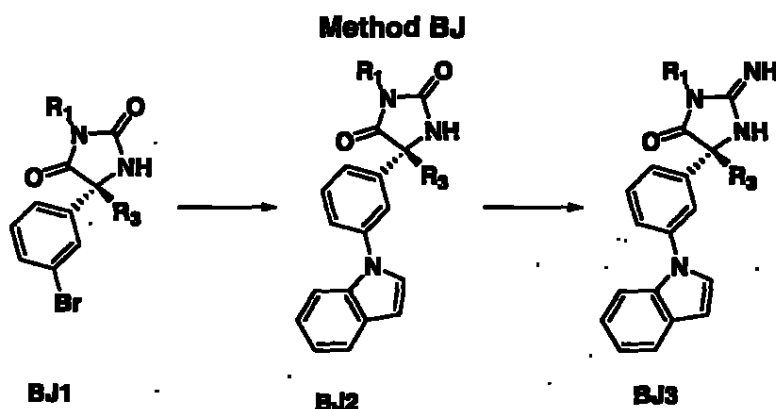
Method BI

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5 A solution of BI1 (0.020 g, 0.040 mmol) in DCM (1 mL) was degassed using freeze/pump/thaw (4x) method. At the end of the fourth cycle Crabtree's catalyst was added and the system was evacuated. While thawing, the system was charged with hydrogen gas, and the reaction was stirred at room temperature for 16 hours under an H₂ atmosphere. The reaction was concentrated, and the brown oil was purified by reverse phase HPLC to furnish BI2 (0.011 g, 0.022 mmol, 55% yield). MS m/e: 368.2 (M+H).

10

**Method BJ, Step 1**

15 A mixture of 2 ml dioxane solution of BJ1 (R¹=Me, R³=Me) (140 mg, 0.5 mmol) generated using Method BK Steps 1 & 2, indole (1.2 eq), potassium t-Butoxide (1.4 eq), Pd₂(dba)₃ (0.02 eq) and 2-di-t-butylphosphinobiphenyl (0.04 eq) in a sealed tube was irradiated in a microwave oven at 120 °C for 10 min and the mixture was separated via a silica gel column to give BJ2 (R¹=Me, R³=Me) (0.73 mg).

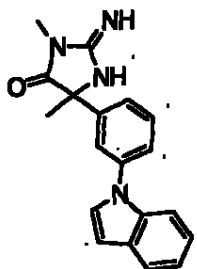
20

Method BJ, Step 2

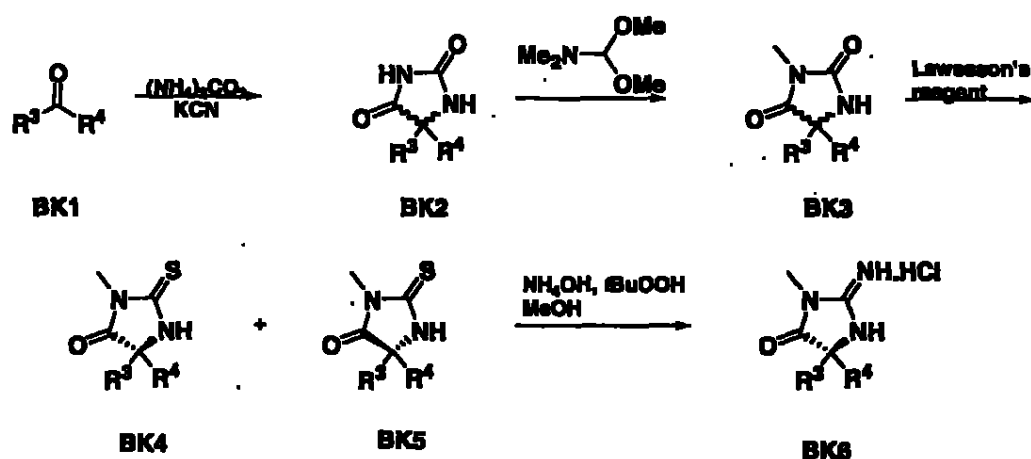
BJ2 (R¹=Me, R³=Me) was converted to BJ3 (R¹=Me, R³=Me) using Method BK, Steps 3 & 4. Obs. Mass for BJ3 (R¹=Me, R³=Me): 319.2.

300

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#	Structure	MW	Obs. m/e
614		318	319

Method BK



5 Method BK, Step 1:

Hydantoin BK2 ($R^3=N$ -benzyl-3-piperidyl, $R^4=n$ -Bu) was prepared according to Method D, Step 1 from the corresponding ketone BK1 ($R^3=N$ -benzyl-3-piperidyl, $R^4=n$ -Bu). Analytical data for BK2 ($R^3=N$ -benzyl-3-piperidyl, $R^4=n$ -Bu): (M+H) = 330.1.

10

Method BK, Step 2:

To a suspension of hydantoin BK2 ($R^3=N$ -benzyl-3-piperidyl, $R^4=n$ -Bu) (138 mg, 0.419 mmol) in DMF (1.5 ml) was added dimethylformamide dimethylacetal (0.11 ml, 0.84 mmol). The resulting mixture was heated in a 100 °C oil bath for 16h and then cooled to RT and concentrated under vacuum. This crude residue was purified by column chromatography (MeOH/DCM) to give

15

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product **BK3** ($R^3=N$ -benzyl-3-piperidyl, $R^4=n$ -Bu) (140 mg, 0.408 mmol, 97%), ($M+H$) = 344.1.

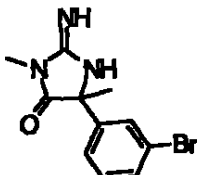
Method BK, Step 3:

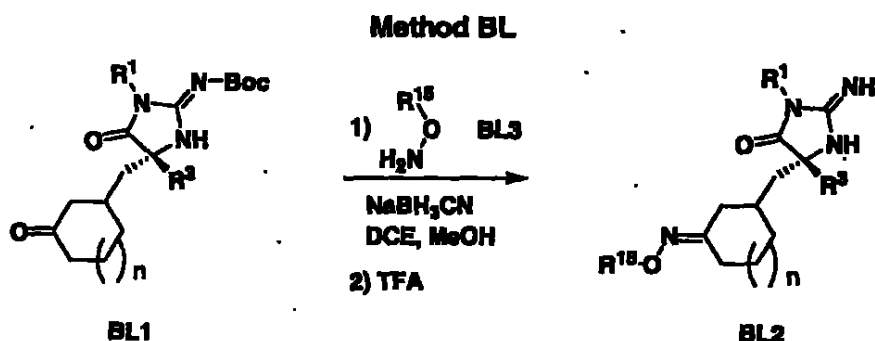
5 To a solution of a portion of **BK3** ($R^3=N$ -benzyl-3-piperidyl, $R^4=n$ -Bu) (70 mg, 0.20 mmol) in toluene (1 ml) was added Lawesson's reagent (107 mg, 0.26 mmol). The resulting mixture was placed in an oil bath at 60 °C for 16h and then at 100 °C for 24h. After cooling to RT, the reaction was quenched by addition of several drops of 1 N HCl and then diluted with EtOAc and 1 N KOH. The
10 phases were separated and the aqueous layer extracted with EtOAc (2X). The organic portions were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. This crude residue was purified by preparative TLC (1000 μ m silica, 15% EtOAc/DCM) to give two separated diastereomers **BK4** ($R^3=N$ -benzyl-3-piperidyl, $R^4=n$ -Bu) (24 mg, 0.067 mmol, 33%, MS: ($M+H$) = 360.2) and
15 **BK5** ($R^3=N$ -benzyl-m-piperidyl, $R^4=n$ -Bu) (22 mg, 0.062 mmol, 31%, MS: ($M+H$) = 360.2).

Method BK, Step 4:

Diastereomer **BK5** ($R^3=N$ -benzyl-3-piperidyl, $R^4=n$ -Bu) was treated
20 with NH_4OH (2 ml) and *t*-butyl hydrogen peroxide (70% aqueous, 2 ml) in MeOH (4 ml) for 24 h. After concentration, the crude sample was purified by preparative TLC (1000 mm silica, 7.5% 7N NH_3 /MeOH in DCM). The resulting sample was dissolved in DCM (1 ml), treated with 4N HCl in dioxane for 5 min, and finally concentrated to give diastereomeric products **BK7** ($R^3=N$ -benzyl-3-piperidyl, $R^4=n$ -Bu) (12 mg, 0.029 mmol, 43%). ^1H NMR (CD_3OD) δ 7.60 (m, 2 H), 7.49 (m, 3 H), 4.39 (ABq, $J_{AB} = 12.8$ Hz, $\Delta\nu_{AB} = 42.1$ Hz, 2 H), 3.69 (m, 1 H), 3.39 (br d, $J = 13.6$ Hz, 1 H), 3.20 (s, 3 H), 2.96 (m, 2 H), 2.45 (m, 1 H), 1.99 (m, 1 H), 1.92-1.78 (m, 3 H), 1.68 (br d, $J = 12.4$ Hz, 1 H), 1.50 (dq, $J_d = 3.6$ Hz, $J_q = 12.8$ Hz, 1 H), 1.36-1.22 (m, 4 H), 1.03 (m, 1 H), 0.90 (t, $J = 7.2$ Hz, 3 H). LCMS:
:5 t_R (doubly protonated) = 0.52 min, (singly protonated) = 2.79 min; ($M+H$) for both peaks = 343.2.

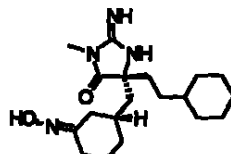
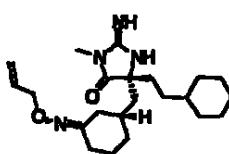
The following compounds were synthesized using similar methods:

#	Structure	M W	Obs. m/e
615		281	282



To a 2ml Methanolic solution of BL1 (n=1, R³=cyclohexylethyl, R¹=Me) (10 mg) was added BL3 (HCl salt, R¹⁵=H, 2 eq) and NaOAc (2 eq) and the mixture was heated to 60 C for 16 h. After removal of solvent, the residue was treated with 20% TFA in DCM for 30 min before the solvent was evaporated and residue purified using a reverse phase HPLC to give BL2 (n=1, R³=cyclohexylethyl, R¹ = Me and R¹⁵ = H).

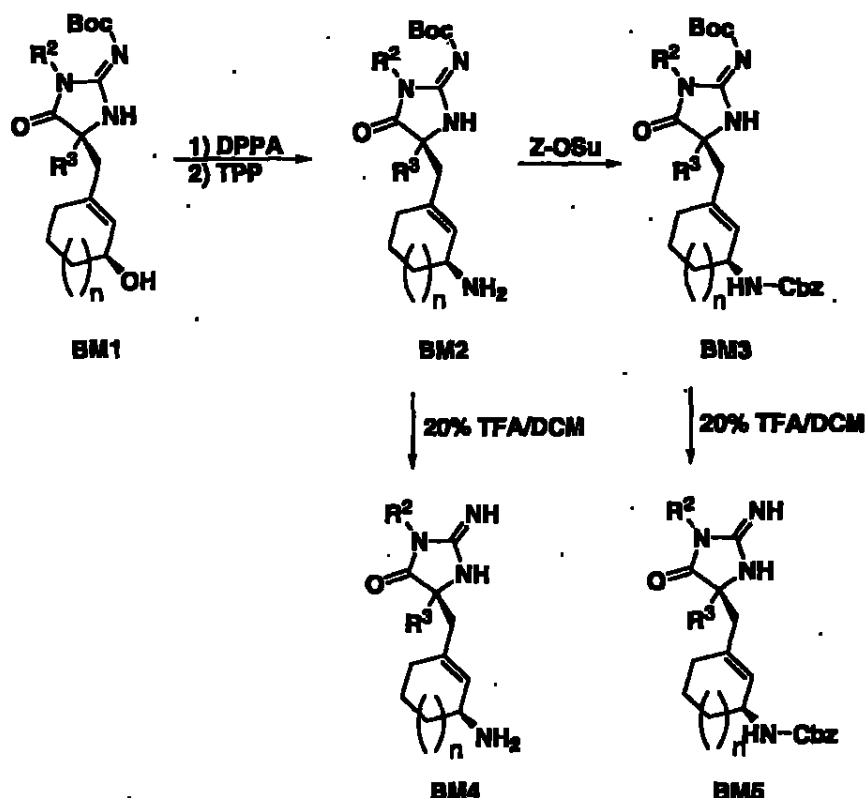
The following compounds were synthesized using similar methods.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
616		348	349	617		368	369

Method BM

203

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**Method BM, Step 1:**

To a toluene solution (3ml) of **BM1** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me) (0.050 mg) was added 1.5 eq of diphenylphosphoryl azide and 1.5 eq of DBU and the solution was stirred at r.t. overnight. The reaction mixture was diluted with EtOAc and washed with 1% aq HOAc before the organic layer was dried and solvent evaporated. The residue was chromatographed using EtOAc/Hex to give a product that was treated with triphenylphosphine (2 eq) in THF (1% water) overnight to give **BM2** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me) after reverse phase purification.

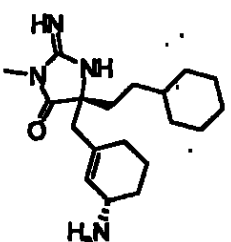
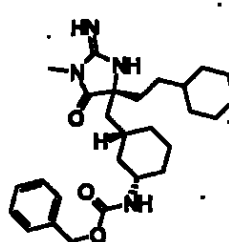
Method BM Step 2:

To a DCM solution of **BM2** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me) was added 1 eq of benzyloxycarbonyl-OSu and the reaction was stirred overnight before the solvent was evaporated and residue chromatographed to give **BM3** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me).

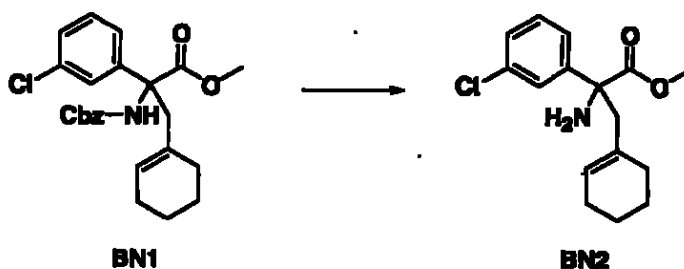
Compound **BM4** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me) and **BM5** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me) were generated from **BM2** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me) and **BM3** ($n=1$, R^3 =cyclohexylethyl, R^2 =Me) through Boc-deprotection.

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The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
618		332	333	619		468	469

Method BN



5

A mixture of Pd(OAc)₂ (9 mg), triethylamine (17 microliter), triethylsilane (11 microliter) and BN1 (20 mg) in DCM was hydrogenated at 1 atm at rt for 1.5 h before the reaction was filtered through a Celite pad to give BN2 after removal of solvent.

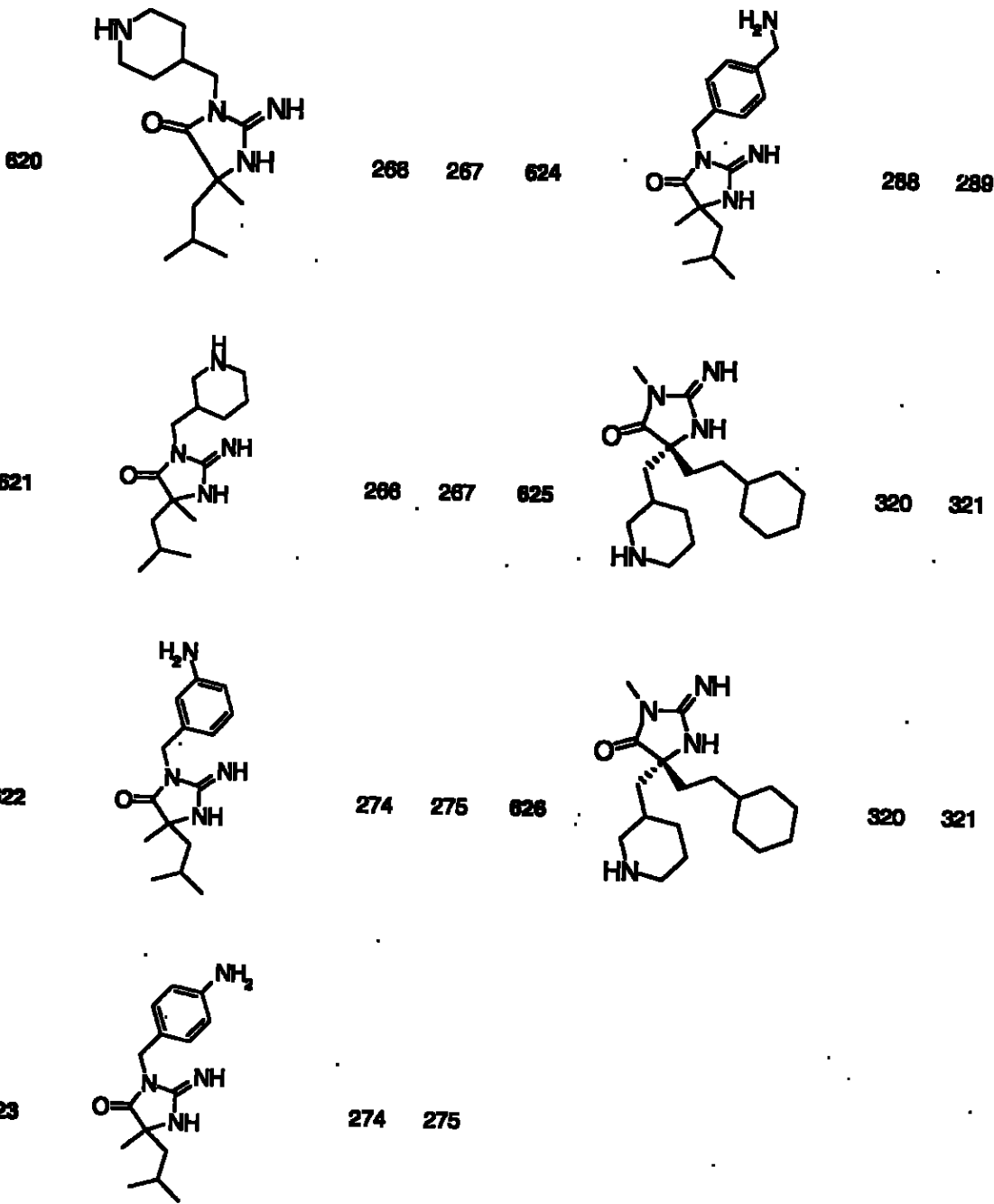
10

Method BO

~~The following compounds were generated through boc-deprotection of the corresponding starting material using 50% TFA in DCM, rt 30 min.~~

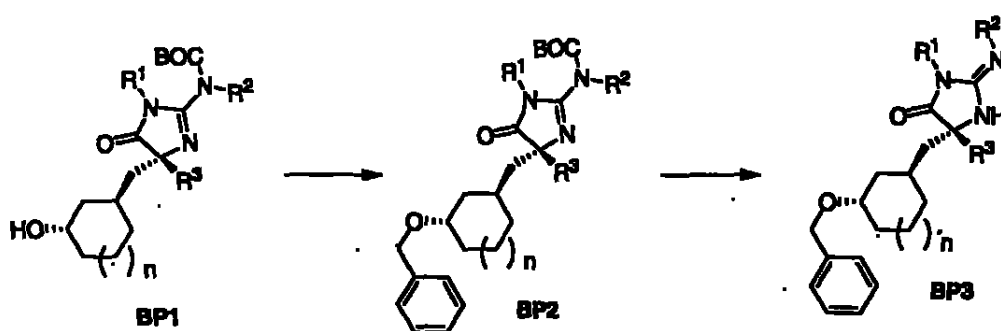
#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
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Method BP

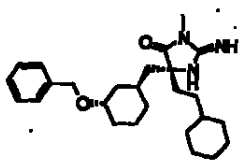
- 290 -

**Method BP, Step 1**

To a solution of BP1 ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3=\text{cyclohexylethyl}$) (0.012 g, 0.028 mmol) in CH_2Cl_2 (0.5 mL) was added 2,6-lutidine (0.010 mL, 0.086 mmol), AgOTf (0.024 g, 0.093 mmol), and benzyl bromide (0.010 mL, 0.084 mmol). The reaction was stirred at room temperature for 16 hours. The solid was filtered, and after concentration the residue was purified by reverse phase HPLC to yield BP2 ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3=\text{cyclohexylethyl}$) (0.010 g, 0.019 mmol). MS m/e : 526.1 ($M+H$).

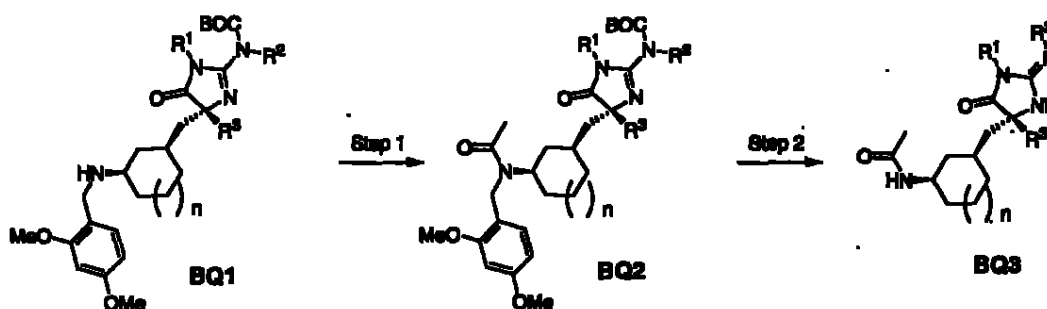
Method BP, Step 2

BP3 ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3=\text{cyclohexylethyl}$) was prepared from BP2 ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3=\text{cyclohexylethyl}$) using 30% TFA/DCM. MS m/e : 426.1 ($M+H$).

#	Structure	M	Obs.
		W	m/e
627		425	426

Method BQ

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Method BQ Step 1:

BQ1 was prepared according to Method AZ.

5 To a solution of BQ1 ($n=1$, $R^1=Me$, $R^2=H$, $R^3=cyclohexylethyl$) (0.004 g, 0.007 mmol) in CH_2Cl_2 (0.3 mL) was added DIEA (0.007 mL, 0.040 mmol), acetic acid (0.001 mL, 0.017 mmol), HOBt (0.003 g, 0.019 mmol), and EDCI (0.003 g, 0.016 mmol). The reaction was stirred at room temperature for 16 hours. The reaction was concentrated and purified by reverse phase HPLC
10 to provide BQ2 ($n=1$, $R^1=Me$, $R^2=H$, $R^3=cyclohexylethyl$) (0.003 g, 0.005 mmol). MS m/e : 627.1 ($M+H$).

Method BQ Step 2:

BQ2 ($n=1$, $R^1=Me$, $R^2=H$, $R^3 = \text{cyclohexylethyl}$) (0.003 g, 0.005 mmol) was treated with 20% TFA/ CH_2Cl_2 (1 mL) in the presence of PS-thiophenol resin (0.030 g, 1.42 mmol/g) for 3 hours. The solution was filtered and concentrated to produce **BQ3** ($n=1$, $R^1=Me$, $R^2=H$, $R^3 = \text{cyclohexylethyl}$) (0.002 g, 0.005 mmol). MS m/e : 377.2 (M+H).

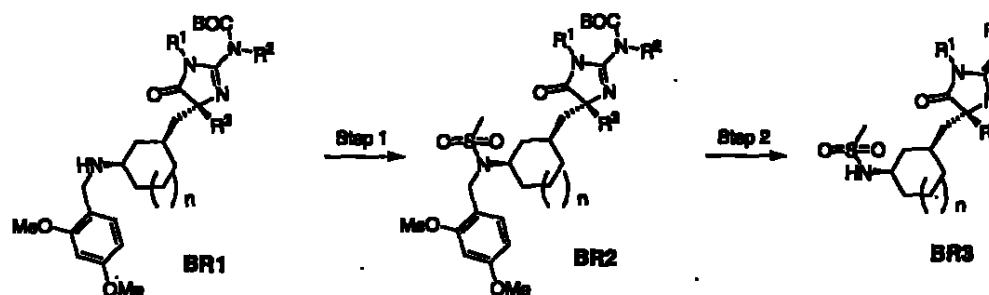
#	Structure	MW	Obs. m/e
628		376	377

20

Method BR

303

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**Method BR, Step 1:**

- 5 To a solution of BR1 ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3=\text{cyclohexylethyl}$) (0.004 g, 0.007 mmol) in pyridine (0.2 ml) was added DMAP (a few crystals) and methanesulfonyl chloride (3 drops). The reaction was stirred at room temperature for 6 days. The reaction was quenched with water and diluted with CH_2Cl_2 . The organic layer was removed, and the aqueous phase was extracted with CH_2Cl_2 (3x). After concentration, the brown residue was purified by reverse phase HPLC to yield BR2 ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3=\text{cyclohexylethyl}$) (0.003 g, 0.004 mmol). MS m/e : 663.2 ($M+H$).

Method BR, Step 2:

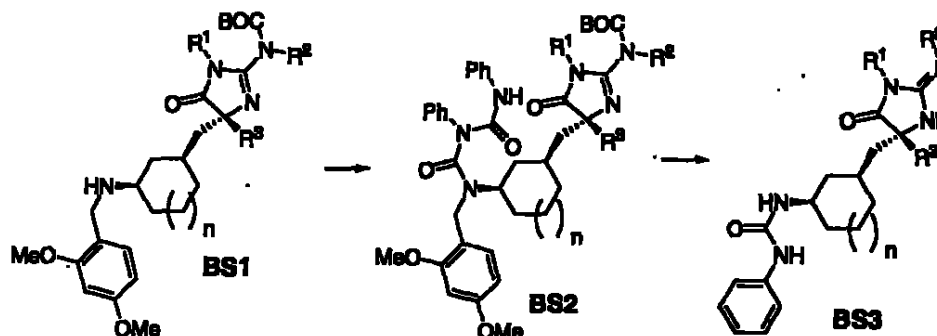
- 15 BR3 ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3=\text{cyclohexylethyl}$) was prepared from BR2 ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3=\text{cyclohexylethyl}$) following a procedure similar to Method BQ Step 2. MS m/e : 413.1 ($M+H$).

#	Structure	MW	Obs. m/e
629		412	413

0

Method BS

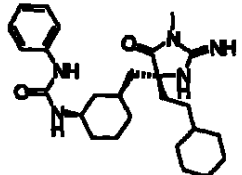
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**Method BS Step 1:**

To a solution of **BS1** ($n=1$, $R^1=Me$, $R^2=H$, $R^3 = \text{cyclohexylethyl}$) (0.003 g, 0.006 mmol) in CH_2Cl_2 (0.3 mL) was added phenyl isocyanate (2 drops). The reaction was stirred at room temperature for 16 hours. The reaction was concentrated and purified by reverse phase HPLC to provide **BS2** ($n=1$, $R^1=Me$, $R^2=H$, $R^3 = \text{cyclohexylethyl}$) (0.002 g, 0.002 mmol). MS m/e : 823.5 ($M+H$).

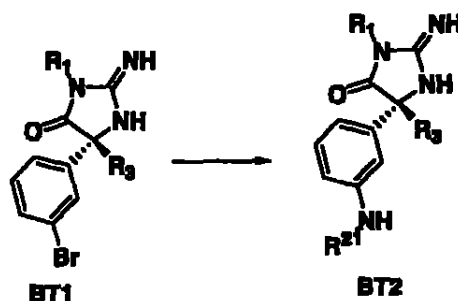
Method BS Step 2:

Compound **BS2** ($n=1$, $R^1=Me$, $R^2=H$, $R^3 = \text{cyclohexylethyl}$) was subjected to the same conditions in Method BQ Step 2. The crude mixture prepared above was treated with LiOH (0.006 g, 0.25 mmol) in MeOH (0.3 mL) for 2 hours. The reaction was concentrated, and the residue was purified by reverse phase HPLC to furnish **BS3** ($n=1$, $R^1=Me$, $R^2=H$, $R^3 = \text{cyclohexylethyl}$) (0.0012 g, 0.002 mmol). MS m/e : 454.1 ($M+H$).

#	Structure	MW	Obs. m/e
630		453	454

Method BT

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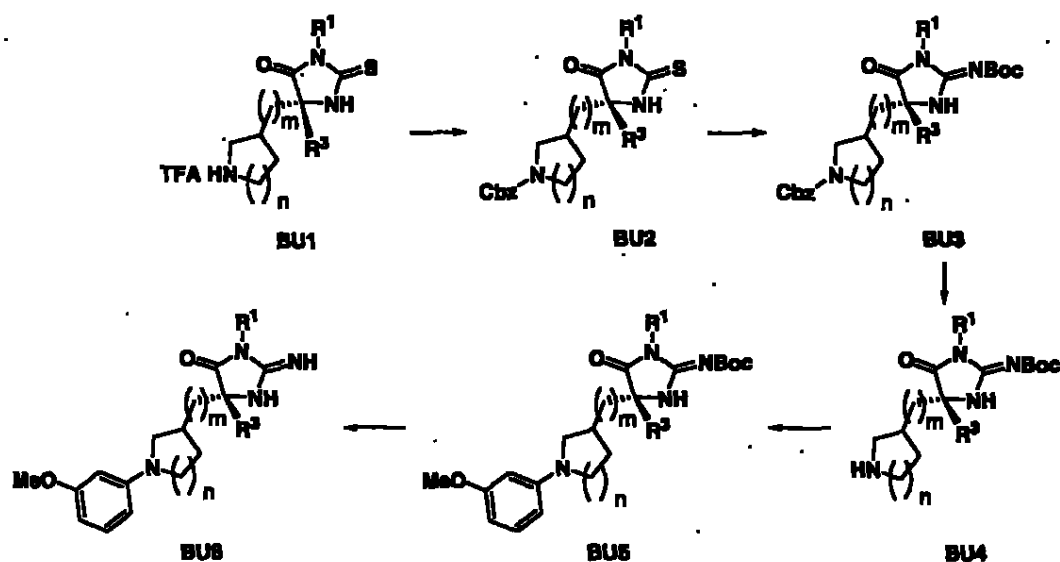
**Method BT:**

To a round bottom flask were added compound BT1 ($R^1=Me$, $R^3=Me$) (100 mg, 0.29 mmol), anhydrous toluene (2 ml), 3-aminopyridine (55 mg, 0.58 mmol) and 2-(di-*tert*-butyl phosphino) biphenyl (17 mg, 0.058). The solution was then degassed by N_2 for 2 minutes before NaO-*t*-Bu (61 mg, 0.638 mmol) and $Pd_2(dba)_3$ (27 mg, 0.029 mmol) were added. The reaction was stirred at 80 °C for 22 hours. After cooling down to room temperature, the reaction was poured to cold water and extracted by CH_2Cl_2 . The combined organic layer was then dried over Na_2SO_4 . After the filtration, the concentrated residue was separated by TLC ($CH_3OH:CH_2Cl_2=1:10$) and reverse phase HPLC (10%-100% acetonitrile in water w/0.1% formic acid) to produce the desired compound BT2 ($R^1=Me$, $R^3=Me$ and $R^{21}=m$ -pyridyl) as a formate salt (23.6 mg, white solid, 20%). ^1H NMR ($CDCl_3$) δ 7.50-6.90 (m, 13 H), 3.14 (s, 3H) MS m/e 358 (M+H).

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
631		347	348	632		356	357
633		357	358	635		357	358



Method BU



5 Method BU, Step 1,

To a round bottomed flask containing BU1 ($m=1$, $n=1$, $R^1=Me$, $R^3=Cyclohexylethyl$) (99 mg, 0.307 mmol) of the trifluoroacetic acid salt of pyrrolidine derivative in 5 ml of DCM was added (86 μ L, 0.614 mmol) of triethylamine followed by addition of (76 mg, 0.307 mmol) N-(benzyloxycarbonyloxy)succinimide. Stir at room temperature for 18h. Dilute the mixture with DCM and extract with sat'd $NaHCO_3$ soln, then water. Collect the organic portion and dry over Na_2SO_4 , filter and concentrate *in vacuo*. Purify by silica gel chromatography (eluting with 0 to 60%

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EtOAc/hexanes) to yield BU2 ($m = 1$, $n = 1$, $R^1 = \text{Me}$, $R^3 = \text{Cyclohexylethyl}$) (130 mg, 0.284 mmol, 93% yield). MS m/e : 458.1 (M+H).

Method BU, Step 2,

5 To a solution of BU2 ($m = 1$, $n = 1$, $R^1 = \text{Me}$, $R^3 = \text{Cyclohexylethyl}$) (130 mg) in 1 ml of MeOH in a reaction vial was added 0.5 ml of a solution of 70% tBuOOH in water and 0.5 ml of NH_4OH . Seal the vial and shake at room temperature for 72h. The mixture was concentrated *in vacuo*. The mixture was diluted with 1 ml of MeOH and a mixture 30 mg of NaHCO_3 and Boc_2O (87 mg, 0.398 mmol) were added. The
10 solution mixture was stirred at room temperature for 18h before it was concentrated and the residue purified by silica gel chromatography using EtOAc/hexanes to yield the BU3 ($m = 1$, $n = 1$, $R^1 = \text{Me}$, $R^3 = \text{Cyclohexylethyl}$) (90 mg, 0.167 mmol, 58% yield). MS m/e : 541.1, 441.1 (M+H).

15 **Method BU, Step 3,**

A solution of BU3 ($m = 1$, $n = 1$, $R^1 = \text{Me}$, $R^3 = \text{Cyclohexylethyl}$) (90mg, 0.167 mmol) in 5 ml of MeOH was hydrogenated using 100 mg of $\text{Pd}(\text{OH})_2 \cdot \text{C}$ (20% w/w) at 1 atm for 1 h. The reaction mixture was filtered through a pad of diatomaceous earth and the pad was washed with MeOH. Concentration of the collected organic portions
20 *in vacuo* yielded BU4 ($m = 1$, $n = 1$, $R^1 = \text{Me}$, $R^3 = \text{Cyclohexylethyl}$) (47 mg 0.116 mmol, 70% yield). MS m/e : 407.1 (M+H).

Method BU, Step 4,

To a vial containing 10 mg of powdered 4 Å molecular sieves was added 3-
5 methoxyphenyl boronic acid (60 mg, 0.395 mmol) then 3 ml of anhydrous MeOH. To this mixture was added pyridine (100 ml, 0.650 mmol), $\text{Cu}(\text{OAc})_2$ (7 mg, 0.038 mmol), and BU4 ($m = 1$, $n = 1$, $R^1 = \text{Me}$, $R^3 = \text{Cyclohexylethyl}$) (7.83 mg, 0.019 mmol) and the mixture was stirred at room temperature for 96 h before it was quenched with 0.25 ml of 7N ammonia in methanol solution. The reaction mixture was extracted with water
10 and DCM and the organic layers were dried and concentrate *in vacuo*. The residue was purified via a reverse-phase HPLC to give a product which was treated with 5ml of 40% of TFA in DCM for 5 h. After removal of the volatiles, the residue was purified using a reverse phase HPLC system to furnish BU5 ($m = 1$, $n = 1$, $R^1 = \text{Me}$,

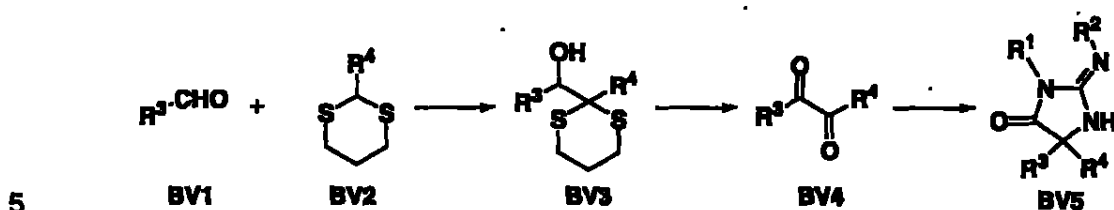
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R^3 =Cyclohexylethyl and R^{21} =m-MeOPh) as the formic acid salt (0.7 mg, 0.0015 mmol, 30.1% yield). MS m/e: 413.1 (M+H).

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
637		358	359	638		412	413

Method BV



Method BV Step 1:

The method was adapted from a literature procedure (Page et al., *Tetrahedron* 1992, 35, 7265-7274)

10 A hexane solution of nBuLi (4.4 mL, 11 mmol) was added to a -78 C solution of BV2 (R^4 = phenyl) (2.0 g, 10 mmol) in THF (47 mL). After 60 minutes at -78 C, a solution of BV1 (R^3 = 3-bromo-4-fluorophenyl) (2.24 g, 11 mmol) was added and the reaction slowly warmed to RT over 18 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with CH_2Cl_2 (2 x), dried over

15 MgSO_4 and concentrated under vacuum. The resulting oil was subjected to silica gel chromatography using 4-10% EtOAc/Hexanes to give a white solid BV3 (R^3 = 3-bromo-4-fluorophenyl and R^4 = phenyl) (1.69 g, 4.23 mmol, 42%). ^1H NMR (CDCl_3) δ 7.61 (m, 2 H), 7.27 (m, 3 H), 6.94 (m, 1 H), 6.92 (m, 1 H), 6.68 (m, 1 H), 3.15 (bs, 1 H), 2.57-2.73 (m, 4 H), 1.89 (m, 2 H).

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Method BV Step 2:

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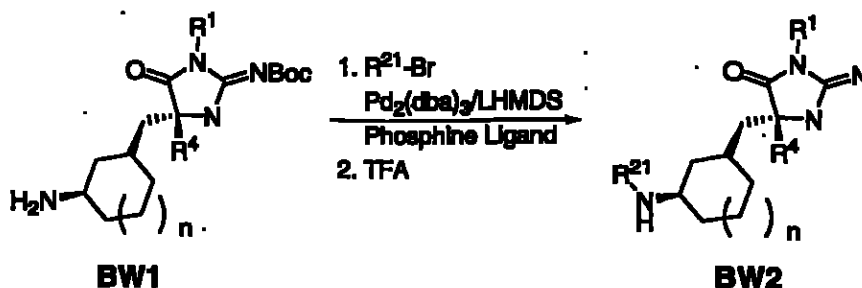
A solution of BV3 (R^3 = 3-bromo-4-fluorophenyl and R^4 = phenyl) (1.89 g, 4.23 mmol) in acetone (40 mL) was slowly added via addition funnel to a 0 °C solution of N-bromosuccinimide (NBS, 11.3 g, 63.3 mmol) in acetone (200 mL) and water (7.5 mL). The mixture was slowly warmed to RT, and quenched after 60 minutes with 10% aqueous Na_2SO_3 . After diluting with CH_2Cl_2 , the layers were separated, and the organic layer washed with water (2x), brine (1x) and dried over $MgSO_4$. Concentration under vacuum afforded an oil which was subjected to silica gel chromatography using 5% EtOAc/Hexanes to give a solid BV4 (R^3 = 3-bromo-4-fluorophenyl and R^4 = phenyl) (690 mg, 2.24 mmol, 53%). ^1H NMR ($CDCl_3$) δ 8.18 (m, 1 H), 7.93 (m, 3 H), 7.66 (m, 1 H), 7.50 (m, 2 H), 7.20 (m, 1 H).

Method BV Step 3:

BV5 (R^3 = 3-bromo-4-fluorophenyl and R^4 = phenyl and R^1 =Me and R^2 = H) was prepared from BV4 (R^3 = 3-bromo-4-fluorophenyl and R^4 = phenyl) using Method AS, Step 4.

#	Structure	MW	Obs. m/e	#	Structure	MW	Obs. m/e
639		361	362	640		361	NA

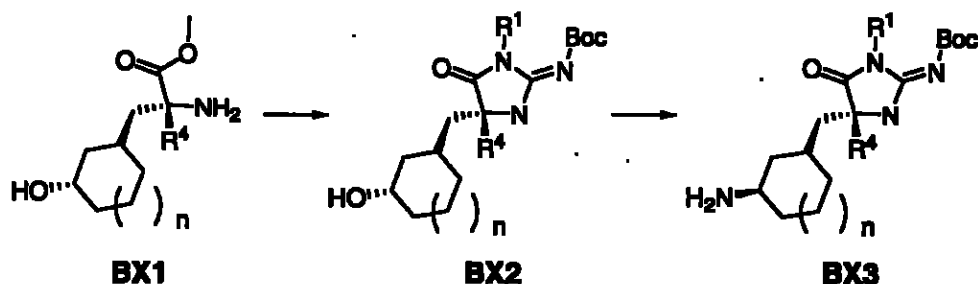
Method BW



- 5 To an oven-dried vial was added $\text{Pd}_2(\text{dba})_3$ (15.4 mg, 0.0168 mmol) and 2-(Di-*t*-butylphosphino)biphenyl (10.0 mg, 0.0336 mmol) followed by addition of a solution of **BW1** ($\text{R}^4 = \text{Me}$; $\text{R}^1 = \text{Me}$ and $n=1$) (56.8 mg, 0.168 mmol) in 2 mL of anhydrous THF. 2-Bromopyridine (17.0 mL, 0.178 mmol) was added followed by addition of 0.80 mL of 1.0 N LHMDS solution in THF. The reaction mixture was stirred at 35 °C for 90 min
- 10 followed by addition of MeOH and filtration through a silica gel pad. Purification by silica gel chromatography (0 to 100 % EtOAc in hexanes) yielded the product which was treated with 5 mL of a 30% TFA in DCM solution to give **BW2** after concentration and purification via a reverse phase column ($\text{R}^4 = \text{Me}$; $\text{R}^1 = \text{Me}$; $\text{R}^{22} = 2\text{-pyridyl}$ and $n=1$) (69.3 mg, 99%). ES_LCMS (m/e): 416.2

15

Method BX



20 Method BX, Step 1

- To a solution of **BX1** ($\text{R}^4 = \text{Me}$ and $n = 1$) (0.78g, 3.63 mmol) in 10 mL of anhydrous DMF, was added N-Boc-N'-methyl thiourea (0.70g, 3.70 mmol), EDCI.HCl (0.90g, 4.71 mmol), and diisopropylethylamine (2.5 mL). The mixture was stirred at RT for 16h before it was quenched with water and extracted with EtOAc (3 x 50 mL). The
- 25 organic solution was dried, concentrated and the residue chromatographed via a silica

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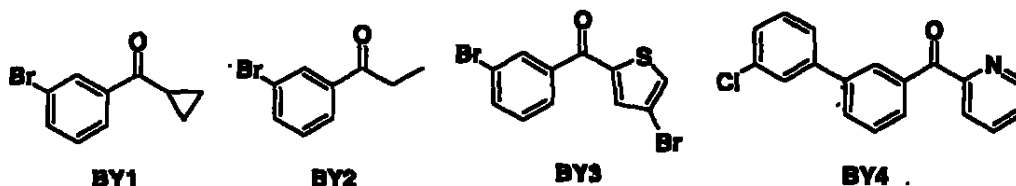
gel column to yield **BX2** ($R^1 = R^4 = \text{Me}$ and $n = 1$) (1.23g, 100%). ES_LCMS (*m/e*): 340.1

Method BX, Step 2

- 5 To a solution of **BX2** ($R^1 = R^4 = \text{Me}$ and $n = 1$) (1.23g, 3.63 mmol) in 40 mL of anhydrous THF was added triphenylphosphine (1.43g, 5.44 mmol) and the mixture was cooled to 0°C followed by slow addition of diisopropylcarbodiimide (1.07 mL, 5.44 mmol). After the mixture was stirred for 15 min at 0°C, nicotinoyl azide (Synthesis, 2004 (17), 2886) (0.66g, 4.71 mmol) was added in one portion and the reaction was
- 10 allowed to warm to RT and stir for 3h. The reaction was diluted with EtOAc (200 mL) and washed with water (3 x 100 mL). The residue from the organic layer was purified through a silica gel column to yield the product azide which was hydrogenation using 20% Pd(OH)₂ / C (0.64 mg) in MeOH to give **BX3** ($R^1 = R^4 = \text{Me}$ and $n = 1$). ES_LCMS (*m/e*): 339.1.
- 15

Method BY

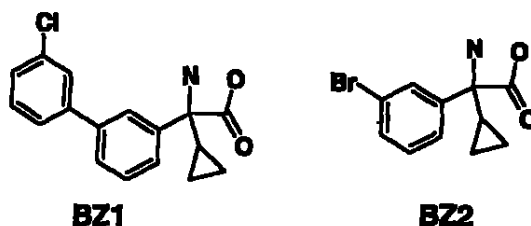
The following compounds were synthesized using methods similar to Methods AO or AP.



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Method BZ

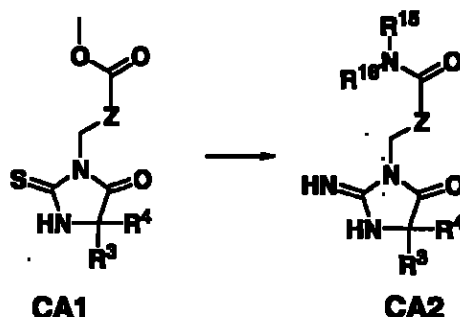
The following aminoacids were generated using methods similar to Method D



5

Method CA

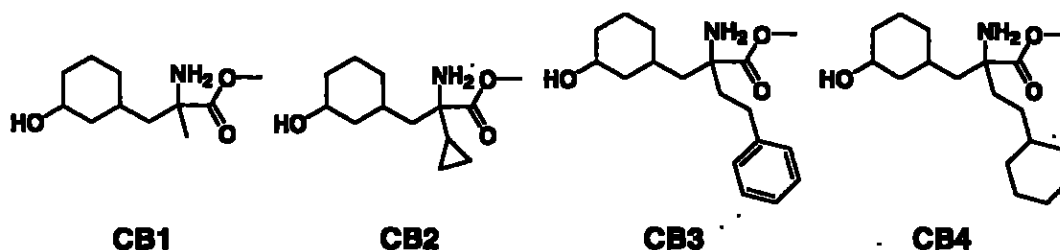
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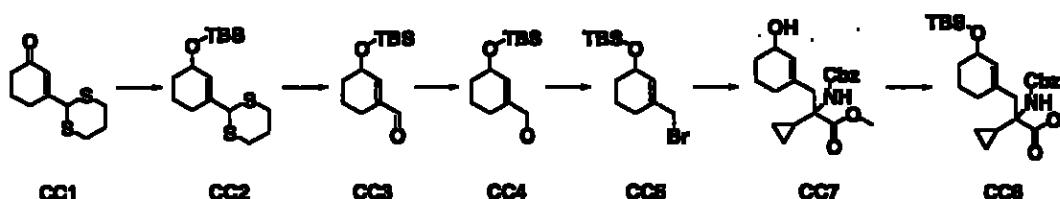
Compound **CA2** ($R^3 = R^4 = \text{Ph}$; $Z = m\text{-phenylene}$, $R^{15} = \text{H}$ and $R^{16} = \text{cyclopentyl}$) was obtained from **CA1** ($R^3 = R^4 = \text{Ph}$; $Z = m\text{-phenylene}$, $R^{15} = \text{H}$ and $R^{16} = \text{cyclopentyl}$) using a method similar to Method G.

Method CB

The following compounds were synthesized using methods similar to Method E and/or AX.



Method CC



15 Method CC, Step 1.

To a methanol solution (20 mL) of **CC1** (5 g) cooled to 0 °C was added sodium borohydride (1 eq) and the reaction was stirred for 30 min before the reaction mixture was evaporated to dryness then extracted with DCM/water. The DCM fractions were pooled, dried (MgSO_4), filtered and concentrated to dryness. The crude product was dissolved in 20 mL of anhydrous DCM. To this solution was added t-butyltrimethylchlorosilane (2 eq.) and imidazole (2 eq.). The reaction was stirred overnight at RT before it was quenched DCM and saturated NaHCO_3 . The organic

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phase was dried (MgSO_4), filtered and evaporated to dryness to give crude product CC2.

Method CC, Step 2.

5 A literature procedure was adapted (Aust. J. Chem. 1990, 43(7), 1195). Compound CC2 (50 g) in 80 mL THF was added to mercuric oxide (1.5 eq.) and borontrifluoride etherate (1.6 eq.) in 540 mL of THF/ H_2O (5:1) and the mixture was stirred under nitrogen for 2 h before the reaction was quenched with saturated NaHCO_3 (aq.) and ether. The ether phase was dried over anhyd. Na_2SO_4 , filtered through a silica pad
10 and concentrated to give crude CC3.

Method CC, Step 3.

To CC3 (10.4 grams) in 200 mL MeOH was added 1.1 eq. of sodium borohydride and the mixture was stirred for 30 min before the reaction mixture was concentrated and
15 the residue partitioned in DCM/ H_2O . The organic phase was dried over Na_2SO_4 , filtered and concentrated. The residue was chromatographed to give product CC4.

Method CC, Step 4.

Compound CC4 (2.5) in 5 mL anhydrous DCM was added Bis(1,2-
20 diphenylphosphino)ethane (DPPE; 1.2 eq.) followed by carbon tetrabromide (1.1 eq.) at 0 °C and the reaction was stirred for 30 min. The reaction was quenched with hexane and poured over a silica pad. The organic solution was evaporated to give product CC5 as an oil. $^1\text{H-NMR}$ (CDCl_3) δ 5.72, br s, 1H; 4.18, t, 1H; 3.83, q, 2H; 2.00-
2.10, m, 2H; 1.76-1.81, m, 2H; 1.43-1.58, m, 2H; 0.84, s, 9H; 0.03, s, 6H.
25

Method CC, Step 5.

Compound CC6 was generated from CC5 using a similar procedure in Method E. Crude compound CC6 was purified by flash chromatography (gradient 0-10% EtOAc in hexane). Two isomers were isolated during purification isomer A which eluted first
30 followed by isomer B.

ISOMER A: $^1\text{H-NMR}$ (CDCl_3) δ 7.26-7.37, m, 5H; 5.57, s, 1H; 5.38, s, 1H; 5.02, q, 2H; 4.08, br s, 1H; 3.67, s, 3H; 3.08, d, 1H; 2.58, d, 1H; 1.80-1.92, m, 1H; 1.60-1.75, m, 3H; 1.32-1.44, m, 3H; 0.83, s, 9H; 0.35-0.45, m, 4H; 0.01, s, 6H.

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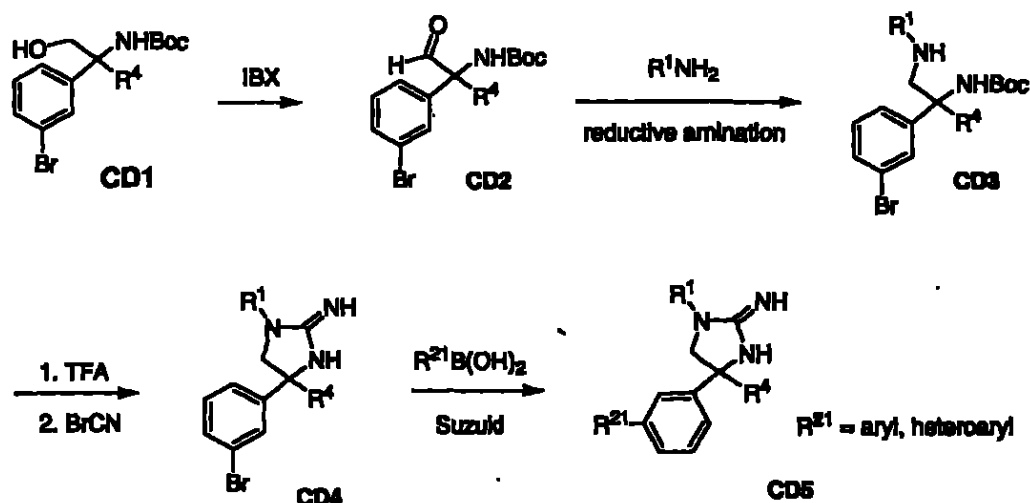
ISOMER B: $^1\text{H-NMR}$ (CDCl_3) δ 7.286-7.36, m, 5H; 5.56, s, 1H; 5.39, s, 1H; 5.06, q, 2H; 4.15, br s, 1H; 3.71, s, 3H; 3.06, d, 1H; 2.70, d, 1H; 1.60-1.90, m, 4H; 1.33-1.48, m, 3H; 0.87, s, 9H; 0.37-0.51, m, 4H; 0.03, s, 6H. Yield 26% isomer A and 22% isomer B.

5

Method CC, Step 6.

Compound CC7 was obtained from CC6 (Isomer B) through treatment with 1 N TBAF in THF for 30 min followed by extraction with ether/water. The organic phase was separated and washed four times with water. The aqueous phase was pooled and washed once with Et_2O (pH ~6 to 7). The organic phase was dried over Na_2SO_4 , filtered and evaporated to give product CC7 in 94% yield. $^1\text{H-NMR}$ (CDCl_3) δ 7.28-7.39, m, 5H; 5.58, br s, 1H; 5.49, br s, 1H; 5.10, d, 1H; 5.02, d, 1H; 4.09, br s, 1H; 3.72, s, 3H; 3.14, d, 1H; 2.70, s, 1H; 1.79-1.87, m, 2H; 1.67-1.79, m, 1H; 1.53-1.67, m, 2H; 1.44-1.53, m, 2H; 1.31-1.39, m, 1H; 0.35-0.54, m, 4H

15

Method CD**Step 1: *tert*-Butyl 2-(3-bromophenyl)-1-oxopropan-2-ylcarbamate**

- To a solution of *tert*-butyl 2-(3-bromophenyl)-1-hydroxypropan-2-ylcarbamate (CD1; $\text{R}^4 = \text{Me}$) (1.5 g, 4.6 mmol) in EtOAc (150 mL) at reflux was added IBX (3.82 g, 13.6 mmol, 3 eq). Reflux was continued for another 2 h and then the mixture was cooled to RT. The white precipitate was filtered and the filtrate was concentrated. The residue was purified by chromatography on silica gel by eluting with EtOAc/hexanes to give

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1.0 g (66%) of *tert*-butyl 2-(3-bromophenyl)-1-oxopropan-2-yl carbamate (CD2; R⁴ = Me) as a colorless oil. ¹H NMR (CDCl₃) δ 9.42 (s, 1H), 7.89 (m, 1H), 7.80 (m, 1H), 7.55-7.40 (m, 2H), 5.85 (bs, 1H), 1.96 (s, 3H), 1.56 (s, 9H).

5 **Step 2: *tert*-Butyl 2-(3-bromophenyl)-1-(methylamino)propan-2-ylcarbamate**

To a solution of *tert*-butyl 2-(3-bromophenyl)-1-oxopropan-2-ylcarbamate (CD2; R⁴ = Me) (1.0 g, 3 mmol) in dichloroethane (50 mL) was added methylamine (0.48 g, 6.1 mmol, 2 eq) in water (40%) and 1 mL of AcOH. The solution was allowed to stir at RT for 1 h followed by the addition of sodium triacetoxymethylborohydride (1.8 g, 8.5 mmol, 2.8 eq). The resulting mixture was stirred at RT for 16 h and quenched with MeOH. After stirring for 30 min the mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel by eluting with EtOAc/MeOH to give 0.62 g (60%) of *tert*-butyl 2-(3-bromophenyl)-1-(methylamino)propan-2-ylcarbamate (CD3; R¹ = Me, R⁴ = Me) as a colorless oil. ¹H NMR (CDCl₃) δ 7.47 (bs, 1H), 7.37 (m, 1H), 7.27 (m, 1H), 7.23 (m, 1H), 5.97 (bs, 1H), 3.18-2.82 (m, 2H), 2.45 (s, 3H), 1.74 (s, 3H), 1.40 (s, 9H). MS (ESI) *m/e* 342.9 (M+H)⁺.

Step 3: 4-(3-Bromophenyl)-1,4-dimethylimidazolidin-2-imine

tert-Butyl 2-(3-bromophenyl)-1-(methylamino)propan-2-ylcarbamate (CD3; R¹ = Me, R⁴ = Me) (0.62 g, 1.8 mmol) was dissolved in 25% TFA in DCM (25 mL) and the mixture was left stirring at RT for 1 h. The mixture was concentrated in vacuo and the residue was redissolved in CHCl₃ (20 mL). The solution was washed with 15% NaOH (10 mL) and the aqueous layer was extracted with CHCl₃ (3 x 10 mL). The combined organic layer was dried over MgSO₄ and concentrated in vacuo to give 0.33 g (76%) of crude 2-(3-bromophenyl)-N¹-methylpropan-1,2-diamine as a colorless oil. ¹H NMR (CDCl₃) δ 7.65 (t, J = 1.7 Hz, 1H), 7.41-7.34 (m, 2H), 7.21 (t, J = 7.8 Hz, 1H), 2.86 (dd, J = 11.7, 0.6 Hz, 1H), 2.64 (dd, J = 11.7, 0.6 Hz, 1H), 2.38 (s, 3H), 1.54 (bs, 3H), 1.43 (s, 9H). MS (ESI) *m/e* 242.9 (M+H)⁺. The compound was used in the next step without further purification.

30 To a solution of 2-(3-bromophenyl)-N¹-methylpropan-1,2-diamine (0.12 g, 0.50 mmol) in EtOH (10 mL) was added BrCN (0.073 g, 0.70 mmol, 1.4 eq). The mixture was stirred at RT for 16 h and then concentrated in vacuo. The residue was redissolved in CHCl₃ (20 mL) and the solution was washed with 15% NaOH (10 mL). The aqueous

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layer was extracted with CHCl_3 (3 x 10 mL) and the combined organic layer was dried (MgSO_4), and concentrated to give 0.14 g (100%) of 4-(3-bromophenyl)-1,4-dimethylimidazolidin-2-imine (CD4; $\text{R}^1 = \text{Me}$, $\text{R}^4 = \text{Me}$) as a colorless oil. ^1H NMR (CDCl_3) δ 7.42 (t, $J = 1.7$ Hz, 1H), 7.35 (dd, $J = 8.1, 1.7$ Hz, 2H), 7.15 (t, $J = 8.1$ Hz, 1H), 3.62 (d, $J = 9.3$ Hz, 1H), 3.53 (d, $J = 9.0$ Hz, 1H), 3.08 (s, 3H), 1.56 (bs, 3H). MS (ESI) m/e 268.1, 270.1 ($\text{M}+\text{H}$) $^+$.

Step 4: 4-(3-(3,4-Difluorophenyl)phenyl)-1,4-dimethylimidazolidin-2-imine

A mixture of 4-(3-bromophenyl)-4-methyloxazolidin-2-imine (0.027 g, 0.1 mmol, 1 eq), 3,4-difluorophenyl boronic acid (0.020 g, 0.13 mmol, 1.3 eq), FibreCat (20 mg), anhydrous ethanol (2 mL), and a 1N K_2CO_3 aqueous solution (0.12 mL, 0.12 mmol, 1.2 eq) was heated in a microwave reactor (Emrys Optimizer) at 110 °C for 15 min. The mixture was transferred to a prepacked column of Si-carbonate (2 g, 0.79 mmol/g), which had been conditioned with MeOH/DCM (1:1). The column was eluted with 1:1 MeOH/DCM (3 x 3 mL) and the eluants were collected and concentrated to give 0.019 g (63%) of 4-(3-(3,4-difluorophenyl)phenyl)-1,4-dimethylimidazolidin-2-imine (CD5; $\text{R}^1 = \text{Me}$, $\text{R}^4 = \text{Me}$, $\text{R}^{21} = 3,4\text{-difluorophenyl}$) as a white solid. ^1H NMR (CDCl_3) δ 7.60 (s, 1H), 7.50-7.20 (m, 6H), 3.48 (m, 2H), 2.79 (s, 3H), 1.66 (s, 3H). MS(ESI) m/e 302.2 ($\text{M}+\text{H}$) $^+$, HPLC (A) $R_t = 5.48$ min.

Alternative for Method CD for compound : $\text{R}^1 = \text{OR}^{18}$

Alternative Method CD, Step 2: *tert*-Butyl 2-(3-bromophenyl)-1-(methoxyamino)propan-2-ylcarbamate

To a solution of *tert*-butyl 2-(3-bromophenyl)-1-oxopropan-2-ylcarbamate (CD2; $\text{R}^4 = \text{Me}$) (2.7 g, 8.2 mmol) in dichloroethane (40 mL) was added methoxyamine hydrochloride (0.89 g, 10.7 mmol, 1.3 eq) and 1 mL of AcOH. The solution was allowed to stir at RT for 16 h. The reaction mixture was concentrated to give the oxime intermediate. The oxime was dissolved in EtOH (20 mL) and borane-pyridine complex (0.74 g, 7.9 mmol) was added dropwise. After stirring at r.t for 20 min, the reaction mixture was concentrated in vacuo. The residue was redissolved in DCM (50 mL) and washed with water (3x20 mL). The organic layer was dried (Na_2SO_4) and concentrated to give 1.6 g (54%) of *tert*-butyl 2-(3-bromophenyl)-1-(methoxyamino)propan-2-ylcarbamate (CD3; $\text{R}^1 = \text{OMe}$, $\text{R}^4 = \text{Me}$). ^1H NMR (CDCl_3) δ

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7.60-7.10 (m, 4H), 5.82 (s, 1H), 3.90 (s, 3H), 3.70 (m, 2H), 1.80 (s, 3H), 1.40 (s, 9H).
The crude compound was used in the next step without further purification.

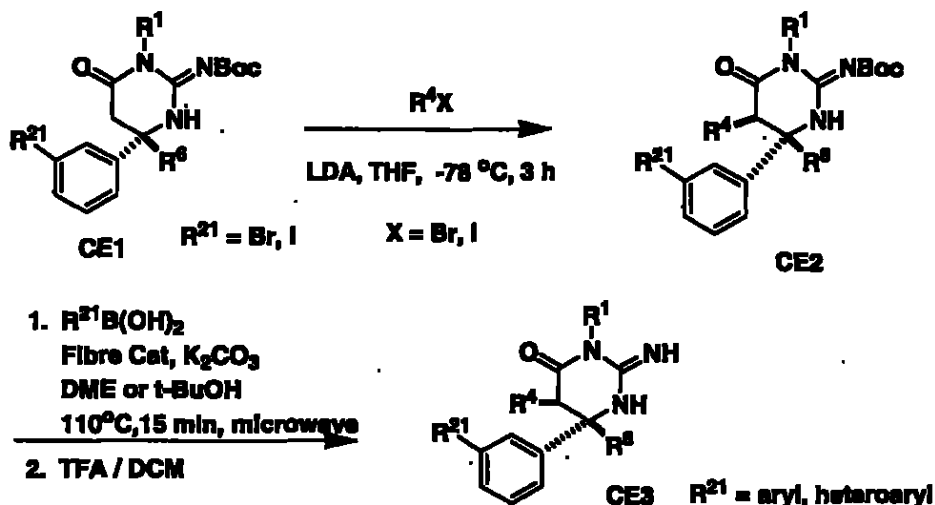
Alternative Method CD, Step 3: 4-(3-Bromophenyl)-1-methoxy-4-methylimidazolidin-2-imine

5 *tert*-Butyl 2-(3-bromophenyl)-1-(methoxyamino)propan-2-yl carbamate (CD3; R¹ = OMe, R⁴ = Me) (1.6 g, 4.4 mmol) was dissolved in 25% TFA in DCM (25 mL) and the mixture was left stirring at RT for 1 h. The mixture was concentrated in vacuo. The residue was redissolved in CHCl₃ (20 mL) and washed with 15% NaOH (10 mL). The
10 aqueous layer was extracted with CHCl₃ (3 x 10 mL). The combined organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was dissolved in EtOH (10 mL) and BrCN (0.096 g, 0.91 mmol) was added. After stirring at RT for 16 h, the mixture was concentrated in vacuo. The residue was redissolved in CHCl₃ (20 mL) and washed with 15% NaOH (10 mL). The aqueous layer was extracted with CHCl₃ (3
15 x 10 mL). The combined organic layer was dried over MgSO₄ and concentrated to give 0.2 g (16%) of 4-(3-bromophenyl)-1-methoxy-4-methylimidazolidin-2-imine (CD4; R¹ = OMe, R⁴ = Me) as a colorless oil. ¹H NMR (CDCl₃) δ 7.65-7.35 (m, 4H), 4.02 (s, 3H), 3.98 (d, 1H), 3.91 (d, 1H), 1.94 (s, 3H).

Alternative Method CD, Step 4: 4-(3-(3-Chlorophenyl)phenyl)-1-methoxy-4-methylimidazolidin-2-imine

A mixture of 4-(3-bromophenyl)-4-methyloxazolidin-2-imine (CD4; R¹ = OMe, R⁴ = Me) (0.027 g, 0.1 mmol, 1 eq), 3-chloro phenylboronic acid (0.023 g, 0.13 mmol, 1.3 eq), FibreCat (0.020 g), anhydrous ethanol (2 mL), and 1N K₂CO₃ aqueous solution (0.12
25 mL, 0.12 mmol, 1.2 eq) was heated in a microwave reactor (Emrys Optimizer) at 110 °C for 15 min. The mixture was transferred to a prepacked column of Si-carbonate (2 g, 0.79 mmol/g), which had been conditioned with MeOH/DCM (1:1). The column was eluted with 1:1 MeOH/DCM (3x3 mL) and the eluants were collected and concentrated to give 0.008 g (25%) of 4-(3-(3-chlorophenyl)phenyl)-1-methoxy-4-
30 methylimidazolidin-2-imine (CD5; R¹ = OMe, R⁴ = Me, R²¹ = 3-ClC₆H₄) as a white solid. ¹H NMR (CDCl₃) δ 7.75-7.60 (m, 5H), 7.58-7.42 (m, 3H), 4.00 (m, 2H), 3.97 (s, 3H), 1.97 (s, 3H). MS(ESI) *m/e* 316.0, 318.0 (M+H)⁺, HPLC (A) R_t = 5.64 min.

Method CE



5 Method CE, Step 1

The synthesis of CE2 ($R^1 = R^4 = \text{Me}$, $R^{21} = \text{Br}$ and $R^6 = \text{Me}$) was adapted from the procedure of Spanu, P. *et. al.*, Tet. Lett., 2003, 44, 671-675. Thus, to a solution of (S)-tert-butyl 4-(3-bromophenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (CE1; $R^1 = R^6 = \text{Me}$, $R^{21} = \text{Br}$) (0.24 g, 0.6 mmol, 1 eq) in THF (4 mL), LDA (2M in heptane/THF, 0.6 mL, 0.12 mmol, 2 eq) was added dropwise via a syringe at -78 °C. After stirring at -78 °C for 30 min, a solution of Iodomethane (0.080 mL, 0.12 mmol, 2 eq) in THF (4 mL) was added dropwise to form an orange-colored enolate solution. The mixture was stirred at -78 °C for 3 h. Water was added to quench the reaction and the suspension was warmed to RT. The mixture was then partitioned between H_2O and Et_2O . The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 25 mL).

The combined organic layers were washed with brine, dried (MgSO_4) and concentrated to give 0.38 g of a brown oil. Chromatography on silica gel using 50% EtOAc/hexanes as eluent gave 0.14 g (54%) of tert-butyl (4S,5R)-4-(3-bromophenyl)-1,4,5-trimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (CE2; $R^1 = R^4 = \text{Me}$, $R^{21} = \text{Br}$ and $R^6 = \text{Me}$) as a white solid. ^1H NMR (CDCl_3 , 300 MHz): δ 10.16 (s, 1H), 7.46 (m, 2H), 7.26 (m, 2H), 3.21 (s, 1H), 3.01 (m, 3H), 3.02 (m, 1H), 1.51 (s, 12H), 1.17 (d, $J = 7.1$ Hz, 3H). MS(ESI): $\text{MH}^+ = 441.7$ HPLC (A) $R_t = 7.20$ min.

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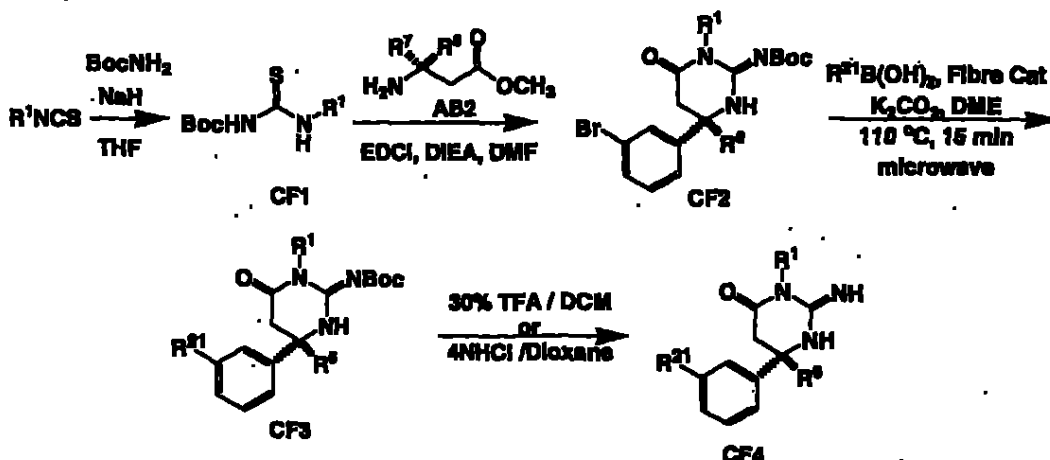
Method CE, Step 2

- A mixture of (S)-tert-butyl 4-(3-bromophenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidene carbamate (CE2; $R^1 = R^4 = \text{Me}$, $R^6 = \text{Me}$, $R^{21} = \text{Br}$) (0.25 g, 0.6 mmol), 5-cyanothien-1-ylboronic acid (0.2 g, 1.3 mmol, 2 eq), Fibrecat (4.26% Pd, 0.7g), and 1N aq. K_2CO_3 (0.5 mL) was heated at 110 °C in a 20 mL Smith process vial using the Emrys microwave synthesizer. After cooling, the reaction mixture was transferred to a pre-packed column of Si-Carbonate column and eluted with MeOH/ CH_2Cl_2 (1:1). The eluent was concentrated to give 0.32 g of a yellow oil, which was purified by silica gel chromatography (20-50% EtOAc/hexanes to give 0.13 g (0.3 mmol, 48% yield, syn:anti ratio: 5:1) of (S)-tert-butyl 4-(3-(5-cyanothien-1-yl)phenyl)-1,4-dimethyl-6-oxotetrahydro-pyrimidin-2(1H)-ylidenecarbamate as a white solid. ^1H NMR (CDCl_3 , 300 MHz): δ 10.15 (s, 1H), 7.58-7.53 (m, 3H), 7.53-7.38 (m, 2H), 7.23 (m, 1H), 3.32 (s, 3H), 3.16(m, 1H), 1.57 (s, 9H), 1.23 (d, $J = 6.9$ Hz, 3H). MS (ESI): $\text{MH}^+ = 438.7$; $\text{M}+56 = 383.1$. HPLC $R_t = 7.28$ min (syn isomer).
- (S)-tert-Butyl 4-(3-(5-cyanothien-1-yl)phenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (23 mg, 0.05 mmol) was treated with 1 mL of 30%TFA/ CH_2Cl_2 at RT for 30 min. The volatiles were removed in vacuo and the residue was re-dissolved in acetonitrile (5 mL) and evaporated again to afford 17 mg of crude iminopyrimidinone as a yellow solid. The crude product was purified by reverse phase HPLC (B) to provide 10 mg (60%) of (S)-6-(3-(5-cyanothien-1-yl)phenyl)-6-ethyl-2-imino-3-methyl-tetrahydropyrimidin-4(1H)-one (CE3; $R^1 = R^4 = \text{Me}$, $R^6 = \text{Me}$, $R^{21} = 5\text{-cyanothien-1-yl}$) as a white solid. ^1H NMR (CDCl_3 , 300 MHz): δ 11.1 (br s, 1H), 10.0 (s, 1H), 7.58-7.53 (m, 3H), 7.44 (m, 1H), 7.40-7.28 (m, 2H), 3.30 (m, 1H), 3.16(s, 3H), 1.60 (s, 3H), 1.27 (d, $J = 7.2$ Hz, 3H). MS (ESI): $\text{MH}^+ = 438.7$; $\text{M}+56 = 339.1$. HPLC $R_t = 7.24$ min (syn isomer).

Method CF

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**Method CF, Step 1.**

To a solution of *t*-butylcarbamate (0.5 g, 4.3 mmol, 1 eq) in anhydrous THF (5.0 mL) at RT was added NaH (0.17 g, 4.3 mmol, 1 eq). The mixture was stirred at RT for 15 min. Then a solution of methyl isocyanate (0.3 g, 4.2 mmol, 1 eq.) in anhydrous THF (5.0 mL) was added dropwise. The reaction mixture was allowed to stir at 25°C for 15 min. The mixture was then poured into 30 mL of ice-water under vigorous stirring. The reaction solution was extracted with Et_2O (2 x 25 mL). The organic layers were combined and washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo to give 0.42 g (50% yield) of *tert*-butyl methylcarbamothioylcarbamate CF1 ($R^1 = \text{Me}$) as a white solid. ^1H NMR (CDCl_3 , 300 MHz): δ 8.3 (br s, 1H), 3.19 (d, 3H, $J = 4.8$ Hz), 1.8 (br s, 1H), 1.5 (s, 9H).

Method CF, Step 2.

To a solution of an HCl salt of AB2 ($R^6 = 3\text{-bromophenyl}$ and $R^7 = \text{Me}$) (0.2 g, 0.7 mmol) and CF1 ($R^1 = \text{Me}$) in DMF (2 mL) at RT was added DIEA (0.5 mL, 2.8 mmol, 4 eq) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide HCl (EDCI, 0.2g, 1.0 mmol, 1.4 eq). After stirring at RT for 16 h, the mixture was diluted with EtOAc (10 mL), washed with brine, dried (MgSO_4), and filtered. The filtrate was evaporated under reduced pressure to afford 0.34 g of crude product as a yellow oil which was purified using silica gel chromatography by eluting with 20% EtOAc/hexanes to give 0.17 g (0.4 mmol, 60%) of (*S*)-*tert*-butyl 4-(3-bromophenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (CF2; $R^1=R^6=\text{Me}$) as a white solid. ^1H NMR (CDCl_3 , 300 MHz): δ 10.63 (s, 1H), 7.42 (m, 2H), 7.24 (m, 2H), 3.21 (s, 3H),

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3.2 (d, 1H, J = 16.3 Hz), 2.87 (d, 1H, J = 16.1 Hz), 1.65 (s, 3H), 1.55 (s, 9H). MS(ESI): MH⁺ = 395.7, 398.7. HPLC R_t = 7.11 min.

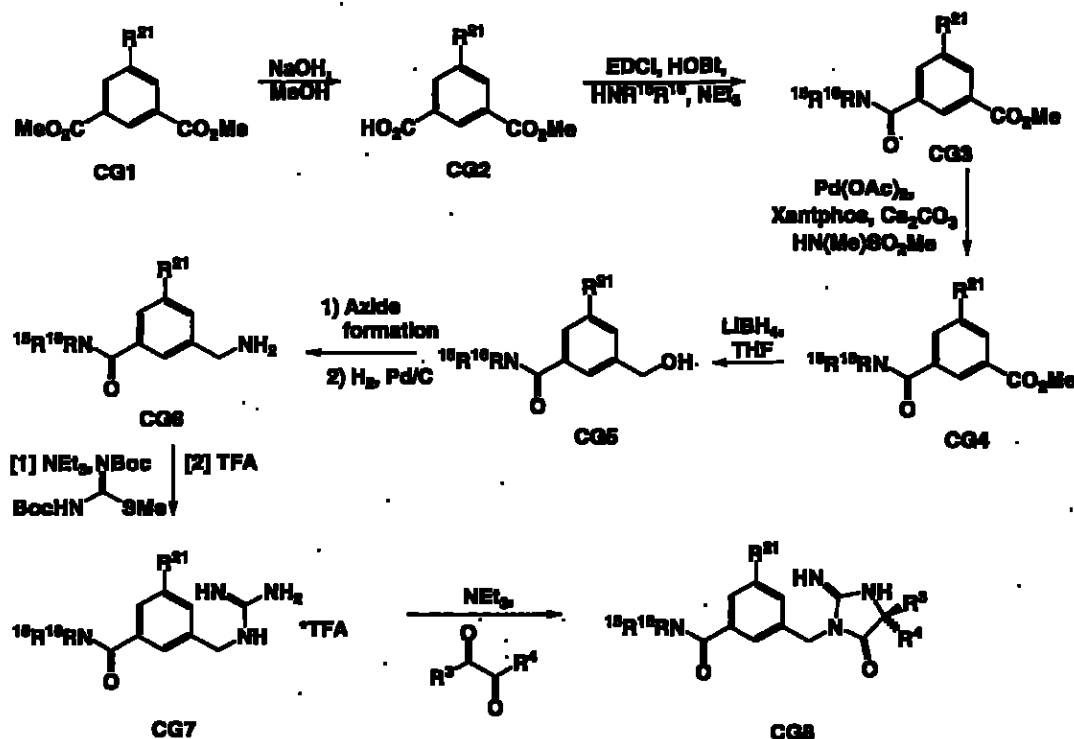
Method CF, Step 3.

- 5 A mixture of (S)-tert-butyl 4-(3-bromophenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (CF2; R¹=R⁸=Me) (0.25 g, 0.6 mmol), 5-chloro-2-hydroxyphenylboronic acid (R²¹ = 5-chloro-2-hydroxyphenyl; 0.2 g, 1.2 mmol, 2 eq), Fibrecat (4.26% of Pd, 0.7 g) and 1N aq. K₂CO₃ (0.5 mL) in dimethoxyethane (DME, 10 mL) or tert-butanol (10 mL) in a 20 mL Smith process vial equipped with stir bar
- 10 was sealed and heated in an Emrys optimizer at 110 °C for 15 min. After cooling, the reaction mixture was transferred to a pre-packed Si-Carbonate column and eluted with MeOH/CH₂Cl₂ (1:1). The eluant was collected and concentrated under reduced pressure to give 0.32g of the crude product as an oil. The crude product was purified by silica gel chromatography (20-50% EtOAc/hexanes gradient) to yield 0.13 g (0.3
- 15 mmol, 48%) of (S)-tert-butyl 4-(3-(3-chloro-6-hydroxyphenyl)-phenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (CF3; R¹ = R⁸ = Me, R²¹ = 3-chloro-6-hydroxyphenyl) as a white solid. ¹HNMR (CDCl₃, 300 MHz): δ 7.48-4.32 (m, 2H), 7.20 (m, 3H), 6.84 (m, 2H), 5.68 (br s, 1H), 3.28 (d, J= 15.7 Hz, 1H), 3.21 (s, 3H), 2.96(d, J = 15.3 Hz, 1H), 1.68 (s, 3H), 1.53 (s, 9H). MS (ESI): MH⁺ = 443.7, 445.7; M⁺-
- 20 56 = 388.0. HPLC R_t (A) = 6.99 min.

Method CF, Step 4.

- (S)-tert-butyl 4-(3-(3-chloro-6-hydroxyphenyl)phenyl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate (CF3; R¹ = R⁸ = Me, R²¹ = 3-chloro-6-hydroxyphenyl) (23 mg, 0.05 mmol) was treated with 1 mL of 30%TFA/CH₂Cl₂ at RT
- 25 for 30 min. The volatiles were removed in vacuo. The residue was redissolved in acetonitrile (5 mL) and evaporated again to afford 17 mg of the crude product as a yellow solid. The crude product was purified via reverse phase HPLC to provide 10 mg (60%) of (S)-6-(3-(3-chloro-6-hydroxy-phenyl)phenyl)-6-ethyl-2-imino-3-methyl-tetrahydropyrimidin-4(1H)-one (CF4; R¹ = R⁸ = Me, R²¹ = 3-chloro-6-hydroxyphenyl)
- 0 as a white solid. ¹HNMR (CDCl₃, 300 MHz): δ 11.4 (br s, 1H), 7.6-4.25 (m, 3H), 7.24-6.84 (m, 3H), 3.68 (br s, 1H), 5.18 (br s, 1H), 3.39 (d, J= 16.1 Hz, 1H), 3.20 (s, 3H), 2.95(d, J = 15.8 Hz, 1H), 1.74 (s, 3H). MS(ESI): MH⁺ = 344.1. HPLC (A) R_t = 5.07 min.

Method CG



Method CG, Step 1;

- 5 A solution of **CG1** ($R^{21} = Br$, 12.29 g, 45 mmol) and $NaOH$ (1.93 g, 49 mmol) in $MeOH$ (70 mL) and water (10 mL) was refluxed for 3 h. After removal of $MeOH$ under vacuum, the aqueous residue was adjusted to pH 3 and the resulting solid filtered off, dried under vacuum to give **CG2** ($R^{21} = Br$, 11.41 g, 98%). ^1H NMR (400 MHz, CD_3OD) δ 8.49 (m, 1 H), 8.27 (m, 1 H), 3.90 (s, 3 H).

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Method CG, Step 2;

- A mixture of **CG2** ($R^{21} = Br$, 11.41 g, 44 mmol), $EDCI$ (8.6 g, 45 mmol), diisopropylamine (6.2 mL, 44.8 mmol), $HOBt$ (6.0 g, 44.4 mmol) and NEt_3 (10 mL, 72 mmol) in CH_2Cl_2 (100 mL) was stirred at RT for 48 h. The reaction was washed with sat. $NaHCO_3$,
 15 water (1x), NH_4Cl (1x), water (1x), brine (1x), dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting material was subjected to silica gel chromatography (0% $\rightarrow$ 40% $EtOAc$ /hexanes) to give **CG3** ($R^{21} = Br$, $R^{15} = R^{16} = Pr$, 3.62 g, 24%).

Method CG, Step 3;

A mixture of CG3 ($R^{21} = \text{Br}$, $R^{15} = R^{16} = \text{Pr}$, 3.6 g, 10.5 mmol), $\text{HN}(\text{Me})\text{SO}_2\text{Me}$ (1.4 mL, 16.3 mmol), $\text{Pd}(\text{OAc})_2$ (355 mg, 1.58 mmol), Xantphos (1.41 g, 2.44 mmol), Cs_2CO_3 (5.17 g, 15.8 mmol) in toluene (40 mL) was degassed under a stream of N_2 for 10 min, then heated at 95 °C for 18 h. The reaction was cooled to RT, filtered through celite, and the filtrate partitioned between EtOAc and water. The organic layer was washed with water (1x), brine (1x), dried over MgSO_4 , filtered, and evaporated under vacuum. The resulting residue was subjected twice to silica gel chromatography (0% → 3% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to give CG4 ($R^{21} = \text{N}(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 2.65 g, 68%).

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Method CG, Step 4;

LiBH_4 (2 M THF, 8 mL, 16 mmol) was added to a solution of CG4 ($R^{21} = \text{N}(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 2.65 g, 7.15 mmol) in THF (40 mL) at 0° C. After 18 h at RT, the reaction was quenched with 1 M HCl and extracted with EtOAc. The organic layer was washed with brine (1x), dried over MgSO_4 , filtered, and evaporated under vacuum. The resulting residue was subjected to silica gel chromatography (0% → 5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to give CG5 ($R^{21} = \text{N}(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 1.77 g, 72%).

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Method CG, Step 5;

A mixture of CG5 ($R^{21} = \text{N}(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 1.77 g, 5.17 mmol), sodium azide (404 mg, 6.21 mmol), and PPh_3 (2.85 g, 10.87 mmol) in CCl_4 (5 mL) and DMF (20 mL) was stirred at 90° C for 5 h, then at RT for 18 h. The reaction was stirred with water (10 mL) for 10 min, then diluted with Et_2O . The organic layer was triturated with water, filtered, dried over MgSO_4 , and evaporated under vacuum. The resulting material was directly used in the next step (azide reduction).

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Method CG, Step 6;

The product from method CG, step 5 was dissolved in EtOH (5 mL) and stirred in the presence of 10% Pd/carbon under an atmosphere of hydrogen (50 psi) for 18 h at RT. The reaction mixture was passed through a PTFE-filter, and the filtrate evaporated under reduced pressure. The resulting material was subjected to preparative thin layer chromatography (5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to give CG6 ($R^{21} = \text{N}(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 130 mg, 7.5% from CG5).

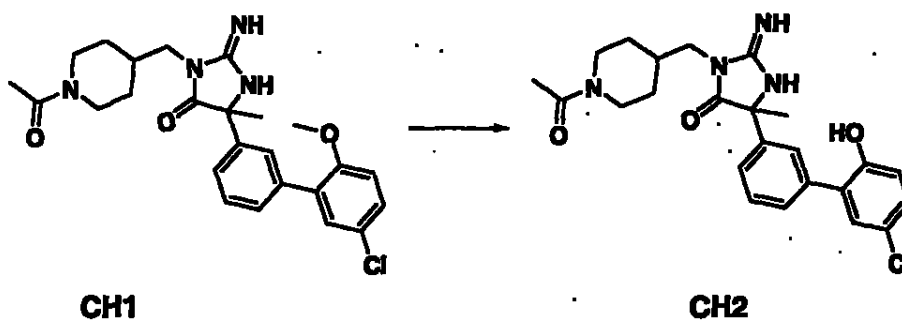
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Method CG, Step 7;

A mixture of CG6 ($R^{21} = N(Me)SO_2Me$, $R^{15} = R^{16} = Pr$, 130 mg, 0.38 mmol), 1,3-di(tert-butoxycarbonyl)-2-methylisothiourea (110 mg, 0.38 mmol), NEt_3 (55 μL , 0.38 mmol) in DMF (1.5 mL) was stirred at RT for 48 h. After removal of the volatiles in vacuo, the resulting material was subjected to preparative thin layer chromatography (5% MeOH/ CH_2Cl_2 as eluent). The resulting Intermediate (140 mg, 0.24 mmol) was treated with 50% TFA/ CH_2Cl_2 at RT for 3 h, followed by removal of all volatiles under vacuum to give CG7 ($R^{21} = N(Me)SO_2Me$, $R^{15} = R^{16} = Pr$, 140 mg, 74% from CG6).

Method CG, Step 8;

A mixture of CG7 ($R^{21} = N(Me)SO_2Me$, $R^{15} = R^{16} = Pr$, 120 mg, 0.24 mmol), benzil (50 mg, 0.24 mmol) and NEt_3 (134 μL , 0.96 mmol) in EtOH (5 mL) was heated at 100 °C for 18 h. After evaporating all volatiles, the residue was partitioned between water and CH_2Cl_2 . The organic layer was washed with brine (1x), dried over $MgSO_4$, filtered and evaporated. The resulting material was subjected to preparative thin layer chromatography (10% MeOH/ CH_2Cl_2 as eluent) to give CG8 ($R^{21} = N(Me)SO_2Me$, $R^{15} = R^{16} = Pr$, $R^3 = R^4 = Ph$, 69 mg, 50%) as the formate salt. ^1H NMR (400 MHz, $CDCl_3$) δ 7.10-7.40 (m, 13 H), 4.72 (m, 2 H), 3.34 (m, 2 H), 3.08 (s, 3 H), 3.00 (m, 2H), 2.60 (s, 3 H), 1.59 (m, 2H), 1.39 (m, 2 H), 0.92 (m, 3 H), 0.84 (m, 3 H); LCMS: 576.3 (M+H).

Method CH

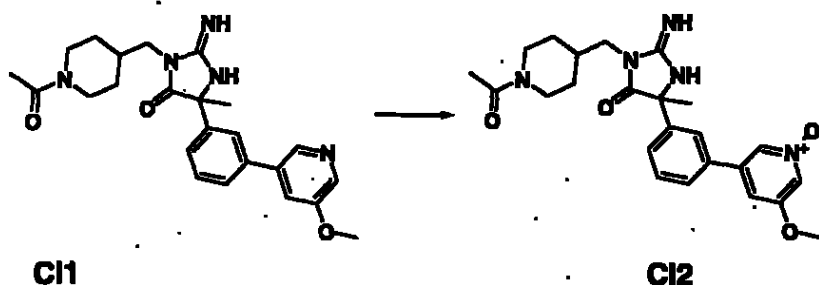
A solution of 0.35 mL of 1 M BBr_3 in DCM (0.35 mmole) was added dropwise to a solution of CH1 (52 mg, 0.11 mole) in 1.5 mL anhydrous DCM in ice bath. The

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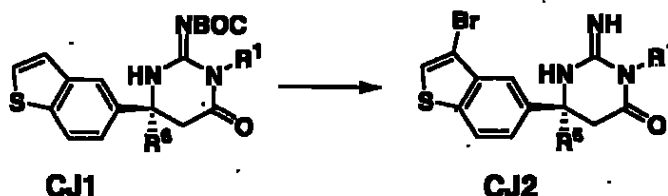
reaction solution was stirred in ice bath for 10 min. and 2 hrs at RT. The reaction was quenched with 5 mL MeOH in ice bath. After concentration the crude was purified on C18 reverse phase column to give CH2 (37.3 mg, 67.% yield) as a formate.

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Method CI

A solution of CI1 (20 mg as a formate; 0.042 mmole) in 4mL of DCM was treated with mCPBA (0.42 mmole) at RT for 2 hrs. The crude mixture was purified on C18 reverse phase column to give compound CI2.

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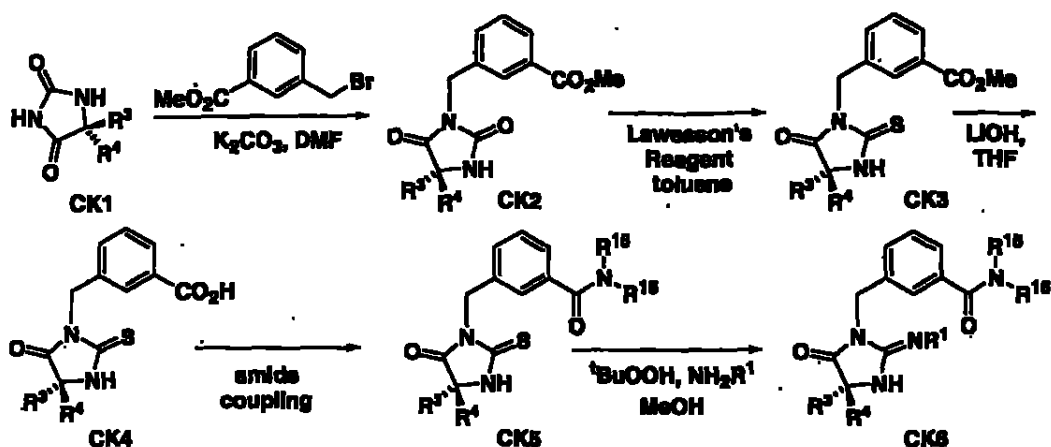
Method CJ

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To a solution of CJ1 ($R^1 = R^8 = \text{Me}$; 324 mg, 0.87 mmole) in 2.5 mL CHCl_3 and 2.5 mL HOAc in ice bath was added NBS (312mg, 1.75 mmole) and the reaction mixture was stirred at RT. Upon reaction completion, the crude mixture was diluted with DCM, and washed with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$, aqueous NaHCO_3 and brine. The crude was purified on flash column to give a product which was treated with 50% TFA in DCM to give CJ2 ($R^1 = R^8 = \text{Me}$ 220mg, 56.% yield) after evaporation.

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Method CK

**Method CK, Step 1;**

Similar to a literature procedure (Moloney et al., *J. Med. Chem.* 1997, 2347-

2362), methyl bromomethylbenzoate (7.00 g, 30.5 mmol) was added to a

- 5 suspension of CK1 ($\text{R}^3 = \text{R}^4 = \text{Ph}$, 7.00 g, 27.8 mmol) and K_2CO_3 (3.85 g, 27.8 mmol) in DMF (50 mL) at RT. After 18 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with NaHCO_3 (1x), water (3x), dried over MgSO_4 , filtered and concentrated under vacuum to give compound CK2 (12.7 g, 100%)

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Method CK, Step 2;

Compound CK3 was obtained from CK2 using method BK, step 3.

Method CK, Step 3;

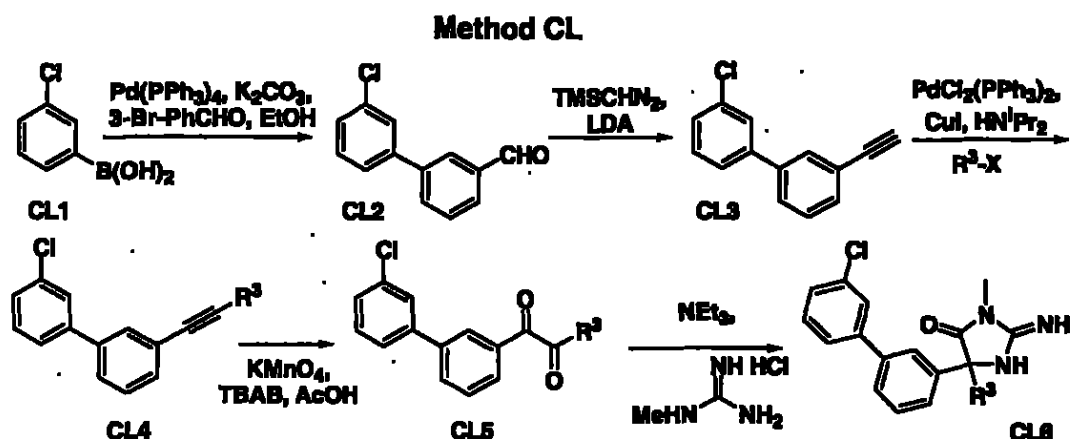
- 15 CK3 (1.18 g, 2.83 mmol) in THF (15 mL) and 2 N LiOH (4 mL, 8 mmol) was stirred overnight at RT. The mixture was quenched with 6 N HCl (2 mL, 12 mmol) and then partitioned between water and EtOAc. The dried EtOAc layer was concentrated *in vacuo* and the residue subjected to reverse-phase HPLC (gradient from 10%→95% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ with 0.1 % HCO_2H , 30 mL/min flow rate
- 20 on a preparative C18 reverse-phase column) to afford CK4.

Method CK, Step 4;

Compounds CK5 were obtained from CK4 using method G, step 2.

- 5 **Method CK, Step 5;**

Compounds CK6 were obtained from CK5 using method A, step 3.



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Method CL, Step 1;

CL2 was obtained from CL1 (3-chlorophenyl boronic acid) following method AW.

Method CL, Step 2;

Trimethylsilyldiazomethane (2 M hexanes, 2.5 mL, 5.0 mmol) was added to a solution of LDA (freshly prepared from DIPA and ⁿBuLi) in THF at -78° C. After 30 min at -78° C, a solution of aldehyde CL2 (900 mg, 4.13 mmol) in THF (5 mL) was added and the reaction slowly warmed to RT over 3 h. The reaction was quenched with water, then extracted with Et₂O (2x 100 mL). The combined organic layers were washed with brine (1x), dried over MgSO₄, filtered, and evaporated under vacuum. The resulting material was subjected to silica gel chromatography (100% hexanes) to give CL3 (752 mg, 86%). ¹H NMR (400 MHz, CDCl₃) δ 7.21-7.65 (m, 8 H), 3.08 (s, 1 H).

Method CL, Step 3;

A mixture of CL3 (202 mg, 0.95 mmol), aryl bromide (Ar = 3,5-pyrimidinyl, 181 mg, 1.14 mmol), Pd(dba)₂ (27 mg, 47.5 μmol), PPh₃ (25 mg, 95 μmol), CuI (18 mg, 95 μmol) and DIPA (400 μL, 285 μmol) in DMF (2 mL) was degassed for 10 min under a stream of N₂, then heated at 100° C for 30 min in a Smith Synthesizer microwave. The reaction was cooled to RT, filtered and diluted with EtOAc. The organic layer was washed with water (1x), brine (1x), dried over MgSO₄, filtered, and evaporated under vacuum. The resulting material was

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subjected to silica gel chromatography (0 → 20% EtOAc/hexanes) to give **CL4** (R^3 = 3,5-pyrimidinyl, 220 mg, 80%).

Method CL, Step 4;

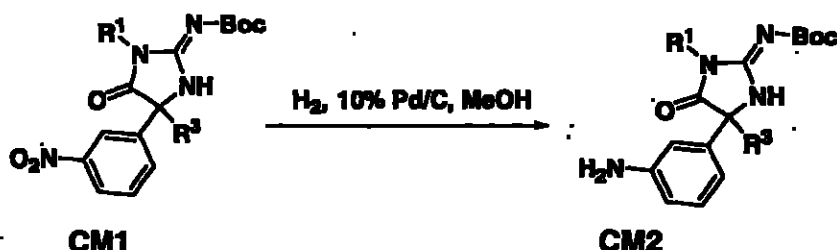
- 5 A mixture of **CL4** (R^3 = 3,5-pyrimidinyl, 210 mg, 0.72 mmol), KMnO_4 (297 mg, 1.88 mmol), tetrabutylammonium bromide (TBAB, 55 mg, 0.17 mmol) in AcOH (263 μL) and CH_2Cl_2 (5 mL) was stirred for 3 h at RT. The reaction mixture was filtered through a plug of silica gel, eluting with MeOH, and the filtrate was concentrated under vacuum. The residue was subjected to preparative thin layer chromatography (5%
10 MeOH/DCM) to give **CL5** (R^3 = 3,5-pyrimidinyl, 154 mg, 66%).

Method CL, Step 5;

Diketone **CL5** was converted into **CL6** as described in Method CG, step 8. LCMS (**CL6**, R^3 = 3,5-pyrimidinyl): 378.2 (M+H).

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Method CM



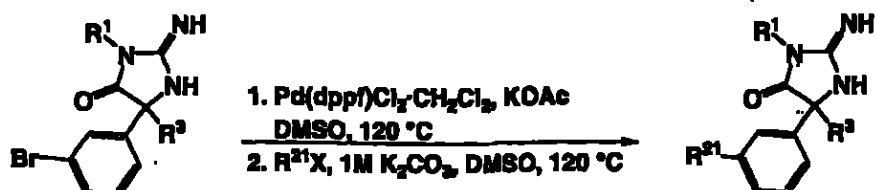
Method CM, Step 1

- 10 To a round bottom flask were added **CM1** (R^1 = Me, R^3 = Ph; 500 mg, 1.22 mmol), methanol (20 mL) and 10% Pd/C (200 mg). The mixture was hydrogenated by a hydrogen balloon for 3 hour 40 min at stirring. After filtration, the concentrated residue was purified by Analogix flash column chromatography
5 (EtOAc/Hexane=0%-50%) to produce **CM2** (R^1 = Me, R^3 = Ph; 443 mg, 92%) as white solid. Observed MW (M+H) 381.2. (400 MHz, CD_3OD): δ = 9.13 (s, br, 1H), 7.36-7.28 (m, 5H), 7.09 (m, 1H), 6.68-6.57 (m, 3H), 3.13 (s, 3H), 1.49 (s, 9H).

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Method CN

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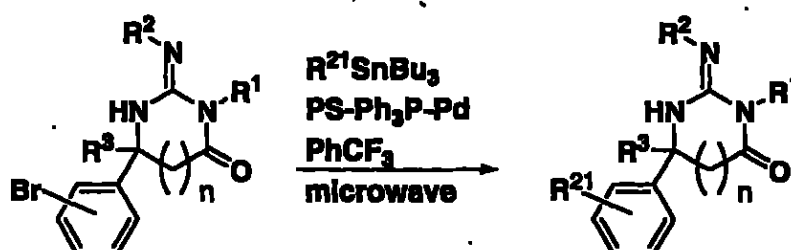
CN1

CN2

To an Ace pressure tube were added CN1 (R^3 =phenyl; R^1 =Me; 100 mg, 0.290 mmol), bis(pinacolato)diboron (81.0 mg, 0.319 mmol), KOAc (85.0 mg, 0.87 mmol), $\text{PdCl}_2(\text{dppf})_2 \cdot \text{CH}_2\text{Cl}_2$ (24 mg, 0.029 mmol) and anhydrous DMSO (1.0 mL). The reaction was then heated to 120 °C (oil bath temperature) at stirring for 2 hour 15 min. After cooling down to RT, the reaction were added 3,5-dibromo pyridine (206 mg, 0.87 mmol), anhydrous DMSO (1.0 mL) and 1M aq. K_2CO_3 (1.45 mL, 1.45 mmol). The reaction was then heated to 120 °C at stirring for 45 min. After cooling down to RT, the reaction was poured to cold water. The aqueous layer was extracted by DCM (3x50 mL) and the combined organic layer was dried over Na_2SO_4 . The concentrated residue was purified first by preparative TLC (7M $\text{NH}_3/\text{MeOH}:\text{DCM}=1:10$) and then preparative HPLC (reverse phase, C-18 column, 0.1% $\text{HCOOH}/\text{CH}_3\text{CN} : 0.1\% \text{HCOOH}/\text{H}_2\text{O} = 10\% - 100\%$) to afford the desired product CN2 (formic acid salt; R^3 =phenyl; R^1 =Me; R^{21} =3'-(5-bromopyridyl); 53.5 mg, 40%) as a white solid. Observed MW ($M+H$) 421.1. (400 MHz, CD_3OD): δ = 8.83-8.50 (m, br. 2H), 8.21 (s, 1H), 7.65 (m, 2H), 7.50 (m, 2H), 7.37 (m, 5H), 3.22 (s, 3H).

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Method CO



CO1

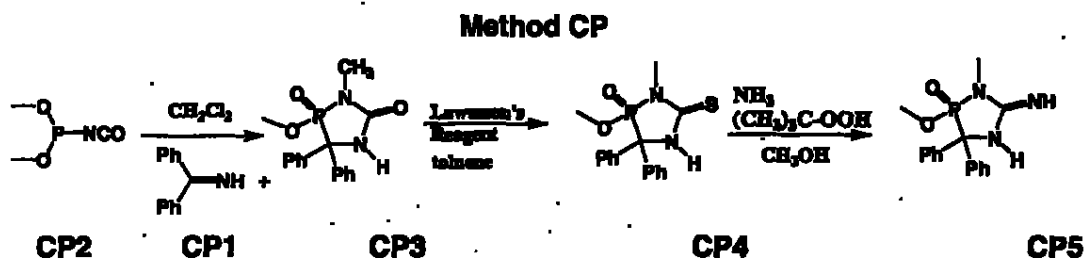
CO2

A microwave tube was charged with CO1 (R^1 = Me, R^2 = H; R^3 = cyclopropyl, n = 0) (30 mg, 0.097 mmol), $\text{PS-Ph}_3\text{P-Pd}$ (49 mg, 0.12 mmol), and $\text{R}^{21}\text{SnBu}_3$ (R^{21} = 2-pyrazinyl) (43 mg, 0.12 mmol) as a solution in 1 mL of PhCF_3 . The tube was sealed, and evacuated and back-filled with N_2 (5X). The mixture was then exposed to microwave

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irradiation (110 °C, 30 min). The resulting mixture was filtered with copious MeOH washes. Concentration of the filtrate gave a crude product that was subjected to RP-HPLC to give CO2 ($R^1 = \text{Me}$, $R^2 = \text{H}$; $R^3 = \text{c-Pr}$, $n = 0$, $R^{21} = 2\text{-pyrazinyl}$) as a formate salt (12 mg, 0.063mmol, 35%). LCMS $R_t = 3.58$ min, $m/e = 308.2$ (M+H).

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10 Method CP; Step 1: 1,4,2-Diazaphospholidin-5-one, 2-methoxy-1-methyl-3,3-diphenyl-2-oxide (CP3)

Using methods similar to those described by I. V. Konovalova et al. (Zhurnal Obshchei Khimii, 50(7), 1653-1654), 1.0 equivalent of phosphorodiamidic acid dimethyl ester (CP2), is added to a solution of benzophenone imine (CP1) in toluene and the mixture is warmed to reflux for 4 h. Removal of solvent and purification by flash chromatography provides the title compound (CP3).

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Method CP, Step 2: 1,4,2-Diazaphospholidin-5-thione, 2-methoxy-1-methyl-3,3-diphenyl-2-oxide (CP4)

20 To a solution of CP3 in toluene (or xylene) is added Lawesson's reagent (1.2 equivalents), and the mixture is stirred at reflux for 2 h. The mixture is cooled and poured into cold water. The organic phase is dried (MgSO_4) and filtered, and solvent is removed. The crude product is purified by flash chromatography to provide the title compound (CP4).

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Method P1, Step 3: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-1-methyl-3,3-diphenyl-2-oxide (CP5)

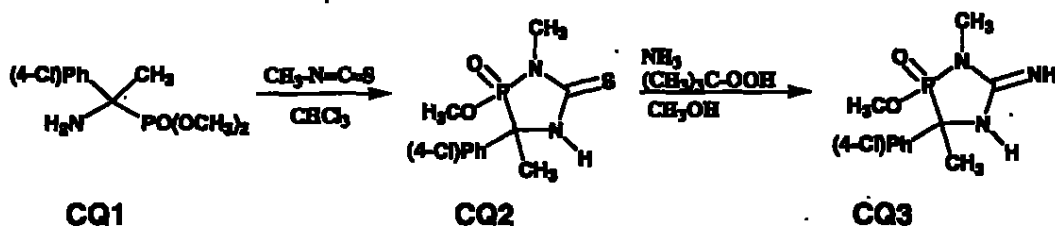
Using a route similar to that described in Method A, step 3, CP4 is used to prepare the title compound (CP5).

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As a variant of Method CP, benzophenone imine (CP1) is treated with 1.0 equivalent of phosphoriscyanatidous acid dimethyl ester $[(CH_3O)_2P-N=C=S]$, giving directly CP4, which is converted to CP5 as described in Method CP, Step 3.

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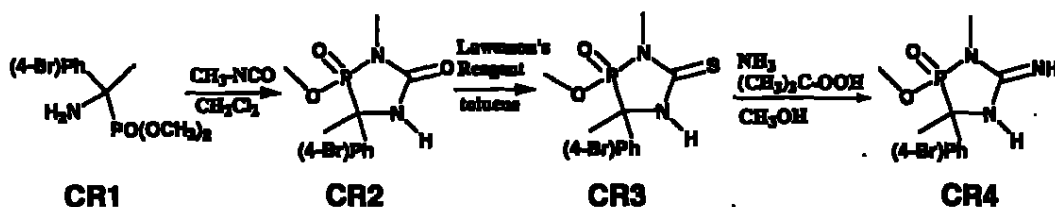
Method CQ

Method CQ, Step 1: 1,4,2-Diazaphospholidin-5-thione, 2-methoxy-1-methyl-3-methyl-3-(4-chlorophenyl)-2-oxide (CQ2)

- 10 Using an approach similar to that described by R. Merten et al. [(Chem. Ber., 102, 2143 (1969)), methylisothiocyanate (1.2 equivalents) is added to a solution of dimethyl [1-amino-1-(4-chlorophenyl)ethyl]phosphonate (CQ1) in chloroform and the mixture is gradually warmed to reflux. After 2 h at reflux, the mixture is cooled and solvent is removed by evaporation. Purification of the crude product by flash chromatography
- 15 provides the title compound.

Method CQ, Step 2: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-1-methyl-3-methyl-3-(4-chlorophenyl)-2-oxide (CQ3)

- 20 Using a route similar to that described in Method A, step 3, CQ2 is used to prepare the title compound.

Method CR

- 25 **Method CR, Step 1: 1,4,2-Diazaphospholidin-5-one, 2-methoxy-1-methyl-3-methyl-3-(4-bromophenyl)-2-oxide (CR2)**

Using an approach similar to that described by R. Merten et al. [(Chem. Ber., 102, 2143 (1969)), methylisocyanate (1.2 equivalents) is added to a solution of dimethyl [1-

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amino-1-(4-bromo)phenyl]ethylphosphonate (CR1) in chloroform and the mixture is gradually warmed to reflux. After 2 h at reflux, the mixture is cooled and solvent is removed by evaporation. Purification of the crude product by flash chromatography provides the title compound (CR2).

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Method CR, Step 2: 1,4,2-Diazaphospholidin-5-thione, 2-methoxy-1-methyl-3-methyl-3-(4-bromo)phenyl-2-oxide (CR3)

To a solution of CR2 in toluene or xylene is added Lawesson's reagent (1.2 equivalents), and the mixture is stirred at reflux for 2 h. The mixture is cooled and poured into cold water. The organic phase is dried (MgSO₄) and filtered, and solvent is removed. The crude product is purified by flash chromatography to provide the title compound.

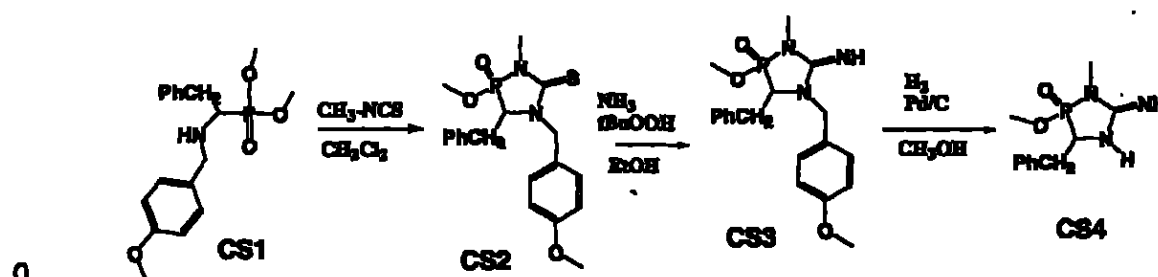
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Method CR, Step 3: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-1-methyl-3-methyl-3-(4-bromo)phenyl-2-oxide (CR4)

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Using a route similar to that described in Method A, step 3, CR3 is used to prepare the title compound.

Method CS



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Method CS, Step 1: 1,4,2-Diazaphospholidin-5-thione, 2-methoxy-4-(4-methoxy)phenylmethyl)-1-methyl-3-phenylmethyl-2-oxide (CS2)

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Using an approach similar to that described by R. Merten et al. [(Chem. Ber., 102, 2143 (1969)), methylisothiocyanate (1.2 equivalents) is added to a solution of dimethyl [1-(4-methoxy)phenylmethylamino]-2-(4-bromo)phenyl]ethylphosphonate (CS1) in chloroform and the mixture is gradually warmed to reflux. After 2 h at reflux, the mixture is cooled and solvent is removed by evaporation. Purification of the crude product by flash chromatography provide the title compound.

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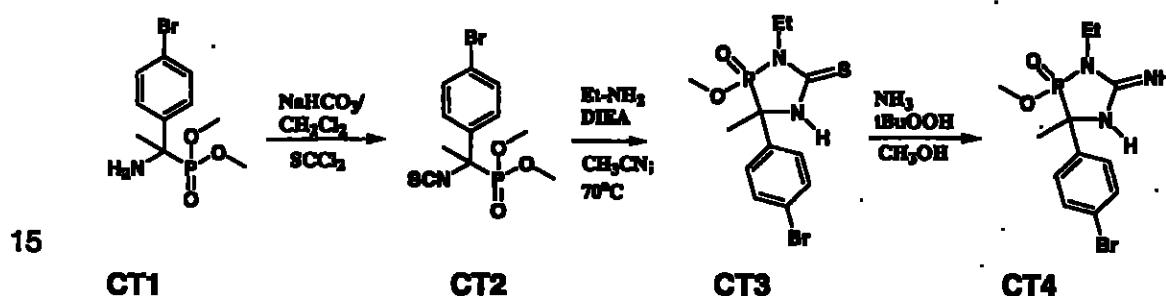
Method CS, Step 2: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-4-(4-methoxy)phenylmethyl-1-methyl-3-phenylmethyl-2-oxide (CS3)

Using a route similar to that described in Method A, step 3, CS2 is used to prepare the title compound.

Method CS, Step 3: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-1-methyl-3-phenylmethyl-2-oxide (CS4).

A solution of CS3 in methanol is hydrogenated at 1 atm in the presence of 5 mol% Pd/C, yielding the title compound after filtration and purification by flash chromatography.

Method CT



Method CT, Step 1: Dimethyl-[(4-bromophenyl)-1-isothiocyanato]ethylphosphonate

20 To a mixture of CT1 in DCM and 0.1 N aqueous sodium bicarbonate (1.0 equivalent) is added thiophosgene (1.5 equivalents), and the mixture is stirred for 4 h at RT. Water is added, and the organic phase is dried (MgSO₄), filtered and concentrated to give the product CT2 which is used without purification.

25 **Method CT, Step 2: 1,4,2-Diazaphospholidin-5-thione, 2-methoxy-1-ethyl-3-(4-bromo)phenyl-2-oxide (CT3)**

To a solution of CT2 in acetonitrile is added ethylamine (2 equivalents) and diisopropylethylamine (2 equivalents) and the solution is slowly warmed to reflux for 2

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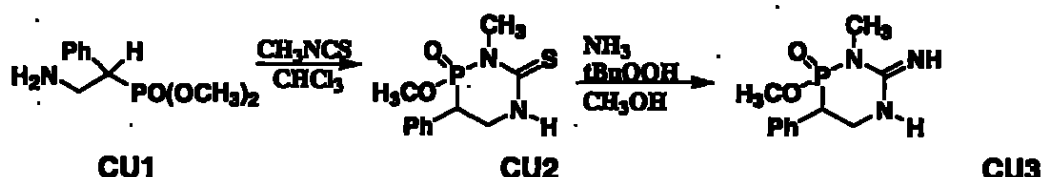
h. After removal of solvent, the product is purified by flash chromatography to give the title product.

Method CT Step 3: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-1-ethyl-3-(4-bromo)phenyl-2-oxide (CT4)

Using a route similar to that described in Method A, step 3, CT3 is used to prepare the title compound.

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Method CU



Method CU, Step 1: 1,5,2-Diazaphosphorine-6(1H)-thione, 1-methyl-2-methoxy-3-phenyl-2-oxide (CU2)

Using an approach similar to that described by R. Merten et al. [(Chem. Ber., 102, 2143 (1969)), methylisothiocyanate (1.2 equivalents) is added to a solution of dimethyl (2-amino-1-phenyl)ethylphosphonate (CU1) in chloroform and the mixture is gradually warmed to reflux. After 2 h at reflux, the mixture is cooled and solvent is removed by evaporation. Purification of the crude product by flash chromatography provides the title compound.

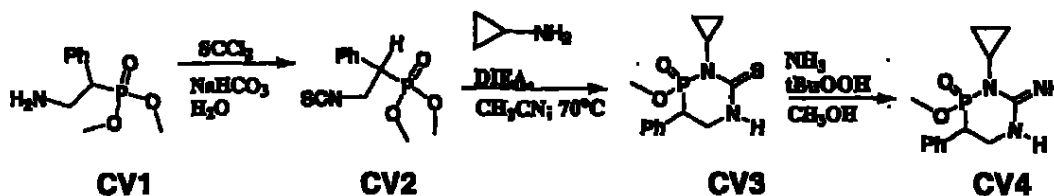
Method CU, Step 2: 1,5,2-Diazaphosphorine-6(1H)-imine, 1-methyl-2-methoxy-3-phenyl-2-oxide (CU3)

Using a route similar to that described in Method A, step 3, CU2 is used to prepare the title compound.

Method CV

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Method CV, Step 1: Dimethyl (2-isothiocyanato-1-phenyl)ethylphosphonate (CV2)

- 5 To a mixture of CV1 in methylene chloride and 0.1 N aqueous sodium bicarbonate (1.0 equivalent) is added thiophosgene (1.5 equivalents), and the mixture is stirred for 4 h at RT. Water is added, and the organic phase is dried (MgSO₄), filtered and concentrated to give the product which is used without purification.

10 **Method CV, Step 2: 1,5,2-Diazaphosphorine-6(1H)-thione, 1-cyclopropyl-2-methoxy-3-phenyl-2-oxide (CV3)**

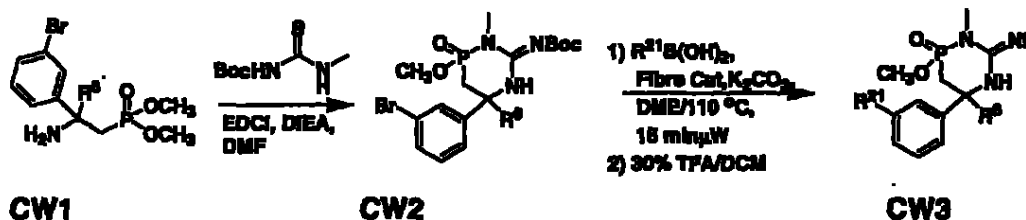
To a solution of CV2 in acetonitrile is added cyclopropylamine (2 equivalents) and diisopropylethylamine (2 equivalents) and the solution is heated at reflux for 2 h. After removal of solvent, the product is purified by flash chromatography to give the title product.

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Method CV Step 3: 1,4,2-Diazaphospholidin-5-imine, 2-methoxy-1-cyclopropyl-3-(4-bromo)phenyl-2-oxide (CV4)

- Using a route similar to that described in Method A, step 3, CV3 is used to prepare the title compound.
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Method CW



- 5 **Method CW; Step 1: Boc-1,5,2-diazaphosphorine-5-imine, 2-methoxy-1-methyl-4-(3-arylphenyl)-2-oxides (CW2)**

Reaction of tert-butyl methylcarbamothioylcarbamate with CW1 (R⁶ = Me) using EDCI and DIEA in DMF affords CW2 (R⁶ = Me) after purification.

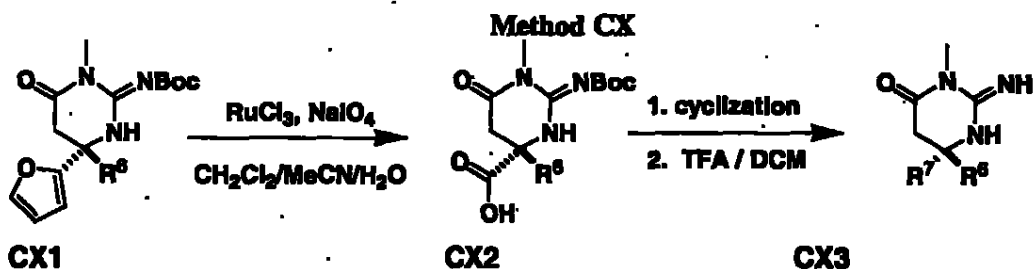
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Method CW; Step 2: 1,5,2-Diazaphosphorine-5-imine, 2-methoxy-1-methyl-4-(3-(m-cyanophenyl)phenyl)-2-oxides (CW3)

Following the procedure of Sauer, D. R. *et al*, *Org. Lett.*, 2004, 6, 2793-2796, Suzuki reaction of CW2 ($R^6 = \text{Me}$) with aryl boronic acids using polymer-support Pd catalysts such as Fibre Cat or PS-PPh₃-Pd under microwave heating conditions provides CW3 ($R^6 = \text{Me}$ and $R^{21} = \text{m-CN-Ph}$) of the invention after subsequent Boc-deprotection.

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Method CX, Step 1, (S)-2-(tert-Butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carboxylic acid

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To a solution of (S)-tert-butyl 4-(furan-2-yl)-1,4-dimethyl-6-oxo-tetrahydropyrimidin-2(1H)-ylidenecarbamate CX1 ($R^6 = \text{Me}$) (1.12 g, 3.64 mmol, prepared using Method CF) in DCM (7 mL) was added MeCN (7 mL) and H₂O (10.5 mL), followed by RuCl₃·H₂O (7.6 mg, 0.036 mmol, 1 mol%), and NaIO₄ (11.6 g, 54.2 mmol, 15 eq). The mixture was stirred at RT for 2 h. The mixture was diluted with DCM (100 mL) and the organic layer was separated, dried (Na₂SO₄), and concentrated to give 0.90 g (86%) of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carboxylic acid CX2 ($R^6 = \text{Me}$) as a brown solid. ¹H NMR (CD₃OD): δ 3.17 (s, 3H), 3.02 (m, 2H), 1.63 (s, 9H), 1.57 (s, 3H).

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Method CX, Step 2, (6S)-2-imino-3,6-dimethyl-6-(3-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)-tetrahydropyrimidin-4(1H)-one (CX3)

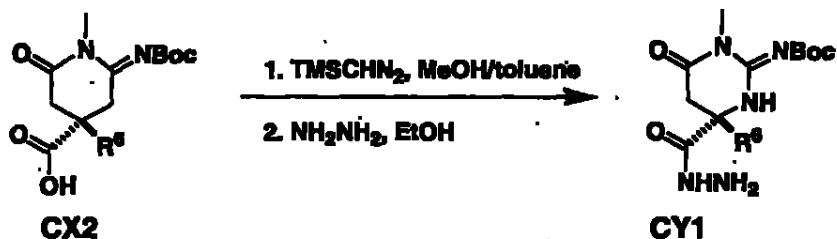
To a solution of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carboxylic acid (CX2, $R^6 = \text{Me}$, 0.035 g, 0.12 mmol) in DMF (0.24 mL) was added TBTU (0.040 mg, 0.12 mmol, 1 eq), HOBT (0.0035 mg, 0.024 mmol, 0.2 eq), and DIEA (0.107 mL, 0.60 mmol, 5 eq). The mixture was stirred at RT for 10 min and then

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N'-hydroxy-3-(trifluoromethyl)benzamidinium (0.028 mg, 0.13 mmol, 1.1 eq) was added. After stirring for another 2 h, the reaction mixture was diluted with EtOAc (20 mL), washed with H₂O (10 mL) and saturated brine (10 mL), and concentrated in vacuo. The crude residue was dissolved in THF (0.4 mL) and then TBAF (1M in THF, 0.099 mL, 0.9 eq) was added. The mixture was stirred at RT for 2 h. EtOAc (20 mL) was added to the reaction mixture, which was washed with H₂O (10 mL) and saturated brine (10 mL), and concentrated in vacuo. The residue was treated with 30% TFA/DCM (1 mL) at RT for 1. The reaction mixture was concentrated in vacuo and the crude product was purified on reverse phase HPLC (B) to give 0.015 g (26%) of (6S)-2-imino-3,6-dimethyl-6-(3-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)-tetrahydropyrimidin-4(1H)-one (CX3; R⁶ = Me, R⁷ = 3-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl) as a white solid. ¹H NMR (CD₃OD): δ 8.40 (m, 2H), 8.04 (d, 1H, J = 6.9 Hz), 7.90 (t, 1H, J = 8.1 Hz), 3.81 (m, 2H), 3.39 (s, 3H), 1.82 (s, 3H). MS (ESI): MH⁺ = 354.2, HPLC (A) R_t = 6.234 min.

Method CY



(S)-2-(tert-Butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carbohydrazide

To a solution of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carboxylic acid CX2 (R⁶ = Me) (0.357 g, 1.25 mmol) in 1:5 MeOH/toluene (3 mL) was added TMSCHN₂ (2M in hexane, 1.9 mL, 3.8 mmol, 3 eq). The mixture was stirred at RT for 2 h. The mixture was concentrated in vacuo to give 0.37 g (100%) of (S)-methyl 2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carboxylate as a brown solid. ¹H NMR (CDCl₃): δ 8.80 (s, 1H), 3.70 (s, 3H), 3.14 (s, 1H), 2.79 (s, 2H), 1.53 (s, 9H), 1.50 (s, 3H).

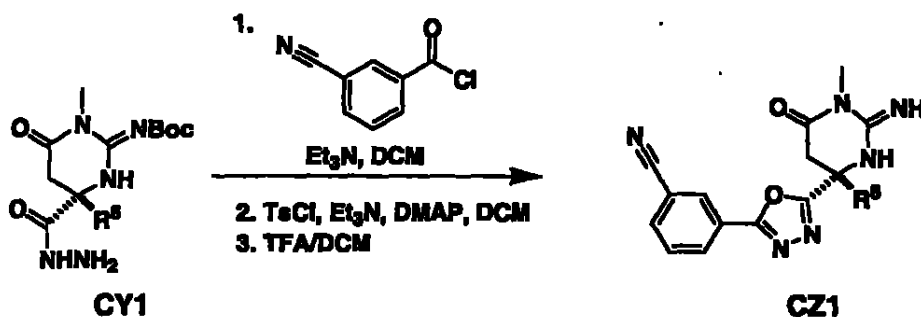
To a solution of (S)-methyl 2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carboxylate (0.074 g, 0.25 mmol) in EtOH (0.5 mL) was added NH₂NH₂ (0.023 mL, 0.75 mmol, 3 eq) and the mixture was stirred at RT for 4 h. The

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mixture was concentrated in vacuo to give 0.074 g (100%) of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carbohydrazide (CY1, $R^8 = \text{Me}$) as a yellow solid. ^1H NMR (CDCl_3) δ 8.95 (s, 1H), 3.11 (s, 3H), 2.28 (m, 2H), 1.50 (s, 9H), 1.47 (s, 3H).

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Method CZ



3-(5-((S)-2-imino-1,4-dimethyl-6-oxo-hexahydropyrimidin-4-yl)-1,3,4-oxadiazol-2-yl)benzonitrile

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To a solution of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carbohydrazide (CY1; $R^8 = \text{Me}$, 0.037 g, 0.12 mmol) in DCM (0.3 mL) at 0 °C was added Et_3N (0.035 mL, 0.24 mmol, 2 eq) followed by 3-cyanobenzoyl chloride (0.027 g, 0.16 mmol, 1.3 eq). The mixture was stirred at RT for 6 h. The mixture was diluted with DCM (20 mL), washed with H_2O (10 mL) and saturated brine (10 mL), and concentrated in vacuo. The residue was then treated with TsCl (0.035 g, 0.18 mmol, 1.5 eq), Et_3N (0.046 mL, 0.31 mmol, 2.6 eq), and DMAP (0.002 g, 0.016 mmol, 0.13 eq) in DCM (0.25 mL) at RT for 16 h. The mixture was diluted with DCM (20 mL), washed with H_2O (10 mL) and saturated brine (10 mL), and concentrated in vacuo.

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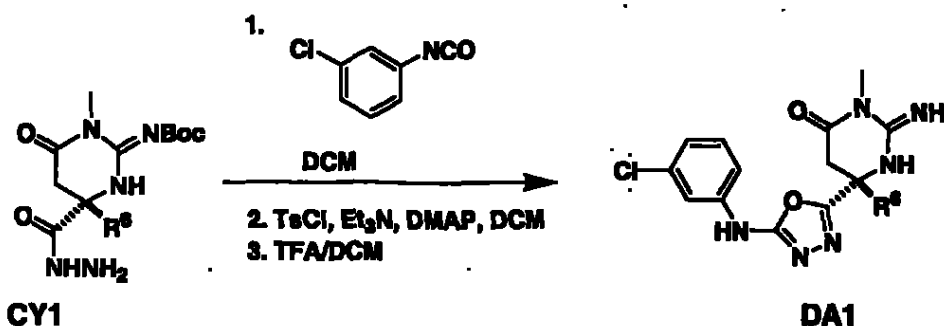
The residue was treated with 30% TFA/DCM (1 mL) at RT for 1 h. The mixture was concentrated in vacuo and the residue was purified on reverse phase HPLC (B) to give 0.006 g (12%) of 3-(5-((S)-2-imino-1,4-dimethyl-6-oxo-hexahydropyrimidin-4-yl)-1,3,4-oxadiazol-2-yl)benzonitrile as a white solid (CZ1; $R^8 = \text{Me}$). ^1H NMR (CD_3OD , 300 MHz): δ 8.49 (m, 2H), 8.12 (d, 1H), 7.92 (t, 1H), 3.75 (m, 2H), 3.36 (s, 3H), 1.82 (s, 3H). MS (ESI): $\text{MH}^+ = 311.2$, HPLC (A) $R_t = 4.175$ min.

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Method DA

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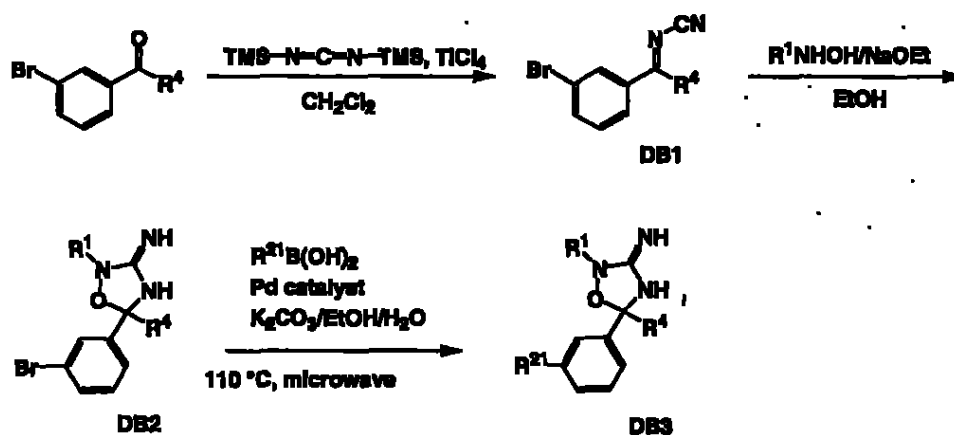
329



(S)-6-(5-(3-chlorophenylamino)-1,3,4-oxadiazol-2-yl)-2-imino-3,6-dimethyl-tetrahydropyrimidin-4(1H)-one

- 5 To a solution of (S)-2-(tert-butoxycarbonyl)-1,4-dimethyl-6-oxo-hexahydropyrimidine-4-carbohydrazide (CY1, $R^6 = \text{Me}$, 0.030 g, 0.10 mmol) in DCM (0.25 mL) was added 3-chlorophenylisocyanate (0.015 mL, 0.20 mmol, 2 eq). The mixture was stirred at RT for 3 h and volatiles were then removed in vacuo. The residue was treated with TsCl (0.020 g, 0.10 mmol, 1 eq), Et_3N (0.083 mL, 0.60 mmol, 6 eq), and DMAP (0.002 g, 0.016 mmol, 0.16 eq) in DCM (0.25 mL) at RT for 16 h. The mixture was diluted with DCM (20 mL), washed with H_2O (10 mL) and saturated brine (10 mL), and concentrated in vacuo. The residue was treated with 30% TFA/DCM (1 mL) at RT for 1 h. The mixture was concentrated in vacuo and the residue was purified on reverse phase HPLC (B) to give 0.006 g (10%) of (S)-6-(5-(3-chlorophenylamino)-1,3,4-oxadiazol-2-yl)-2-imino-3,6-dimethyl-tetrahydropyrimidin-4(1H)-one (DA1; $R^6 = \text{Me}$). ^1H NMR (CD_3OD , 300 MHz): δ 7.78 (t, 1H), 7.47 (m, 2H), 7.17 (dt, 1H), 3.53 (m, 2H), 3.36 (s, 3H), 1.78 (s, 3H). MS (ESI): $\text{MH}^+ = 335.3$, HPLC (A) $R_t = 5.710$ min.

Method DB



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Method DB, Step 1; (1-(3-bromophenyl)ethylidene)cyanamide (DB1, $R^4 = \text{Me}$)

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Following the procedure of Cuccia, S.J.; Fleming, L.B.; France, D.J. *Synth. Comm.* 2002, 32 (19), 3011-3018: 3-Bromoacetophenone (2.0 g, 10 mmol, 1 eq), was dissolved in 20 mL DCM. A 1.0 N solution of titanium tetrachloride in DCM (20 mL, 20 mmol, 2 eq) was added dropwise over 15 min and the resulting mixture was stirred at 25 °C for 1 h. Bis-trimethylsilylcarbodiimide (5.0 mL, 22 mmol, 2.2 eq) in 5 mL of DCM was added over 15 min and the reaction was stirred for 16 h under argon. The reaction was poured onto 200 mL of an ice/water mixture and extracted with 3 x 200 mL of DCM. The combined organic phase was dried over MgSO₄, filtered, and concentrated to give 2.3 g (100%) of (1-(3-bromophenyl)ethylidene)cyanamide (DB1, R¹ = Me) as a white solid: ¹H NMR (CDCl₃) δ 8.16 (t, J = 1.8 Hz, 1H), 7.94 (dd, J = 1.7, 1.1 Hz, 1H), 7.76 (dd, J = 1.7, 1.1 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 2.82 (s, 3H).

Method DB, Step 2; 5-(3-Bromophenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine (DB2, R¹ = Me)

To a solution of the HCl salt of methylhydroxylamine (0.19 g, 2.2 mmol, 1 eq) in ethanol (25 mL) at 25 °C was added a 21% solution of NaOEt in ethanol (0.75 mL, 2.0 mmol, 0.9 eq) followed by (1-(3-bromophenyl)ethylidene)cyanamide (0.50 g, 2.2 mmol, 1 eq). After stirring at 25 °C for 10 min, the solvent was removed *in vacuo*. The residue was redissolved in CH₂Cl₂ (25 mL), the mixture was filtered, and the solvent was removed *in vacuo* to give 0.5 g (83%) of 5-(3-bromophenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine (DB2, R¹ = Me, R⁴ = Me) as a colorless oil: ¹H NMR (CDCl₃) δ 7.63 (t, J = 1.8 Hz, 1H), 7.52 (dd, J = 2.0, 1.1 Hz, 1H), 7.38 (dd, J = 2.0, 1.1 Hz, 1H), 7.29 (t, J = 7.9 Hz, 1H), 3.28 (s, 3H), 1.88 (s, 3H). MS (ESI) *m/e* 270.0, 272.0 (M+H)⁺.

Method DB, Step 3; 5-(3-(3-Chlorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine

To a solution of 5-(3-bromophenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine (25 mg, 0.093 mmol) and 3-chlorophenyl boronic acid (17 mg, 0.11 mmol) in ethanol (1 mL) was added a 1 M aqueous solution of K₂CO₃ (0.22 mL, 0.22 mmol) and PS-PPh₃-Pd (46 mg, 0.0046 mmol). The sample was heated in an Emrys Optimizer Microwave at 110 °C for 10 min. The resin was filtered off and rinsed alternately three times with CH₂Cl₂ (5 mL) and CH₃OH (5 mL). The combined filtrates were concentrated and the residue was purified by reverse phase prep-HPLC to give 12.3 mg (44%) of 5-(3-(3'-

3A6

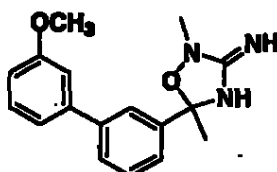
- 330 -

chlorophenyl)-phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine (DB3; $R^1 = \text{Me}$, $R^4 = \text{Me}$, $R^{21} = 3\text{-chlorophenyl}$) as a colorless oil: ^1H NMR (CDCl_3) δ 7.69 (s, 1H), 7.58 (m, 2H), 7.49 (m, 3H), 7.37 (m, 2H), 3.29 (s, 3H), 1.94 (s, 3H). MS (ESI) m/e 302.0, 304.0 (M^+H)⁺.

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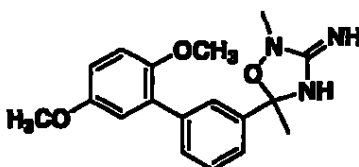
Using a similar procedure, the following compounds were also prepared.

5-(3-(3-Methoxyphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine



10 ^1H NMR (CDCl_3) δ 7.72 (s, 1H), 7.62 (dt, 1H), 7.49 (m, 2H), 7.38 (t, $J = 8.2\text{Hz}$, 1H), 7.20 (m, 1H), 7.14 (t, 1H), 6.93 (m, 1H), 3.88 (s, 3H), 3.27 (s, 3H), 1.95 (s, 3H). MS m/e 298.1 (M^+H)

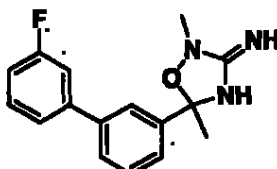
5-(3-(2,5-Dimethoxyphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine



15

^1H NMR (CDCl_3) δ 7.67 (s, 1H), 7.57 (m, 1H), 7.45 (m, 2H), 6.92 (m, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 3.27 (s, 3H), 1.95 (s, 3H). MS m/e 328.1 (M^+H)

5-(3-(3-Fluorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine



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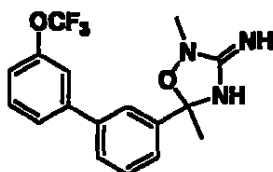
^1H NMR (CDCl_3) δ 7.71 (s, 1H), 7.60 (m, 1H), 7.50 (m, 2H), 7.41 (m, 2H), 7.31 (m, 1H), 7.08 (m, 1H), 3.29 (s, 3H), 1.94 (s, 3H). MS m/e 286.0 (M^+H)

5-(3-(3-Trifluoromethoxyphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine

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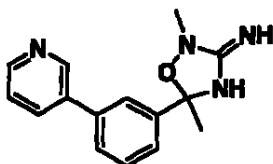
297

- 331 -



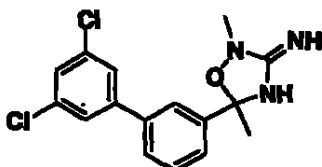
$^1\text{H NMR}$ (CDCl_3) δ 7.70 (s, 1H), 7.59 (m, 1H), 7.55 (m, 1H), 7.50 (m, 2H), 7.46-7.48 (m, 2H), 7.26 (m, 1H), 3.29 (s, 3H), 1.95 (s, 3H). MS m/e 352.1 (M^+H)

5 5-(3-(3-Pyridyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine



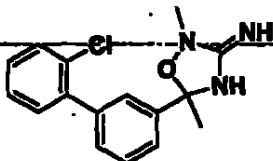
$^1\text{H NMR}$ (CD_3OD) δ 9.17 (s, 1H), 8.84 (m, 2H), 8.08 (m, 1H), 7.99 (s, 1H), 7.88 (m, 1H), 7.72 (m, 2H), 3.37 (s, 3H), 2.00 (s, 3H). MS m/e 269.1 (M^+H)

10 5-(3-(3,5-Dichlorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine



$^1\text{H NMR}$ (CDCl_3) δ 7.66 (s, 1H), 7.54 (m, 1H), 7.52 (m, 2H), 7.47 (m, 2H), 7.38 (m, 1H), 3.30 (s, 3H), 1.94 (s, 3H). MS m/e 336.1 (M^+H)

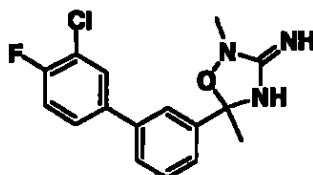
5 5-(3-(2-Chlorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine



$^1\text{H NMR}$ (CDCl_3) δ 7.59 (m, 1H), 7.50 (m, 4H), 7.34 (m, 3H), 3.28 (s, 3H), 1.95 (s, 3H). MS m/e 302.1 (M^+H)

) 5-(3-(3-Chloro-4-fluorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazolidin-3-imine

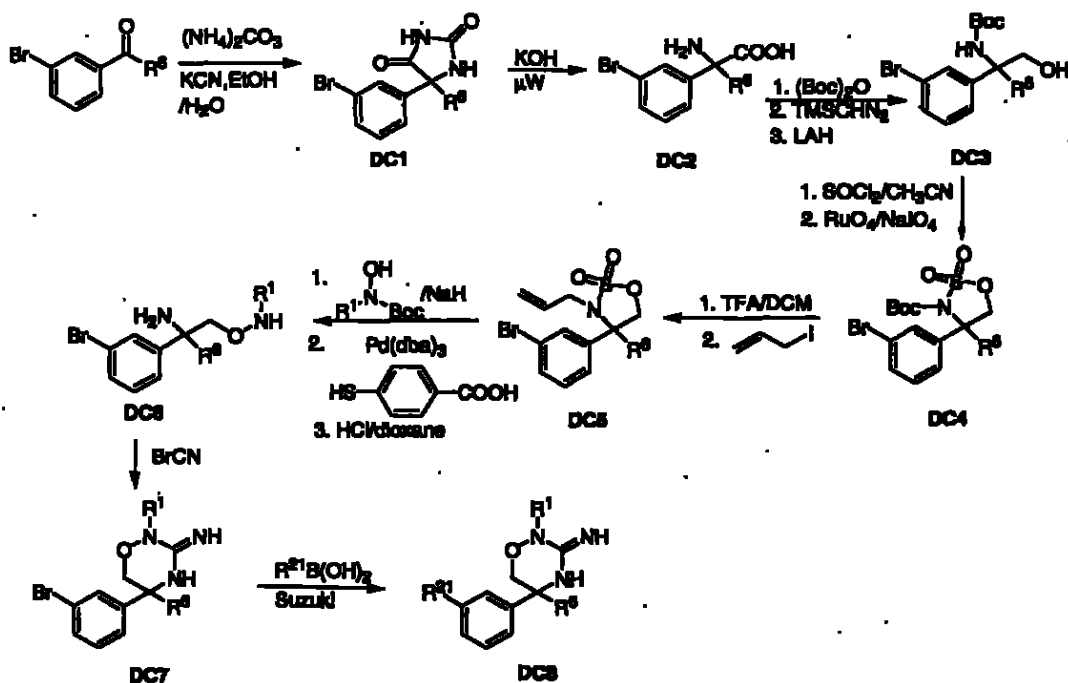
- 332 -



^1H NMR (CDCl_3) δ 7.65 (m, 2H), 7.48-7.54 (m, 4H), 7.22 (m, 1H), 3.30 (s, 3H), 1.94 (s, 3H). MS m/e 320.1 (M^+H)

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Method DC



Method DC, Step 1, 5-(3-Bromophenyl)-5-methylimidazolidine-2,4-dione

- 10 A mixture of 3-bromoacetophenone (10 g, 50 mmol), KCN (8.16 g, 130 mmol, 2.5 eq) and $(\text{NH}_4)_2\text{CO}_3$ (21.7 g, 225 mmol, 4.5 eq) in EtOH/ H_2O (1:1, 110 mL) was heated at 60 °C for 16 h. The reaction mixture was cooled to 0 °C. The resulting precipitate was filtered, washed with water, hexane, and then dried to give 12.6 g (93%) of 5-(3-bromophenyl)-5-methylimidazolidine-2,4-dione as an off-white solid (DC1; $\text{R}^6 = \text{Me}$).
- 15 ^1H NMR (CD_3OD) δ 7.64 (s, 1H), 7.45 (t, $J = 9.7$ Hz, 2H), 7.26 (t, $J = 7.6$ Hz, 1H), 1.68 (s, 3H).

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Method DC, Step 2, 2-Amino-2-(3-bromophenyl)propanoic acid

5-(3-Bromophenyl)-5-methylimidazolidine-2,4-dione (DC1; $R^8 = \text{Me}$) (1.5 g, 5.6 mmol) was dissolved in 15 mL of 1N KOH, heated to 185 °C in a microwave reactor (Emrys Optimizer) for 2 h. Afterward, the mixture was carefully acidified using conc. HCl to pH ~2. The mixture was extracted once with Et₂O (20 mL). The aqueous layer was concentrated in vacuo to give 1.6 g (100%) of 2-amino-2-(3-bromophenyl)-2-propanoic acid (DC2; $R^8 = \text{Me}$) as an off white solid. ¹H NMR (CD₃OD) δ 7.75 (t, J = 2.0, 1H), 7.66 (m, 1H), 7.56 (m, 1H), 7.45 (t, J = 8.1 Hz, 1H), 1.99 (s, 3H).

Method DC, Step 3, 2-(3-Bromophenyl)-2-(tert-butoxycarbonyl)propanoic acid

To a solution of 2-amino-2-(3-bromophenyl)-propanoic acid (DC2; $R^8 = \text{Me}$) (10.5 g, 43 mmol) in 1N KOH (105 mL) and dioxane (70 mL) at 0 °C was added (Boc)₂O (20.6 g, 95 mmol, 2.2 eq). The mixture was stirred at RT for 16 h. The reaction mixture was concentrated to 100 mL. EtOAc (100 mL) was added and the mixture was cooled to 0 °C. After acidifying with 2N KHSO₄ to pH 2 – 3, the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined EtOAc layer was washed with H₂O (2 x 50 mL), dried (Na₂SO₄), and concentrated to give 11.7 g (79%) of 2-(3-bromophenyl)-2-(tert-butoxycarbonyl) propanoic acid as a white solid. ¹H NMR (CDCl₃) δ 7.61 (s, 1H), 7.41 (m, 2H), 7.24 (m, 1H), 1.98 (s, 3H), 1.44 (s, 9H).

To a solution of 2-(3-bromophenyl)-2-(tert-butoxycarbonyl) propanoic acid (11.3 g, 32.8 mmol) in MeOH (35 mL) was added toluene (175 mL) followed by TMSCHN₂ (2M in hexane, 44 mL, 98 mmol, 3 eq). The mixture was stirred at RT for 16 h. Solvents were evaporated and the residue was chromatographed on silica by eluting with EtOAc/hexanes to give 11.8 g (100%) of methyl 2-(3-bromophenyl)-2-(tert-butoxycarbonyl)propanoate as a yellow oil. ¹H NMR (CDCl₃) δ 7.59 (t, J = 1.8 Hz, 1H), 7.36-7.44 (m, 2H), 7.21 (t, J = 8.0 Hz, 1H), 5.92 (s, 1H), 3.70 (s, 3H), 1.97 (s, 3H), 1.36 (br s, 9H).

To a solution of methyl 2-(3-bromophenyl)-2-(tert-butoxycarbonyl) propanoate (11.8 g, 33 mmol) in THF (150 mL) at -78 °C was added LAH powder (3.1 g, 82.0 mmol, 2.5 eq). The mixture was stirred at -78 °C and allowed to warm to RT over 16 h. The mixture was cooled to 0 °C and the reaction was quenched by slowly adding 3 mL of H₂O. The mixture was diluted with DCM (500 mL) followed by the addition of 1N NaOH (6 mL) and H₂O (9 mL). After stirring at 0 °C for 30 min, the mixture was filtered

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and the filtrate was concentrated to give 10 g (95%) of *tert*-butyl 2-(3-bromophenyl)-1-hydroxypropan-2-ylcarbamate (DC3; R⁶ = Me) as a colorless oil. ¹H NMR (CDCl₃) δ 7.49 (t, J = 1.8 Hz, 1H), 7.35-7.39 (m, 1H), 7.27-7.30 (m, 1H), 7.21 (t, J = 7.8 Hz, 1H), 3.72 (m, 2H), 1.57 (s, 3H), 1.41 (br s, 9H).

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Method DC, Step 4; 3-(*tert*-Butoxycarbonyl)-4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide

To a solution of SOCl₂ (5.7 mL, 2.5 eq) in dry CH₃CN (37 mL) under argon was cooled to -40 °C was added *tert*-butyl 2-(3-bromophenyl)-1-hydroxypropan-2-ylcarbamate (DC3; R⁴ = Me) (10.3 g, 31 mmol) in dry CH₃CN (27 mL) was added dropwise, followed by the addition of dry pyridine (12.4 mL, 160 mmol, 5 eq). The mixture was then allowed to warm to RT in 1 h. The mixture was concentrated to about 30 mL. EtOAc (30 mL) was added and the precipitate was filtered off. The filtrate was concentrated in vacuo to give 10.4 g (89%) of 3-(*tert*-butoxycarbonyl)-4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2-oxide as a colorless oil. ¹H NMR (CDCl₃) δ 7.64 (t, J = 2.0 Hz, 1H), 7.36-7.53 (m, 2H), 7.24 (m, 1H), 4.52 (q, J = 9.5 Hz, 2H), 1.86 (s, 3H), 1.42 (br s, 9H).

To a solution of 3-(*tert*-butoxycarbonyl)-4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2-oxide (10.4 g, 28 mmol) in CH₃CN (50 mL) at 0 °C was added RuO₄ (0.5% in stabilized aq., 50 mg, 0.1% by weight) in H₂O (10 mL) and NaIO₄ (8.9 g, 41.5 mmol, 1.5 eq) in H₂O (35 mL). The mixture was stirred at RT for 2 h. The mixture was partitioned between Et₂O (200 mL) and H₂O (50 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (3 x 50 mL). The combined organic layer was dried (Na₂SO₄), and concentrated to give 10.8 g (100%) of 3-(*tert*-butoxycarbonyl)-4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (DC4; R⁶ = Me) as a white solid (~ 10.8 g, yield: 100%). ¹H NMR (CDCl₃) δ 7.56 (t, J = 1.8 Hz, 1H), 7.48-7.52 (m, 1H), 7.38-7.44 (m, 1H), 7.30 (t, J = 8.0 Hz, 1H), 4.41 (dd, J₁ = 9.3 Hz, J₂ = 20.4 Hz, 2H), 2.01 (s, 3H), 1.39 (s, 9H).

Method DC, Step 5; 3-Allyl-4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide

3-(*tert*-Butoxycarbonyl)-4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (DC4; R⁶ = Me) (10.8 g, 28 mmol) was dissolved in 25% TFA in DCM (40 mL, 5 eq)

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and the mixture was left standing at RT for 3 h. The mixture was concentrated in vacuo to give 7.3 g (91%) of 4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide as a yellow oil. ¹H NMR (CDCl₃) δ 7.59 (t, J = 1.8 Hz, 1H), 7.48-7.52 (m, 1H), 7.39-7.42 (m, 1H), 7.30 (t, J = 8.1 Hz, 1H), 4.59 (m, 2H), 1.82 (s, 3H).

- 5 To a solution of 4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (7.3 g, 25 mmol) in DCM (77 mL) was added allyl iodide (9.1 mL, 100 mmol, 4 eq), followed by BnBu₃NCl (0.39 g, 1.3 mmol) and 40% NaOH (28 mL). The mixture was stirred at RT for 16 h. The organic layer was separated and the solvent was evaporated. Silica gel chromatography using 5-20% EtOAc/hexanes gave 8.3 g (100%) of 3-allyl-4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (DC5; R⁸ = Me) as a colorless oil. ¹H NMR (CDCl₃) δ 7.64 (t, J = 1.8 Hz, 1H), 7.48-7.54 (m, 2H), 7.31 (t, J = 8.0 Hz, 1H), 5.77-5.89 (m, 1H), 5.19-5.33 (m, 2H), 4.38 (dd, J₁ = 8.7 Hz, J₂ = 23.7 Hz, 2H), 3.46-3.68 (m, 2H), 1.83 (s, 3H).

15 **Method DC, Step 6; N-(2-(3-bromophenyl)-2-amino)prop-1-oxy)-methylamine**

- To a suspension of NaH (60%, 0.14 g, 1.5 eq) in 0.5 mL of anhydrous DMF was added tert-butyl hydroxy(methyl)carbamate (0.52 g, 1.5 eq) in 1.5 mL of DMF. After stirring at RT for 15 min, a solution of 3-allyl-4-(3-bromophenyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (DC5; R⁸ = Me) (0.78 g, 2.3 mmol) in 6 mL of anhydrous DMF was added dropwise. The mixture was stirred at RT for 16 h. The mixture was partitioned between EtOAc (10 mL) and 1N HCl (3 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over Na₂SO₄ and concentrated to give 0.45 g (41%) of a product which was used without purification.

- 20 To a solution of the above product (3.86 g, 8.1 mmol) in THF (30 mL) was added a pre-stirred (15 min) mixture of Pd₂(dba)₃ (0.51 g, 0.41 mmol) and 1,4-bis(diphenylphosphino)butane (0.25 g, 0.41 mmol) in THF (5 mL), followed by thiosalicylic acid (2.2 g, 1.2 eq). The mixture was stirred at RT for 16 h. Solvent was evaporated and the residue was chromatographed on silica by eluting with 50% EtOAc/hexanes to give 1.3 g (37%) product as a oil which was dissolved in 4M HCl/dioxane (11 mL) and the mixture was stirred at RT for 2 h. Solvent was evaporated in vacuo and the residue was diluted with CHCl₃ (10 mL) followed by treatment with 1N NaOH to pH ~ 12. The organic layer was separated and the

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aqueous layer was extracted with CHCl_3 (3 x 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated to give 0.56 g (76%) of N-(2-(3-bromophenyl)-2-amino)prop-1-oxy)-methylamine (DC6; $\text{R}^6 = \text{Me}$, $\text{R}^1 = \text{Me}$) as a colorless oil. ^1H NMR (CDCl_3) δ 7.74 (t, $J = 1.8$ Hz, 1H), 7.41-7.50 (m, 2H), 7.26 (t, $J = 8.0$ Hz, 1H), 3.85 (dd, $J_1 = 9.6$ Hz, $J_2 = 28.8$ Hz, 2H), 2.72 (s, 3H), 1.48 (s, 3H).

Method DC, Step 7; 5-(3-Bromophenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine

To a solution of N-(2-(3-bromophenyl)-2-amino)prop-1-oxy)-methylamine (DC6; $\text{R}^6 = \text{Me}$, $\text{R}^1 = \text{Me}$) (0.76 g, 2.9 mmol) in EtOH (10 mL) was added BrCN (0.46 g, 4.4 mmol, 1.5 eq). After stirring at RT for 16 h, the mixture was concentrated. The residue was redissolved in CHCl_3 (20 mL) and washed with 2N NaOH (10 mL). The aqueous layer was extracted with CHCl_3 (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated to give 0.82 g (100%) of 5-(3-bromophenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine (DC7; $\text{R}^6 = \text{Me}$, $\text{R}^1 = \text{Me}$) as a light yellow oil. ^1H NMR (CDCl_3) δ 10.59 (s, 1H), 8.12 (br s, 1H), 7.46 (m, 2H), 7.29 (m, 2H), 4.14 (dd, $J_1 = 11.5$ Hz, $J_2 = 57.7$ Hz, 2H), 3.39 (s, 3H), 1.89 (s, 3H).

Method DC, Step 8; 5-(3-(3-Cyanophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine

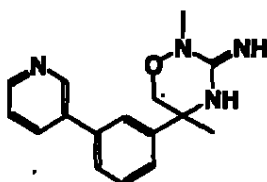
A mixture of 5-(3-bromophenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine (DC7; $\text{R}^6 = \text{Me}$, $\text{R}^1 = \text{Me}$) (0.025 g, 0.088 mmol, 1 eq), 3-cyanophenylboronic acid (0.019 g, 0.13 mmol, 1.5 eq), FibreCat (40 mg), anhydrous ethanol (1.5 mL), and a 1N K_2CO_3 aqueous solution (0.12 mL, 0.12 mmol, 1.4 eq) in a microwave vial was heated in a microwave reactor (Emrys Optimizer) at 110 °C for 15 min. The mixture was filtered, concentrated and purified by prep HPLC (B) to give 0.012 g (44%) of 5-(3-(3-cyanophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine (DC8; $\text{R}^6 = \text{Me}$, $\text{R}^1 = \text{Me}$, $\text{R}^{21} = 3\text{-cyanophenyl}$) as a white solid. ^1H NMR (CDCl_3) δ 10.67 (s, 1H), 8.05 (br s, 1H), 7.85 (m, 2H), 7.50-7.66 (m, 5H), 7.35 (m, 1H), 4.22 (dd, $J_1 = 11.8$ Hz, $J_2 = 48.6$ Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). MS m/e 307.3 (M^+H).

Using a similar procedure, the following compounds were also prepared:

5-(3-(3-Pyridyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine

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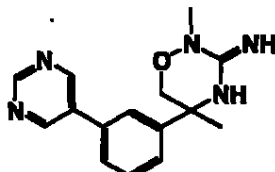
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¹H NMR (CDCl₃) δ 10.85 (s, 1H), 9.13 (s, 1H), 8.78 (m, 1H), 8.65 (m, 1H), 7.92 (m, 2H), 7.81 (s, 1H), 7.60 (m, 2H), 7.44 (m, 1H), 4.26 (dd, J₁ = 11.8 Hz, J₂ = 37.4 Hz, 2H), 3.41 (s, 3H), 1.77 (s, 3H). MS *m/e* 283.2 (M⁺H)

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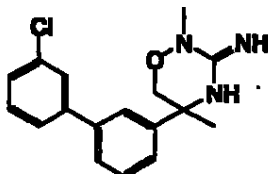
5-(3-(5-Pyrimidyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



¹H NMR (CDCl₃) δ 10.77 (br s, 1H), 10.42 (s, 1H), 9.26 (s, 1H), 9.07 (s, 1H), 7.84 (br s, 1H), 7.57-7.63 (m, 3H), 7.46 (m, 1H), 4.23 (dd, J₁ = 11.5 Hz, J₂ = 45.9 Hz, 2H), 3.41 (s, 3H), 1.77 (s, 3H). MS *m/e* 284.2 (M⁺H)

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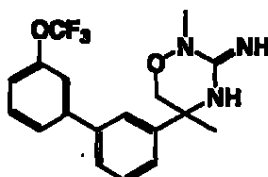
5-(3-(3-Chlorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



¹H NMR (CDCl₃) δ 10.63 (s, 1H), 8.00 (br s, 1H), 7.48-7.55 (m, 5H), 7.31-7.74 (m, 3H), 4.20 (dd, J₁ = 11.5 Hz, J₂ = 54.4 Hz, 2H), 3.39 (s, 3H), 1.76 (s, 3H). MS *m/e* 316.2 (M⁺H)

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5-(3-(3-Trifluoromethoxyphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



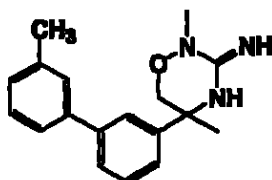
¹H NMR (CDCl₃) δ 10.72 (s, 1H), 8.03 (br s, 1H), 7.55 (m, 1H), 7.51 (m, 2H), 7.48 (m, 2H), 7.41 (m, 1H), 7.32-7.34 (dt, J₁ = 1.6 Hz, J₂ = 7.2 Hz, 1H), 7.21-7.23 (m, 1H),

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4.21 (dd, $J_1 = 11.8$ Hz, $J_2 = 53.0$ Hz, 2H), 3.39 (s, 3H), 1.76 (s, 3H). MS m/e 366.2 (M^+H)

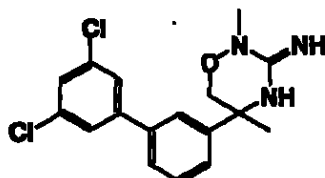
5-(3-(3-Tolyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



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^1H NMR ($CDCl_3$) δ 10.61 (s, 1H), 8.07 (br s, 1H), 7.53 (m, 2H), 7.45 (m, 1H), 7.33-7.37 (m, 3H), 7.28-7.32 (m, 1H), 7.17-7.19 (m, 1H), 4.20 (dd, $J_1 = 11.8$ Hz, $J_2 = 58.2$ Hz, 2H), 3.38 (s, 3H), 2.42 (s, 3H), 1.76 (s, 3H). MS m/e 296.4 (M^+H)

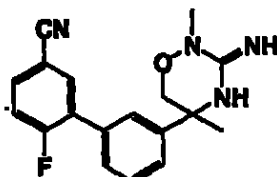
10 5-(3-(3,5-Dichlorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



^1H NMR ($CDCl_3$) δ 10.71 (s, 1H), 8.06 (br s, 1H), 7.47 (m, 3H), 7.43 (m, 2H), 7.35 (m, 2H), 4.20 (dd, $J_1 = 11.7$ Hz, $J_2 = 54.9$ Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). MS m/e 350.2 (M^+H)

5

5-(3-(2-Fluoro-5-cyanophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine

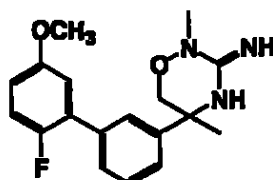


^1H NMR ($CDCl_3$) δ 10.50 (s, 1H), 7.86 (br s, 1H), 7.77 (dd, $J_1 = 2.1$ Hz, $J_2 = 6.9$ Hz, 1H), 7.65 (m, 1H), 7.50 (m, 2H), 7.42 (m, 1H), 7.27 (t, $J = 5.0$ Hz, 2H), 4.20 (dd, $J_1 = 12.0$ Hz, $J_2 = 50.4$ Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). MS m/e 325.1 (M^+H)

5-(3-(2-Fluoro-5-methoxyphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine

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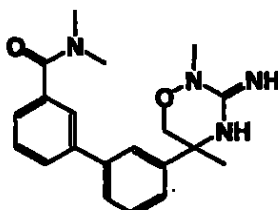
355



¹H NMR (CDCl₃) δ 10.53 (s, 1H), 7.94 (br s, 1H), 7.47 (m, 3H), 7.37 (m, 1H), 7.07 (t, J = 9.5 Hz, 1H), 6.93 (m, 1H), 6.86 (m, 1H), 4.19 (dd, J₁ = 11.7 Hz, J₂ = 58.5 Hz, 2H), 3.82 (s, 3H), 3.38 (s, 3H), 1.75 (s, 3H). MS *m/e* 330.1 (M⁺H)

5

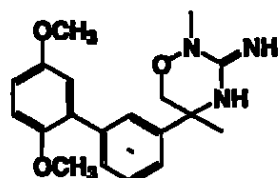
5-(3-(3-Dimethylaminocarbonylphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



¹H NMR (CDCl₃) δ 10.58 (s, 1H), 7.95 (br s, 1H), 7.26-7.65 (m, 8H), 4.20 (dd, J₁ = 11.5 Hz, J₂ = 54.7 Hz, 2H), 3.38 (s, 3H), 3.14 (s, 3H), 3.02 (s, 3H), 1.75 (s, 3H). MS *m/e* 353.2 (M⁺H)

10

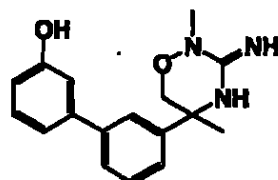
5-(3-(2,5-Dimethoxyphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



¹H NMR (CDCl₃) δ 10.50 (s, 1H), 7.99 (br s, 1H), 7.40-7.50 (m, 3H), 7.29-7.33 (m, 1H), 6.84-6.94 (m, 3H), 4.18 (dd, J₁ = 11.5 Hz, J₂ = 65.4 Hz, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.37 (s, 3H), 1.74 (s, 3H). MS *m/e* 342.2 (M⁺H)

15

5-(3-(3-Hydroxyphenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



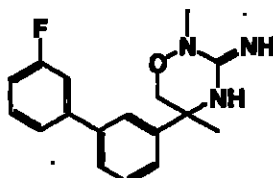
20

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- 340 -

^1H NMR (CDCl_3) δ 9.75 (s, 1H), 7.39-7.54 (m, 3H), 7.21-7.30 (m, 2H), 7.10-7.12 (m, 2H), 6.82-6.84 (m, 1H), 5.83 (br s, 2H), 4.15 (dd, $J_1 = 11.5$ Hz, $J_2 = 35.7$ Hz, 2H), 3.36 (s, 3H), 1.74 (s, 3H). MS m/e 298.3 (M^+H)

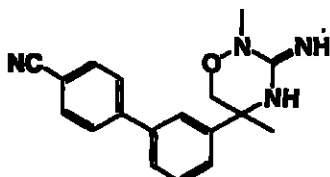
5 **5-(3-(3-Fluorophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine**



^1H NMR (CDCl_3) δ 10.77 (s, 1H), 8.15 (s, 1H), 7.25-7.56 (m, 7H), 7.01-7.08 (m, 1H), 4.20 (dd, $J_1 = 11.5$ Hz, $J_2 = 53.0$ Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). MS m/e 300.2 (M^+H)

10

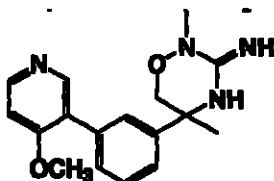
5-(3-(4-Cyanophenyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



^1H NMR (CDCl_3) δ 10.67 (s, 1H), 8.01 (br s, 1H), 7.74 (s, 4H), 7.63 (s, 1H), 7.48-7.56 (m, 2H), 7.33-7.35 (m, 1H), 4.23 (dd, $J_1 = 11.5$ Hz, $J_2 = 47.2$ Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). MS m/e 307.2 (M^+H)

5

5-(3-(4-Methoxy-3-pyridyl)phenyl)-2,5-dimethyl-1,2,4-oxadiazinan-3-imine



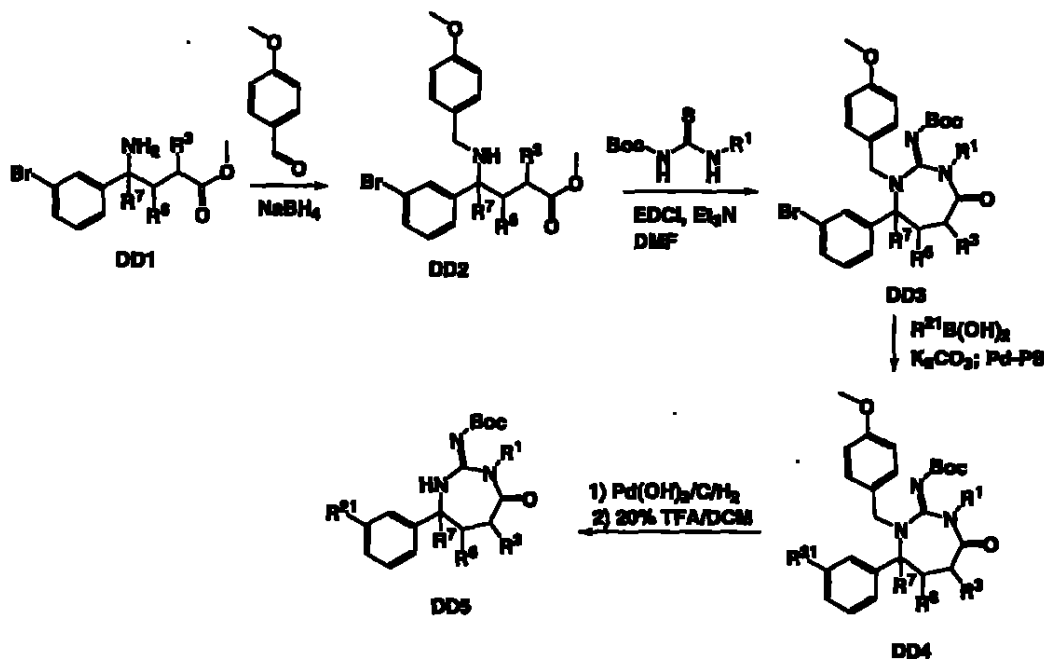
^1H NMR (CDCl_3) δ 10.55 (s, 1H), 8.74 (d, $J = 6.0$ Hz, 1H), 8.64 (s, 1H), 7.83 (br s, 1H), 7.49-7.53 (m, 3H), 7.37-7.42 (m, 2H), 4.20 (dd, $J_1 = 11.5$ Hz, $J_2 = 49.4$ Hz, 2H), 4.11 (s, 3H), 3.39 (s, 3H), 1.76 (s, 3H). MS m/e 313.2 (M^+H)

)

Method DD

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**Method DD, Step 1;**

To a 10 mL MeOH solution of DD1 ($R^3 = R^6 = H$, $R^7 = Me$, 1 g) was added p-methoxybenzaldehyde (1 eq) and 4 Å molecular sieves (4 g). The solution was stirred overnight before sodium borohydride (1 eq) was added and reaction stirred for 1 h. The reaction mixture was filtered and solvent evaporated. The residue was chromatographed using MeOH/DCM to afford compound DD2 ($R^3 = R^6 = H$, $R^7 = Me$).

Method DD, Step 2;

Procedure similar to Method CF, step 2 was used for generation of DD3 ($R^1 = Me$, $R^3 = R^6 = H$, $R^7 = Me$).

Method DD, Step 3;

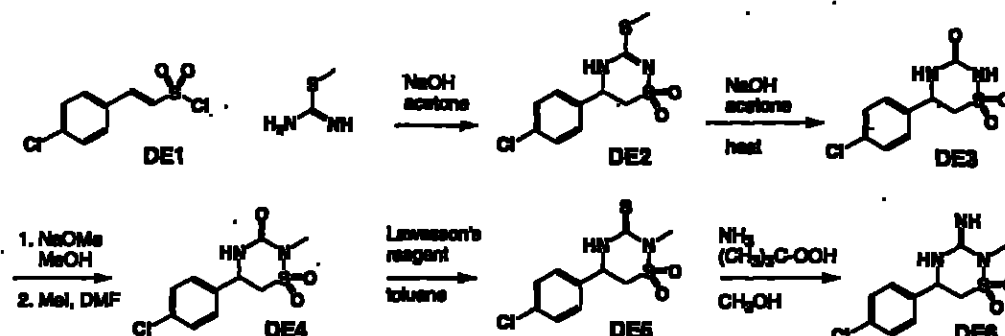
Procedure similar to Method CF, step 3 was used for generation of DD4 ($R^1 = Me$, $R^3 = R^6 = H$, $R^7 = Me$) from DD3

Method DD, Step 4;

Compound DD4 was hydrogenated using $Pd(OH)_2/C$ in Methanol. After removal of the catalyst and solvent the crude product was treated with 20% TFA in DCM to give product DD5 ($R^1 = Me$, $R^3 = R^6 = H$, $R^7 = Me$) after purification.

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Method DE



5 Method DE, Step 1: 5-(4-Chlorophenyl)-3-methylsulfany-5,6-dihydro-4H-[1,2,4]thiadiazine 1,1-dioxide

2-(4-Chlorophenyl)ethanesulfonyl chloride **DE1** is treated with 1.2 equivalents of S-methyl isothioureahemisorbate and a slight excess of 1N NaOH in acetone. After 12 h at RT the mixture is concentrated in vacuo and the precipitate collected to give the title compound.

10

Method DE, Step 2: N-(2-(4-Chlorophenyl)ethene-1-sulfonyl)-S-methylisothioureahemisorbate

Using a method similar to that described by K. Hasegawa and S. Hirooka (Bull. Chem. Soc. Jap., 1972, 45, 1893), N-(2-(4-chlorophenyl)ethylene-1-sulfonyl)thioureahemisorbate **DE2** in DMF is treated with 1N NaOH (2.4 equivalents) and dimethyl sulfate (1.2 equivalents) at 0-10 °C. After 3 h at RT, the reaction mixture is poured into ice water. The precipitate is collected, washed with water and dried to give the title compound **DE3**.

15

Method DE, Step 2: 5-(4-Chlorophenyl)-1,1-dioxo-5,6-dihydro-4H-[1,2,4]thiadiazine 3-one

Using a method similar to that described by K. Hasegawa and S. Hirooka (Bull. Chem. Soc. Jap., 1972, 45, 1893), 5-(4-chlorophenyl)-3-methylsulfany-5,6-dihydro-4H-[1,2,4]thiadiazine 1,1-dioxide **DE2** in acetone is treated with 1N NaOH and the mixture is refluxed for 2 h. The acetone is evaporated and the mixture is acidified with conc. HCl to afford the title compound **DE3**.

5

Method DE, Step 3: 5-(4-Chlorophenyl)-2-methyl-1,1-dioxo-5,6-dihydro-4H-[1,2,4]thiadiazine 3-one

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- Using a method similar to that described by A. Etienne et al. (Bull. Soc. Chim. Fr.; 1974, 1395) 5-(4-chlorophenyl)-1,1-dioxo-[1,2,4]thiadiazinan-3-one DE3 is treated with sodium methoxide (1 equivalent) in methanol. Add methyl iodide (1.2 equivalent) in DMF and allow to stir for 12 h. Pour the mixture into ice water and collect the precipitate of the title compound DE4.

Method DE, Step 4: 5-(4-Chlorophenyl)-2-methyl-1,1-dioxo-[1,2,4]thiadiazinan-3-thione

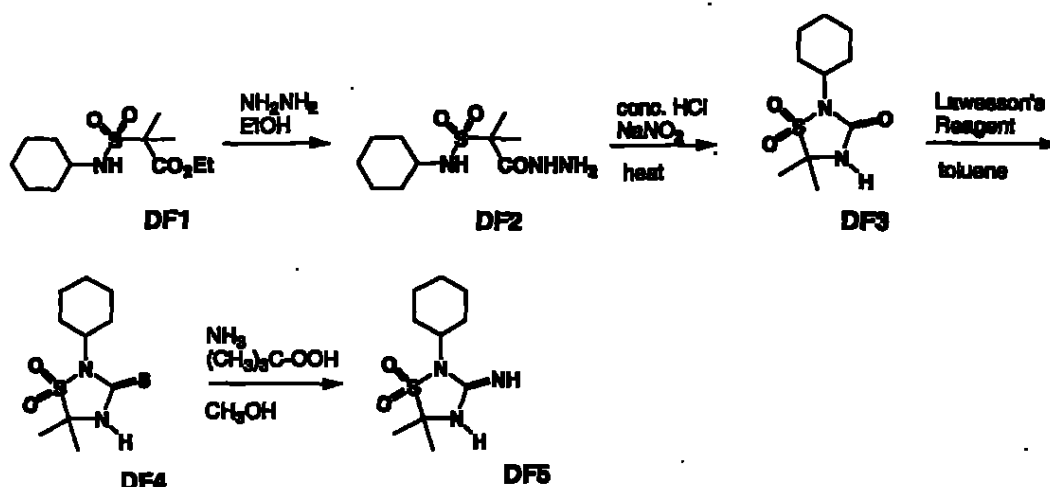
- To a solution of DE4 in toluene (or xylene) is added Lawesson's reagent (1.2 equivalents), and the mixture is stirred at reflux for 2 h. The mixture is cooled and poured into cold water. The organic phase is dried (MgSO₄) and filtered, and solvent is removed. The crude product is purified by flash chromatography to provide the title compound (DE5).

- Method DE, Step 5: 5-(4-Chlorophenyl)-2-methyl-1,1-dioxo-[1,2,4]thiadiazinan-3-ylideneamine**

Using a route similar to that described in Method A, step 3, DE5 is used to prepare the title compound (DE6).

- As a variant of this method, DE2 is treated with ammonia and the resultant product is treated with sodium hydride and methyl iodide in DMF to give the product DE6

Method DF



Method DF, Step 1: 2-Hydrazinocarbonylpropane-2-sulfonic acid cyclohexylamide

- 5 Using a method similar to that described by S. Palk and E.H. White (Tetrahedron, 1996, 52, 5303), 2-cyclohexylsulfamoyl-2-methylpropionic acid ethyl ester DF1 (which is prepared by the method of A. De Blic et al. (Synthesis, 1982, 281)) in ethanol is treated with 1.2 equivalent of 95% hydrazine under N₂ and the mixture is allowed to stand at RT for 12 h. The reaction mixture is concentrated to give the title compound
- 10 DF2 which is used directly in Step 2.

Method DF, Step 2: 2-Cyclohexyl-5,5-dimethyl-1,2,4-thiadiazolidin-3-one-1,1-dioxide

- A solution of DF2 in CH₂Cl₂ is refluxed under a N₂ for 10 h. The solvent is removed in vacuo and the crude product is purified by flash chromatography to provide the title compound DF3.
- 15

Method DF, Step 3: 2-Cyclohexyl-5,5-dimethyl-1,2,4-thiadiazolidin-3-thione-1,1-dioxide

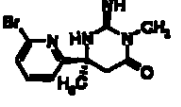
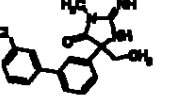
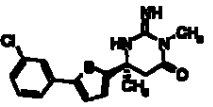
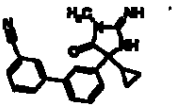
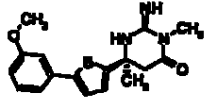
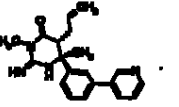
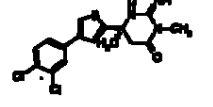
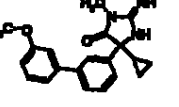
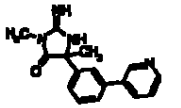
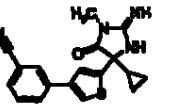
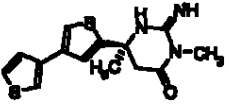
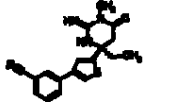
- 20 To a solution of DF3 in toluene (or xylene) is added Lawesson's reagent (1.2 equivalents), and the mixture is stirred at reflux for 2 h. The mixture is cooled and poured into cold water. The organic phase is dried (MgSO₄) and filtered, and solvent is removed. The crude product is purified by flash chromatography to provide the title compound (DF4).

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Method DF, Step 4: 2-Cyclohexyl-5,5-dimethyl-1,2,4-thiadiazolidin-3-imine-1,1-dioxide

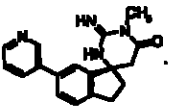
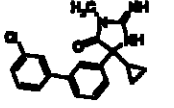
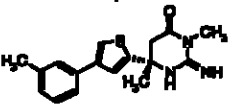
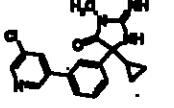
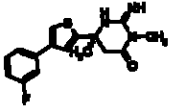
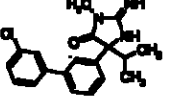
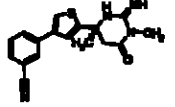
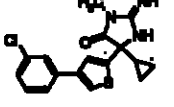
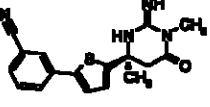
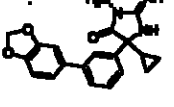
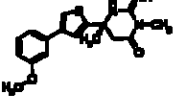
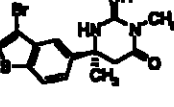
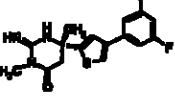
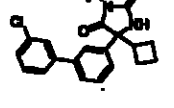
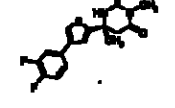
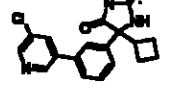
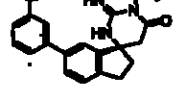
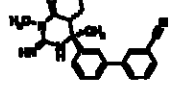
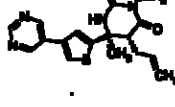
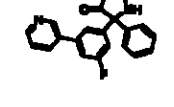
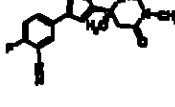
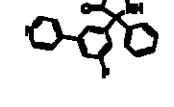
Using a route similar to that described in Method A, step 3, DF4 is used to prepare the title compound (DF5).

The following table contains example compounds which were synthesized with procedure(s) similar to methods listed in the corresponding column and whose LCMS data (obs. mass) are also listed.

#	Compounds	Method	Obs. Mass	#	Compounds	Method	Obs. Mass
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1482		CF	333.9	1483		AW	331.2
1483		CF	328.9	1484		CE	335.2
1484		CF	367.8	1485		AW	336.2
1485		AW	281	1486		AW	337.2
1486		CF	308	1487		CF	338.2

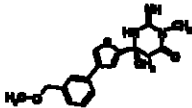
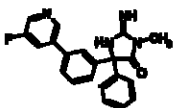
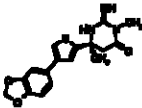
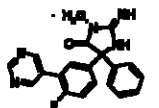
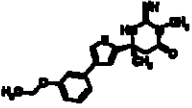
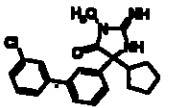
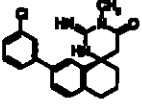
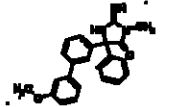
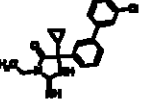
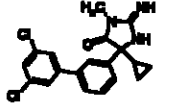
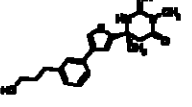
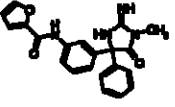
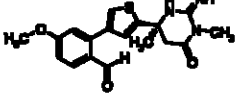
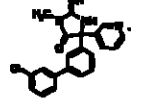
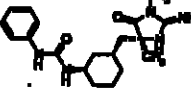
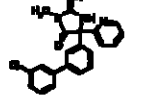
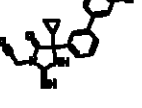
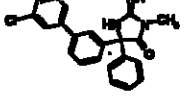
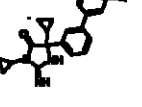
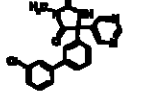
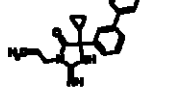
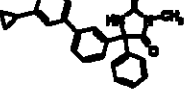
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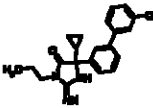
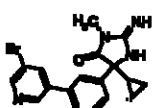
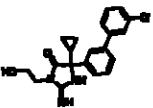
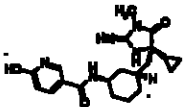
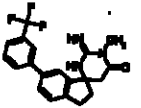
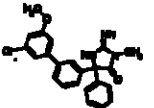
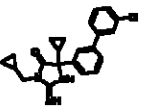
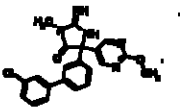
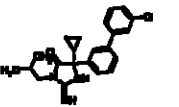
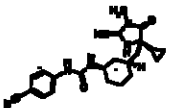
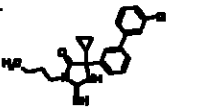
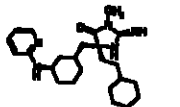
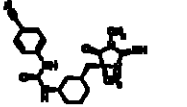
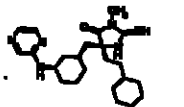
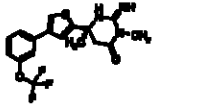
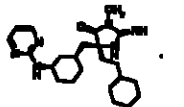
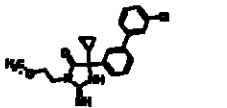
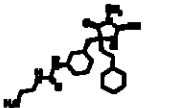
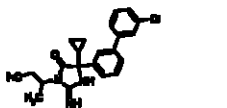
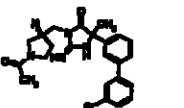
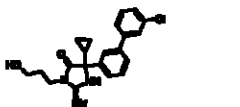
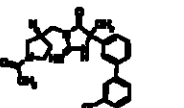
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1501		CF	325	1672		AW	350.2
1502		CF	330	1673		CJ	352.2
1503		CF	336	1674		AW	354.2
1504		CF	338	1675		AW	355.2
1505		AB	340	1676		CE	359.2
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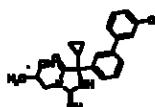
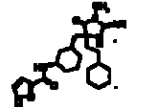
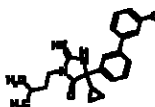
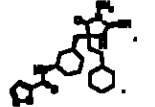
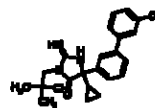
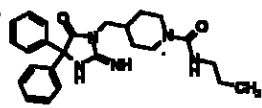
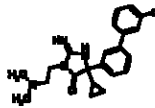
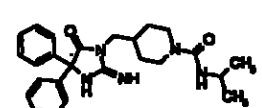
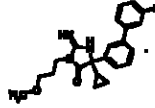
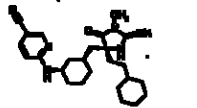
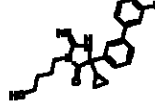
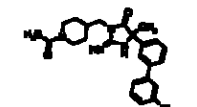
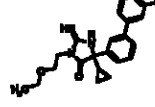
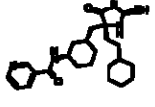
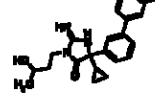
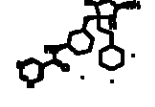
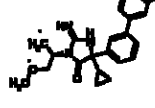
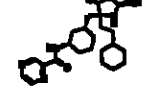
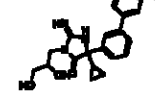
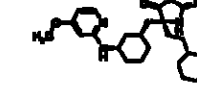
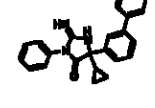
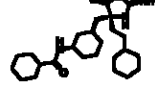
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1509		CF	344	1580		AW	362.2
1510		CF	344	1581		AW	366.2
1511		AB	354	1582		AW	372.2
1512		A	354	1583		AW	374.2
1513		CF	358	1584		BQ	375.2
1514		CF	358	1585		CL	377.2
1515		BS	358	1586		BK	377.2
1516		A	364	1587		AW	377.2
1517		A	366	1588		CG	378.2
1518		A	366	1589		AW	383.2

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1619		A	388	1690		CO	385.2
1620		A	370	1691		BQ	388.2
1621		AB	374	1692		AW	408.2
1622		A	380	1693		CL	408.2
1623		A	382	1694		BS	409.2
1624		A	382	1695		BW	412.2
1625		BS	383	1696		BW	413.2
1626		CF	384	1697		BW	413.2
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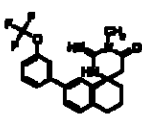
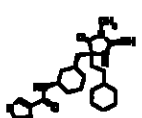
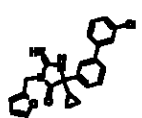
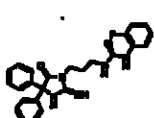
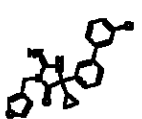
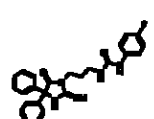
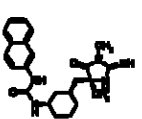
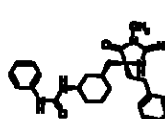
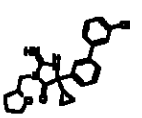
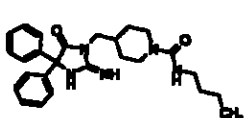
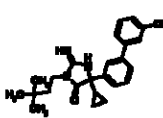
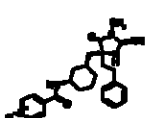
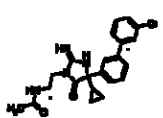
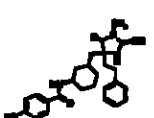
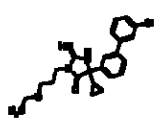
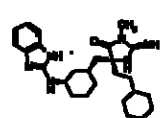
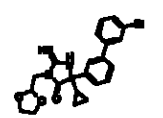
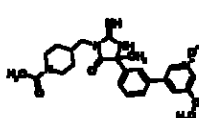
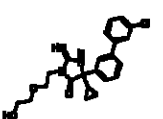
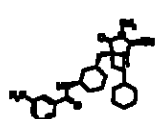
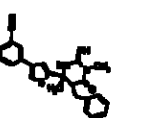
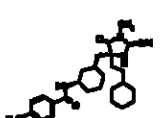
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1530		A	384	1701		BQ	429.2
1531		A	386	1702		BQ	430.2
1532		A	388	1703		R	434.2
1533		A	387	1704		R	434.2
1534		A	388	1705		BW	437.2
1535		A	388	1706		AW	438.2
1536		A	388	1707		BQ	440.2
1537		A	388	1708		BQ	441.2
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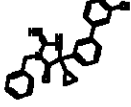
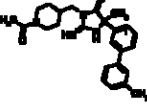
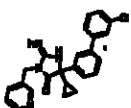
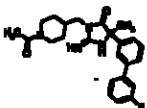
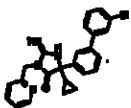
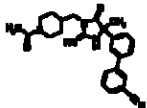
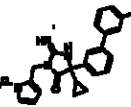
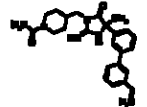
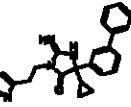
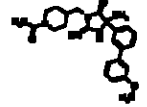
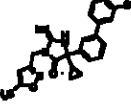
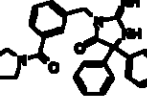
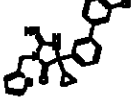
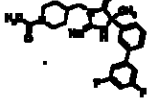
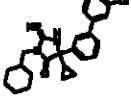
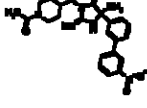
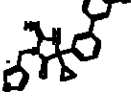
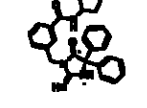
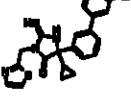
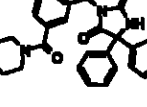
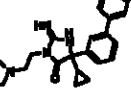
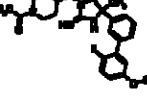
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1541		AB	404	1712		BQ	448.2
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1545		A	410	1716		R	448.2
1546		A	410	1717		BQ	450.2
1547		A	411	1718		BQ	450.2
1548		A	412	1719		BW	451.2
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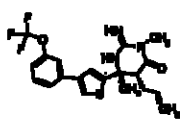
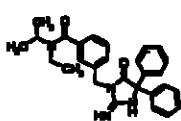
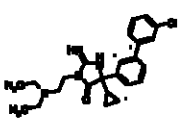
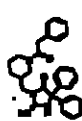
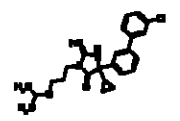
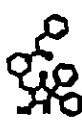
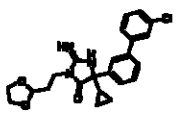
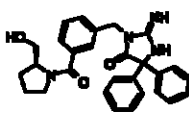
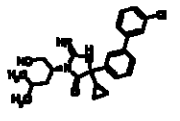
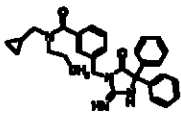
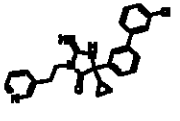
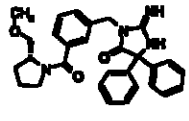
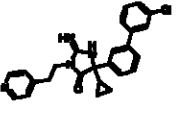
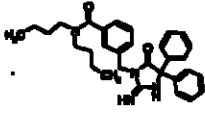
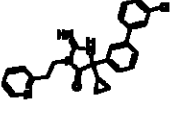
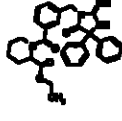
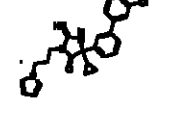
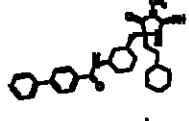
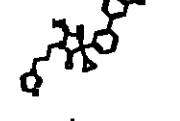
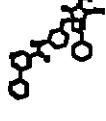
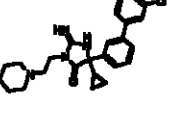
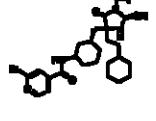
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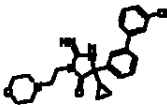
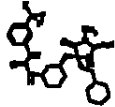
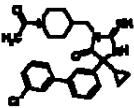
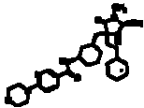
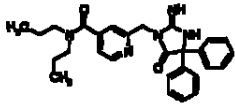
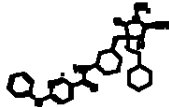
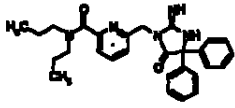
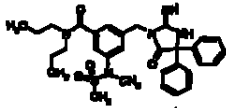
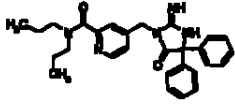
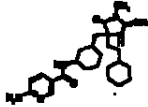
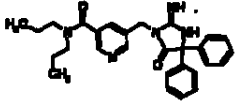
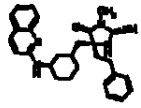
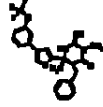
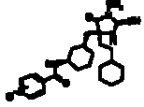
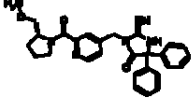
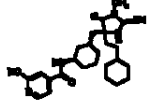
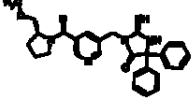
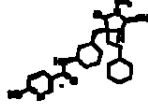
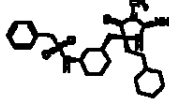
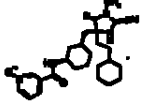
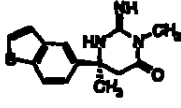
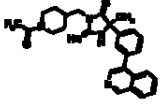
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1556		A	420	1727		AW	435.2
1557		A	421	1728		CK	439.2
1558		A	422	1729		AW	441.2
1559		A	422	1730		AW	450.3
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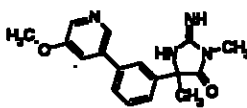
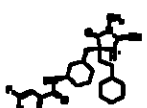
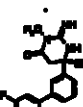
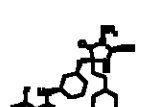
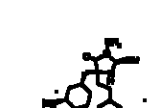
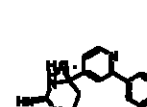
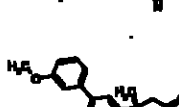
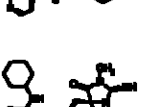
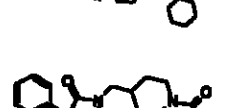
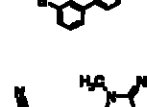
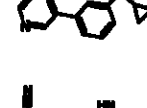
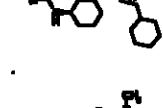
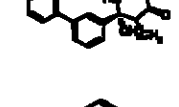
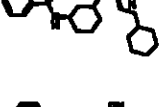
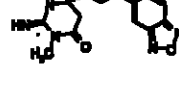
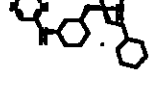
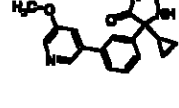
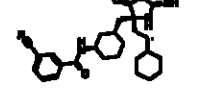
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1565		A	426	1736		L	457.3
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1568		A	431	1739		CK	463.3
1569		A	431	1740		CK	467.3
1570		A	431	1741		CK	525.3
1571		A	433	1742		BQ	515.3
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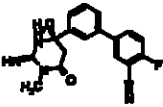
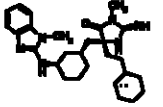
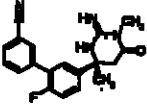
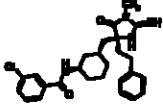
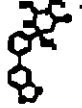
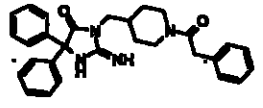
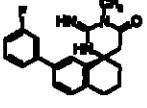
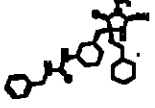
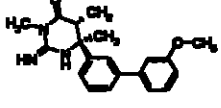
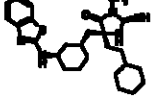
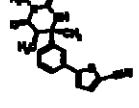
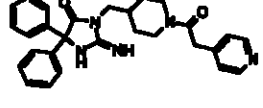
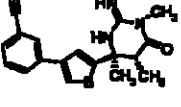
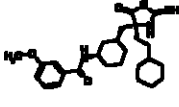
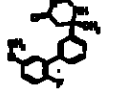
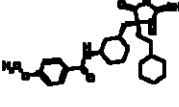
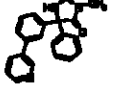
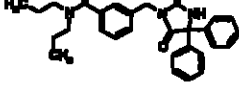
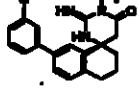
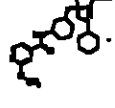
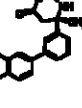
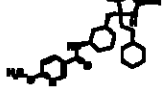
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1578		CG	470	1749		BQ	455.3
1579		CG	470	1750		BW	456.3
1580		CE	474	1751		BQ	458.3
1581		CG	484	1752		BQ	458.3
1582		CG	484	1753		BS	458.3
1583		BR	489	1754		BQ	458.3
1584		CF	274.1	1755		AW	458.3

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1585		AW	311.1	1758		BQ	458.3
1586		AB	312.1	1767		BQ	458.3
1587		AB	319.1	1788		BQ	458.3
1588		CF	320.1	1769		BQ	458.3
1589		CF	325.1	1780		B6	480.3
1590		AB	326.1	1781		R	480.3
1591		AW	332.1	1782		BW	482.3
1592		CE	333.1	1783		BW	482.3
1593		CF	338.1	1784		BW	483.3
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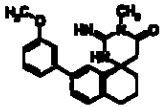
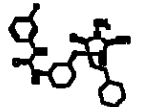
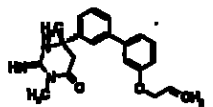
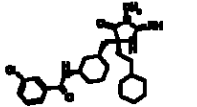
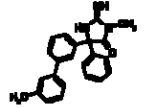
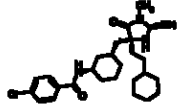
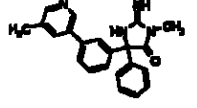
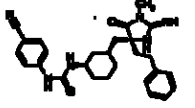
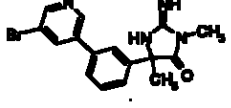
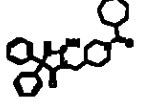
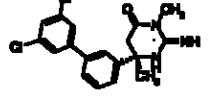
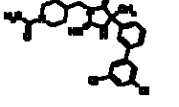
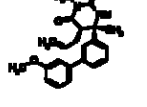
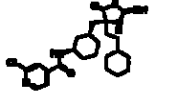
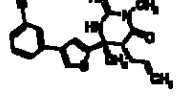
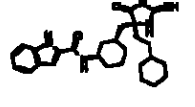
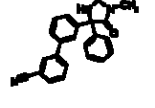
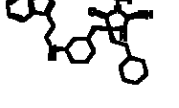
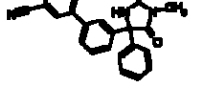
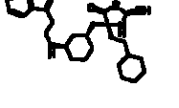
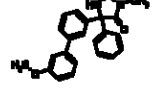
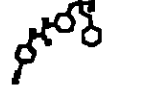
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1586		CF	337.1	1767		BW	465.3
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1589		AB	338.1	1770		BS	468.3
1590		CE	338.1	1771		BW	468.3
1591		CF	338.1	1772		Q	468.3
1592		CE	339.1	1773		BQ	469.3
1593		AB	342.1	1774		BQ	469.3
1594		AW	343.1	1775		CG	469.3
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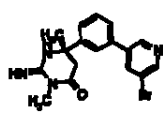
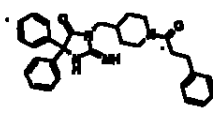
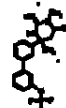
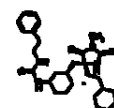
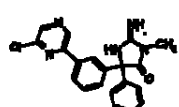
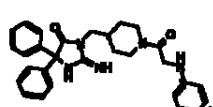
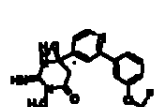
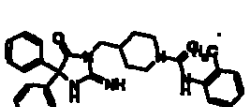
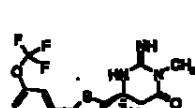
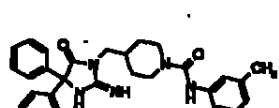
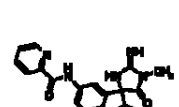
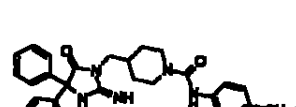
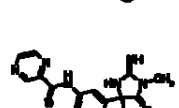
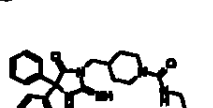
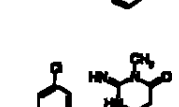
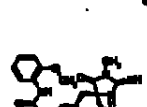
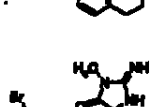
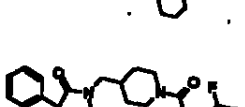
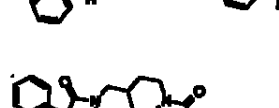
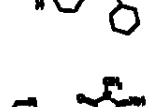
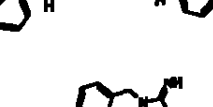
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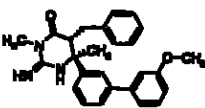
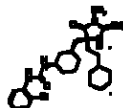
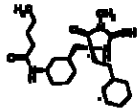
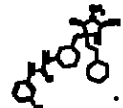
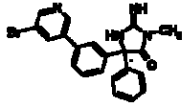
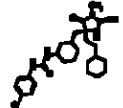
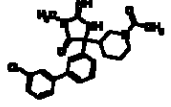
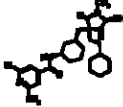
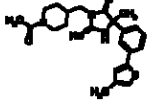
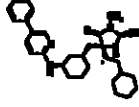
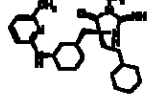
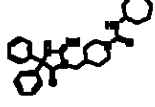
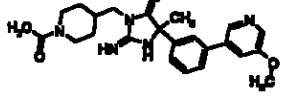
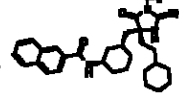
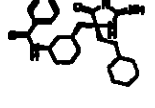
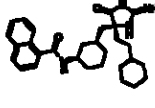
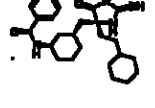
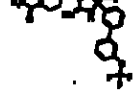
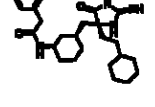
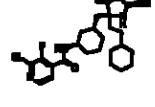
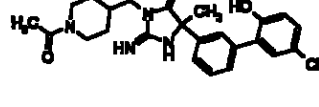
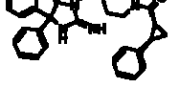
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1811		AW	369.1	1782		Q	473.3
1812		AB	362.1	1783		AW	473.3
1813		CE	364.1	1784		BQ	474.3
1814		CE	365.1	1785		BO	478.3
1815		AW	367.1	1786		AZ	478.3
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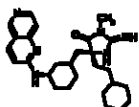
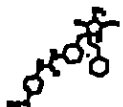
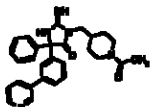
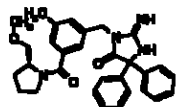
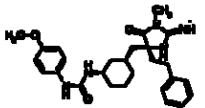
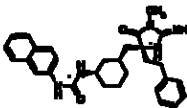
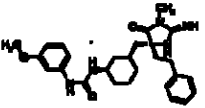
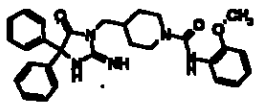
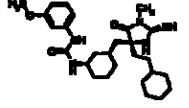
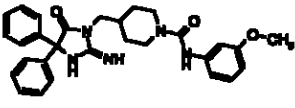
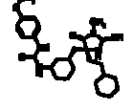
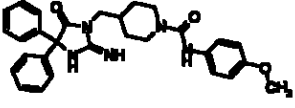
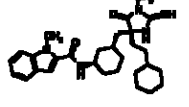
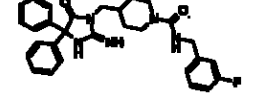
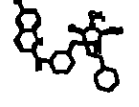
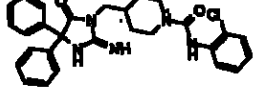
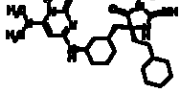
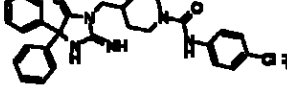
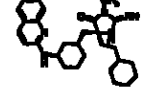
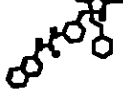
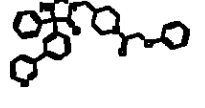
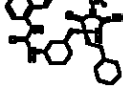
- 357 -

1618		CF	373.1	1788		Q	481.3
1619		AB	375.1	1790		BS	482.3
1620		AW	375.1	1791		Q	482.3
1621		CF	375.1	1792		R	482.3
1622		CF	384.1	1793		I	482.3
1623		BQ	385.1	1794		I	482.3
1624		BQ	387.1	1795		R	482.3
1625		AB	388.1	1796		BS	484.3
1626		CO	398.1	1797		R	486.3
1627		BW	412.1	1798		F	488.3
1628		BW	412.1	1799		CK	487.3

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294

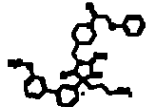
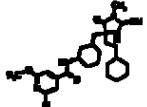
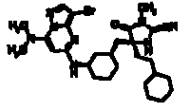
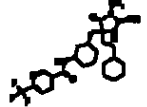
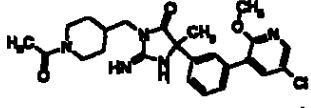
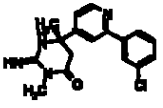
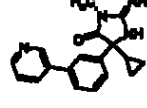
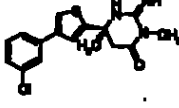
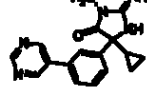
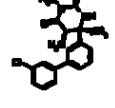
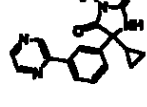
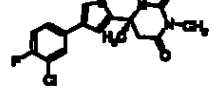
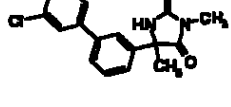
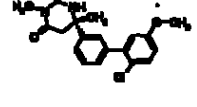
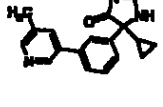
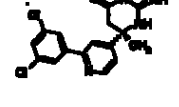
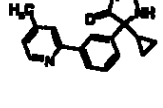
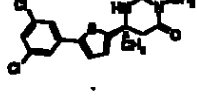
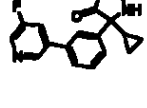
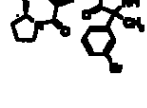
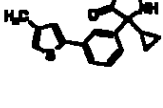
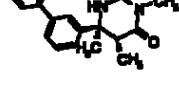
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1831		AW	421.1	1802		BS	488.3
1832		AM	425.1	1803		BQ	488.3
1833		AW	425.1	1804		BW	488.3
1834		BW	428.1	1805		R	488.3
1835		AW	438.1	1806		BQ	488.3
1836		BQ	439.1	1807		BQ	488.3
1837		BQ	440.1	1808		AW	489.3
1838		BQ	453.1	1809		BQ	489.3
1839		CH	455.1	1810		Q	493.3

- 359 -

1840		BW	483.1	1811		BS	497.3
1841		Q	488.1	1812		CG	497.3
1842		BS	478.1	1813		BS	496.3
1843		BS	478.1	1814		R	496.3
1844		BS	484.1	1815			498.3
1845		BS	484.1	1816			498.3
1846		BQ	482.1	1817		R	500.3
1847		BW	482.1	1818		R	502.3
1848		BW	486.1	1819			502.3
1849		BW	486.1	1820		BS	504.3
1850		Q	500.1	1821		BS	504.3

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1851		AW	569.1	1822		BQ	504.3
1852		BW	573.1	1823		BQ	508.3
1853		AW	470.1	1824		CF	329.1, 331.1
1854		AW	307.2	1825		CF	334.0, 336.0
1855		AW	308.2	1826		CF	342.1, 344.1
1856		CP	308.2	1827		CF	352.0, 353.9
1857		AW	315.2	1828		CF	358.1, 360.1
1858		AW	321.2	1829		CF	363.1, 365.1
1859		CO	321.2	1830		CF	367.9, 369.9
1860		AW	325.2	1831		A	501.1 499
1861		AW	328.2	1832		CE	309

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Human Cathepsin D FRET assay.

- 5 This assay can be run in either continuous or endpoint format. The substrate used below has been described (Y.Yasuda et al., J. Biochem. , 125, 1137 (1999)). Substrate and enzyme are commercially available.

- 10 The assay is run in a 30ul final volume using a 384 well Nunc black plate. 8 concentrations of compound are pre-incubated with enzyme for 30mins at 37C followed by addition of substrate with continued incubation at 37C for 45 mins. The rate of increase in fluorescence is linear for over 1h and is measured at the end of the incubation period using a Molecular Devices FLEX station plate reader. KIs are interpolated from the IC50s using a Km value of 4uM and the substrate concentration of 2.5uM.

Reagents

- Na-Acetate pH 5
1% Brij-35 from 10% stock (Calbiochem)
20 DMSO
Purified (>95%) human liver Cathepsin D (Athens Research & Technology Cat# 16-12-030104)
Peptide substrate(Km=4uM) Mca-Gly-Lys-Pro-Ile-Leu-Phe-Phe-Arg-Leu-Lys(Dnp)-D-Arg-NH₂ Bachem Cat # M-2455
Pepstatin is used as a control inhibitor (Ki~0.5nM) and is available from Sigma.
25 Nunc 384 well black plates

Final Assay buffer conditions

- 100mM Na Acetate pH 5.0
0.02% Brij-35
30 1% DMSO

Compound is diluted to 3x final concentration in assay buffer containing 3% DMSO. 10ul of compound is added to 10ul of 2.25nM enzyme(3x) diluted in assay buffer without DMSO, mixed briefly, spun, and incubated at 37C for 30mins. 3x substrate

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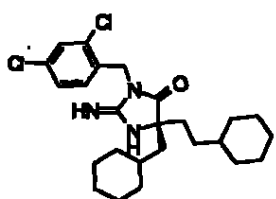
(7.5uM) is prepared in 1x assay buffer without DMSO. 10ul of substrate is added to each well mixed and spun briefly to initiate the reaction. Assay plates are incubated at 37 C for 45mins and read on 384 compatible fluorescence plate reader using a 328nm Ex and 393nm Em.

- 5 Compounds of the present invention exhibit hCathD KI data ranges from about 0.1 to about 500 nM, preferably about 0.1 to about 100 nM more preferably about 0.1 to about 75 nM.

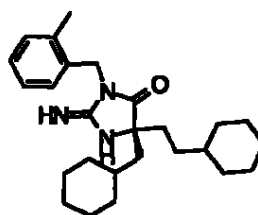
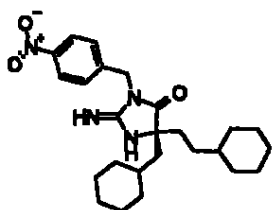
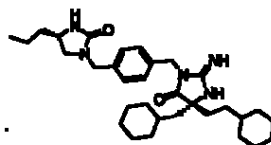
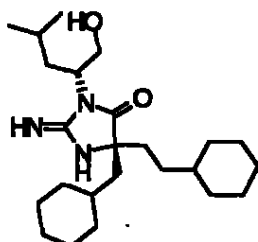
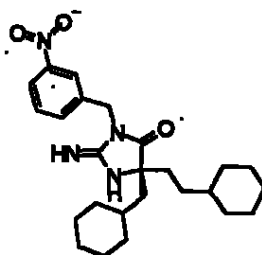
The following are examples of compounds that exhibit hCathD KI data under 75 nM.

10

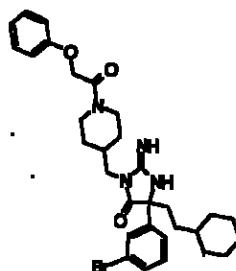
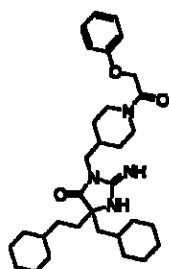
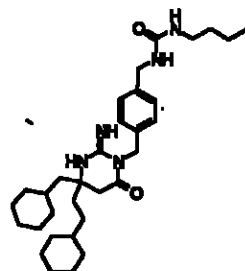
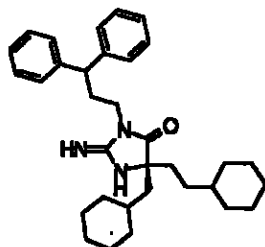
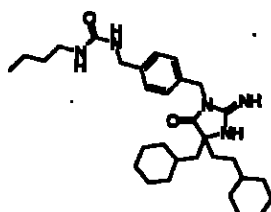
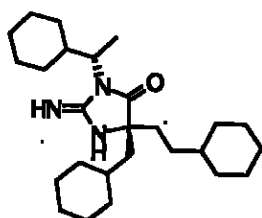
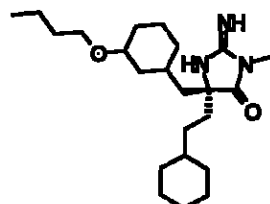
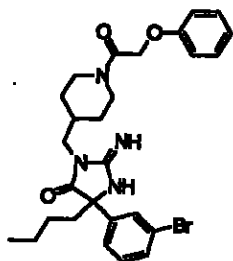
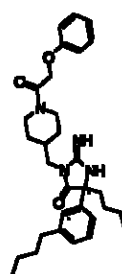
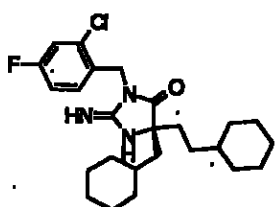
structure



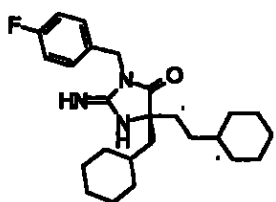
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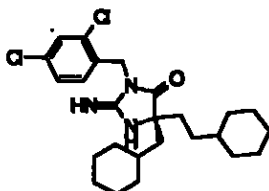
379



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The following compound



5 has a hCath D KI value of 0.45 nM.

BACE-1 Cloning, Protein Expression and Purification.

A predicted soluble form of human BACE1 (sBACE1, corresponding to amino acids 1-454) was generated from the full length BACE1 cDNA (full length human BACE1 cDNA in pCDNA4/mycHisA construct; University of Toronto) by PCR using the advantage-GC cDNA PCR kit (Clontech, Palo Alto, CA). A HindIII/PmeI fragment from pCDNA4-sBACE1myc/His was blunt ended using Klenow and subcloned into the Stu I site of pFASTBAC1(A) (Invitrogen). A sBACE1mycHis recombinant bacmid was generated by transposition in DH10Bac cells (GIBCO/BRL). Subsequently, the sBACE1mycHis bacmid construct was transfected into sf9 cells using CellFectin (Invitrogen, San Diego, CA) in order to generate recombinant baculovirus. Sf9 cells were grown in SF 900-II medium (Invitrogen) supplemented with 3% heat inactivated FBS and 0.5X penicillin/streptomycin solution (Invitrogen). Five milliliters of high titer plaque purified sBACEmyc/His virus was used to infect 1L of logarithmically growing sf9 cells for 72 hours. Intact cells were pelleted by centrifugation at 3000xg for 15 minutes. The supernatant, containing secreted sBACE1, was collected and diluted 50% v/v with 100 mM HEPES, pH 8.0. The diluted medium was loaded onto a Q-

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sepharose column. The Q-sepharose column was washed with Buffer A (20 mM HEPES, pH 8.0, 50 mM NaCl).

Proteins, were eluted from the Q-sepharose column with Buffer B (20 mM HEPES, pH 8.0, 500 mM NaCl). The protein peaks from the Q-sepharose column were pooled and loaded onto a Ni-NTA agarose column. The Ni-NTA column was then washed with Buffer C (20 mM HEPES, pH 8.0, 500 mM NaCl). Bound proteins were then eluted with Buffer D (Buffer C+250 mM imidazole). Peak protein fractions as determined by the Bradford Assay (Blorad, CA) were concentrated using a Centricon 30 concentrator (Millipore). sBACE1 purity was estimated to be ~90% as assessed by SDS-PAGE and Commassle Blue staining. N-terminal sequencing indicated that greater than 90% of the purified sBACE1 contained the prodomain; hence this protein is referred to as sproBACE1.

Peptide Hydrolysis Assay.

The inhibitor, 25 nM EuK-biotin labeled APP_{sw} substrate (EuK-KTEEISEVNLDAEFRHDKC-biotin; CIS-Bio International, France), 5 μ M unlabeled APP_{sw} peptide (KTEEISEVNLDAEFRHDK; American Peptide Company, Sunnyvale, CA), 7 nM sproBACE1, 20 mM PIPES pH 5.0, 0.1%Brij-35 (protein grade, Calbiochem, San Diego, CA), and 10% glycerol were preincubated for 30 min at 30°C. Reactions were initiated by addition of substrate in a 5 μ l aliquot resulting in a total volume of 25 μ l. After 3 hr at 30° C reactions were terminated by addition of an equal volume of 2x stop buffer containing 50 mM Tris-HCl pH 8.0, 0.5 M KF, 0.001% Brij-35, 20 μ g/ml SA-XL665 (cross-linked allophycocyanin protein coupled to streptavidin; CIS-Bio International, France) (0.5 μ g/well). Plates were shaken briefly and spun at 1200xg for 10 seconds to pellet all liquid to the bottom of the plate before the incubation. HTRF measurements were made on a Packard Discovery® HTRF plate reader using 337 nm laser light to excite the sample followed by a 50 μ s delay and simultaneous measurements of both 620 nm and 665 nm emissions for 400 μ s.

IC₅₀ determinations for inhibitors, (*I*), were determined by measuring the percent change of the relative fluorescence at 665 nm divided by the relative fluorescence at 620 nm, (665/620 ratio), in the presence of varying concentrations of *I* and a fixed concentration of enzyme and substrate. Nonlinear regression analysis of this data was performed using GraphPad Prism 3.0 software selecting four parameter logistic equation, that allows for a variable slope. $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) /$

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381

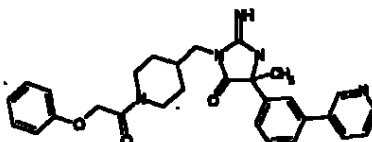
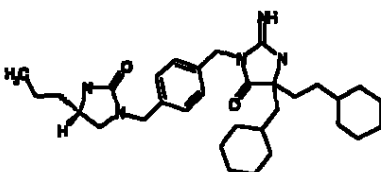
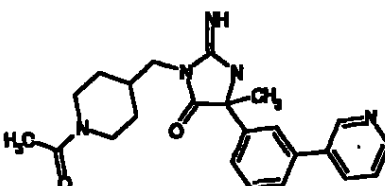
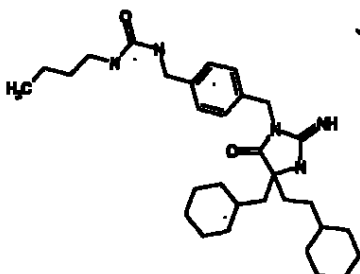
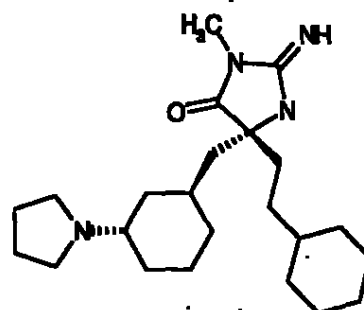
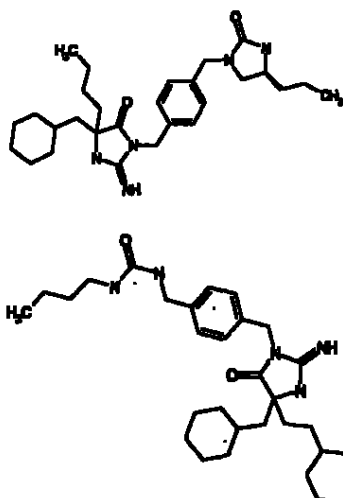
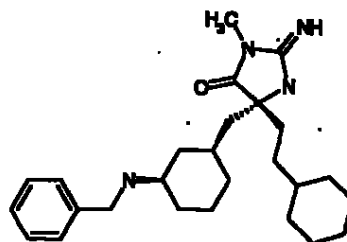
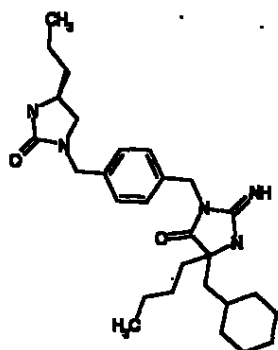
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$(1+10^{((\text{LogEC}_{50}-X) \cdot \text{Hill Slope}))}$); X is the logarithm of concentration of I, Y is the percent change in ratio and Y starts at bottom and goes to top with a sigmoid shape.

Compounds of the present invention have an IC_{50} range from about 0.001 to about 500 μM , preferably about 0.001 to about 100 μM , more preferably about 0.001 to about 20 μM .

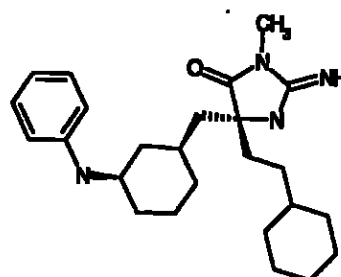
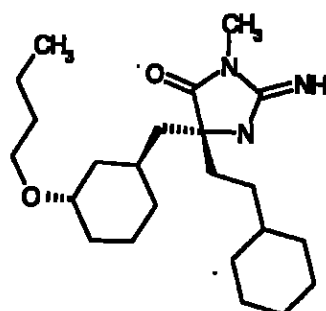
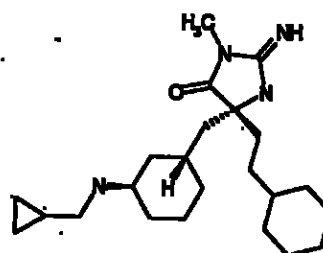
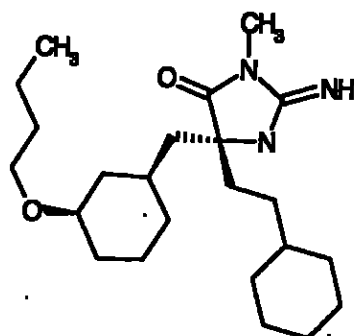
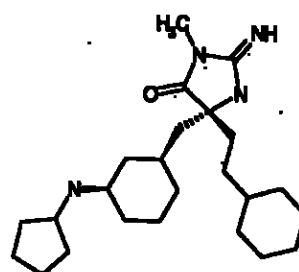
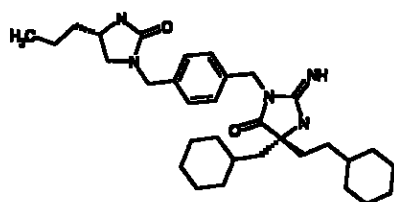
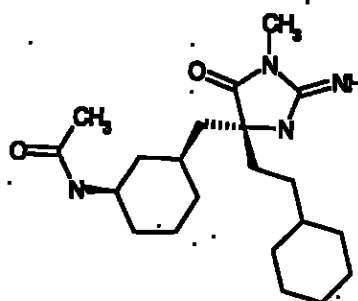
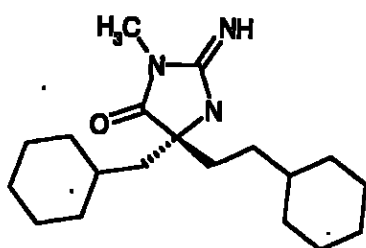
5

Examples of compounds with human BACE 1 $\text{IC}_{50} < 1 \mu\text{M}$ are listed below:



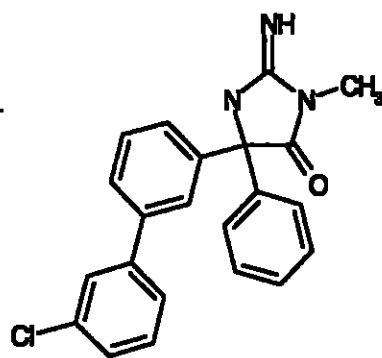
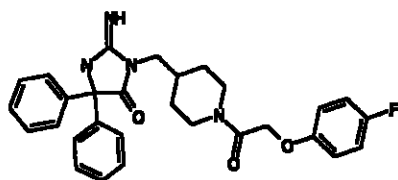
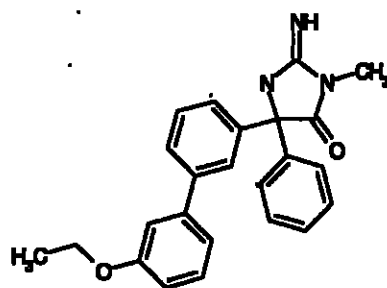
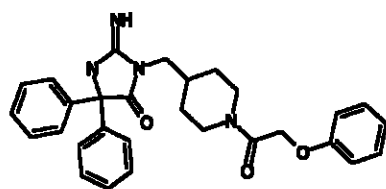
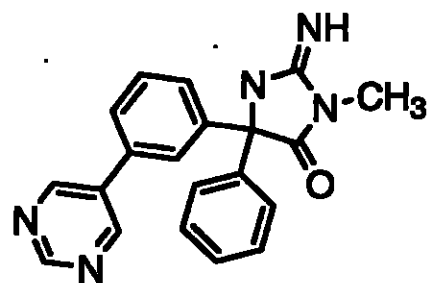
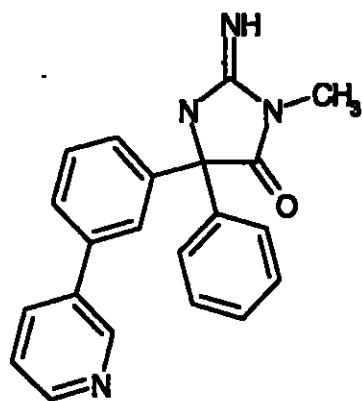
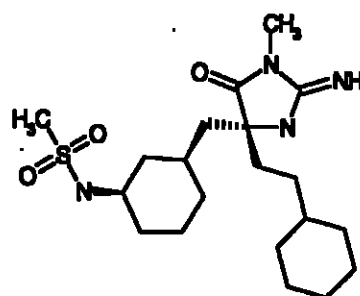
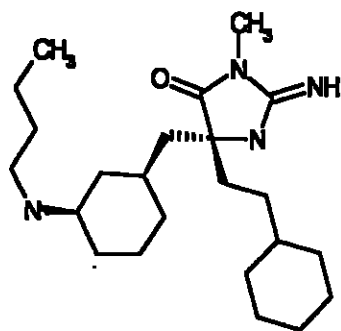
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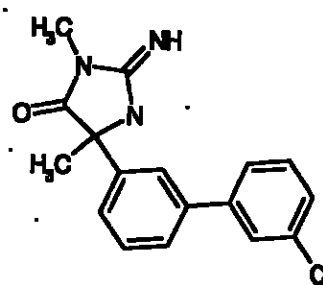
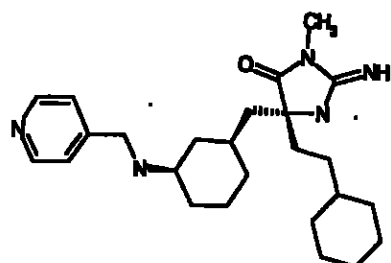
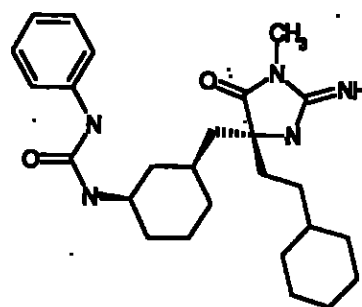
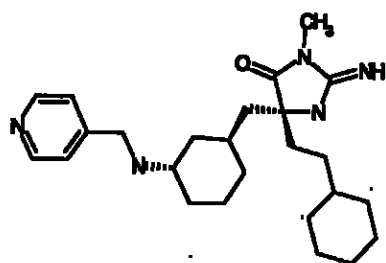
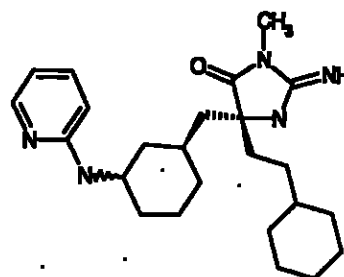
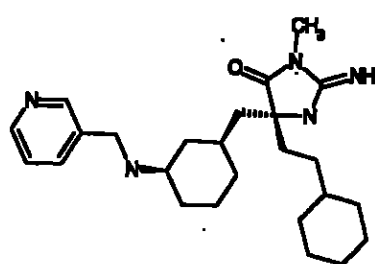
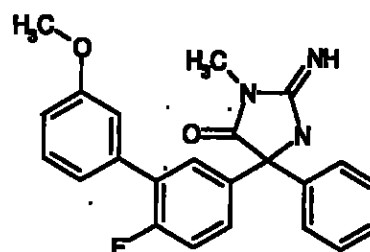
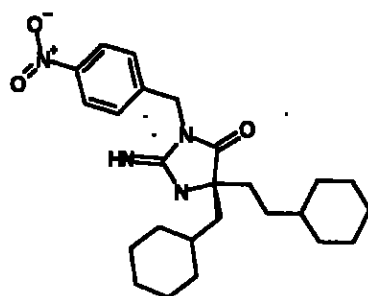
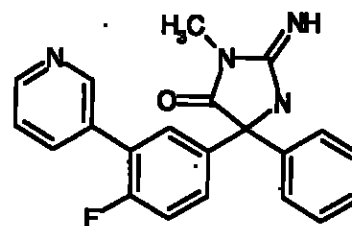
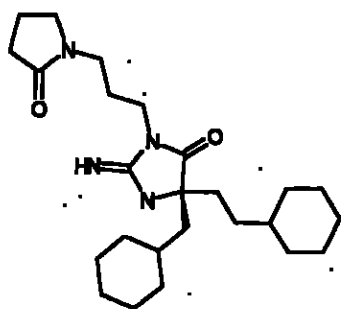


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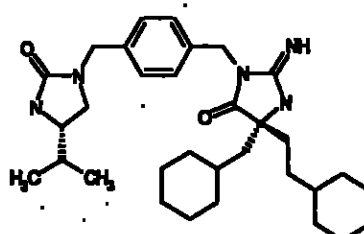
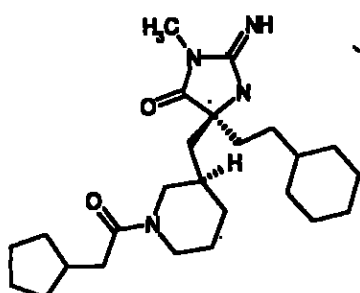
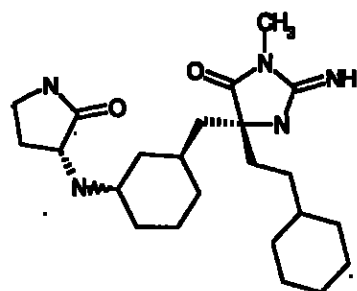
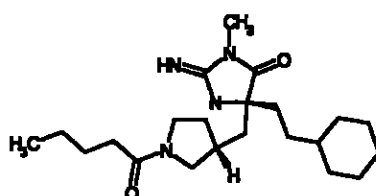
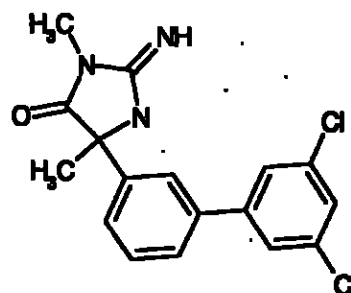
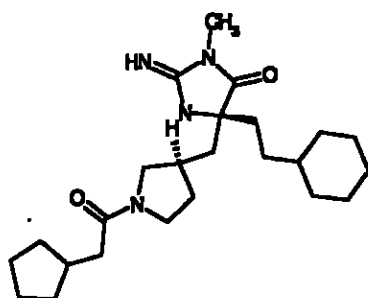
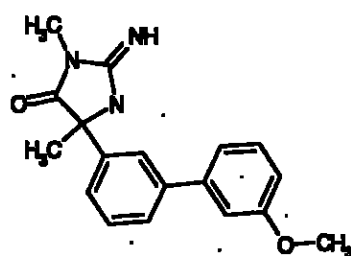
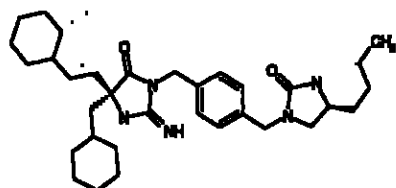


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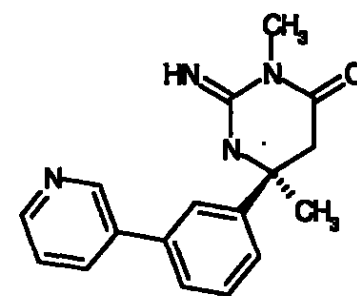
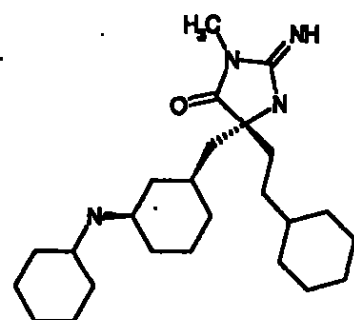
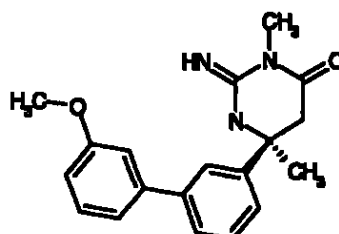
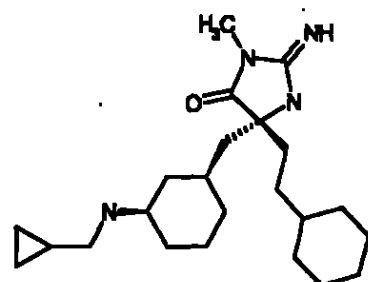
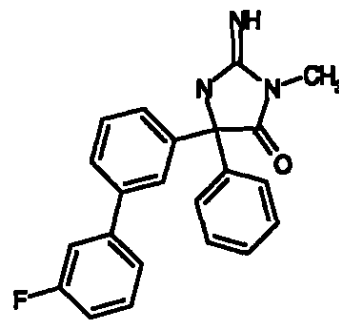
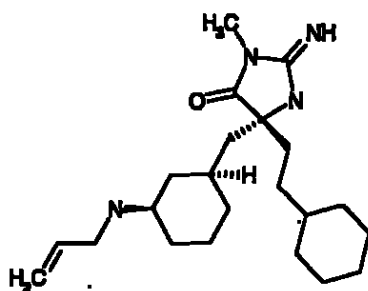
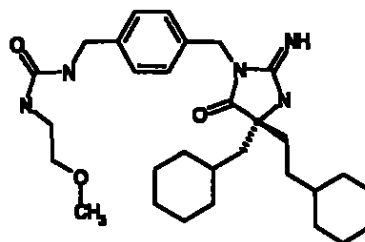
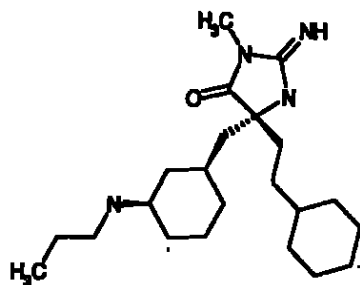
306
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2515

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**Human mature Renin enzyme assay:**

Human Renin was cloned from a human kidney cDNA library and C-terminally epitope-tagged with the V5-6His sequence into pCDNA3.1. pCDNA3.1-Renin-V5-6His was stably expressed in HEK293 cells and purified to >80% using standard Ni-Affinity chromatography. The prodomain of the recombinant human renin-V5-6His

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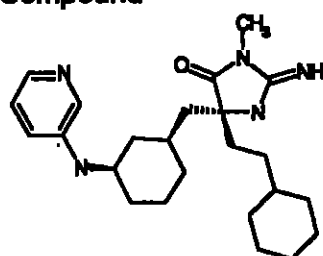
- 372 -

was removed by limited proteolysis using immobilized TPCK-trypsin to give mature-human renin. Renin enzymatic activity was monitored using a commercially available fluorescence resonance energy transfer(FRET) peptide substrate, RS-1 (Molecular Probes, Eugene, OR) in 50mM Tris-HCl pH 8.0, 100mM NaCl, 0.1%Brij-35 and 5% DMSO buffer for 40mins at 30 degrees celsius in the presence or absence of different concentrations of test compounds. Mature human Renin was present at approximately 200nM. Inhibitory activity was defined as the percent decrease in renin induced fluorescence at the end of the 40min incubation compared to vehicle controls and samples lacking enzyme.

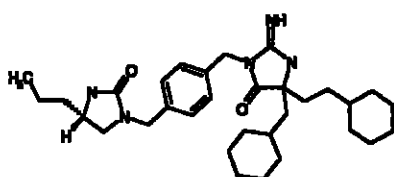
10

% of hRenin at 100 μ M

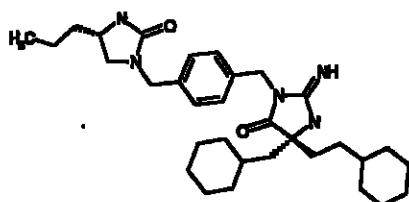
Compound



68.8



75.3



76.9

In the aspect of the invention relating to a combination of at least one compound of formula I with at least one cholinesterase inhibitor, acetyl- and/or butyrylcholinesterase inhibitors can be used. Examples of cholinesterase inhibitors are tacrine, donepezil, rivastigmine, galantamine, pyridostigmine and neostigmine, with tacrine, donepezil, rivastigmine and galantamine being preferred. Preferably, these combinations are directed to the treatment of Alzheimer's disease.

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In the aspect of the invention relating to a combination of at least one compound of formula I with at least one muscarinic m_1 agonist or m_2 antagonist can be used. Examples of m_1 agonists are known in the art. Examples of m_2 antagonists are also known in the art; in particular, m_2 antagonists are disclosed in US patents
5 5,883,096; 6,037,352; 5,889,006; 6,043,255; 5,952,349; 5,935,958; 6,066,836; 5,977,138; 6,294,554; 6,043,255; and 6,458,812; and in WO 03/031412, all of which are incorporated herein by reference.

In other aspects of the invention relating to a combination of at least one compound of formula I and at least one other agent, for example a beta secretase
10 inhibitor; a gamma secretase inhibitor; an HMG-CoA reductase inhibitor such as atorvastatin, lovastatin, simvastatin, pravastatin, fluvastatin and rosuvastatin; non-steroidal anti-inflammatory agents such as, but not necessarily limited to ibuprofen, relafen or naproxen; N-methyl-D-aspartate receptor antagonists such as memantine; anti-amyloid antibodies including humanized monoclonal antibodies; vitamin E;
15 nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; antibiotics such as doxycycline; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; GABA_A inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity. Preferably, these combinations are directed to the
20 treatment of Alzheimer's disease.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about
25 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's
30 Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and

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emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 300 mg/day, preferably 1 mg/day to 50 mg/day, in two to four divided doses.

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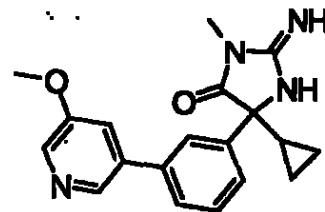
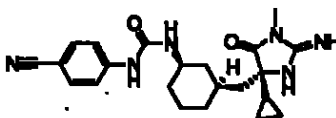
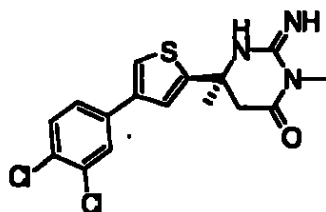
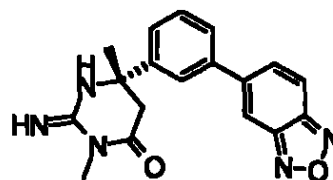
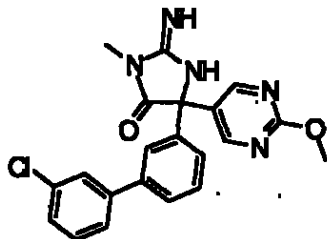
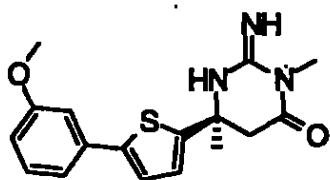
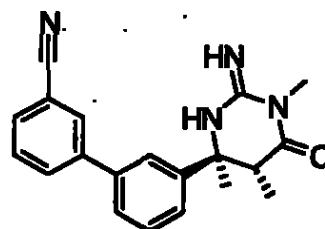
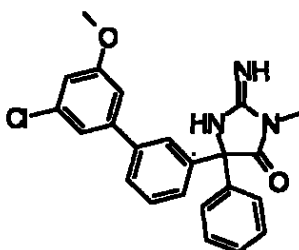
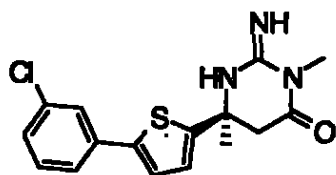
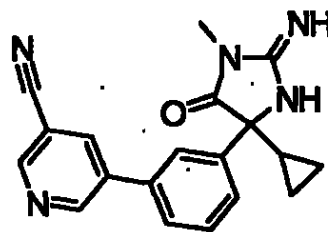
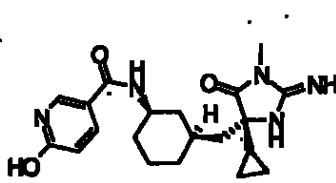
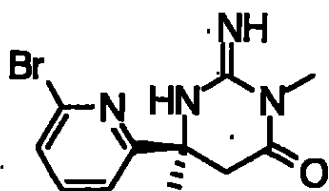
When a compound of formula I is used in combination with a cholinesterase inhibitor to treat cognitive disorders, these two active components may be co-administered simultaneously or sequentially, or a single pharmaceutical composition comprising a compound of formula I and a cholinesterase inhibitor in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional oral or parenteral dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. The dosage of the cholinesterase inhibitor can be determined from published material, and may range from 0.001 to 100 mg/kg body weight.

When separate pharmaceutical compositions of a compound of formula I and a cholinesterase inhibitor are to be administered, they can be provided in a kit comprising in a single package, one container comprising a compound of formula I in a pharmaceutically acceptable carrier, and a separate container comprising a cholinesterase inhibitor in a pharmaceutically acceptable carrier, with the compound of formula I and the cholinesterase inhibitor being present in amounts such that the combination is therapeutically effective. A kit is advantageous for administering a combination when, for example, the components must be administered at different time intervals or when they are in different dosage forms.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

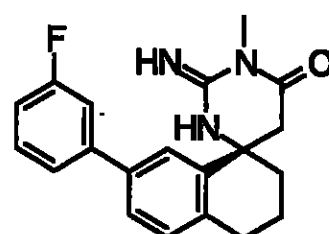
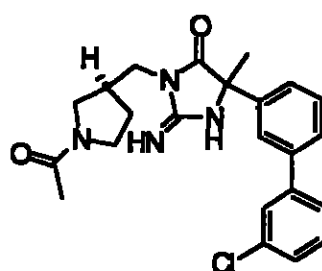
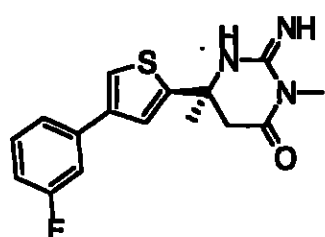
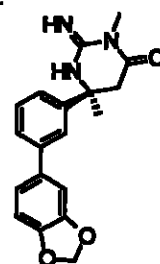
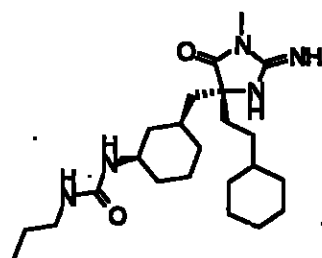
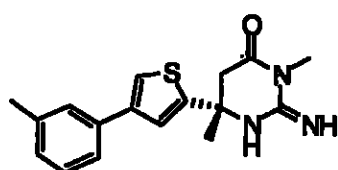
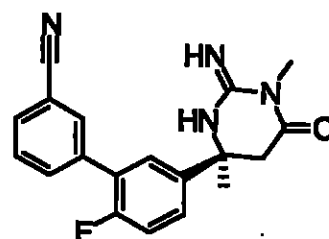
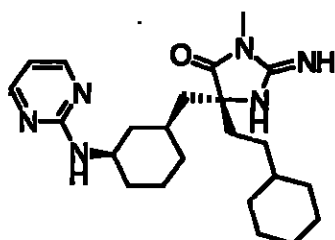
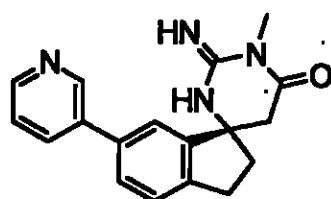
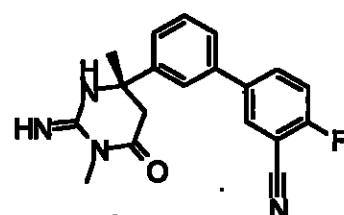
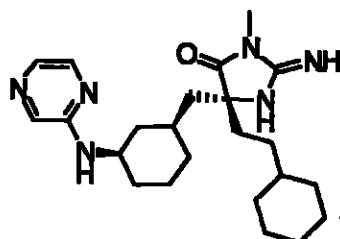
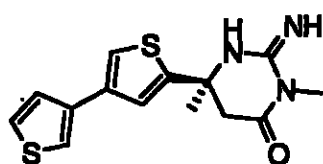
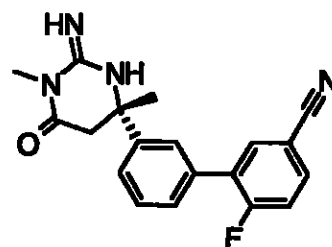
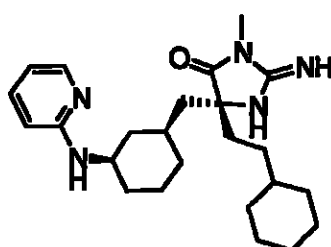
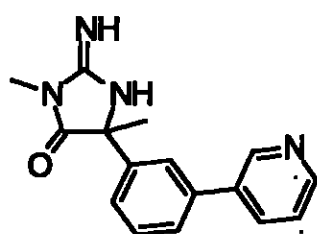
We claim:

1. A compound selected from the group consisting of



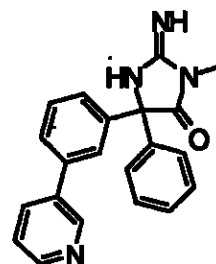
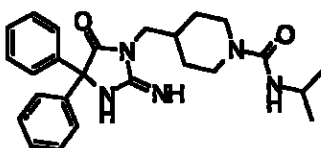
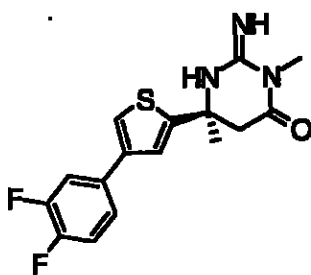
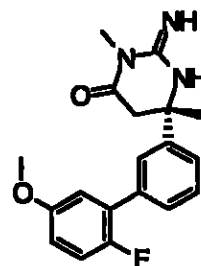
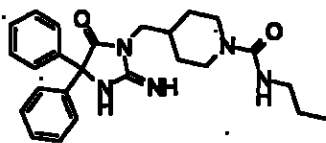
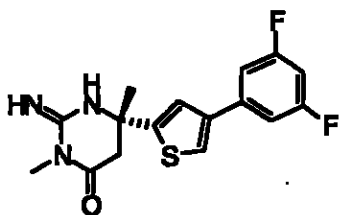
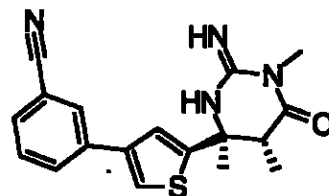
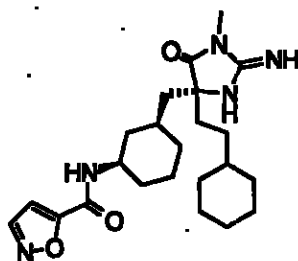
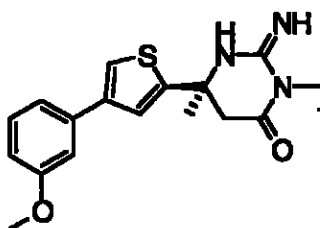
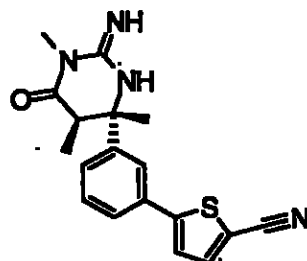
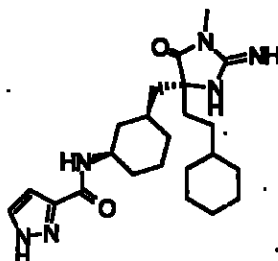
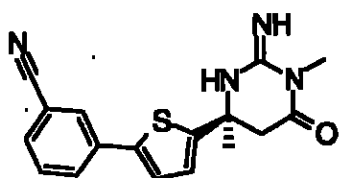
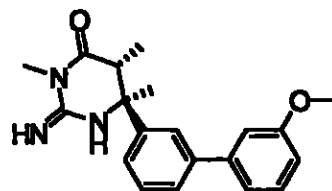
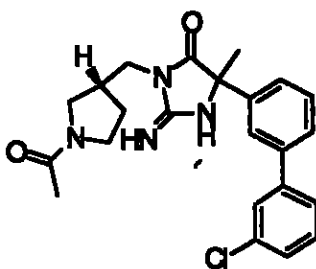
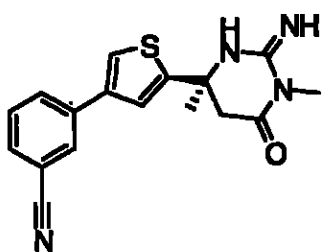
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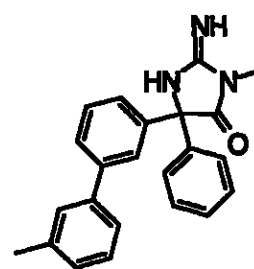
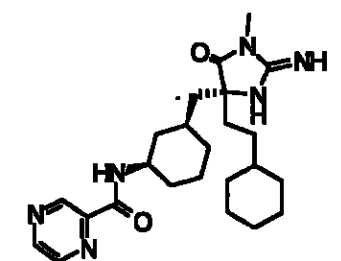
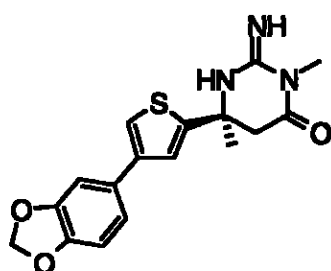
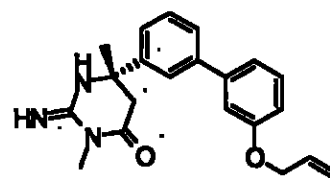
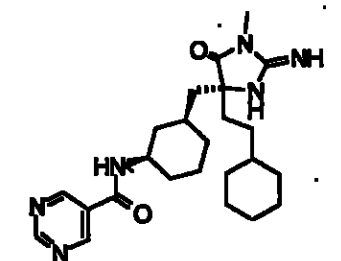
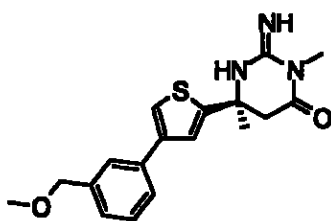
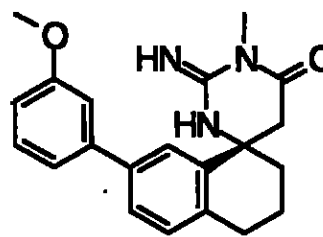
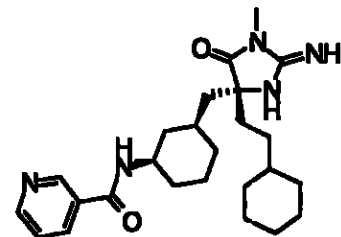
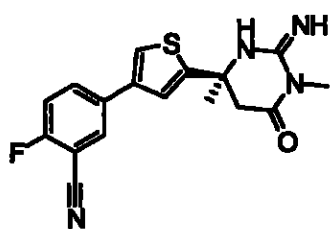
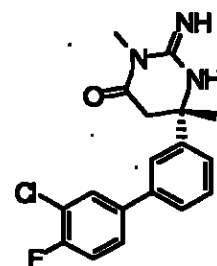
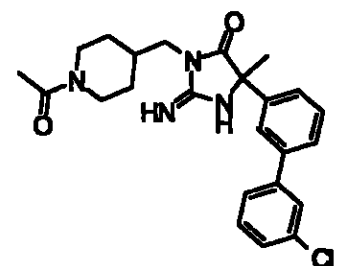
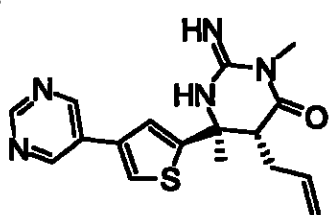
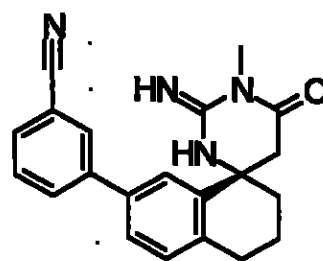
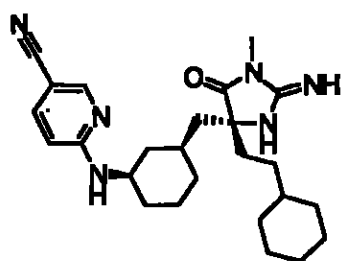
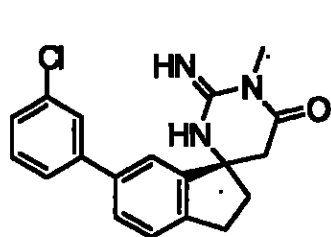


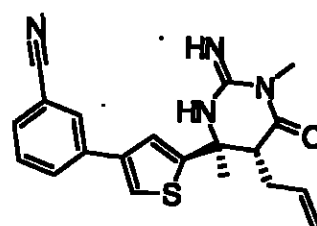
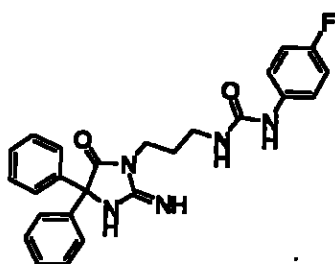
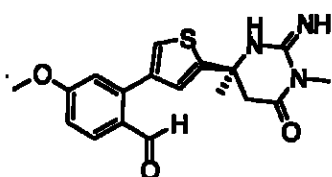
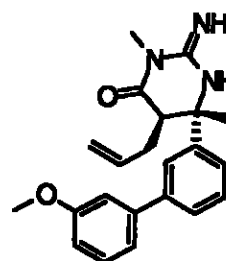
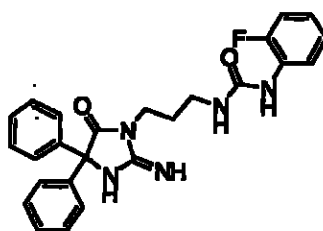
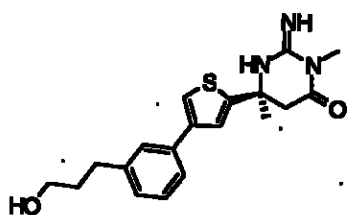
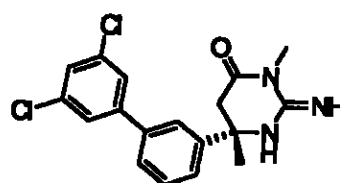
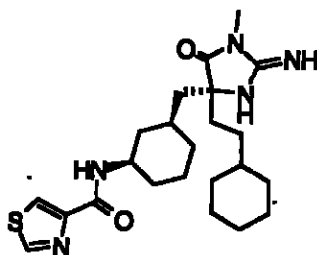
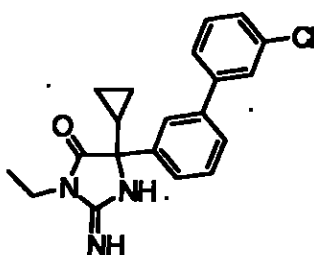
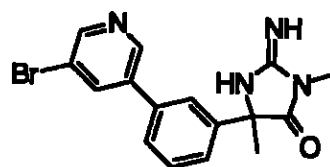
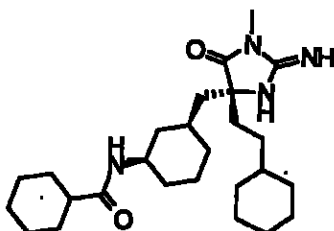
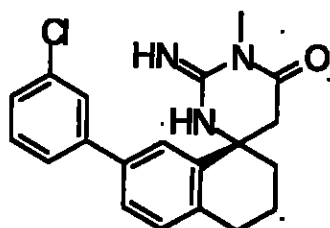
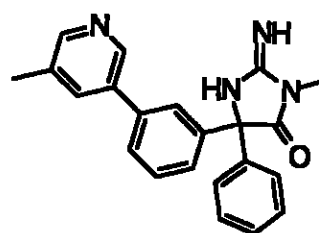
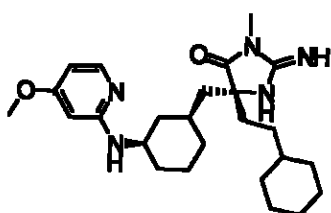
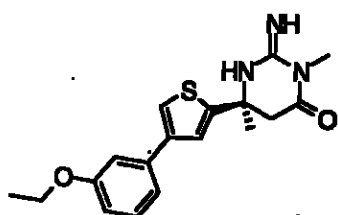
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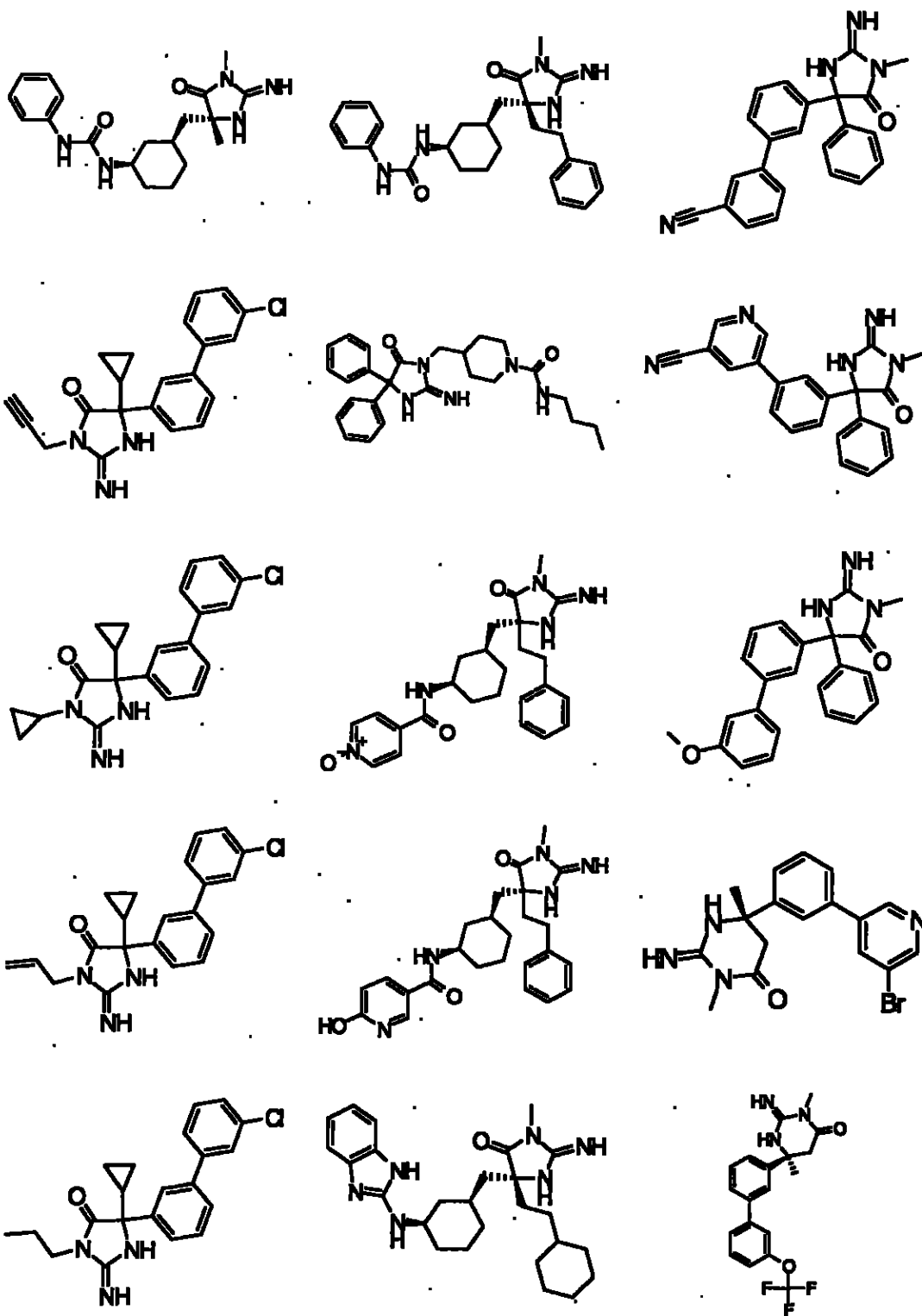
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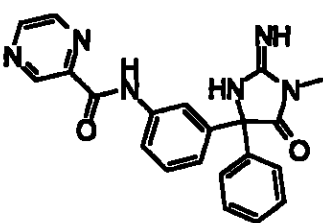
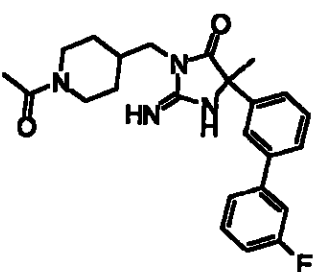
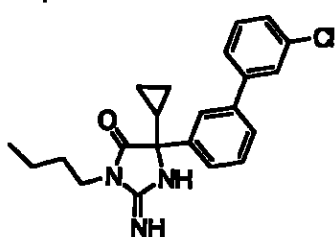
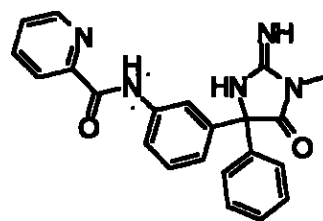
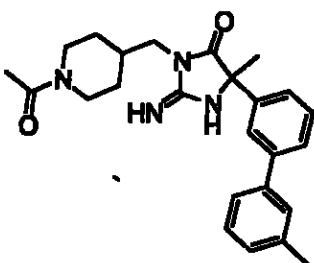
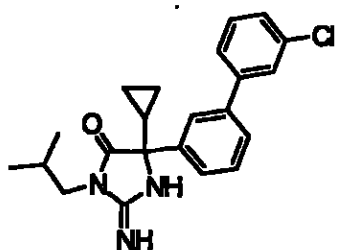
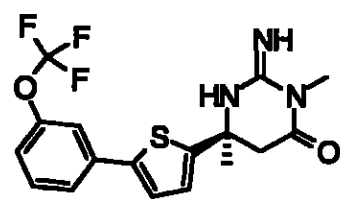
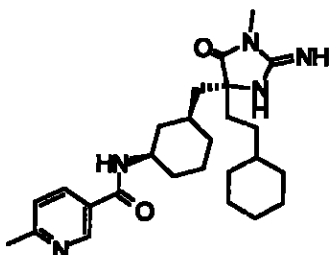
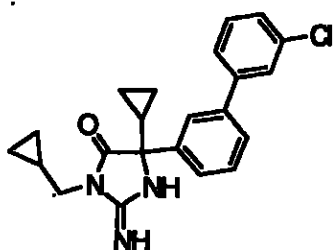
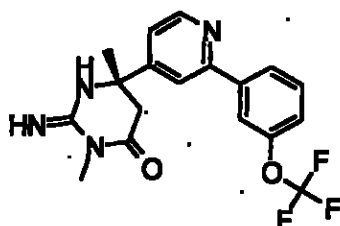
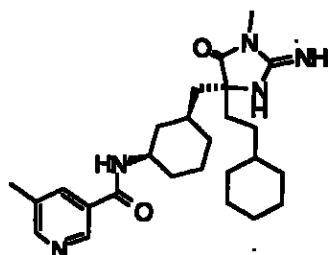
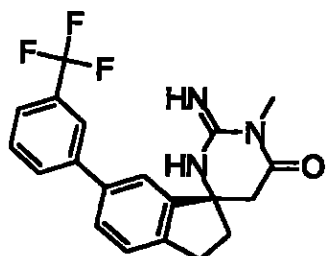
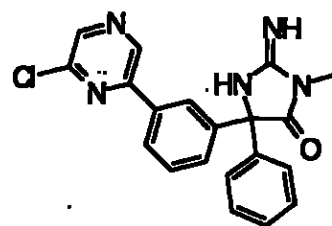
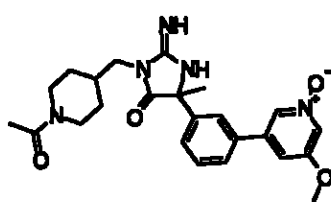
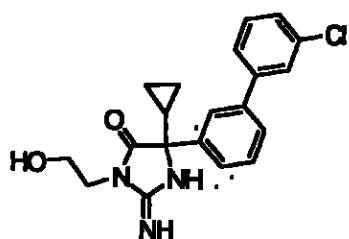
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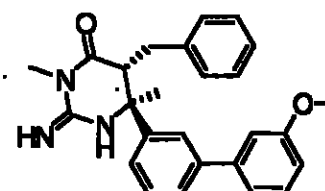
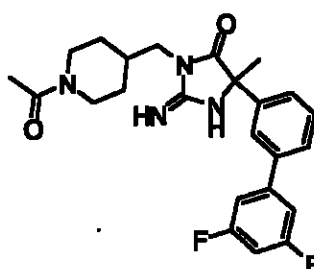
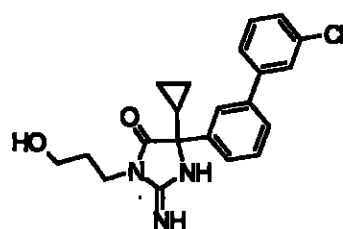
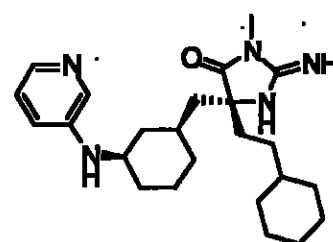
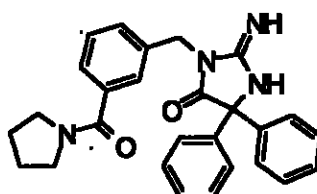
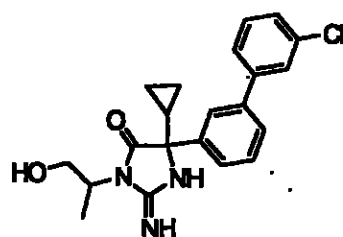
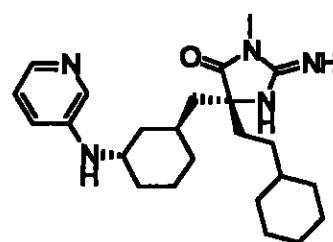
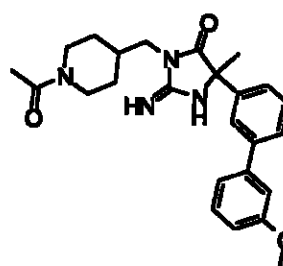
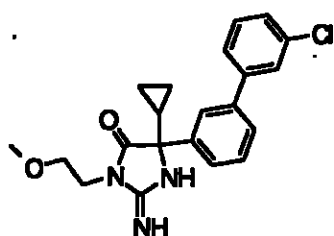
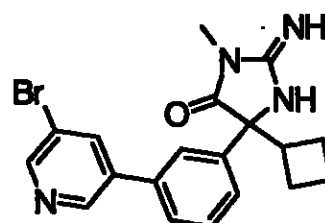
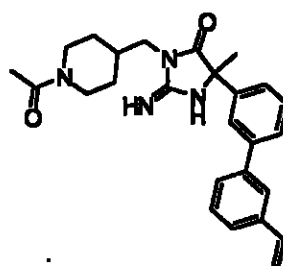
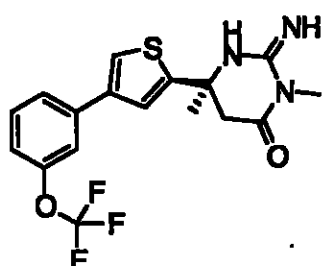
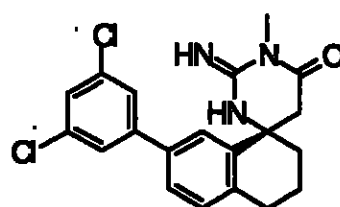
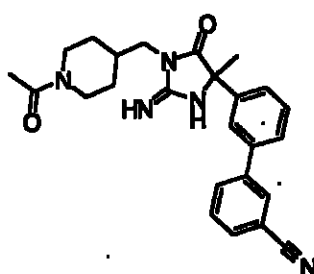
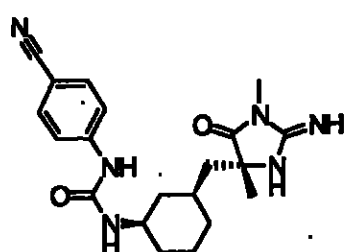
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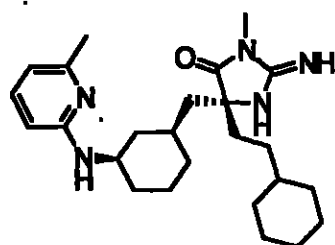
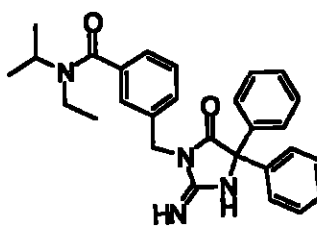
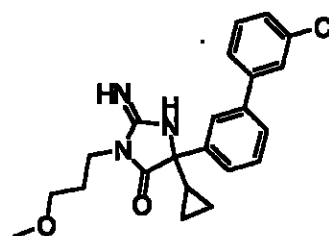
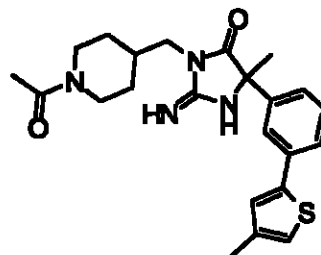
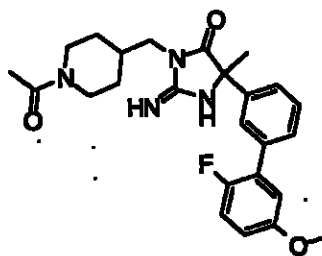
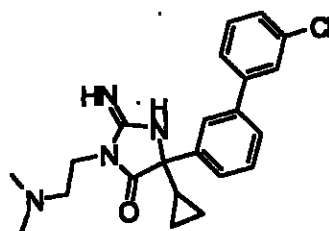
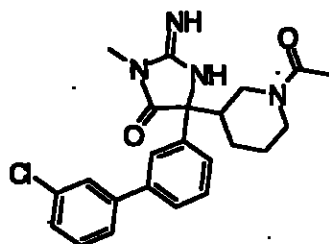
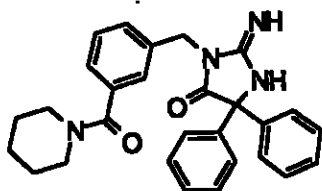
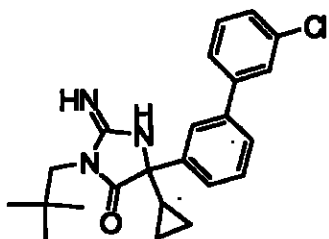
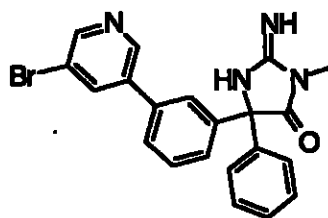
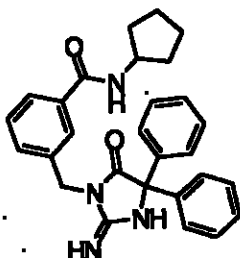
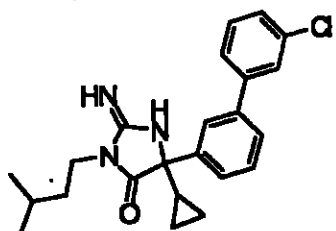
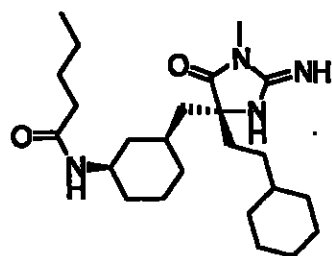
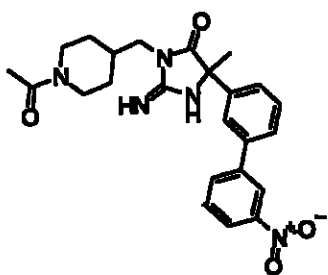
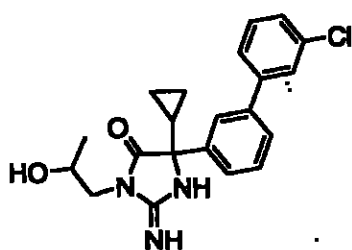
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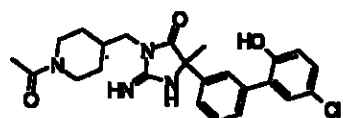
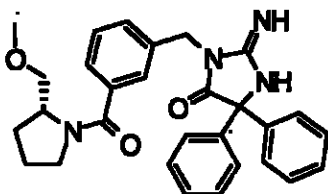
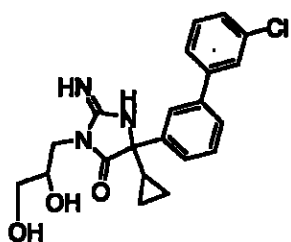
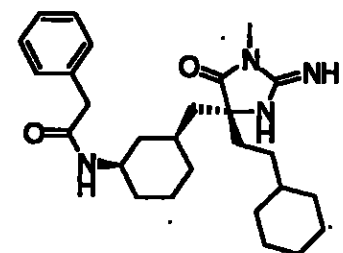
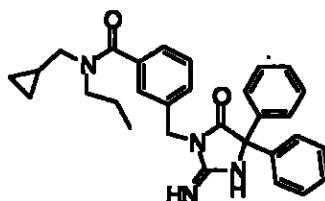
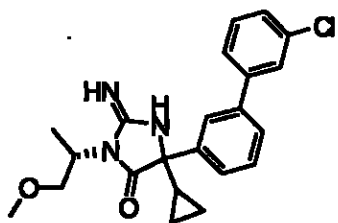
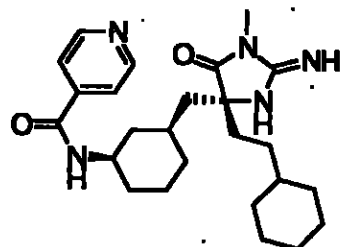
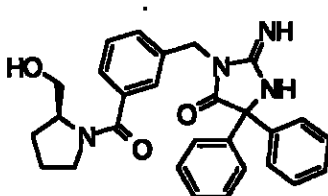
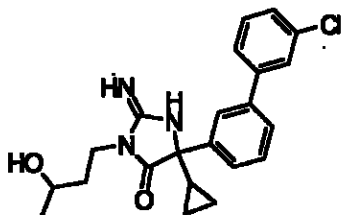
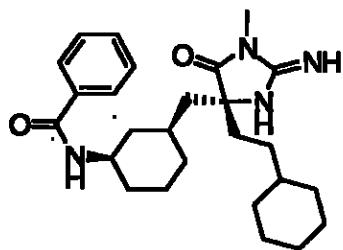
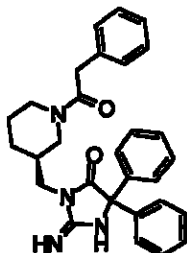
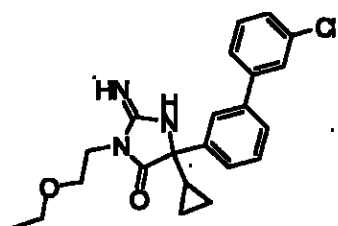
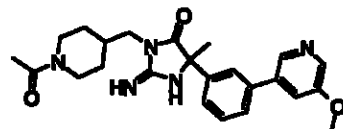
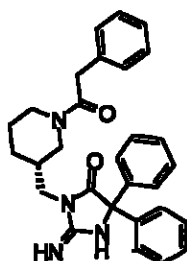
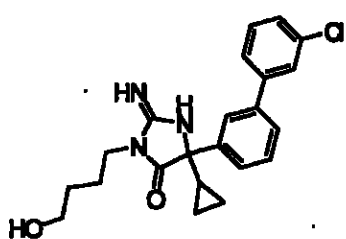
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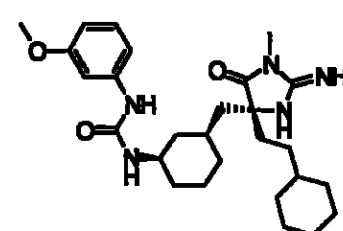
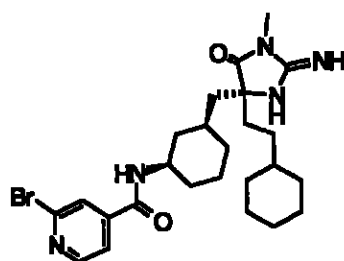
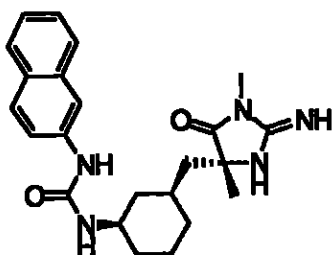
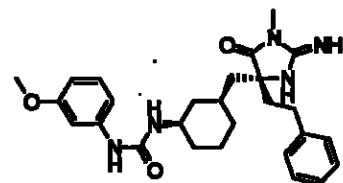
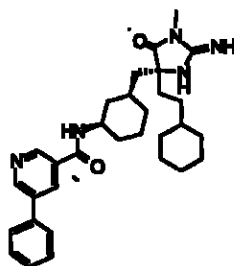
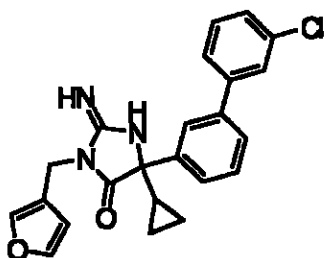
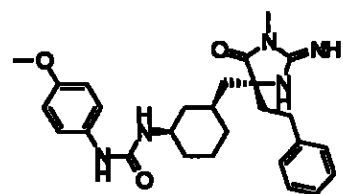
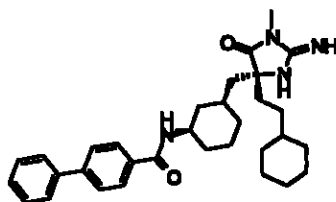
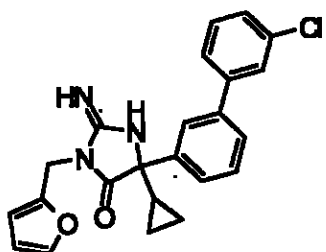
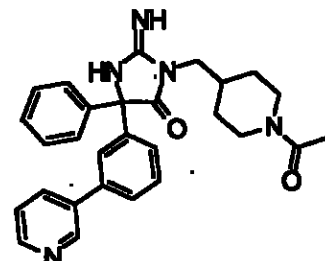
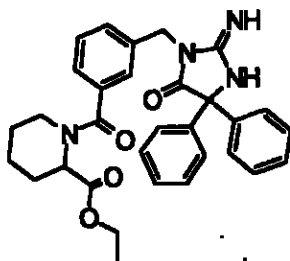
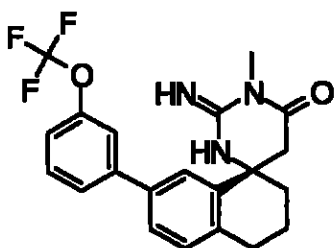
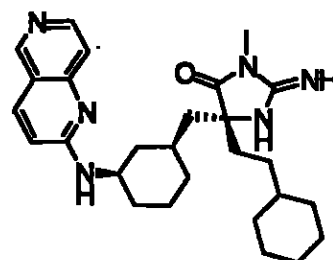
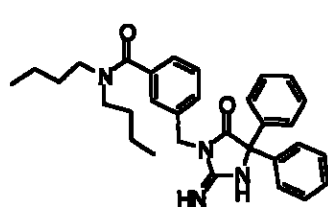
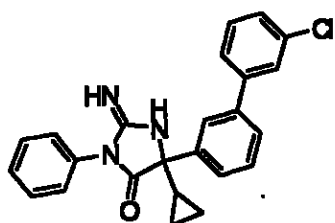
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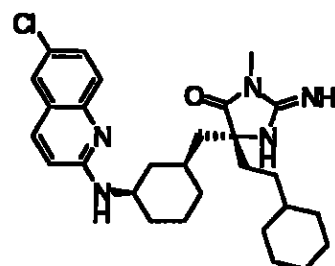
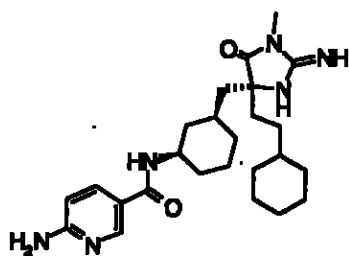
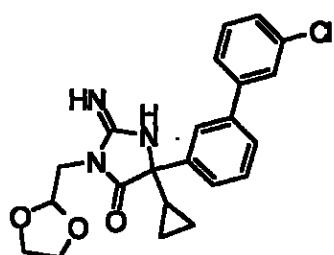
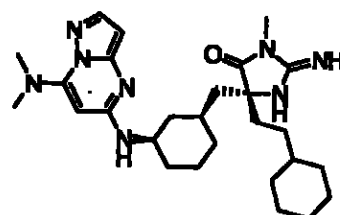
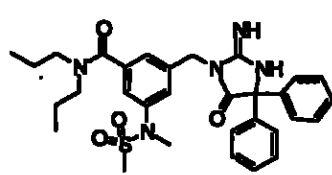
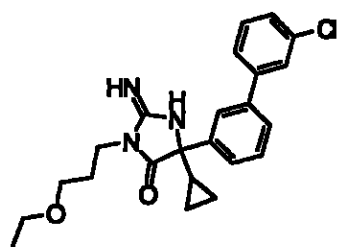
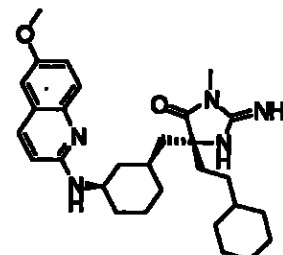
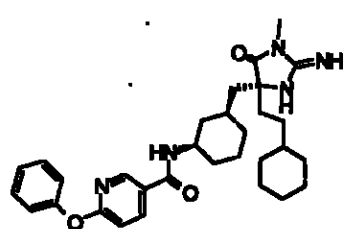
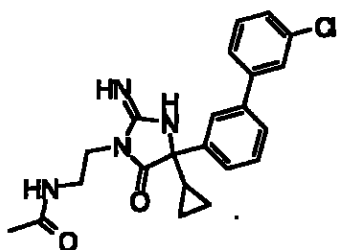
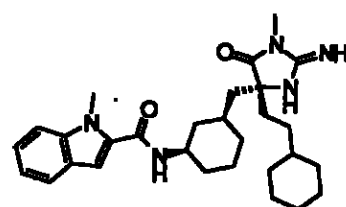
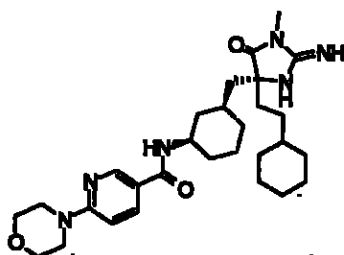
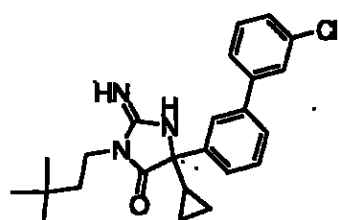
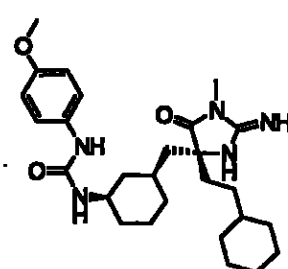
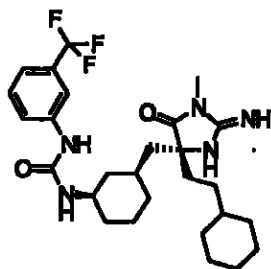
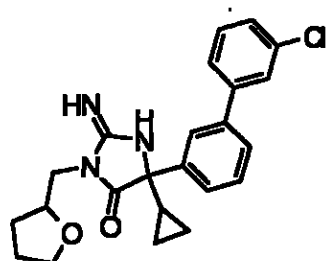


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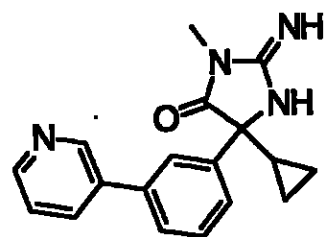
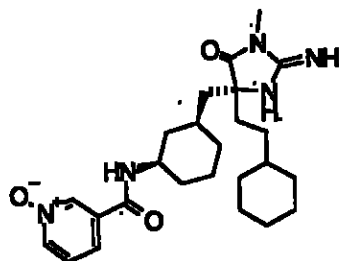
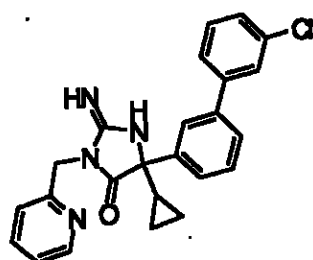
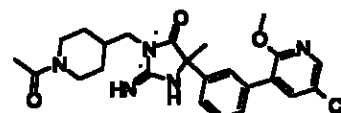
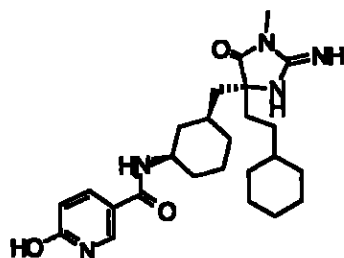
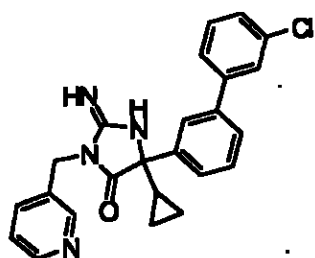
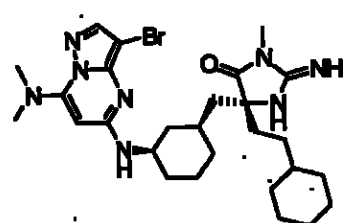
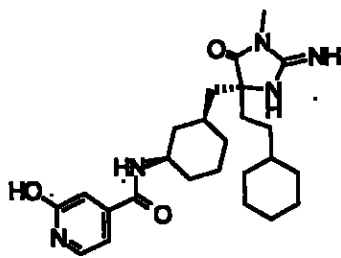
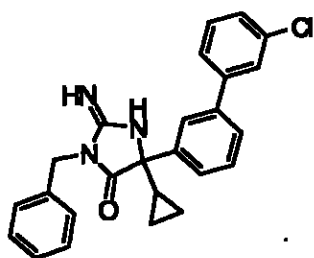
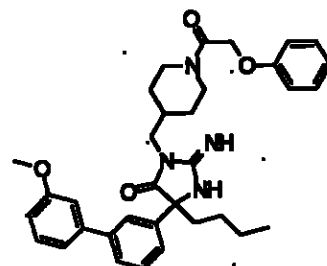
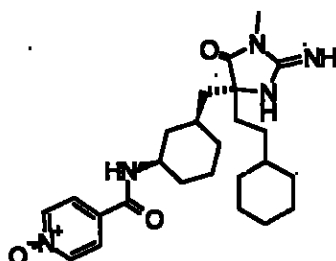
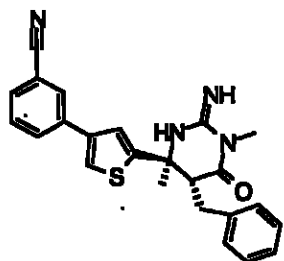
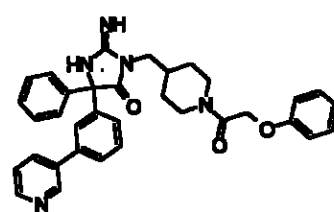
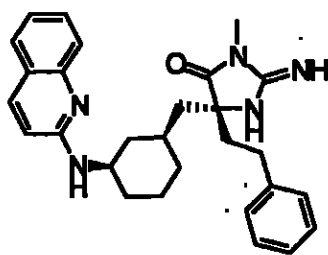
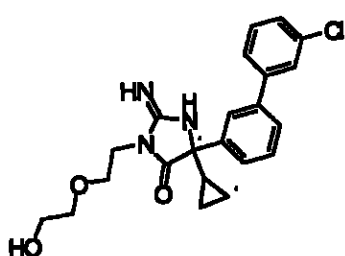
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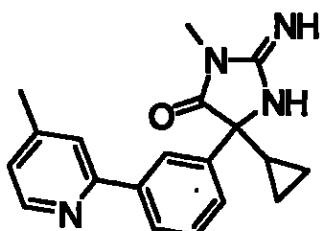
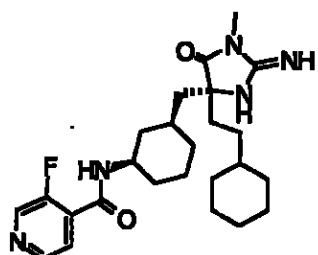
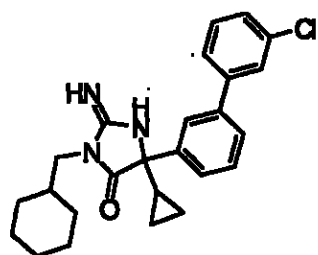
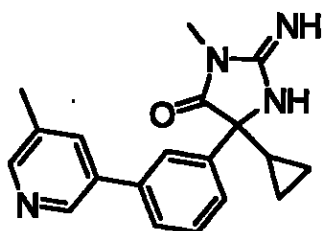
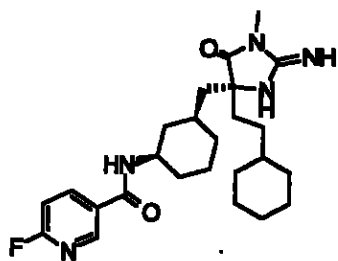
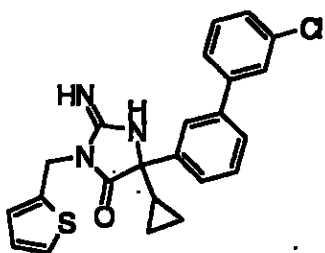
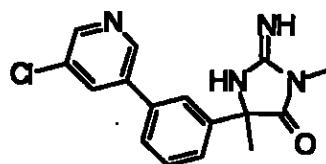
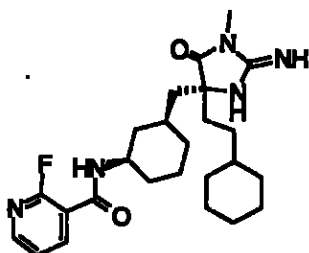
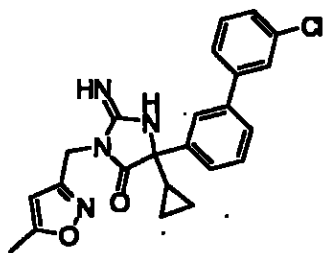
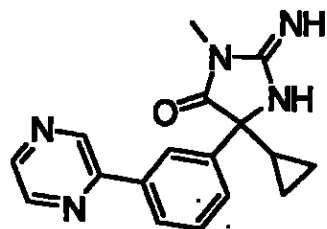
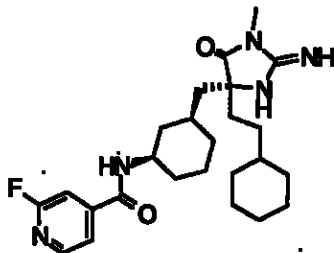
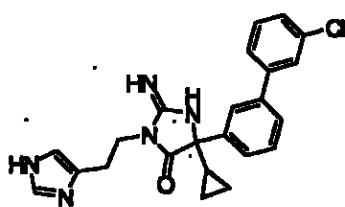
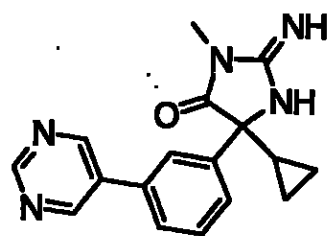
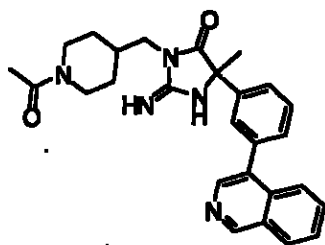
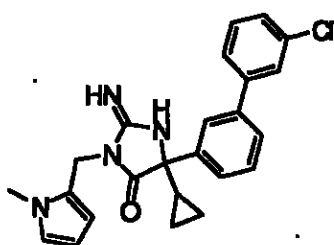


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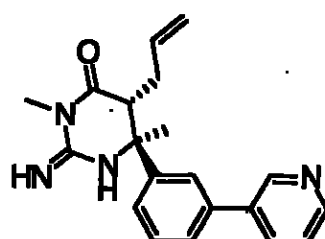
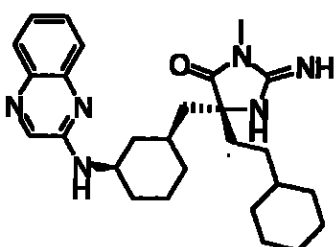
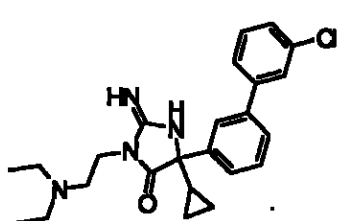
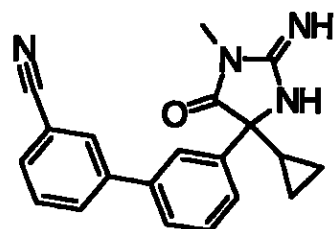
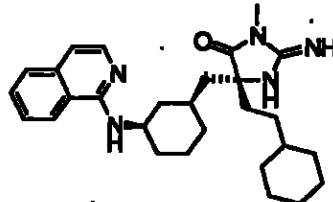
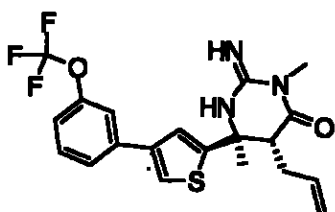
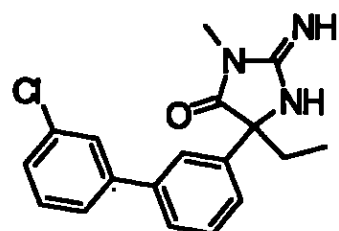
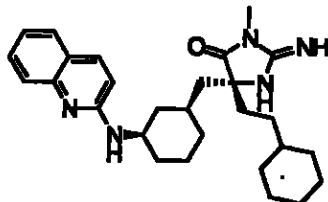
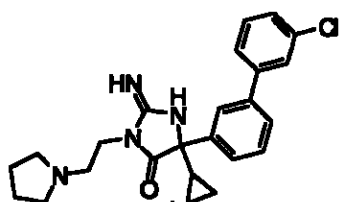
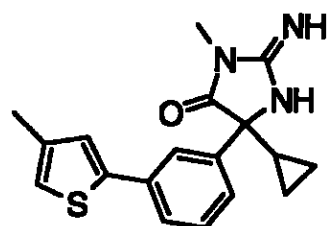
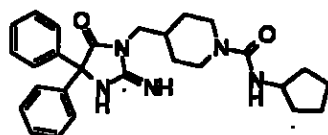
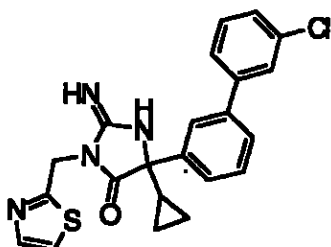
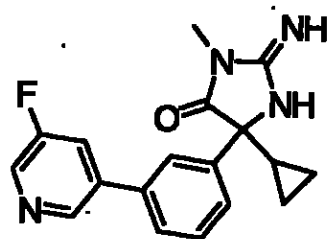
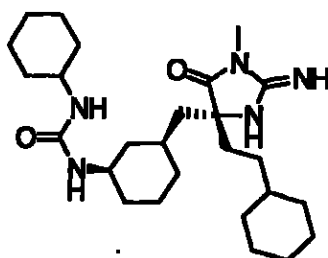
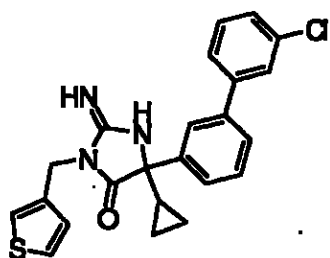
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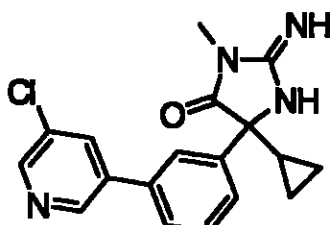
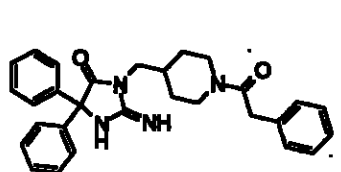
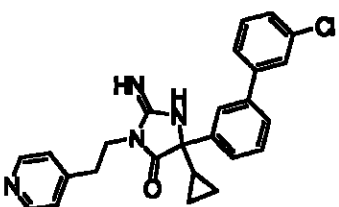
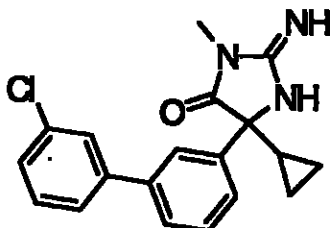
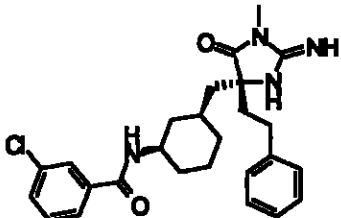
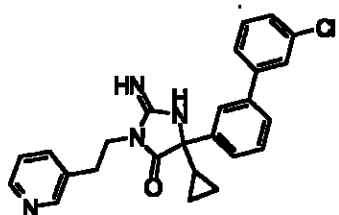
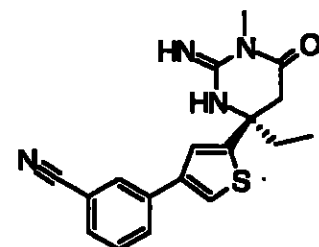
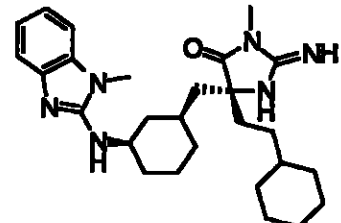
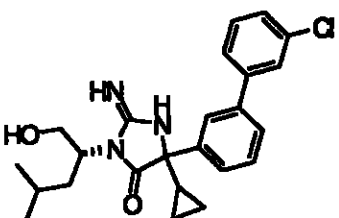
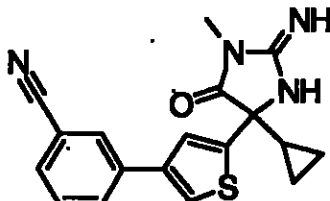
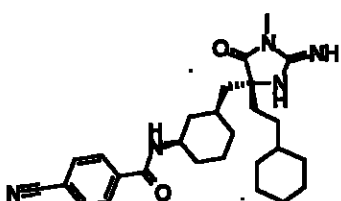
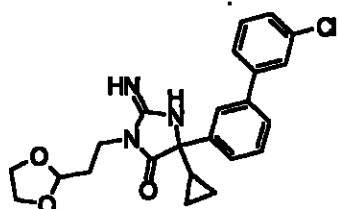
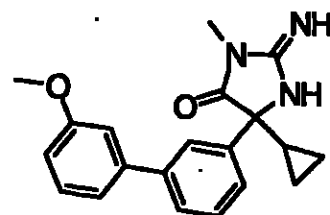
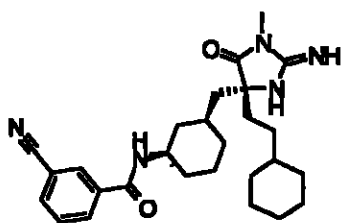
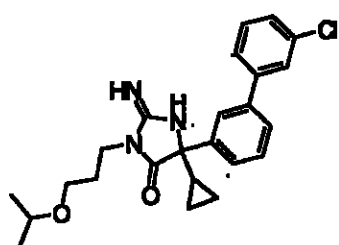
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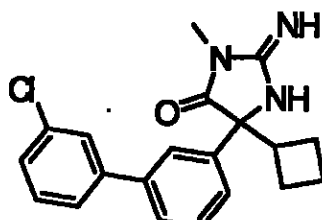
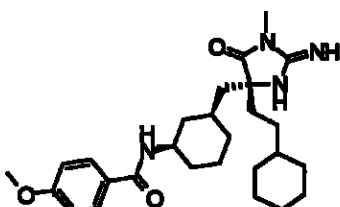
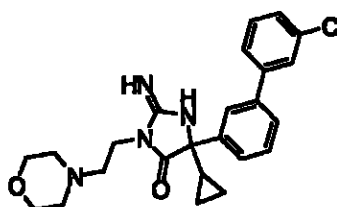
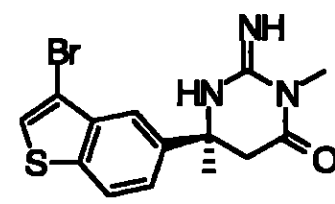
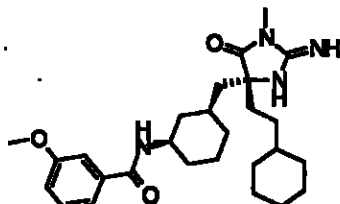
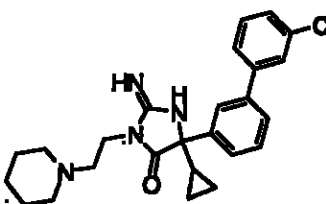
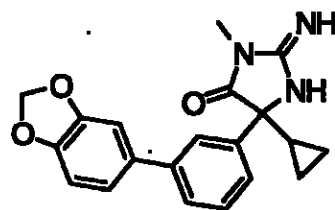
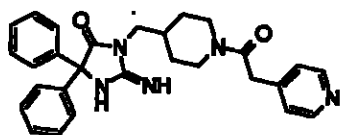
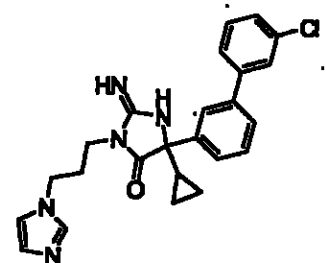
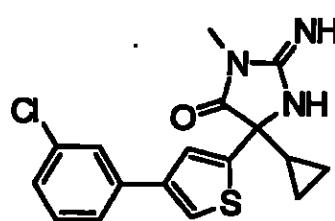
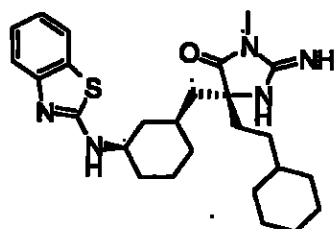
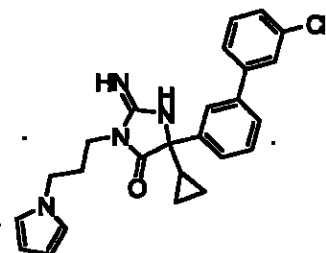
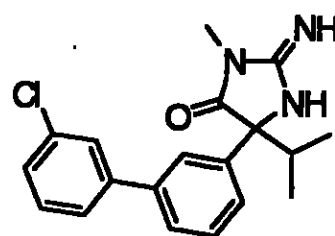
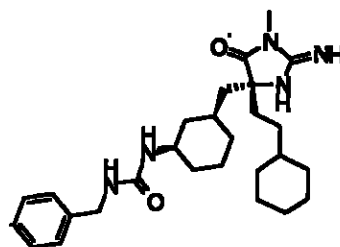
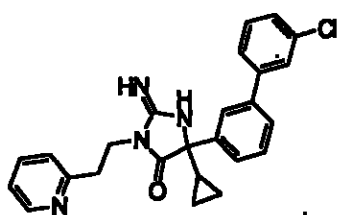
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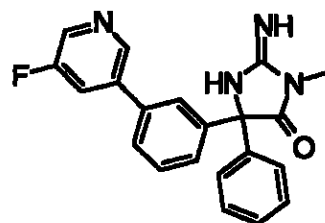
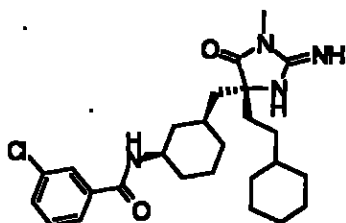
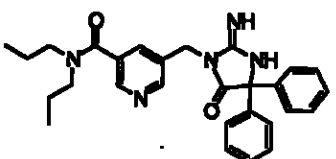
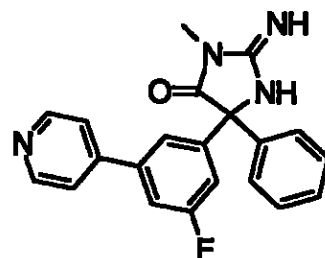
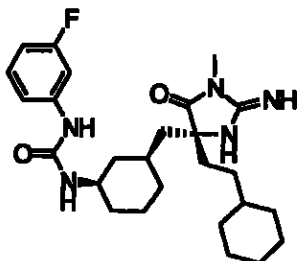
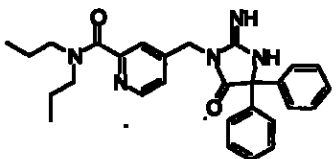
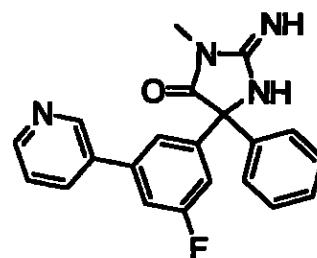
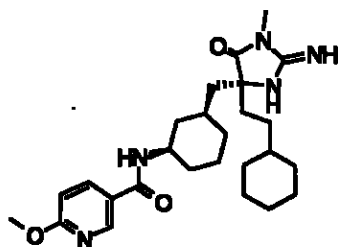
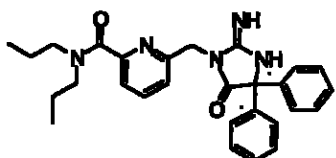
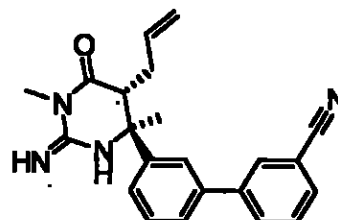
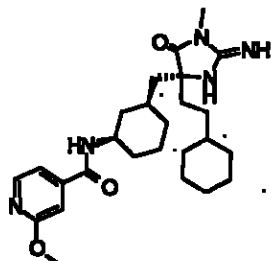
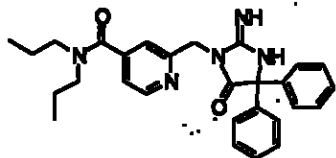
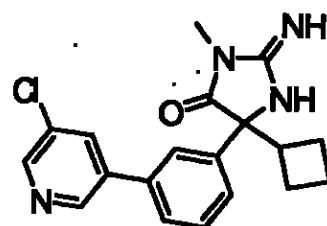
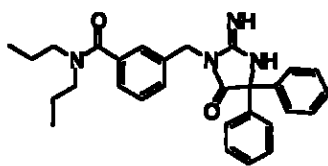
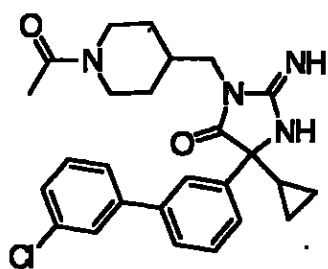
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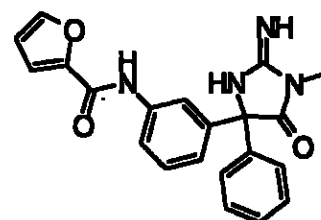
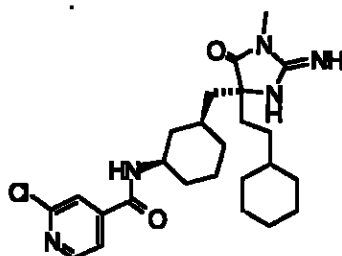
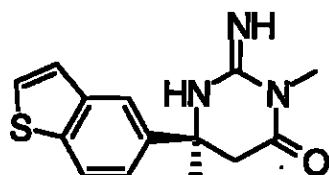
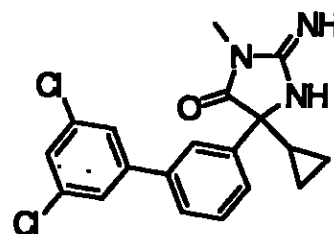
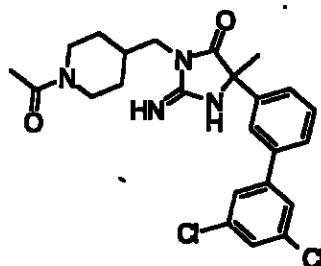
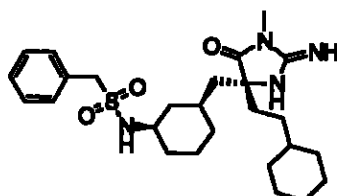
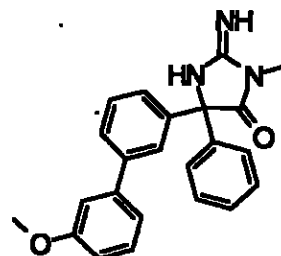
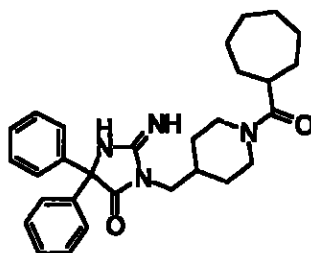
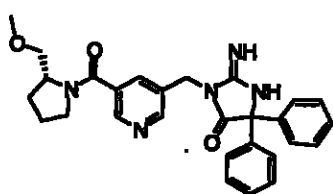
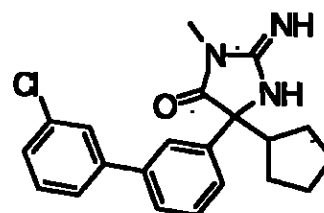
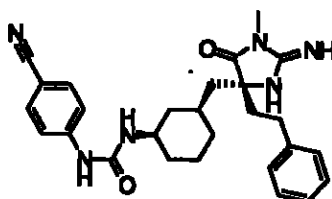
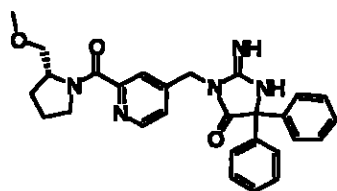
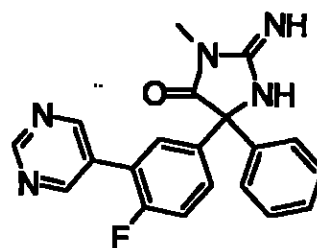
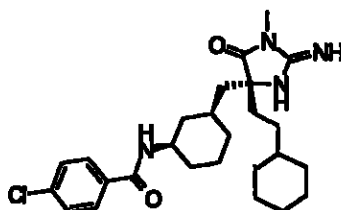
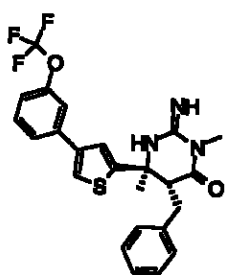
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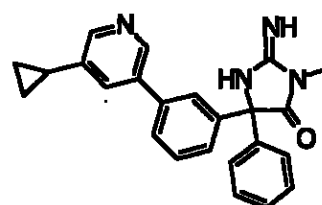
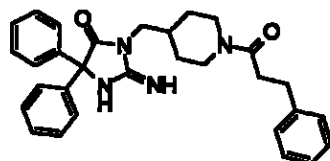
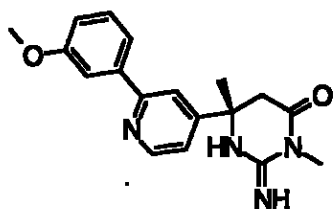
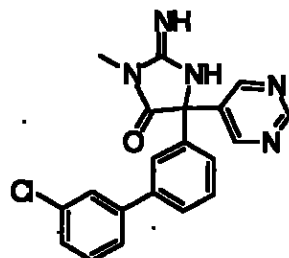
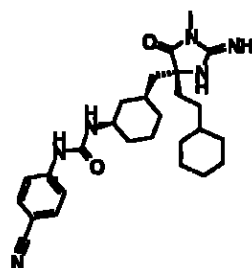
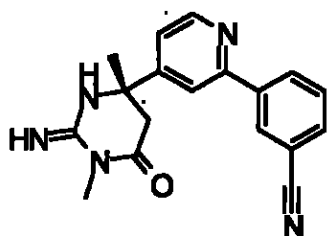
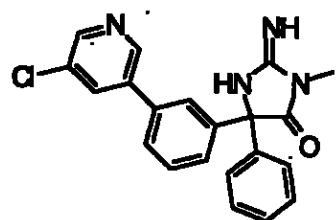
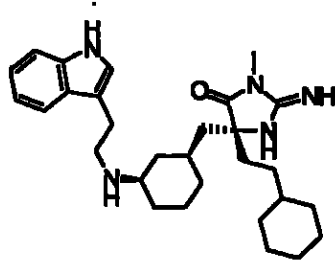
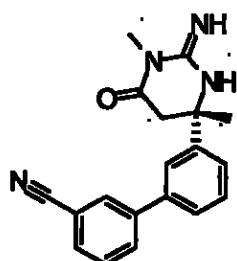
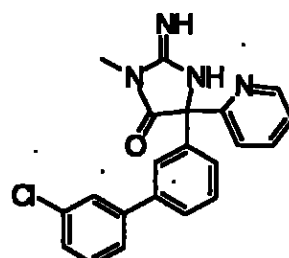
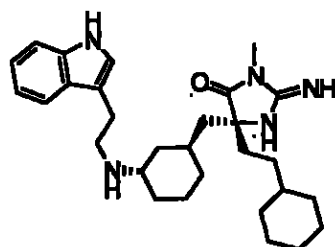
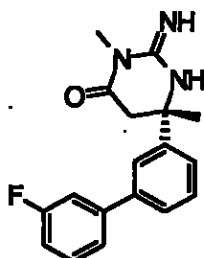
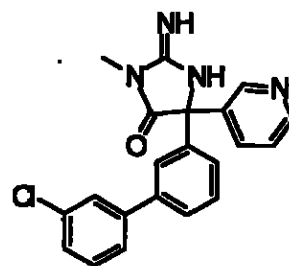
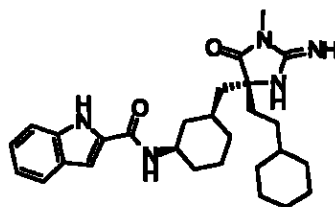
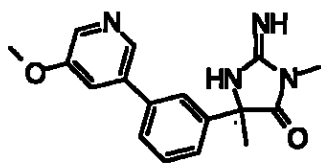
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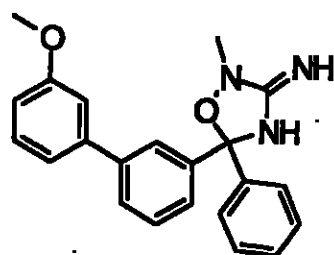
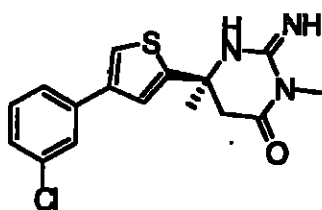
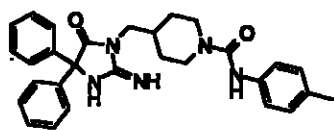
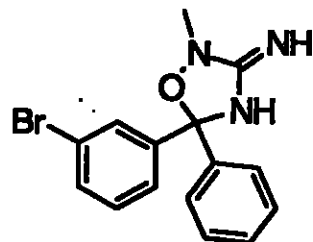
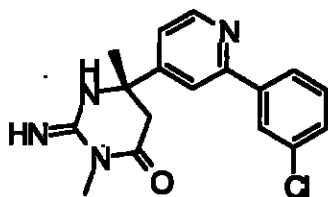
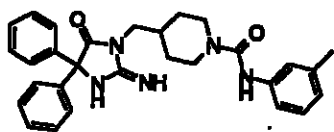
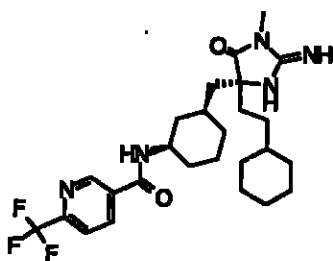
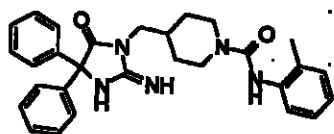
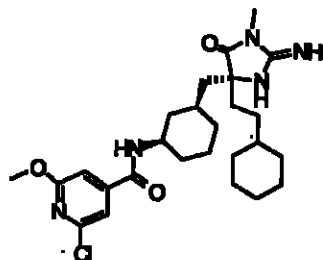
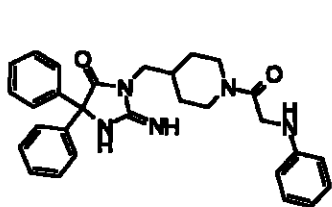
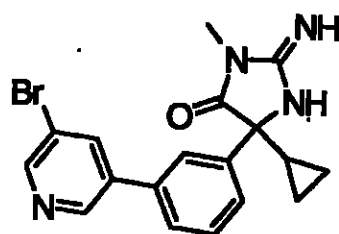
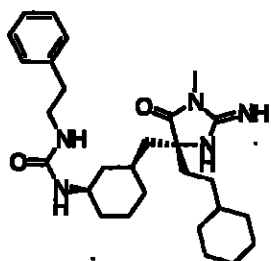
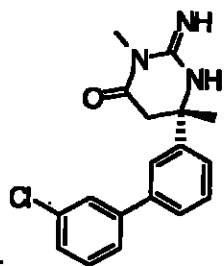
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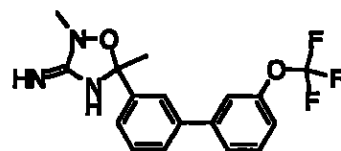
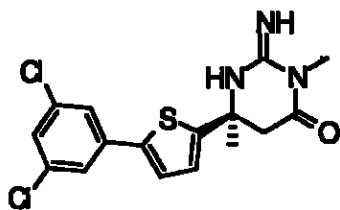
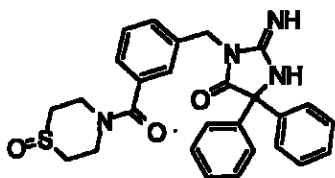
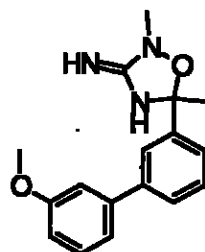
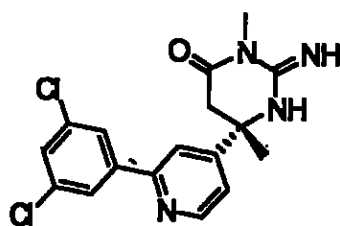
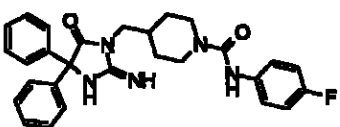
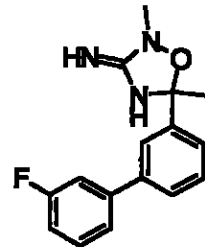
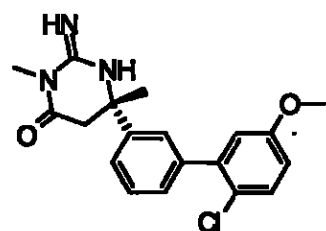
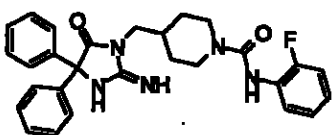
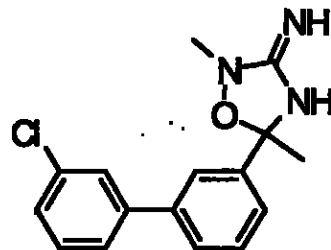
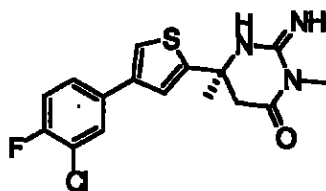
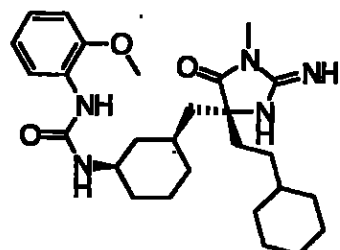
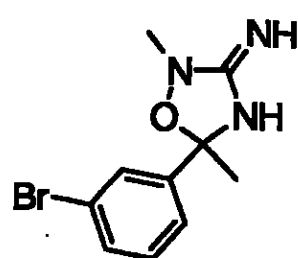
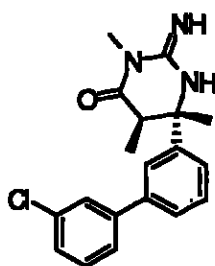
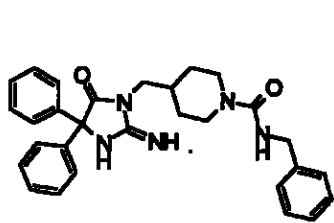
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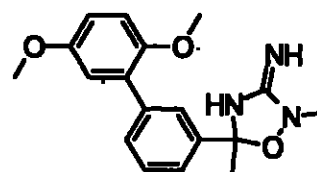
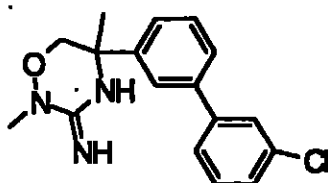
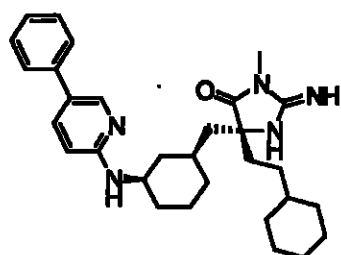
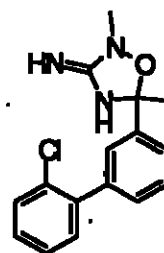
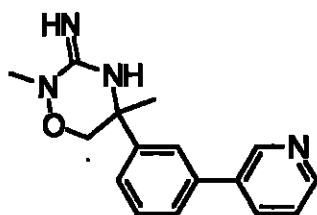
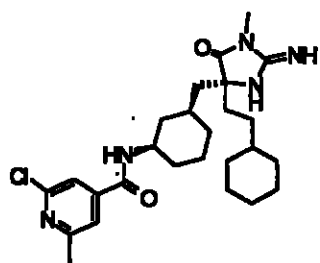
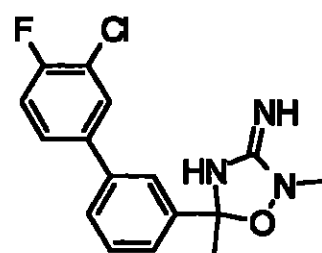
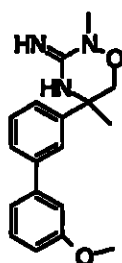
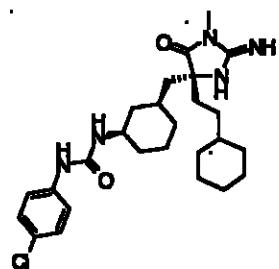
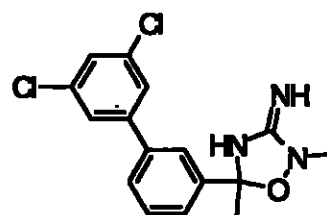
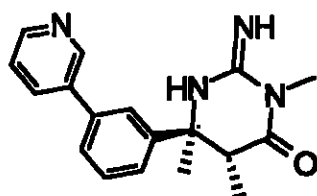
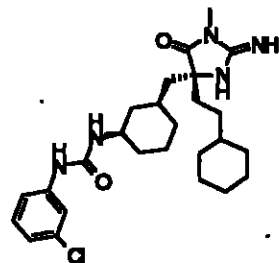
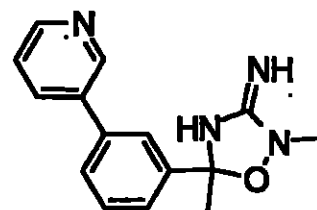
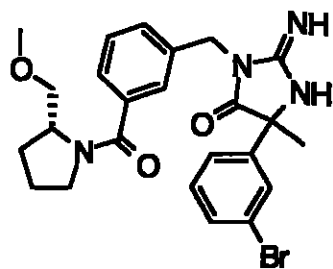
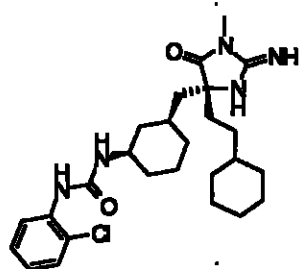
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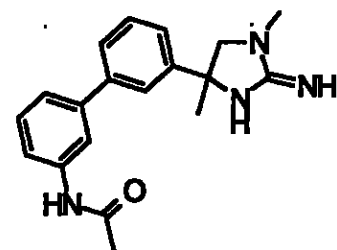
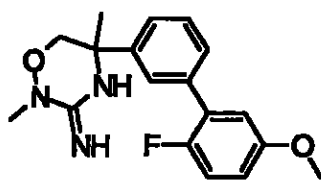
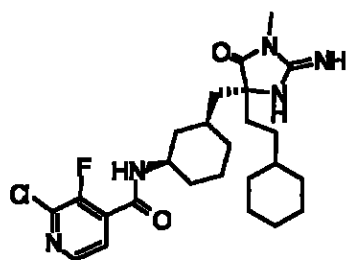
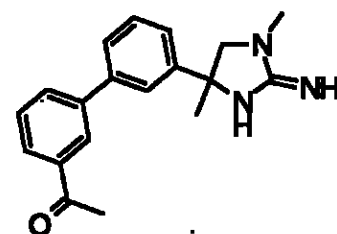
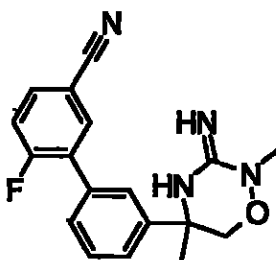
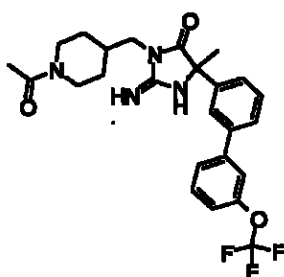
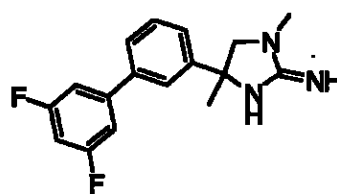
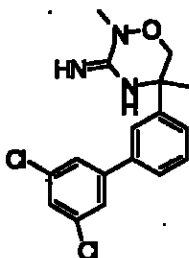
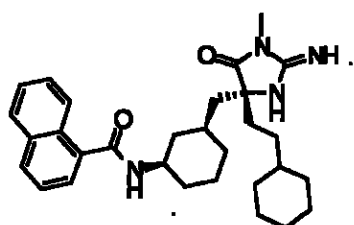
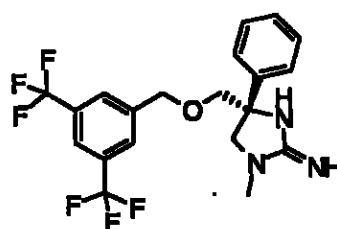
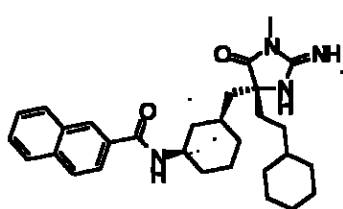
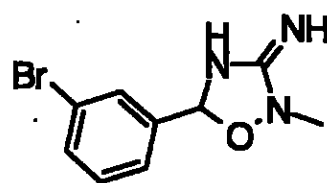
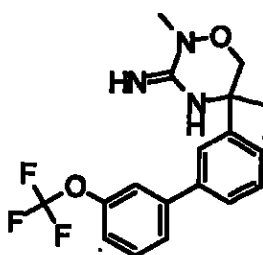
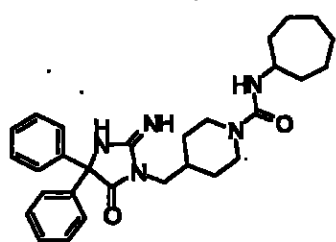
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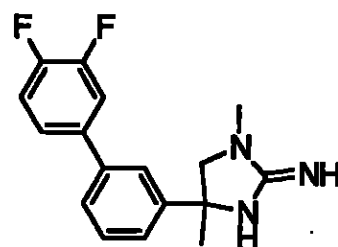
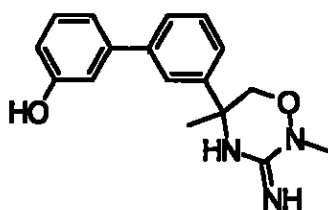
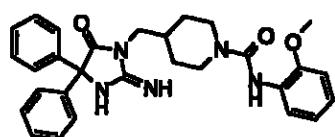
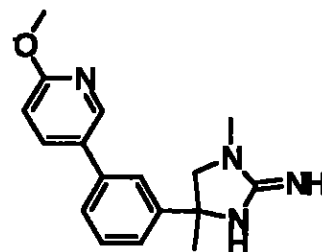
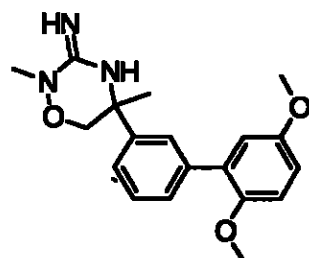
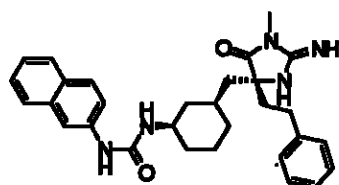
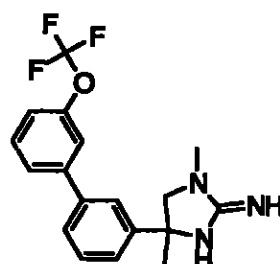
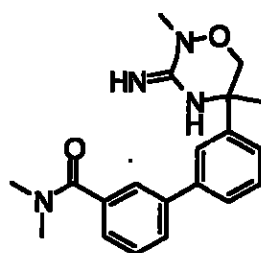
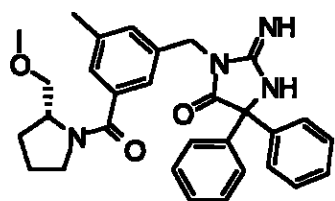
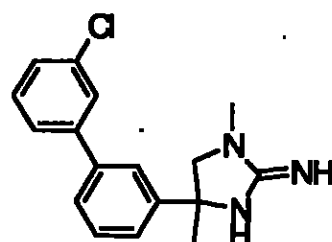
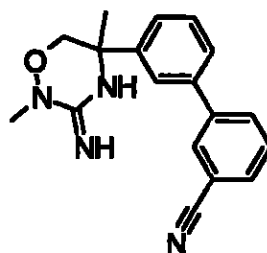
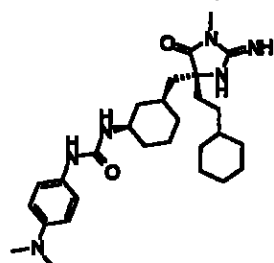
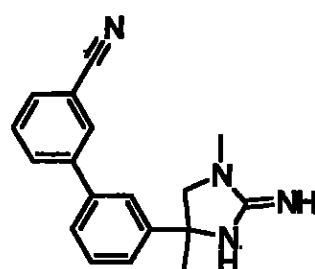
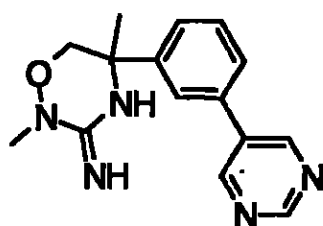
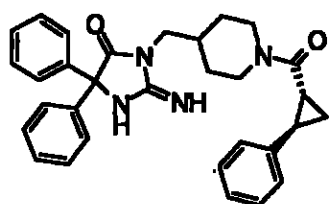
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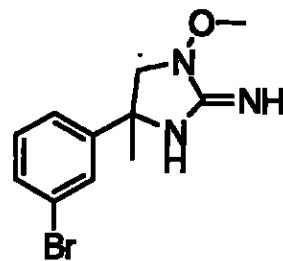
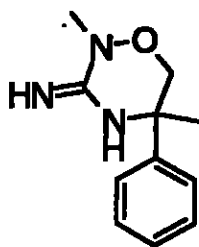
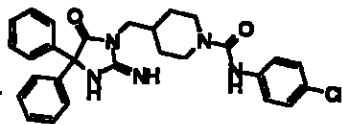
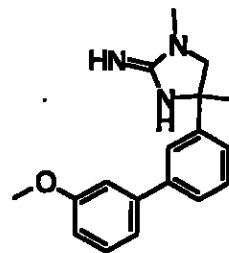
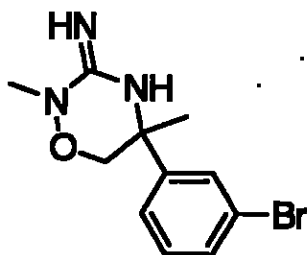
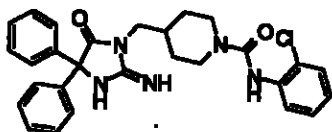
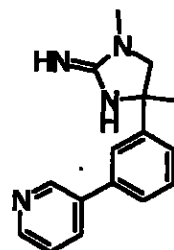
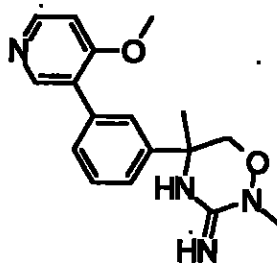
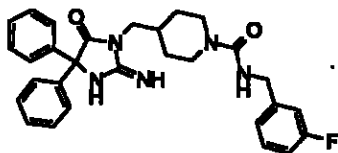
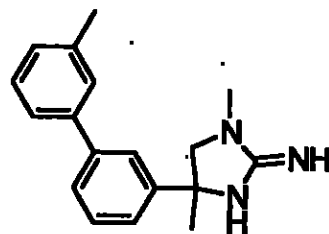
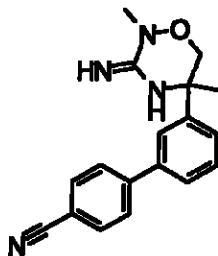
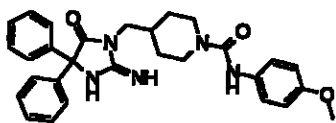
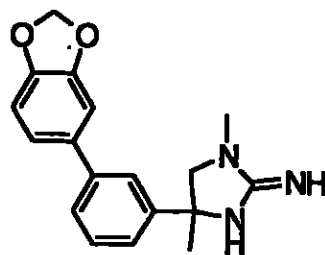
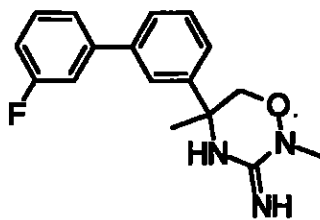
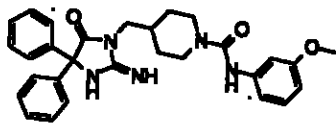
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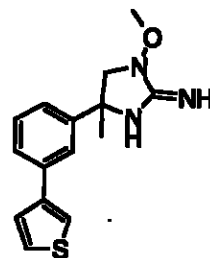
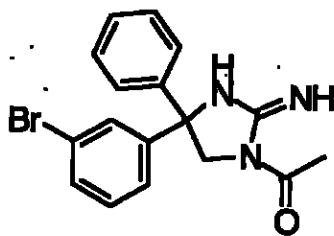
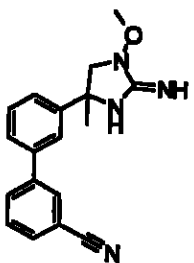
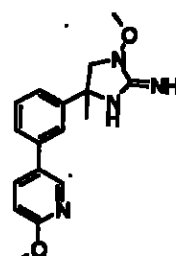
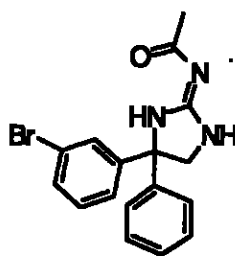
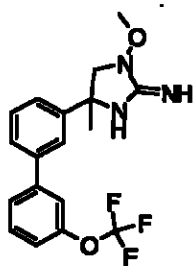
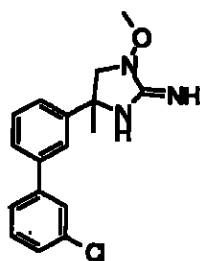
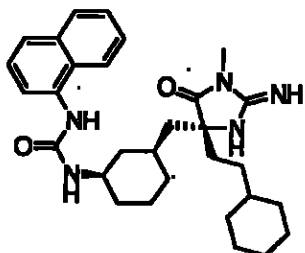
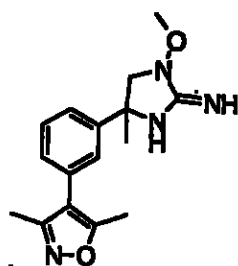
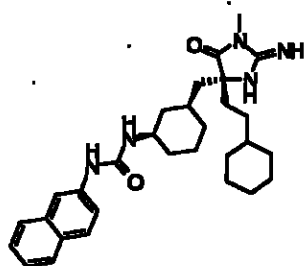
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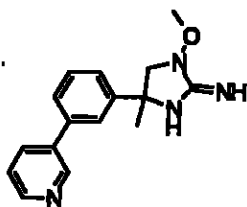


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and



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2. A pharmaceutical composition comprising an effective amount of a compound of claim 1 and a pharmaceutically effective carrier.
3. A method of inhibiting aspartyl protease comprising administering to a patient
5 In need of such treatment an effective amount of a compound of claim 1.
4. A method of treating cardiovascular diseases, cognitive and neurodegenerative diseases, and the methods of inhibiting of Human Immunodeficiency Virus, plasmeplins, cathepsin D and protozoal enzymes comprising administering to a patient
10 in need of such treatment an effective amount of a compound of claim 1.
5. The method of claim 4 wherein a cognitive or neurodegenerative disease is treated.
- 15 6. The method of claim 5 wherein Alzheimer's disease is treated.
7. A pharmaceutical composition comprising an effective amount of a compound of claim 1, and an effective amount of a cholinesterase inhibitor or a muscarinic m₁ agonist or m₂ antagonist in a pharmaceutically effective carrier.
20
8. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1 in combination with an effective amount of a cholinesterase inhibitor.
25
9. The method of claim 8 wherein Alzheimer's disease is treated.
10. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of a
30 compound of claim 1 in combination with an effective amount of a gamma secretase inhibitor, an HMG-CoA reductase inhibitor or non-steroidal anti-inflammatory agent.
11. The method of claim 10 wherein Alzheimer's disease is treated.

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12. The method of claim 10 wherein said HMG-CoA reductase inhibitor is atorvastatin, lovastatin, simvastatin, pravastatin, fluvastatin or rosuvastatin.
13. The method of claim 10 wherein said non-steroidal anti-inflammatory agent is
5 ibuprofen, relafen or naproxen.
14. A pharmaceutical composition comprising an effective amount of a compound of claim 1, and an effective amount of a gamma secretase inhibitor; an HMG-CoA reductase inhibitor or a non-steroidal anti-inflammatory agent.
10
15. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of at least one compound of claim 1 in combination with an effective amount of one or more compounds selected from the group consisting of a cholinesterase inhibitor,
15 muscarinic m_1 agonist or m_2 antagonist, gamma secretase inhibitor, an HMG-CoA reductase inhibitor and non-steroidal anti-inflammatory agent.

INHIBIDORES HETEROCÍCLICOS DE ASPARTIL PROTEASA

CAMPO DE LA INVENCION

Esta invención se refiere a inhibidores heterocíclicos de aspartil proteasa, a las composiciones farmacéuticas que comprenden dichos compuestos, a su uso en el tratamiento de enfermedades cardiovasculares, a enfermedades cognitivas y neurodegenerativas, y a su uso como inhibidores del Virus de Inmunodeficiencia Humana, plasmepsinas, catepsina D y enzimas protozoarias.

ANTECEDENTES

Se conocen ocho proteasas aspárticas humanas de la familia A1 (de tipo pepsina) actualmente: pepsina A y C, renina, BACE, BACE 2, Napsina A, catepsina D en estados patológicos.

La función que cumple el sistema de renina-angiotensina (RAS) en la regulación de la presión sanguínea y del electrolito de los fluidos ha quedado bien establecida (Oparil, S, et al. N Engl J Med 1974; 291:381-401/446-57). El octapéptido Angiotensina-II, un potente vasoconstrictor y estimulador para la liberación de aldosterona adrenérgica, fue procesado a partir del precursor deca péptido Angiotensina-I, el cual fue procesado a su vez a partir del angiotensinógeno mediante la enzima renina. La angiotensina-II demostró también que cumplía varios roles en el crecimiento celular del músculo liso vascular, en la inflamación, en la generación de especies de oxígeno reactivo en trombosis, influenciando la aterogénesis y el deterioro vascular. Clínicamente, el beneficio de la interrupción de la generación de angiotensina-II a través del antagonismo de la conversión de angiotensina-I ha quedado bien establecida y existe en una variedad de fármacos inhibidores ACE en el mercado. El bloqueo de la conversión precoz del angiotensinógeno a angiotensina-I, es decir, la inhibición de la enzima renina, se espera que tendrá efectos similares pero no idénticos. Debido a que la renina es una proteasa aspartilo cuyo único sustrato natural es el angiotensinógeno, se cree que se producirían menos frecuentemente efectos adversos para controlar la elevada presión sanguínea y los síntomas relacionados regulados por angiotensina-II a través de su inhibición.

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Otra proteasa, la Catepsina-D, está involucrada en la biogénesis lisosomal y en la diana (targeting), de proteínas, y puede estar también involucrada en el procesamiento de antígenos en la presentación de fragmentos peptídicos. Ha sido

conectada con numerosas enfermedades incluyendo la enfermedad de Alzheimer, enfermedad del tejido conectivo, distrofia muscular y cáncer de mama.

La enfermedad de Alzheimer (AD) es una enfermedad neurodegenerativa progresiva que es finalmente fatal. El avance de la enfermedad está asociado con la pérdida gradual de la función cognitiva relacionada con la memoria, razonamiento, orientación y opinión. Los cambios de comportamiento incluyendo confusión, depresión y agresión se manifiestan también como avances de la enfermedad. La disfunción cognitiva de comportamiento se considera que el resultado de la función neuronal alterada de la pérdida neuronal en el hipocampo en la corteza cerebral. Los tratamientos para AD corrientemente disponibles son paliativos, y aunque mejoran los desórdenes cognitivos del comportamiento, no previenen el avance de la enfermedad. Por lo tanto, existe una necesidad médica no lograda para descubrir tratamientos para AD que detengan el avance de la enfermedad.

Los sellos distintivos patológicos de AD son la deposición de placas β -amiloides extracelulares ($A\beta$) y enmarañamientos neurofibrilares intracelulares constituidos por la proteína tau anormalmente fosforilada. Los individuos con AD exhiben depósitos $A\beta$ característicos, en regiones cerebrales que se saben que son importantes para la memoria y el conocimiento. Se cree que $A\beta$ es el agente causante fundamental de la pérdida de células neuronales y de la disfunción que está asociada con la declinación cognitiva y de comportamiento. Las placas amiloides consisten predominantemente en péptidos $A\beta$ constituidos por 40 – 42 residuos aminoácidos, que derivan del procesamiento de la proteína precursora amiloide (APP). El APP se procesa mediante múltiples actividades de proteasa distintas. Los péptidos $A\beta$ son el resultado de la disociación de APP mediante β -secretasa en la posición que corresponde al N-término de $A\beta$, y al C-término mediante la actividad de γ -secretasa. La APP disociada por la actividad de α -secretasa que da como resultado el fragmento no-amiloidogénico, secretado que se conoce como APP soluble.

Se ha identificado una aspartil proteasa conocida como BACE-1 como responsable de la actividad de la β -secretasa para la disociación de APP en la posición que corresponde al N-término de los péptidos $A\beta$.

Evidencia genética y bioquímica acumulada, apoya el rol central de $A\beta$ en la etiología de AD. Por ejemplo, $A\beta$ ha demostrado que es tóxica para las células neuronales in vitro cuando se inyecta a cerebro de roedores. Además, se conocen formas heredadas de AD de comienzo precoz, en las cuales están presentes

mutaciones bien definidas de APP o de las presenilinas. Estas mutaciones aumentan la producción de A β y se consideran las causantes de AD.

Debido a que los péptidos A β se forman como resultado de la actividad de la β -secretasa, la inhibición de BACE-1 debería inhibir la formación de los péptidos A β . Por lo tanto la inhibición de BACE-1 es una realización terapéutica para el tratamiento de AD y otras enfermedades cognitivas neurodegenerativas causadas por la deposición de placas A β .

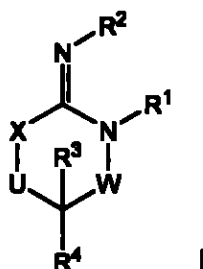
El virus de inmunodeficiencia humana (HIV), es el agente causante del síndrome de deficiencia de inmunidad adquirida (SIDA). Se ha demostrado químicamente que los compuestos tales como indinavir, ritonavir y saquinavir los cuales son inhibidores de la aspartil proteasa HIV dan como resultado una disminución de la carga viral. De este modo, los compuestos descritos aquí resultarían útiles para el tratamiento de SIDA. Tradicionalmente, un objetivo mayor para los investigadores ha sido la proteasa HIV-1, una aspartil proteasa relacionada con la renina.

Además, el virus de tipo I de leucemia de células T humana (HTLV-I) es un retrovirus humano que ha sido clínicamente asociado con leucemia de células T en adultos y otras enfermedades crónicas. Tal como otros retrovirus, el HTLV-I requiere una aspartil proteasa para procesar las proteínas precursoras virales, que producen viriones maduros. Esto hace que las proteasas sean un objetivo atractivo para el diseño inhibitorio. "Moore, et al. Purificación de HTLV-I Proteasa y Síntesis de Inhibidores para el tratamiento de la Infección de HTLV-I, 55ª de la Reunión Regional del Sudeste de la Sociedad Química Americana, Atlanta, GA, US Noviembre 16-19, 2003 (2003), 1073. CODEN; 69EUCH Conferencia, AN 2004:137641 CAPLUS".

Las plasmepsinas son enzimas aspartil proteasa esenciales del parásito de la malaria. Los compuestos para la inhibición de las plasmepsinas de proteasas aspartilo, particularmente I, II, IV y HAP, están siendo desarrolladas para el tratamiento de malaria. "Freire, et al. en la WO 2002074719. Na Byoung-Kuk, et al. Aspartil Proteasas de Plasmodium vivax altamente conservadas en aislados silvestres Korean Journal de Parasitology (Junio de 2004), 42(2) 61-6. Journal code: 9435800". Además, los compuestos usados para las dianas, plasmepsinas aspartil proteasas (por ejemplo. I, II, IV y HAP), han demostrado ser útiles para matar los parásitos de la malaria, y por lo tanto para tratar agentes que la sufren.

COMPENDIO DE LA INVENCION

La presente invención se refiere a compuestos que tienen la fórmula estructural I



o a un estereoisómero, tautómero, o sal o solvato de los mismos farmacéuticamente aceptables, en la cual

W es un enlace, $-C(=S)-$, $-S(O)-$, $-S(O)_2-$, $-C(=O)-$, $-O-$, $-C(R^6)(R^7)-$, $-N(R^5)-$ o $-C(=N(R^5))-$;

X es $-O-$, $-N(R^5)-$ o $-C(R^6)(R^7)-$; con la condición de que cuando X es $-O-$, U no sea $-O-$, $-S(O)-$, $-S(O)_2-$, $-C(=O)-$ o $-C(=NR^5)-$;

U es un enlace, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-O-$, $-P(O)(OR^{15})-$, $-C(=NR^5)-$, $-(C(R^6)(R^7))_b-$ o $-N(R^5)-$; donde b es 1 ó 2; con la condición de que cuando W es $-S(O)-$, $-S(O)_2-$, $-O-$, o $-N(R^5)-$, U no sea $-S(O)-$, $-S(O)_2-$, $-O-$, o $-N(R^5)-$; con la condición de que cuando X es $-N(R^5)-$ y W es $-S(O)-$, $-S(O)_2-$, $-O-$, o $-N(R^5)-$, entonces U no sea un enlace;

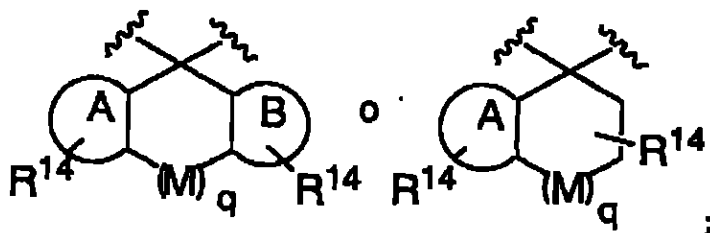
R^1 , R^2 y R^5 están independientemente seleccionados del grupo que consiste en H, alquilo, alquenilo, cicloalquilol, cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, arilcicloalquilo, $-OR^{15}$, $-CN$, $-C(O)R^8$, $-C(O)OR^9$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-C(O)N(R^{11})(R^{12})$, $-S(O)N(R^{11})(R^{12})$, $-S(O)_2N(R^{11})(R^{12})$, $-NO_2$, $-N=C(R^6)_2$ y $-N(R^6)_2$, con la condición de que R^1 y R^5 no estén ambos seleccionados de $-NO_2$, $-N=C(R^6)_2$ y $-N(R^6)_2$;

R^3 , R^4 , R^6 y R^7 están independientemente seleccionados del grupo que consiste en H, alquilo, cicloalquilo, cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, halo, $-CH_2-O-Si(R^9)(R^{10})(R^{10})$, $-SH$, $-CN$, $-OR^9$, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^{11})(R^{12})$, $-SR^{10}$, $-S(O)N(R^{11})(R^{12})$, $-S(O)_2N(R^{11})(R^{12})$, $-N(R^{11})(R^{12})$, $-N(R^{11})C(O)R^8$, $-N(R^{11})S(O)R^{10}$, $-N(R^{11})C(O)N(R^{12})(R^{13})$, $-N(R^{11})C(O)OR^9$ y $-C(=NOH)R^8$; con la condición de que cuando U es $-O-$ o $-N(R^5)-$, entonces R^3 , R^4 , R^6 y R^7 no son halo, $-SH$, $-OR^9$, $-SR^{10}$, $-S(O)N(R^{11})(R^{12})$, $-S(O)_2N(R^{11})(R^{12})$, $-N(R^{11})(R^{12})$, $-N(R^{11})C(O)R^8$, $-N(R^{11})S(O)R^{10}$, $-N(R^{11})C(O)N(R^{12})(R^{13})$, o $-N(R^{11})C(O)OR^9$; con la condición de que cuando W es $-O-$

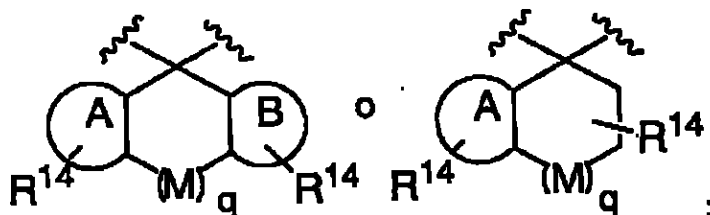
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o $-N(R^5)-$, entonces R^3 y R^4 no son halo, $-SH$, $-OR^8$, $-SR^{18}$, $-S(O)N(R^{11})(R^{12})$, $-S(O)_2N(R^{11})(R^{12})$, $-N(R^{11})(R^{12})$, $-N(R^{11})C(O)R^8$, $-N(R^{11})S(O)R^{10}$, $-N(R^{11})C(O)N(R^{12})(R^{13})$, o $-N(R^{11})C(O)OR^8$; con la condición de que cuando X es $-N(R^5)-$, W es $-C(O)-$ y U es un enlace, R^3 , R^4 y R^5 no son halo, $-CN$, $-SH$, $-OR^8$, $-SR^{18}$, $-S(O)N(R^{11})(R^{12})$ o $-S(O)_2N(R^{11})(R^{12})$; o R^3 , R^4 , R^6 y R^7 , conjuntamente con el carbono al cual están unidos, forman un grupo cicloalquilo de 3-7 miembros que está opcionalmente sustituido con R^{14} o un éter cicloalquilico de 3-7 miembros opcionalmente sustituido con R^{14} ;

o R^3 y R^4 o R^6 y R^7 conjuntamente con el carbono al cual están unidos se combinan para formar grupos multicíclicos tales como;



en los cuales M es $-CH_2-$, S , $-N(R^{18})-$ u O , A y B son independientemente arilo o heteroarilo y q es 0, 1 ó 2 con la condición de que cuando q es 2, una M debe ser un átomo de carbono y cuando q es 2, M es opcionalmente un doble enlace; y con la condición de que cuando R^3 , R^4 , R^6 y R^7 formen dichos grupos multicíclicos;



y entonces grupos adyacentes R^3 y R^4 o R^6 y R^7 no pueden combinarse para formar dichos grupos multicíclicos;

R^8 está independientemente seleccionado del grupo que consiste en H , alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, $-OR^{18}$, $-N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$ y $-N(R^{15})C(O)OR^{16}$;

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R^9 está independientemente seleccionado del grupo que consiste en H, alquilo, cicloalquilo, cicloalquilalquilo, cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilalquilo, heteroarilo y heteroarilalquilo;

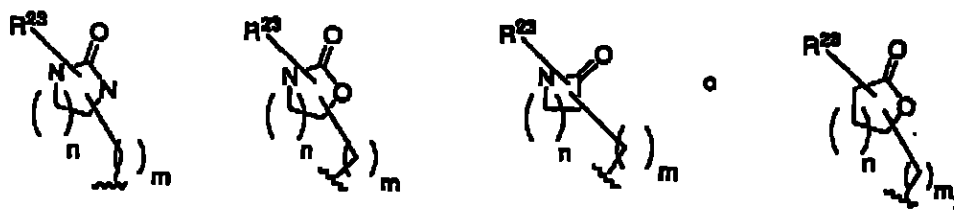
R^{10} está independientemente seleccionado del grupo que consiste en H, alquilo, alquenilo, cicloalquilo, cicloalquilalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, y $-N(R^{15})(R^{16})$;

R^{11} , R^{12} y R^{13} están independientemente seleccionados del grupo que consiste en H, alquilo, cicloalquilo, cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, $-C(O)R^8$, $-C(O)OR^8$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-C(O)N(R^{15})(R^{16})$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$ y $-CN$;

R^{14} representa 1-5 sustituyentes independientemente seleccionados del grupo que consiste en alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, halo, $-CN$, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$ y $-N(R^{15})C(O)OR^{16}$;

R^{15} , R^{16} y R^{17} están independientemente seleccionados del grupo que consiste en H, alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, arilcicloalquilo, arilheterocicloalquilo, R^{18} -alquilo, R^{18} -cicloalquilo, R^{18} -cicloalquilalquilo, R^{18} -heterocicloalquilo, R^{18} -heterocicloalquilalquilo, R^{18} -arilo, R^{18} -arilalquilo, R^{18} -heteroarilo y R^{18} -heteroarilalquilo; o

R^{15} , R^{16} y R^{17} son



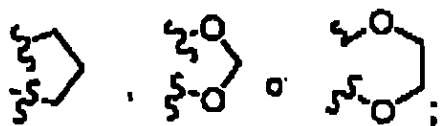
donde R^{23} es 0 a 5 sustituyentes, m es 0 a 6 y n es 1 a 5;

R^{18} representa 1-5 sustituyentes independientemente seleccionados del grupo que consiste en alquilo, alquenilo, arilo, arilalquilo, arilalquenilo, arilalquinilo, $-NO_2$,

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halo, heteroarilo, HO-alcoxialquilo, $-\text{CF}_3$, $-\text{CN}$, alquilo-CN, $-\text{C}(\text{O})\text{R}^{19}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^{19}$, $-\text{C}(\text{O})\text{NHR}^{20}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}_2\text{C}(\text{O})\text{N}(\text{alquilo})_2$, $-\text{C}(\text{O})\text{N}(\text{alquilo})(\text{arilo})$, $-\text{C}(\text{O})\text{N}(\text{alquilo})(\text{heteroarilo})$, $-\text{SR}^{19}$, $-\text{S}(\text{O})_2\text{R}^{20}$, $-\text{S}(\text{O})\text{NH}_2$, $-\text{S}(\text{O})\text{NH}(\text{alquilo})$, $-\text{S}(\text{O})\text{N}(\text{alquilo})(\text{alquilo})$, $-\text{S}(\text{O})\text{NH}(\text{arilo})$, $-\text{S}(\text{O})_2\text{NH}_2$, $-\text{S}(\text{O})_2\text{NHR}^{19}$, $-\text{S}(\text{O})_2\text{NH}(\text{heterocicloalquilo})$, $-\text{S}(\text{O})_2\text{N}(\text{alquilo})_2$, $-\text{S}(\text{O})_2\text{N}(\text{alquilo})(\text{arilo})$, $-\text{OCF}_3$, $-\text{OH}$, $-\text{OR}^{20}$, $-\text{O-heterocicloalquilo}$, $-\text{O-cicloalquilalquilo}$, $-\text{O-heterocicloalquilalquilo}$, $-\text{NH}_2$, $-\text{NHR}^{20}$, $-\text{N}(\text{alquilo})_2$, $-\text{N}(\text{arilalquilo})_2$, $-\text{N}(\text{arilalquilo})(\text{heteroarilalquilo})$, $-\text{NHC}(\text{O})\text{R}^{20}$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NH}(\text{alquilo})$, $-\text{NHC}(\text{O})\text{N}(\text{alquilo})(\text{alquilo})$, $-\text{N}(\text{alquilo})\text{C}(\text{O})\text{NH}(\text{alquilo})$, $-\text{N}(\text{alquilo})\text{C}(\text{O})\text{N}(\text{alquilo})(\text{alquilo})$, $-\text{NHS}(\text{O})_2\text{R}^{20}$, $-\text{NHS}(\text{O})_2\text{NH}(\text{alquilo})$, $-\text{NHS}(\text{O})_2\text{N}(\text{alquilo})(\text{alquilo})$, $-\text{N}(\text{alquilo})\text{S}(\text{O})_2\text{NH}(\text{alquilo})$ y $-\text{N}(\text{alquilo})\text{S}(\text{O})_2\text{N}(\text{alquilo})(\text{alquilo})$;

o dos porciones R^{18} en carbonos adyacentes pueden estar ligadas conjuntamente para formar;



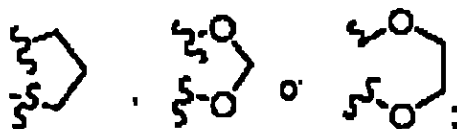
R^{19} es alquilo, cicloalquilo, arilo, arilalquilo o heteroarilalquilo;

R^{20} es alquilo, cicloalquilo, arilo, halo arilo sustituido, arilalquilo, heteroarilo o heteroarilalquilo;

y donde cada uno de los grupos alquilo, cicloalquilo, cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, alquenilo y alquinilo en R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} y R^{14} están independientemente no sustituidos o están sustituidos con 1 a 5 grupos R^{21} independientemente seleccionados del grupo que consiste en alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, halo, $-\text{CN}$, $-\text{OR}^{15}$, $-\text{C}(\text{O})\text{R}^{15}$, $-\text{C}(\text{O})\text{OR}^{15}$, $-\text{C}(\text{O})\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{SR}^{15}$, $-\text{S}(\text{O})\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{CH}(\text{R}^{15})(\text{R}^{16})$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{C}(=\text{NOR}^{15})\text{R}^{16}$, $-\text{P}(\text{O})(\text{OR}^{15})(\text{OR}^{16})$, $-\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{alquilo-N}(\text{R}^{15})(\text{R}^{16})$, $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$, $-\text{CH}_2\text{-N}(\text{R}^{15})\text{C}(\text{O})\text{R}^{16}$, $-\text{CH}_2\text{-N}(\text{R}^{15})\text{C}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{CH}_2\text{-R}^{15}$, $-\text{CH}_2\text{N}(\text{R}^{15})(\text{R}^{16})$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{CH}_2\text{-N}(\text{R}^{15})\text{S}(\text{O})_2\text{R}^{16}$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})_2\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{N}(\text{R}^{15})\text{S}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{CH}_2\text{-N}(\text{R}^{15})\text{C}(\text{O})\text{N}(\text{R}^{16})(\text{R}^{17})$, $-\text{N}(\text{R}^{15})\text{C}(\text{O})\text{OR}^{16}$, $-\text{CH}_2\text{-}$

$N(R^{15})C(O)OR^{16}$, $-S(O)R^{15}$, $=NOR^{15}$, $-N_3$, $-NO_2$ y $-S(O)_2R^{15}$; y cada uno de los grupos alquilo, cicloalquenilo, cicloalquilo, cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, alquenilo y alquinilo en R^{21} están independientemente no sustituidos o sustituidos con 1 a 5 grupos R^{22} independientemente seleccionados del grupo que consiste en alquilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, arilo, heteroarilo, halo, $-CF_3$, $-CN$, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-alquilo-C(O)OR^{15}$, $C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, $-alquilo-N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-N_3$, $=NOR^{15}$, $-NO_2$, $-S(O)R^{15}$ y $-S(O)_2R^{15}$;

o dos porciones R^{21} o dos porciones R^{22} en carbonos adyacentes pueden estar ligadas conjuntamente para formar



y cuando R^{21} o R^{22} están seleccionados del grupo que consiste en $-C(=NOR^{15})R^{16}$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$ y $-CH_2-N(R^{15})C(O)OR^{16}$, R^{15} y R^{16} conjuntamente pueden ser una cadena C_2 a C_4 , en la cual opcionalmente, uno, dos o tres carbonos del anillo pueden ser reemplazados con $-C(O)-$ o $-N(H)-$ y R^{15} y R^{16} , conjuntamente con los átomos a los cuales están unidos, forman un anillo de 5 a 7 miembros, opcionalmente sustituido con R^{23} ;

R^{23} representa 1 a 5 grupos independientemente seleccionados del grupo que consiste en alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, halo, $-CN$, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, $-C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$,

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$-N(R^{24})(R^{25})$, $-alquilo-N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$, $-CH_2-N(R^{24})C(O)R^{25}$,
 $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$, $-N(R^{24})S(O)_2N(R^{25})(R^{26})$,
 $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$, $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$,
 $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ y $-S(O)_2R^{24}$; y donde cada uno de
los grupos alquilo, cicloalquilo, cicloalquilalquilo, heterocicloalquilo,
heterocicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, alqueno y
alquinilo en R^{23} están independientemente no sustituidos o están sustituidos con 1 a 5
grupos R^{27} independientemente seleccionados del grupo que consiste en alquilo,
cicloalquilo, heterocicloalquilo, arilo, heteroarilo, halo, $-CF_3$, $-CN$, $-OR^{24}$, $-C(O)R^{24}$,
 $-C(O)OR^{24}$, alquilo- $C(O)OR^{24}$, $C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$,
 $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, $-alquilo-$
 $N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$, $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$,
 $-CH_2-N(R^{24})S(O)_2R^{25}$, $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$,
 $-N(R^{24})C(O)N(R^{25})(R^{26})$, $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-$
 $N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ y $-S(O)_2R^{24}$;

R^{24} , R^{25} y R^{26} están independientemente seleccionados del grupo que consiste
en H, alquilo, cicloalquilo, cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo,
arilo, arilalquilo, heteroarilo, heteroarilalquilo, arilcicloalquilo, R^{27} -alquilo, R^{27} -
cicloalquilo, R^{27} -cicloalquilalquilo, R^{27} -heterocicloalquilo, R^{27} -heterocicloalquilalquilo,
 R^{27} -arilo, R^{27} -arilalquilo, R^{27} -heteroarilo y R^{27} -heteroarilalquilo;

R^{27} representa 1-5 sustituyentes independientemente seleccionados del grupo
que consiste en alquilo, arilo, arilalquilo, $-NO_2$, halo, $-CF_3$, $-CN$, alquilo- CN , $-C(O)R^{28}$,
 $-C(O)OH$, $-C(O)OR^{28}$, $-C(O)NHR^{28}$, $-C(O)N(alquilo)_2$, $-C(O)N(alquilo)(arilo)$,
 $-C(O)N(alquilo)(heteroarilo)$, $-SR^{28}$, $-S(O)_2R^{28}$, $-S(O)NH_2$, $-S(O)NH(alquilo)$,
 $-S(O)N(alquilo)(alquilo)$, $-S(O)NH(arilo)$, $-S(O)_2NH_2$, $-S(O)_2NHR^{28}$, $-S(O)_2NH(arilo)$,
 $-S(O)_2NH(heterocicloalquilo)$, $-S(O)_2N(alquilo)_2$, $-S(O)_2N(alquilo)(arilo)$, $-OH$, $-OR^{28}$,
 $-O-heterocicloalquilo$, $-O-cicloalquilalquilo$, $-O-heterocicloalquilalquilo$, $-NH_2$, $-NHR^{28}$,
 $-N(alquilo)_2$, $-N(arilalquilo)_2$, $-N(arilalquilo)(heteroarilalquilo)$, $-NHC(O)R^{28}$,
 $-NHC(O)NH_2$, $-NHC(O)NH(alquilo)$, $-NHC(O)N(alquilo)(alquilo)$,
 $-N(alquilo)C(O)NH(alquilo)$, $-N(alquilo)C(O)N(alquilo)(alquilo)$, $-NHS(O)_2R^{28}$,
 $-NHS(O)_2NH(alquilo)$, $-NHS(O)_2N(alquilo)(alquilo)$, $-N(alquilo)S(O)_2NH(alquilo)$ y
 $-N(alquilo)S(O)_2N(alquilo)(alquilo)$;

R^{28} es alquilo, cicloalquilo, arilalquilo o heteroarilalquilo; y

R^{29} es alquilo, cicloalquilo, arilo, arilalquilo, heteroarilo o heteroarilalquilo;

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con la condición de cuando W es $-C(O)-$ y U es un enlace, R^1 no sea fenilo opcionalmente sustituido, y que cuando U es $-C(O)-$ y W es un enlace, R^5 no sea fenilo opcionalmente sustituido;

con la condición de que ni R^1 ni R^5 sea $-C(O)$ -alquil-azetidinona o alquil disustituido con $(-COOR^{15}$ o $-C(O)N(R^{15})(R^{16})$) y $(-N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, o $-N(R^{15})C(O)OR^{16}$);

con la condición de que cuando R^1 es metilo, X es $-N(R^5)-$, R^2 es H, W es $-C(O)-$ y U es un enlace, (R^3, R^4) no sea (H, H), (fenilo, fenilo), (H, fenilo), (bencilo, H), (bencilo, fenilo), (i-butilo, H), (i-butilo, fenilo), (OH-fenilo, fenilo), (halo-fenilo, fenilo), o $(CH_3O$ -fenilo, NO_2 -fenilo); y cuando W es un enlace y U es $-C(O)-$, (R^3, R^4) no sea (H, H), (fenilo, fenilo), (H, fenilo), (bencilo, H), (bencilo, fenilo), (i-butilo, H), (i-butilo, fenilo), (OH-fenilo, fenilo), (halo-fenilo, fenilo), o $(CH_3O$ -fenilo, NO_2 -fenilo);

con la condición de que cuando X es $-N(R^5)-$, R^1 y R^5 son cada uno H, W es $-C(O)-$ y U es un enlace, (R^3, R^4) no sea (fenilo opcionalmente sustituido, bencilo opcionalmente sustituido), (fenilo opcionalmente sustituido, heteroarilalquilo) o (heteroarilo, heteroarilalquilo);

con la condición de que cuando U es un enlace, W es $-C(O)-$, y R^3 y R^4 forman un anillo con el carbono al cual están unidos, R^1 no sea 2- CF_3 -3-CN-fenilo;

con la condición de que cuando X es $-N(R^5)-$, U es $-O-$ y W es un enlace o $-C(R^6)(R^7)-$, (R^3, R^4) no sea (H, $-NHC(O)$ -alquil-heteroarilo) o (H, alquil- $NHC(O)$ -alquil-heteroarilo); y

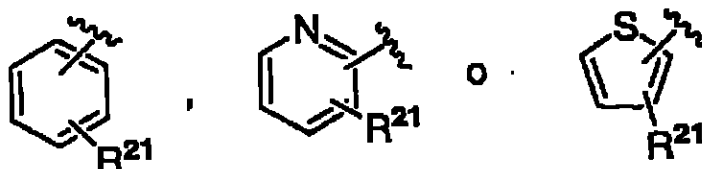
con la condición de que cuando X es $-N(R^5)-$, R^1 y R^5 no sea $-alquilaril$ -aril- $SO_2-N(R^{15})(R^{16})$ donde R^{15} es H y R^{16} es heteroarilo;

con la condición de que cuando R^1 es R^{21} -arilo o R^{21} -arilalquilo, donde R^{21} es $-OCF_3$, $-S(O)CF_3$, $-S(O)_2CF_3$, $-S(O)$ alquilo, $-S(O)_2$ alquilo, $-S(O)_2CHF_2$, $-S(O)_2CF_2CF_3$, $-OCF_2CHF_2$, $-OCHF_2$, $-OCH_2CF_3$, $-SF_3$ o $-S(O)_2NR^{15}R^{16}$; donde R^{15} y R^{16} están independientemente seleccionados del grupo que consiste en H, alquilo, alquenilo, cicloalquilo, heterocicloalquilo, arilo y heteroarilo, R^{16} -alquilo, R^{16} -cicloalquilo, R^{16} -heterocicloalquilo, R^{16} -arilo y R^{16} -heteroarilo; U es un enlace o $-CH_2$; y X es $-N(R^5)-$; entonces R^5 es H;

con la condición de que cuando U es un enlace,

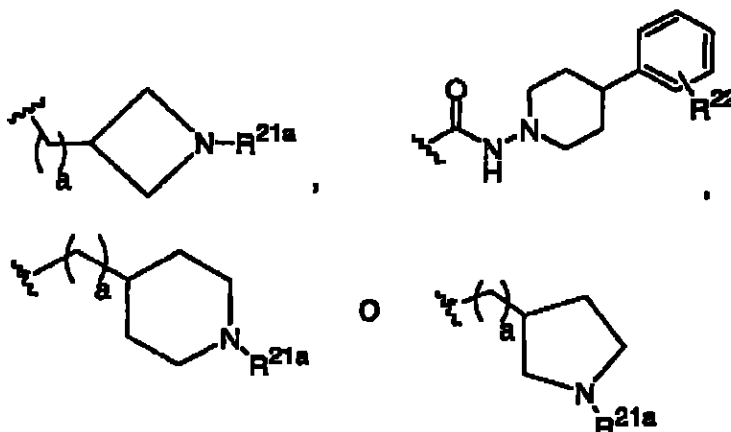
R^3 y R^4 son alquilo,

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donde R^{21} es halo, $-CN$, alquilo, alcoxi, haloalquilo o haloalcoxi, o R^3 y R^4 , conjuntamente con el carbono al cual están unidos forman un grupo cicloalquilo de 3-7 miembros

y R^1 es

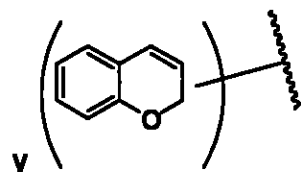


donde a es 0 a 6 y R^{22} es alquilo, alcoxi, halo, $-CN$, $-OH$, $-NO_2$ o haloalquilo;

entonces R^{21a} no sea H , $-C(O)_2R^{15}$, donde R^{15} está seleccionado del grupo que consiste en alquilo, cicloalquilo y alquilo sustituido con fenilo, alquilo o alquilo- R^{22} , donde R^{22} está seleccionado del grupo que consiste en

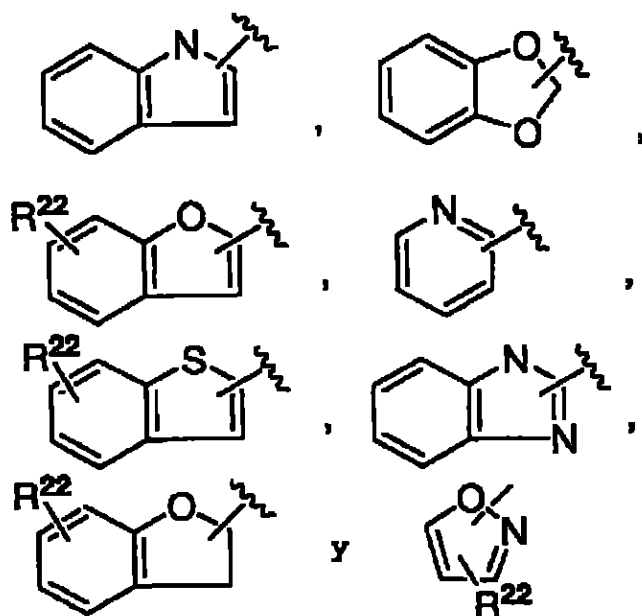
fenilo,

fenilo sustituido con alquilo,



y donde R^{22} está seleccionado del grupo que consiste en H , metoxi, nitro, oxo, $-OH$, halo y alquilo,

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En otro aspecto, la invención se refiere a una composición farmacéutica que comprende por lo menos un compuesto de fórmula I y un portador farmacéuticamente aceptable.

En otro aspecto, la invención comprende el método para inhibir aspartil proteasa que comprende administrar por lo menos un compuesto de fórmula I a un paciente que necesita dicho tratamiento.

Más específicamente, la invención comprende: el método de tratamiento de una enfermedad cardiovascular tal como hipertensión, insuficiencia renal, o una enfermedad modulada por la inhibición de renina; el método de tratamiento de Virus de Inmunodeficiencia Humana; el método de tratamiento de una enfermedad cognitiva, o neurodegenerativa tal como la Enfermedad de Alzheimer; el método para inhibir las plasmepsinas I y II para el tratamiento de malaria; el método para inhibir Catepsina D para el tratamiento de la Enfermedad de Alzheimer, cáncer de mama, y cáncer ovárico; y el método para inhibir enzimas protozoarias, por ejemplo la inhibición de plasmodium falciparum para el tratamiento de infecciones fúngicas. Dicho método de tratamiento comprende administrar por lo menos un compuesto de fórmula I a un paciente que necesita dicho tratamiento. En particular, la invención comprende el método para el tratamiento de la enfermedad de Alzheimer que comprende administrar por lo menos un compuesto de fórmula I a un paciente que necesita dicho tratamiento.

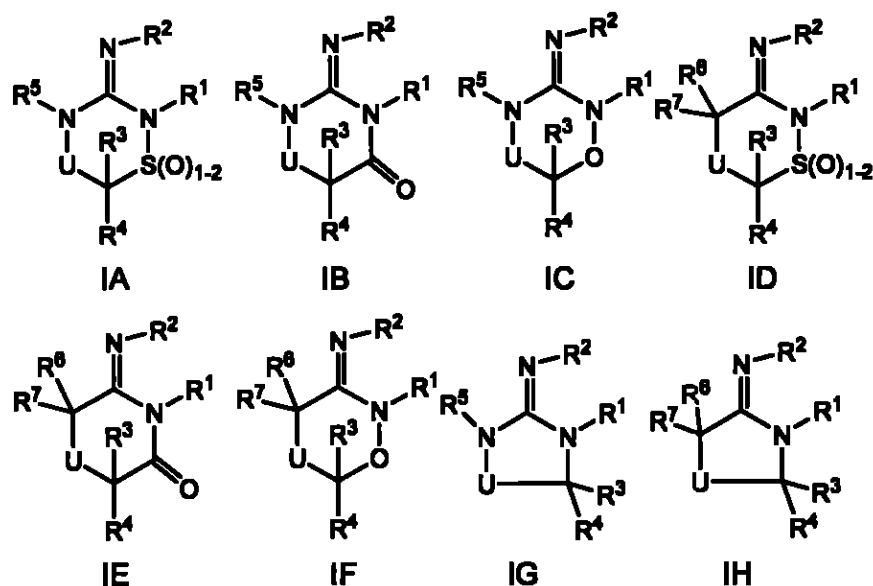
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En otro aspecto, la invención comprende el método de tratamiento de la enfermedad de Alzheimer, que comprende administrar a un paciente que necesita dicho tratamiento una combinación de por lo menos un compuesto de fórmula I y un inhibidor de colinesterasa o un antagonista muscarínico m_1 o antagonista m_2 .

En un aspecto final, la invención se refiere a un equipo que comprende en recipientes separados en un solo paquete, composiciones farmacéuticas para ser usadas en combinación, donde uno de los recipientes comprende un compuesto de fórmula I en un portador farmacéuticamente aceptable y un segundo recipiente que comprende un inhibidor de colinesterasa o un antagonista muscarínico en un portador farmacéuticamente aceptable, siendo las cantidades combinadas cantidades que son eficaces para tratar una enfermedad cognitiva o una enfermedad neurodegenerativa tal como la enfermedad de Alzheimer.

DESCRIPCIÓN DETALLADA:

Los compuestos de fórmula I en los cuales X, W y U son tal como se definieron anteriormente incluyen las siguientes estructuras independientemente preferidas:



En los compuestos de fórmulas IA a IF, U es preferiblemente un enlace o $-C(R^6)(R^7)-$. En los compuestos de fórmula IG y de IH, U es preferiblemente $-C(O)-$.

Se comprenderá que debido a que la definición de R^1 es igual que la definición de R^5 , cuando X es $-N(R^5)-$, los compuestos de fórmula I en los cuales W es un

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enlace y U es un enlace, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-O-$, $-C(R^6)(R^7)-$ o $-N(R^5)-$ son equivalentes a los compuestos de fórmula I en los cuales U es un enlace y W es un enlace, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-O-$, $-C(R^6)(R^7)-$ o $-N(R^5)-$.

Compuestos más preferidos de la invención son aquellos de fórmula IB en los cuales U es un enlace o aquellos de fórmula IB en los cuales U es $-C(R^6)(R^7)-$.

Otro grupo de compuestos preferidos de fórmula I es aquel en el cual R^2 es H.

R^3 , R^4 , R^6 y R^7 están preferiblemente seleccionados del grupo que consiste en alquilo, cicloalquilo, cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, halo, $-CH_2-O-Si(R^9)(R^{10})(R^{10})$, $-SH$, $-CN$, $-OR^9$, $-C(O)R^9$, $-C(O)OR^9$, $-C(O)N(R^{11})(R^{12})$, $-SR^{10}$, $-S(O)N(R^{11})(R^{12})$, $-S(O)_2N(R^{11})(R^{12})$, $-N(R^{11})(R^{12})$, $-N(R^{11})C(O)R^9$, $-N(R^{11})S(O)R^{10}$, $-N(R^{11})C(O)N(R^{12})(R^{13})$, $-N(R^{11})C(O)OR^9$ y $-C(=NOH)R^9$.

R^3 , R^4 , R^6 y R^7 están preferiblemente seleccionados del grupo que consiste en arilo, heteroarilo, heteroarilalquilo, arilalquilo, cicloalquilo, heterocicloalquilo, heterocicloalquilalquilo, alquilo y cicloalquilalquilo.

En un grupo de compuestos preferidos

U es un enlace o $-C(O)-$;

W es un enlace o $-C(O)-$;

X es $-N(R^5)-$;

R^1 es H, alquilo, R^{21} -alquilo, arilalquilo, R^{21} -arilalquilo, cicloalquilalquilo, R^{21} -cicloalquilalquilo, heterocicloalquilalquilo o R^{21} -heterocicloalquilalquilo,

R^2 es H;

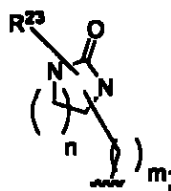
R^3 es alquilo, cicloalquilalquilo, cicloalquilo, arilo, arilalquilo, R^{21} -alquilo, R^{21} -cicloalquilalquilo, R^{21} -cicloalquilo, R^{21} -arilo o R^{21} -arilalquilo;

R^4 es alquilo, cicloalquilalquilo, cicloalquilo, arilo, arilalquilo, R^{21} -alquilo, R^{21} -cicloalquilalquilo, R^{21} -cicloalquilo, R^{21} -arilo o R^{21} -arilalquilo;

R^5 es H, alquilo, R^{21} -alquilo, arilalquilo, R^{21} -arilalquilo, cicloalquilalquilo, R^{21} -cicloalquilalquilo, heterocicloalquilalquilo o R^{21} -heterocicloalquilalquilo;

R^6 es alquilo, cicloalquilalquilo, cicloalquilo, arilo, arilalquilo, R^{21} -alquilo, R^{21} -cicloalquilalquilo, R^{21} -cicloalquilo, R^{21} -arilo o R^{21} -arilalquilo;

R^7 es alquilo, cicloalquilalquilo, cicloalquilo, arilo, arilalquilo, R^{21} -alquilo, R^{21} -cicloalquilalquilo, R^{21} -cicloalquilo, R^{21} -arilo o R^{21} -arilalquilo;



R^{15} , R^{16} y R^{17} es H, R^{18} -alquilo, alquilo o

R^{21} es alquilo, arilo, halo, $-OR^{15}$, $-NO_2$, $-C(O)R^{15}$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$ o

$-CH(R^{15})(R^{16})$;

n es 1;

m es 1;

R^{18} es $-OR^{20}$

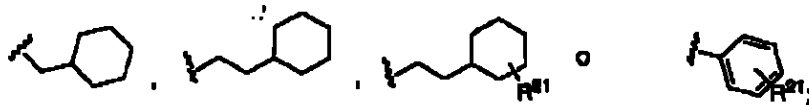
R^{20} es arilo;

y

R^{23} es alquilo.

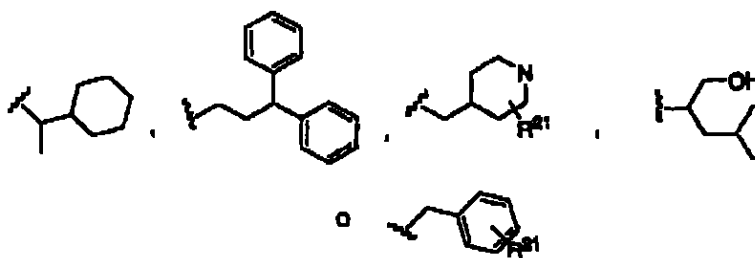
En un grupo de compuestos preferidos

R^3 , R^4 , R^6 y R^7 son



y

R^1 y R^5 es H, CH_3 ,



Un grupo adicional de compuestos preferidos:

U es un enlace o $-C(O)-$;

W es un enlace o $-C(O)-$;

X es $-N(R^5)-$;

R^1 es H, alquilo, R^{21} -alquilo, arilalquilo, R^{21} -arilalquilo, cicloalquilalquilo, R^{21} -cicloalquilalquilo, heterocicloalquilalquilo o R^{21} -heterocicloalquilalquilo,

R^2 es H;

R^3 es alquilo, cicloalquilalquilo, cicloalquilo, arilo, arilalquilo, R^{21} -alquilo, R^{21} -cicloalquilalquilo, R^{21} -cicloalquilo, R^{21} -arilo, R^{21} -arilalquilo, heteroarilalquilo, heteroarilo, heterocicloalquilo, heterocicloalquilalquilo, R^{21} -heteroarilalquilo, R^{21} -heteroarilo, R^{21} -heterocicloalquilo o R^{21} -heterocicloalquilalquilo;

R^4 es alquilo, cicloalquilalquilo, cicloalquilo, arilo, arilalquilo, R^{21} -alquilo, R^{21} -cicloalquilalquilo, R^{21} -cicloalquilo, R^{21} -arilo, R^{21} -arilalquilo, heteroarilalquilo, heteroarilo, heterocicloalquilo, heterocicloalquilalquilo, R^{21} -heteroarilalquilo, R^{21} -heteroarilo, R^{21} -heterocicloalquilo o R^{21} -heterocicloalquilalquilo;

R^5 es H, alquilo, R^{21} -alquilo, arilalquilo, R^{21} -arilalquilo, cicloalquilalquilo, R^{21} -cicloalquilalquilo, heterocicloalquilalquilo o R^{21} -heterocicloalquilalquilo;

R^6 es alquilo, cicloalquilalquilo, cicloalquilo, arilo, arilalquilo, R^{21} -alquilo, R^{21} -cicloalquilalquilo, R^{21} -cicloalquilo, R^{21} -arilo, R^{21} -arilalquilo, heteroarilalquilo, heteroarilo, heterocicloalquilo, heterocicloalquilalquilo, R^{21} -heteroarilalquilo, R^{21} -heteroarilo, R^{21} -heterocicloalquilo o R^{21} -heterocicloalquilalquilo;

R^7 es alquilo, cicloalquilalquilo, cicloalquilo, arilo, arilalquilo, R^{21} -alquilo, R^{21} -cicloalquilalquilo, R^{21} -cicloalquilo, R^{21} -arilo, R^{21} -arilalquilo, heteroarilalquilo, heteroarilo, heterocicloalquilo, heterocicloalquilalquilo, R^{21} -heteroarilalquilo, R^{21} -heteroarilo, R^{21} -heterocicloalquilo o R^{21} -heterocicloalquilalquilo;

R^{15} , R^{16} y R^{17} es H, cicloalquilo, cicloalquilalquilo, R^{18} -alquilo, alquilo, arilo,

R^{18} -arilo, R^{18} -arilalquilo, arilalquilo,

n es 1 ó 2;

m es 0 ó 1;

R^{18} es $-OR^{20}$ o halo;

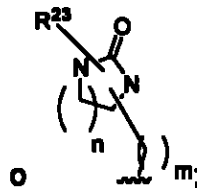
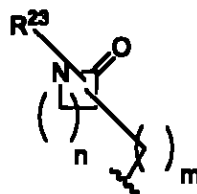
R^{20} es arilo o arilo halo sustituido;

R^{21} es alquilo, arilo, heteroarilo, R^{22} -alquilo, R^{22} -arilo, R^{22} -heteroarilo, halo, heterocicloalquilo, $-N(R^{15})(R^{16})$, $-OR^{15}$, $-NO_2$, $-C(O)R^{15}$, $-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$ o $-CH(R^{15})(R^{16})$;

R^{22} es $-OR^{15}$ o halo

y

R^{23} es H o alquilo.



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Se observa que los carbonos de fórmula I pueden ser reemplazados por 1 a 3 átomos de silicón siempre que se satisfagan todos los requisitos de valencia.

Tal como se usaron anteriormente, y a través de toda la memoria, términos siguientes, a menos que se indique lo contrario, tendrán los siguientes significados:

"Paciente" incluye seres humanos y animales.

"Mamífero" significa seres humanos y otros animales mamíferos.

"Alquilo" significa un grupo hidrocarbonado alifático que puede ser recto o ramificado y que comprende aproximadamente 1 hasta aproximadamente 20 átomos de carbono en la cadena. Los grupos alquilo preferidos contienen aproximadamente 1 hasta aproximadamente 12 átomos de carbono en la cadena. Los grupos alquilo más preferidos contienen aproximadamente 1 hasta aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo tal como metilo, etilo o propilo, están unidos a una cadena alquilo lineal. "Alquilo inferior" significa un grupo que tiene aproximadamente 1 hasta aproximadamente 6 átomos de carbono en la cadena, que puede ser recta o ramificada. Ejemplos no limitativos de grupos alquilo apropiados incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, t-butilo, n-pentilo, heptilo, nonilo y decilo. Los grupos alquilo R^{21} -sustituidos incluyen fluormetilo, trifluormetilo y ciclopropilmetilo.

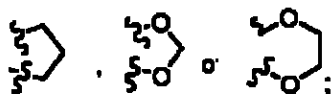
"Alquenilo" significa un grupo hidrocarbonado alifático que contiene por lo menos un doble enlace de carbono a carbono y que puede ser de cadena recta o ramificada y que comprende aproximadamente 2 hasta aproximadamente 15 átomos de carbono en la cadena. Los grupos alquenilo preferidos tienen aproximadamente 2 hasta aproximadamente 12 átomos de carbono en la cadena; y más preferiblemente aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo tales como metilo, etilo o propilo, están unidos a una cadena alquenilo lineal. "Alquenilo inferior" significa aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena, la cual puede ser recta o ramificada. Ejemplos no limitativos de grupos alquenilo apropiados incluyen etenilo, propenilo, n-butenilo, 3-metilbut-2-enilo, n-pentenilo, octenilo y decenilo.

"Alquinilo" significa un grupo hidrocarbonado alifático que contiene por lo menos un triple enlace de carbono a carbono y que puede ser de cadena recta o ramificada y que comprende aproximadamente 2 hasta aproximadamente 15 átomos de carbono en la cadena. Los grupos alquinilo preferidos tienen aproximadamente 2

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hasta aproximadamente 12 átomos de carbono en la cadena; y más preferiblemente aproximadamente 2 hasta aproximadamente 4 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior tales como metilo, etilo o propilo están unidos a una cadena alquilo lineal. "Alquilo inferior" significa aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena que puede ser recta o ramificada. Ejemplos no limitativos de grupos alquilo apropiados incluyen etinilo, propinilo, 2-butinilo, 3-metilbutinilo, n-pentinilo, y decinilo.

"Ariilo" significa un sistema de anillo aromático monocíclico o multicíclico que comprende aproximadamente 6 hasta aproximadamente 14 átomos de carbono, preferiblemente aproximadamente 6 hasta aproximadamente 10 átomos de carbono. El grupo ariilo puede estar opcionalmente sustituido con uno o más sustituyentes (por ejemplo R^{18} , R^{21} , R^{22} , etc.) que pueden ser iguales o diferentes, y que son tal como se han definido aquí o dos sustituyentes en carbonos adyacentes pueden estar ligados conjuntamente para formar.



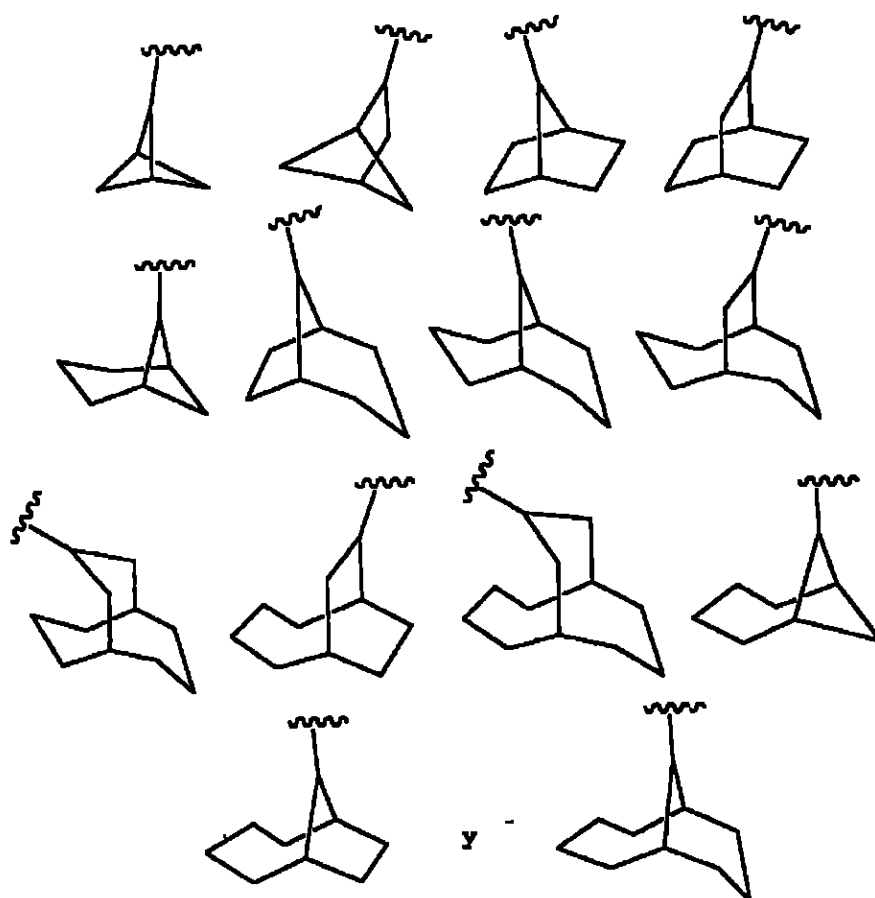
Ejemplos no limitativos de grupos ariilo apropiados incluyen fenilo y naftilo.

"Heteroarilo" significa un sistema de anillo monocíclico o multicíclico aromático que comprende aproximadamente 5 hasta aproximadamente 14 átomos en el anillo, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos en el anillo, en el cual uno a ocho de los átomos del anillo es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre, solos o en combinación. Los heteroarilos preferidos contienen aproximadamente 5 hasta aproximadamente 6 átomos en el anillo. El "heteroarilo" puede estar opcionalmente sustituido con uno o más sustituyentes R^{21} que pueden ser iguales o diferentes, y que son tal como se definen aquí. Los prefijos aza, oxa o tia antes de nombre de raíz heteroarilo significan que por lo menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, está presente como átomo del anillo. Un átomo de nitrógeno de un heteroarilo puede estar opcionalmente oxidado al correspondiente N-óxido. Ejemplos no limitativos de heteroarilos apropiados incluyen piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, isoxazolilo, isotiazolilo, oxazolilo, tiazolilo, pirazolilo, furazanilo, pirrolilo, pirazolilo, triazolilo, 1,2,4-tiadiazolilo, pirazinilo, piridazinilo, quinoxalinilo, ftalazinilo, imidazo[1,2-

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a]piridinilo, imidazo[2,1-b]tiazolilo, benzofurazanilo, indolilo, azaindolilo, benzimidazolilo, benzotienilo, quinolinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidilo, pirrolopiridilo, imidazopiridilo, isoquinolinilo, benzoazaindolilo, 1,2,4-triazinilo, benzotiazolilo y similares.

"Cicloalquilo" se refiere a un sistema de anillo mono- o multicíclico no aromático que comprende aproximadamente 3 hasta aproximadamente 10 átomos de carbono, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos de carbono. Los anillos cicloalquilo preferidos contienen aproximadamente 5 hasta aproximadamente 7 átomos de anillo. El cicloalquilo puede estar opcionalmente sustituido con uno o más sustituyentes R^{21} , los cuales pueden ser iguales o diferentes, y son tal como se han definido anteriormente. Ejemplos no limitativos de cicloalquilos monocíclicos apropiados incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares. Ejemplos no limitativos de cicloalquilos multicíclicos apropiados incluyen 1-decalina, norbornilo, adamantilo y similares. Otros ejemplos no limitativos de cicloalquilo incluyen los siguientes



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"Cicloalquiléter" significa un anillo no aromático de 3 a 7 miembros que comprende un átomo de oxígeno y 2 a 7 átomos de carbono. Los átomos de carbono del anillo pueden estar sustituidos, con la condición de que los sustituyentes adyacentes al oxígeno del anillo no incluyan halo o sustituyentes unidos al anillo a través de un átomo de oxígeno, nitrógeno o azufre.

"Cicloalquenilo" significa un sistema de anillo no aromático mono o multicíclico que comprende aproximadamente 3 hasta aproximadamente 10 átomos de carbono, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos de carbono que contiene por lo menos un doble enlace de carbono a carbono. El anillo cicloalquenilo puede estar opcionalmente sustituido con uno más sustituyentes R²¹ que pueden ser iguales o diferentes, y que son tal como se han definido anteriormente. Los anillos cicloalquenilo preferidos contienen aproximadamente 5 hasta aproximadamente 7 átomos de anillo. Ejemplos no limitativos de cicloalquenilos monocíclicos apropiados incluyen ciclopentenilo, ciclohexenilo, cicloheptenilo, y similares. Ejemplos no limitativos de un cicloalquenilo multicíclico apropiado es norbornilenilo.

"Heterociclenilo" significa un sistema de anillo monocíclico o multicíclico no aromático que comprende aproximadamente 3 hasta aproximadamente 14 átomos en el anillo, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos en el anillo donde uno o más de los átomos en el sistema de anillo es un elemento distinto de carbono, por ejemplo un átomo de nitrógeno, oxígeno o azufre, solo o en combinación, y que contiene por lo menos un doble enlace de carbono a carbono o un doble enlace de carbono-nitrógeno. No existen átomos de oxígeno y/o azufre adyacentes presentes en el sistema de anillo. Los anillos heterociclenílicos precedidos contienen aproximadamente 5 hasta aproximadamente 6 átomos en el anillo. El prefijo aza, oxa o tia antes del nombre de raíz heterociclenilo significa que está presente como átomo del anillo por lo menos un átomo de nitrógeno, oxígeno o azufre, respectivamente. El heterociclenilo puede estar opcionalmente sustituido con uno o más sustituyentes del sistema de anillo donde "sustituyente del sistema de anillo" es tal como se ha definido anteriormente. El átomo de nitrógeno o azufre o el heterociclenilo puede estar opcionalmente oxidado al correspondiente N-óxido, S-óxido o S,S-dióxido. Ejemplos no limitativos de grupos azaheterociclenílicos monocíclicos apropiados incluyen 1,2,3,4-tetrahidropiridina, 1,2-dihidropiridilo, 1,4-dihidropiridilo, 1,2,3,6-tetrahidropiridina, 1,4,5,6-tetrahidropirimidina, 2-pirrolinilo, 3-

pirrolinilo, 2-imidazolinilo, 2-pirazolinilo, y similares. Ejemplos no limitativos de grupos oxaheterociclenílicos apropiados incluyen 3,4-dihidro-2H-pirano, dihidrofurano, fluordihidrofurano, y similares. Un ejemplo no limitativo de un grupo oxaheterociclenilo multícíclico apropiado es 7-oxabicyclo[2.2.1]heptenilo. Ejemplos no limitativos de anillos tiaheterociclenilo monocíclicos apropiados incluyen dihidrotiofenilo, dihidrotiopiranilo, y similares.

"Halo" significa grupos flúor, cloro, bromo, o yodo. Se prefiere flúor, cloro o bromo, y son aún más preferidos flúor y cloro.

"Haloalquilo" significa un alquilo tal como el definido anteriormente en el cual uno o más átomos de hidrógeno en el alquilo son reemplazados con un grupo halo definido anteriormente.

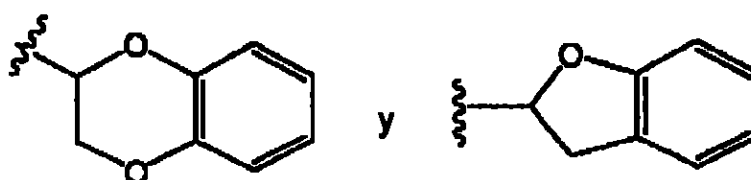
"Heterociclilo" (o heterocicloalquilo) significa un sistema de anillo mono monocíclico o multícíclico no aromático saturado que comprende aproximadamente 3 hasta aproximadamente 14 átomos en el anillo, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos en el anillo, en el cual 1-3, preferiblemente 1 o 2 de los átomos en el sistema de anillo son un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre, solos o en combinación. No existe ningún átomo de oxígeno y/o azufre adyacente presente en el sistema de anillo. Los heterociclilos preferidos contienen aproximadamente 5 hasta aproximadamente 6 átomos de anillo. El prefijo aza, oxa o tia antes del nombre de raíz heterociclilo significa que está presente como átomo del anillo por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente. El heterociclilo puede estar opcionalmente sustituido con uno o más sustituyentes R²¹ que pueden ser iguales o diferentes, y que son tal como se han definido aquí. El átomo de nitrógeno o azufre del heterociclilo puede estar opcionalmente oxidado al correspondiente N-óxido, S-óxido o S,S-dióxido. Ejemplos no limitativos de anillos heterociclilo monocíclicos apropiados incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,3-dioxolanilo, 1,4-dioxanilo, tetrahidrofurano, tetrahidrotiofenilo, tetrahidrotiopiranilo, y similares.

"Aralquilo" significa un grupo aril-alquilo en el cual el arilo y el alquilo son tan como se han descrito previamente. Los aralquilos preferidos comprenden un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilo apropiados incluyen bencilo, 2-fenetilo y naftalenilmetilo. El enlace con la porción principal se efectúa a través del alquilo.

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"Arlcicloalquilo" significa un grupo derivado de un arilo y cicloalquilo fusionados tal como se define aquí. Los arlcicloalquilos preferidos son aquellos en los cuales arilo es fenilo y cicloalquilo consiste en aproximadamente 5 hasta aproximadamente 6 átomos de anillo. El arlcicloalquilo puede estar opcionalmente sustituido con 1-5 sustituyente R^{21} . Ejemplos no limitativos de arlcicloalquilos apropiados incluyen indanilo y 1,2,3,4-tetrahidronaftilo y similares. El enlace con la porción principal se efectuó a través de un átomo de carbono no aromático.

"Arlheterocicloalquilo" significa un grupo derivado de un arilo y heterocicloalquilo fusionados tal como se definen aquí. Los arlcicloalquilos preferidos son aquellos en los cuales arilo es fenilo y heterocicloalquilo consiste en aproximadamente 5 hasta aproximadamente 6 átomos del anillo. El arlheterocicloalquilo puede estar opcionalmente sustituido con 1-5 sustituyentes R^{21} . Ejemplos no limitativos del arlheterocicloalquilo apropiados incluyen



El enlace con la porción principal se efectúa a través de un átomo de carbono no aromático.

De manera similar, "heteroarilalquilo" "cicloalquilalquilo" y "heterocicloalquilalquilo" significa un grupo heteroaril-, cicloalquil- o heterocicloalquil- alquilo- en el cual el heteroarilo, cicloalquilo, heterocicloalquilo y alquilo son tal como se han descrito previamente. Los grupos preferidos contienen un grupo alquilo inferior. El enlace con la porción principal se efectúa a través del alquilo.

"Acilo" significa un grupo $H-C(O)-$, alquilo- $C(O)-$, alqueno- $C(O)-$, alquino- $C(O)-$ o cicloalquilo- $C(O)-$ en el cual los varios grupos son tal como se han descrito previamente. El enlace con la porción principal se efectúa a través del carbonilo. Los acilos preferidos contienen un alquilo inferior. Ejemplos no limitativos de grupos acilo apropiados incluyen formilo, acetilo, propanoilo, 2-metilpropanoilo, butanoilo y ciclohexanoilo.

"Alcoxi" significa un grupo alquilo- $O-$ en el cual el grupo alquilo está como se ha descrito previamente. Ejemplos no limitativos de grupos alcoxi apropiados incluyen metoxi, etoxi, n-propoxi, isopropoxi, n-butoxi y heptoxi. El enlace con la porción principal se efectúa a través del oxígeno del éter.

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45A

"Alcoxialquilo" significa un grupo derivado de un alcoxi y un alquilo tal como se definen aquí. El enlace con la porción principal se efectúa a través del alquilo.

"Arlalquenilo" significa un grupo derivado de un arilo y un alquenilo tal como se definen aquí. Los arlalquenilos preferidos son aquellos en los cuales arilo es fenilo y el alquenilo consiste en aproximadamente 3 hasta aproximadamente 6 átomos. El arlalquenilo puede estar opcionalmente sustituido con uno o más sustituyentes R^{27} . El enlace con la porción principal se efectúa a través de un átomo de carbono no aromático.

"Arlalquinilo" significa un grupo derivado de un arilo y alquinilo tal como se definen aquí. Los arlalquinilos preferidos son aquellos en los cuales arilo es fenilo y el alquinilo consiste en aproximadamente 3 hasta aproximadamente 5 átomos. El arlalquinilo puede estar opcionalmente sustituido con uno o más sustituyentes R^{27} . El enlace con la porción principal se efectúa a través de un átomo de carbono no aromático.

El sufijo "eno" en el alquilo, arilo, heterocicloalquilo, etc. indica una porción divalente, por ejemplo, $-\text{CH}_2\text{CH}_2-$ es etileno, y $\xi-\text{C}_6\text{H}_4-\xi$ es para-fenileno.

El término "opcionalmente sustituido" significa sustitución opcional con los grupos radicales o porciones especificadas, en una posición o posiciones disponibles.

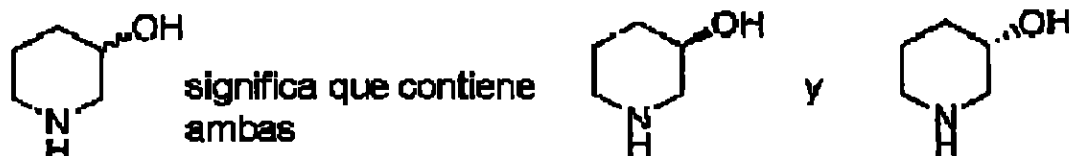
Las sustitución en la porción cicloalquilalquilo, heterocicloalquilalquilo, arilalquilo, o heteroarilalquilo incluye sustitución en la porción del anillo y/o en la porción alquilo del grupo.

Cuando una variable aparece más de una vez en un grupo, por ejemplo, R^8 en $-\text{N}(\text{R}^8)_2$, o una variable aparece más de una vez en la estructura del a fórmula I, por ejemplo, R^{15} puede aparecer tanto en R^1 como en R^3 , las variables pueden ser iguales o diferentes.

Con referencia a la cantidad de porciones (por ejemplo, sustituyentes, grupos o anillos) en un compuesto, a menos que se defina lo contrario, las frases "uno o más" y "por lo menos una" significan que puede haber tantas porciones como se permita químicamente, y la determinación de la cantidad máxima de dichas porciones está dentro de los conocimientos de un experto en la materia: Con respecto a las composiciones y métodos que comprenden el uso de "por lo menos un compuesto de fórmula I", uno a tres compuestos de la fórmula I pueden administrarse al mismo tiempo, preferiblemente uno.

Tal como se usa aquí, el término "composición" abarca un producto que comprende los ingredientes especificados en las cantidades especificadas, así como también cualquier producto que es el resultado, directo o indirecto, de la combinación de los ingredientes especificados en las cantidades especificadas.

La línea ondulada ~~~~ como enlace indica en general una mezcla de, o cualquiera de, los posibles isómeros, por ejemplo que contienen estereoquímica (R)- y (S)-. Por ejemplo,



Las líneas trazadas en los sistemas de anillo, tales como por ejemplo:



indica que la línea (enlace) indicado puede estar unido a cualquiera de los átomos de carbono del anillo sustituibles.

Tal como es bien conocido en el arte, un enlace trazado desde un átomo particular donde no se describe ninguna porción en el extremo terminal del enlace, indica un grupo metilo unido a través de ese enlace al átomo, a menos que se indique lo contrario. Por ejemplo:

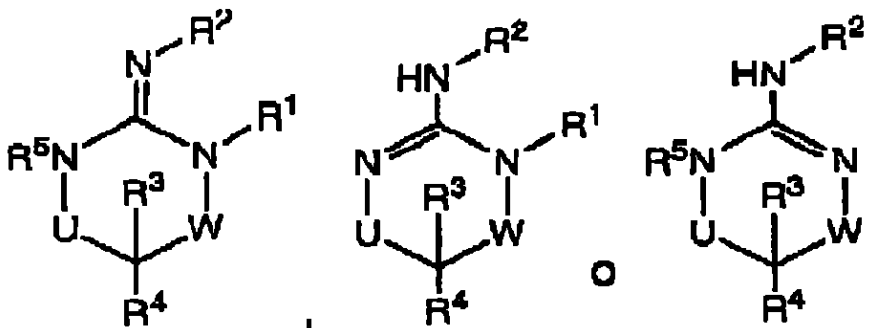


Al observar que cualquier heteroátomo con valencias no satisfechas en el texto, esquemas, ejemplos, formulas estructurales, y cualquiera de las Tablas presentes, se considera que tiene el átomo o átomos de hidrógeno para satisfacer las valencias.

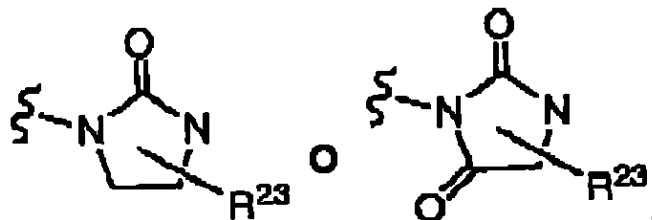
Los expertos en la materia reconocerán que ciertos compuestos de formula I son tautoméricas, y todas dichas formas tautoméricas están contempladas aquí como parte de la presente invención. Por ejemplo, un compuesto en el cual X es

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$-N(R^5)-$ y R^1 y R^5 cada una H puede estar representado por cualquiera de las siguientes estructuras:



Cuando R^{21} y R^{22} , son, por ejemplo, $-N(R^{15})C(O)N(R^{16})(R^{17})$ y R^{15} y R^{16} forman un anillo, la porción formada, es por ejemplo,



Los profármacos y solvatos de los compuestos de la invención están también contemplados aquí. El término "profármaco", tal como se emplea aquí, denota un compuesto que es un precursor de una droga, el cual, mediante administración a un sujeto, es sometido a conversión química mediante procesos metabólicos o químicos para proveer un compuesto de fórmula I o una sal y/o un solvato del mismo. Una discusión de los profármacos se provee T. Higuchi y V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) Volumen 14 de A.C.S. Symposium Series, y en *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association y Pergamon Press, incorporándose ambos aquí como referencia.

"Solvato" significa una asociación física de un compuesto de ésta invención con una o más moléculas de solvente. Ésta asociación física involucra varios grados de unión iónica y covalente incluyendo unión de hidrógeno. En algunos casos, el solvato será capaz de aislación, por ejemplo cuando se incorporan uno o más moléculas de solvente en los retículos cristalinos del sólido cristalino "solvato" abarca tanto los solvatos de fase en solución como los aislables. Ejemplos no limitativos de solvatos apropiados incluyen etanolatos, metanolatos, y similares. "Hidrato" es un solvato en el cual la molécula de solvente es H_2O .

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"Cantidad eficaz" o "cantidad terapéuticamente eficaz" describe una cantidad de compuesto o composición de la presente invención que es eficaz para inhibir la aspartil proteasa y/o para inhibir BACE-1 y producir por lo tanto el efecto terapéutico deseado en un paciente apropiado.

Los compuestos de fórmula I forman sales que están también dentro del alcance de la invención. La referencia que se hace aquí a un compuesto de fórmula I incluye referencia a las sales del mismo, a menos que se indique lo contrario. El término "sal(s)", tal como se emplea aquí, denota sales ácidas formadas con ácidos inorgánicos y/o orgánicos, así como también sales básicas formadas con bases inorgánicas y/o orgánicas, además, cuando un compuesto de fórmula I contiene a ambas, una porción básica tal como pero sin limitarla a una piridina o un imidazol, y una porción ácida, tal como, pero sin limitarla a un ácido carboxílico, zwitteriones ("sales internas") puede formarse y se incluirá dentro del término "sales(s)" que se usa aquí. Se prefieren las sales farmacéuticamente aceptables (es decir, no tóxicas, fisiológicamente aceptables) aunque también son útiles otras sales. Las sales de los compuestos de fórmula I pueden formarse, por ejemplo, por reacción de 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 precipita la sal o en un medio acuoso seguido de liofilización. Los ácidos (y bases) que se consideran generalmente apropiados para la formación de sales farmacéuticamente útiles a partir de compuestos farmacéuticos básicos (o ácidos) han sido discutidos por ejemplo por S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Yerson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; en *The Orange Book* (Food & Drug Administration, Washington, D.C. en su red); y P. Heinrich Stahl, Camille G. Wermuth (Eds.), *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (2002) Int'l. Union of Pure y Applied Chemistry, pp. 330-331, Estas descripciones se incorporan aquí como referencia.

Ejemplos de sales de adición de ácido incluyen acetatos, adipatos, alginatos, ascorbatos, aspartatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, alcanforatos, alcanforsulfonatos, ciclopentanopropionatos, digluconatos, dodecilsulfatos, etansulfonatos, fumaratos, glucoheptanoatos, glicerofosfatos, hemisulfatos heptanoatos, hexanoatos, clorhidratos, bromihidratos, iodihidratos, 2-hidroxietansulfonatos, lactatos, maleatos, metansulfonatos, sulfatos de metilo, 2-

naftalensulfonatos, nicotinatos, nitratos, oxalatos, pamoatos, pectinatos, persulfatos, 3-fenilpropionatos, fosfatos, picratos, pivalatos, propionatos, salicilatos, succinatos, sulfatos, sulfonatos (tales como los mencionados aquí), tartratos, tiocianatos, toluensulfonatos (conocidos también como tosilatos) undecanoatos, y similares.

Ejemplos de sales básicas incluyen sales de amonio, sales de metales alcalinos tales como sales de sodio, litio, y potasio, sales de metales alcalino térreos tales como sales de calcio y magnesio, sales de aluminio, sales de zinc, sales con bases orgánicas (por ejemplo, aminas orgánicas) tales como benzatinas, dietilamina, diciclohexilaminas, hidrabaminas (formadas con N.N-bis(deshidroabietil)etilendiamina), N-metil-D-glucaminas, N-metil-D-glucamidas, t-butil aminas, piperazina, fenilciclohexilamina, colina, trometamina y sales con amino ácidos tales como arginina, lisina y similares. Los grupos que contienen nitrógeno básico pueden cuaternizarse con agentes tales como haluros de alquilo inferior (por ejemplo cloruros, bromuros y yoduros de metilo, etilo, propilo y butilo), sulfatos de dialquilo (por ejemplo sulfatos de dimetilo, dietilo, dibutilo, y diamilo), haluros de cadena larga (por ejemplo cloruros, bromuros y yoduros de decilo, laurilo, miristilo y estearilo), haluros de aralquilo (por ejemplo bromuros de bencilo y fenetilo), y otros.

Todas dichas sales ácidas y sales básicas son sales farmacéuticamente aceptables dentro del alcance de la invención, y todas dichas sales ácidas y básicas se consideran equivalentes a las formas libres de los compuestos correspondientes para los propósitos de la invención.

Todos los estereoisómeros (por ejemplo, los isómeros geométricos, los isómeros ópticos y similares) de los presentes compuestos (incluyendo aquellos de las sales, solvatos y profármacos de los compuestos así como también las sales y solvatos de los profármacos) tal como aquellos que pueden existir debido a los carbonos asimétricos en varios sustituyentes, incluyendo las formas enantioméricas (que pueden existir incluso en ausencia de carbonos asimétricos), formas rotaméricas, atropisómeras, y formas diastereoméricas, están contempladas dentro del alcance de esta invención. Los estereoisómeros individuales de los compuestos de la invención pueden estar por ejemplo, sustancialmente libres de otros isómeros, o pueden estar mezclados por ejemplo, en forma de racematos o con todos los restantes, o con otros estereoisómeros seleccionados. Los centros quirales de la presente invención pueden tener la configuración S o R tal como se ha definido en las Recomendaciones de IUPAC 1974. El uso de los términos "sal", "solvato"

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"profármaco" y similares, puede aplicarse igualmente a la sal, solvato y a los profármacos de enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de los compuestos de la invención.

Las formas polimórficas de los compuestos de fórmula I, y de las sales, solvatos y profármacos de los compuestos de fórmula I, se incluirán en la presente invención.

Los compuestos de fórmula I pueden prepararse usando procedimientos conocidos en el arte. Los métodos preparativos para preparar materiales de partida y compuestos de fórmula I se mostrarán a continuación como esquemas de reacción generales (Método A, Método B, etc.) seguidos de procedimientos específicos, pero los expertos en la materia reconocerán que son también apropiados otros procedimientos. En los Esquemas y en los Ejemplos siguientes, se usarán las siguientes abreviaturas:

metilo: Me; etilo: Et; propilo: Pr; butilo: Bu; bencilo: Bn; butiloxycarbonilo terciario: Boc o BOC

cromatografía líquida de alta presión: HPLC

espectrometría de masa por cromatografía líquida: LCMS

temperatura ambiente: RT o rt

día: d; hora: h; minutos: min

tiempo de retención: R_t

micro-onda: μW

saturado: sat.; anhidro: anhid.

1-hidroxibenzotriazol: HOBt

clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida: EDCI

acetato de etilo: EtOAc

benciloxycarbonilo: CBZ

[1-(clorometil)-4-flúor-1,4-diazoniabicyclo[2.2.2] octano bis(tetraflúor-borato)]:
Selectfluor

1,8-diazabicyclo[5,4,0]undec-7-eno: DBU

tetrahidrofurano: THF; N,N-dimetilformamida: DMF; metanol: MeOH; éter dietílico: Et₂O; ácido acético: AcOH; acetonitrilo: MeCN; ácido trifluoracético: TFA; diclorometano: DCM; dimetoxietano: DME; difenilfosfinoferroceno (dppf);

n-butilitio: n-BuLi; diisopropilamida de litio: LDA

1-hidroxi-7-azabenzotriazol: HOAt

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4-N,N-dimetilaminopiridina: DMAP; diisopropiletilamina: DIEA; N-metilmorfolina: NMM

Resina sulfónica de tolueno microporosa (resina MP-TsOH)

tris-(2-aminoetil)aminometil poliestireno (PS-trisamina)

poliestireno de isocianato de metilo (PS-NCO)

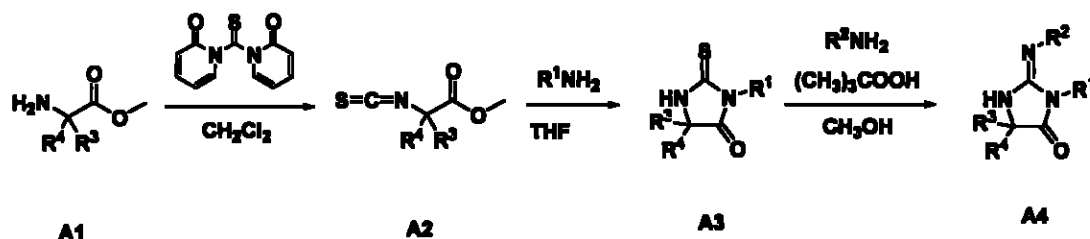
Saturado (sat.); anhidro (anhyd); temperatura ambiente (rt); hora (h); Minutos (Min), Tiempo de Retención (R_t); peso molecular (PM); mililitro (mL); gram (g). miligramo (mg); equivalente (eq); día (d); microondas (μW); microlitro(μL);

Todos los datos de RMN se recogieron en espectrómetros de RMN de 400 MHz a menos que se indique lo contrario. La espectrometría de Masa-Electro-rocío-LC con una columna C-18 y 5% a 95% de MeCN en agua como fase móvil se usó para determinar la masa molecular y el tiempo de retención. Las tablas contienen los compuestos con los datos del tiempo de retención/PM observado y/o RMN.

Para consistencia interna en los esquemas de reacción que se muestran en los Métodos A a DF, el producto de cada método se muestra como estructura A4, B4, C3, etc., donde ciertas variables son tal como se han definido para ese método, pero que tal como resultará aparente, por ejemplo A4 tiene la misma estructura que C3. Es decir, pueden usarse diferentes métodos para preparar compuestos similares.

Los compuestos de la invención pueden producirse por procedimientos conocidos por los expertos en la materia y tal como se muestran en los esquemas de reacción siguientes y en las preparaciones y ejemplos que se describen a continuación. Las Tablas contienen los compuestos con los valores m/e observados a partir de los datos de espectrometría de masa y/o RMN. Estos compuestos pueden obtenerse con métodos de síntesis similares a los que se enumeran en la última columna usando los reactivos apropiados.

Método A



Método A, Etapa 1:

A una solución de A1 (R³ = CH₃ & R⁴ = CH₂CH(CH₃)₂) (10 mmoles, 1 eq) en 30 ml de CH₂Cl₂ anhidro se le agregó tiocarbonil dipiridona (1,2 eq). Después

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de agitar durante la noche la solución se diluyó con CH_2Cl_2 , se lavó con HCl 1N, H_2O (2x), y una solución acuosa saturada de NaCl (2x). La solución orgánica se secó sobre Na_2SO_4 , se filtró y se concentró. El material crudo se purificó a través de cromatografía evaporativa para proporcionar **A2** ($\text{R}^3 = \text{CH}_3$ & $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$).

Método A, Etapa 2:

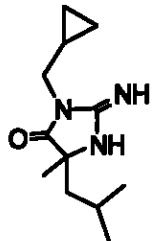
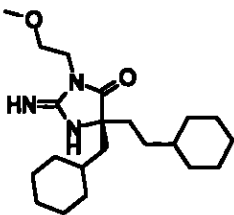
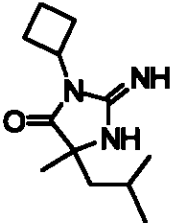
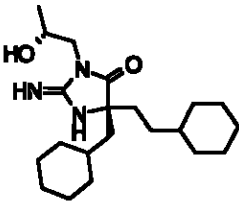
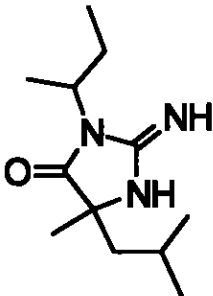
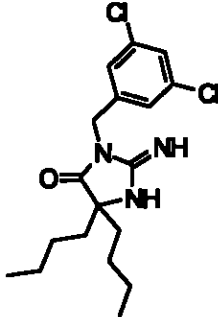
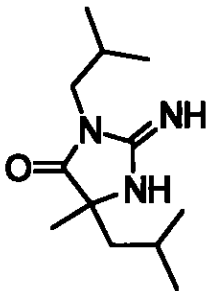
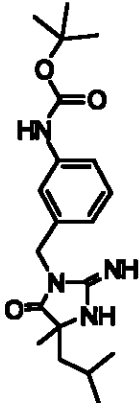
Se agregó una solución de 3,5-difluorbencil amina (0,15 mmoles, 1,5 eq) en THF (0,15 mL) a una solución de **A2** ($\text{R}^3 = \text{CH}_3$ & $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (0,1 mmoles, 1 eq) en CH_2Cl_2 anhidro (1 mL). La mezcla de reacción se reflujo durante la noche. La solución de reacción se agregó a una resina MP-TsOH (2–3 eq) y se diluyó con CH_3CN . La suspensión se agitó durante la noche. La mezcla se filtró y el filtrado se concentró para proporcionar **A3** ($\text{R}^1 = 3,5$ -difluorbencilo, $\text{R}^3 = \text{CH}_3$, & $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$).

Método A, Etapa 3:

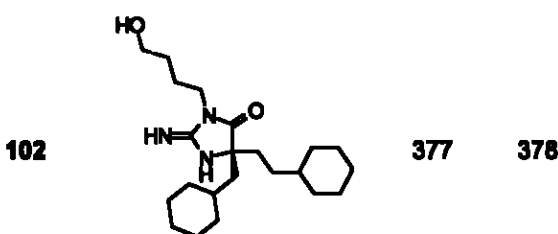
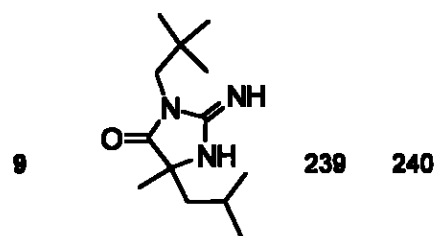
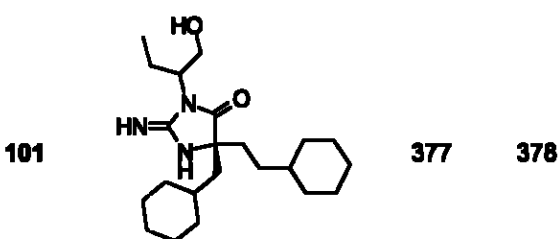
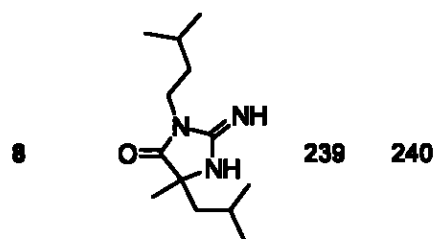
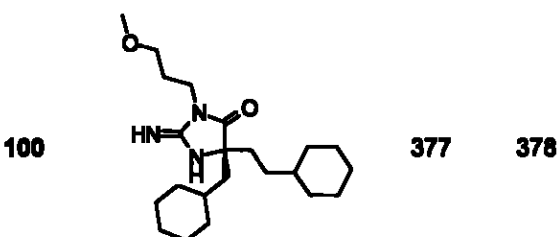
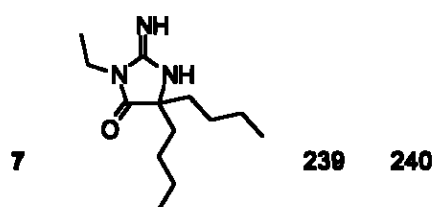
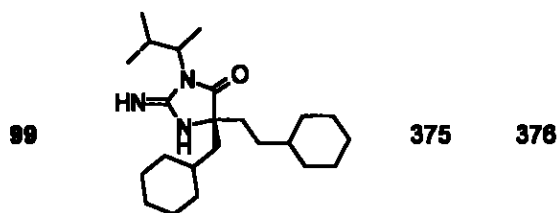
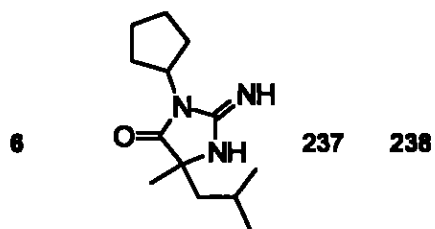
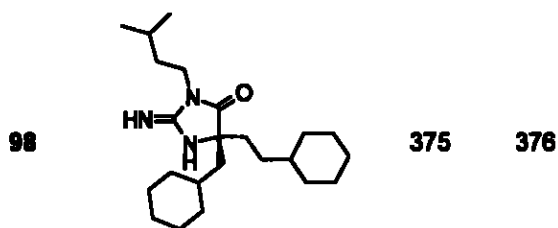
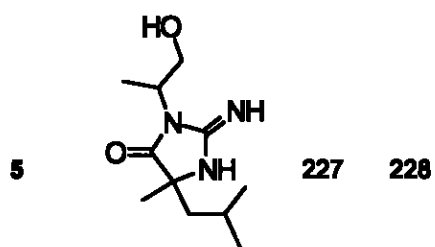
A una solución de **A3** ($\text{R}^1 = 3,5$ -difluorbencilo, $\text{R}^3 = \text{CH}_3$, & $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (10 mg) en CH_3OH (1 mL) se le agregó NH_4OH (0,44 mL) y peróxido de hidrógeno de *t*-butilo (0,1 mL) y la mezcla de reacción se agitó durante 2 días. La solución se concentró, el residuo resultante se disolvió en CH_3OH (1,2 mL) y luego se trató con resina de ácido sulfónico. La suspensión se agitó durante la noche y la resina se lavó con CH_3OH (4 x 10 min) antes de tratarla con NH_3 2N en CH_3OH durante 1 hora. La suspensión se filtró y el filtrado se concentró para proporcionar el material crudo el cual se purificó por HPLC/LCMS preparativa fluyendo con un gradiente de $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ para proporcionar **A4** ($\text{R}^1 = 3,5$ -difluorbencilo, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{CH}_3$, & $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$). RMN (CD_3OD): δ 6,9, m, 3H; δ 4,8–4,9, m; δ 1,75, d, 2H; δ 1,5, m, 1H; δ 1,42, s, 3H; δ 0,85, d, 3H; δ 0,65, d, 3H. ES_LCMS (m/e) 296,1.

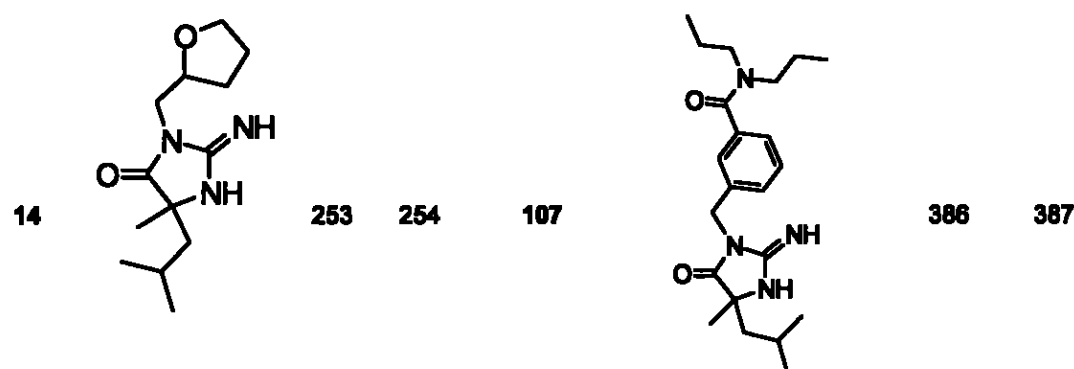
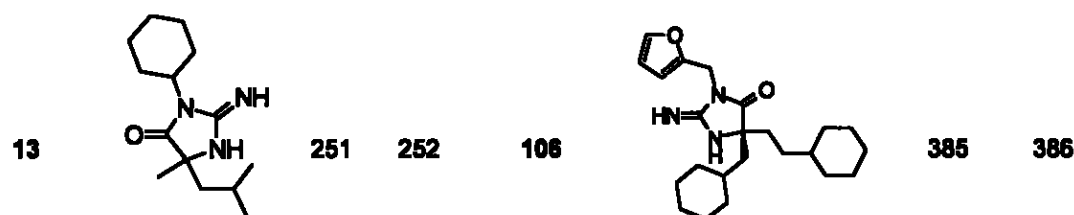
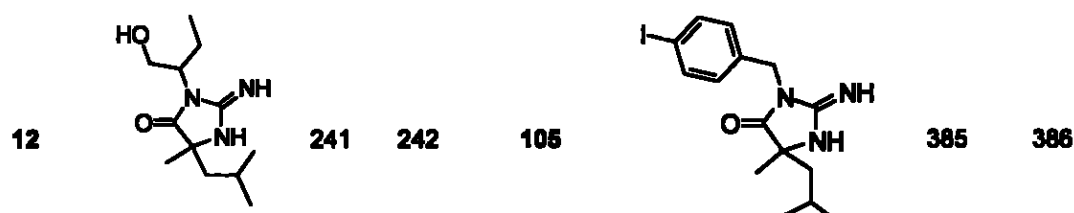
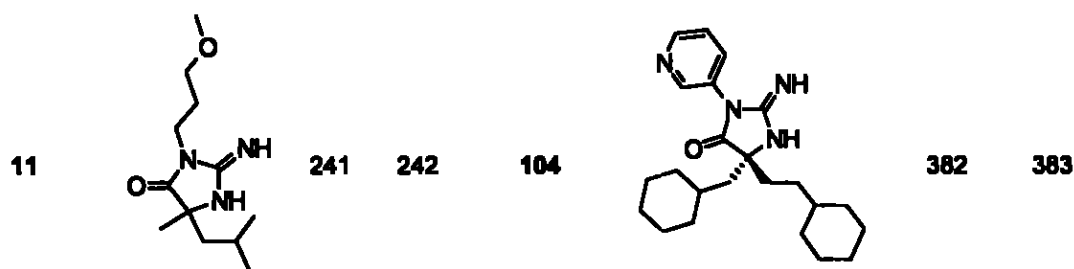
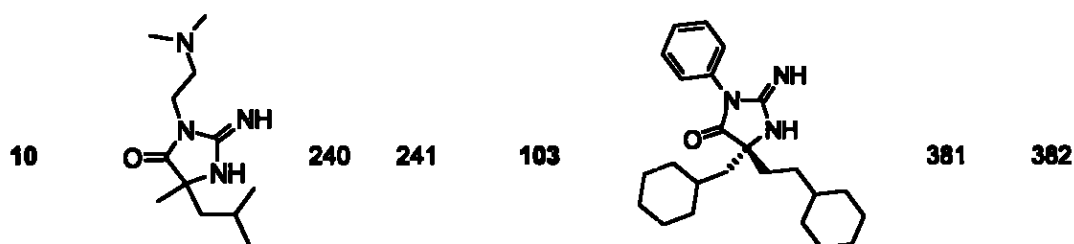
Se sintetizaron los siguientes compuestos usando métodos similares.

451
462

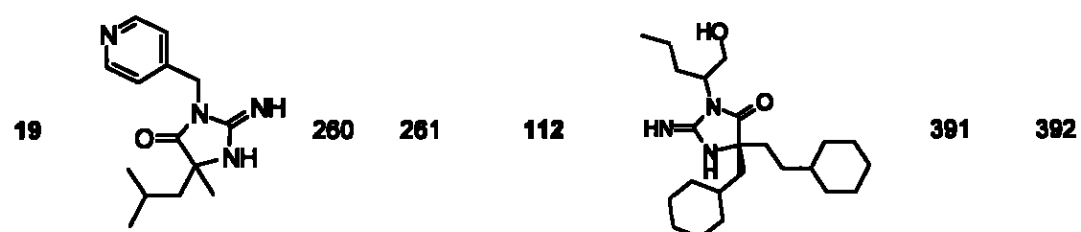
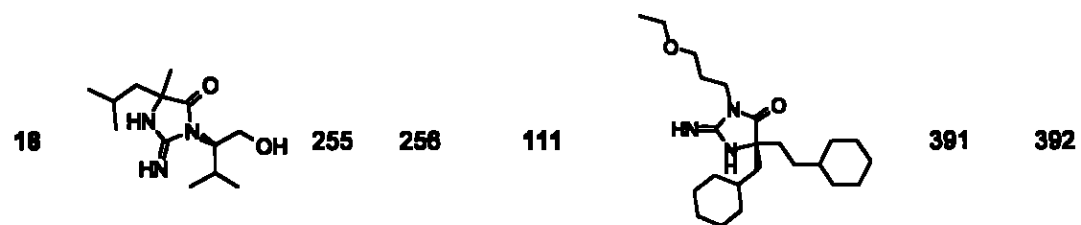
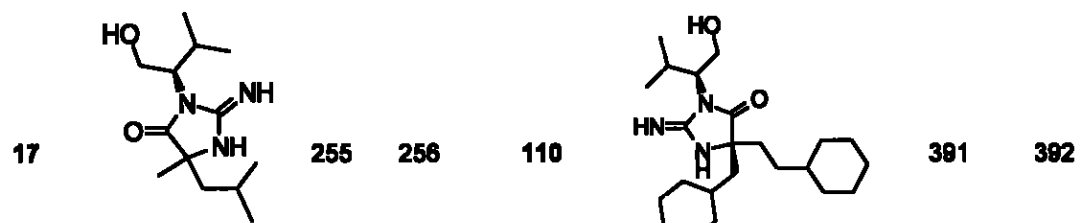
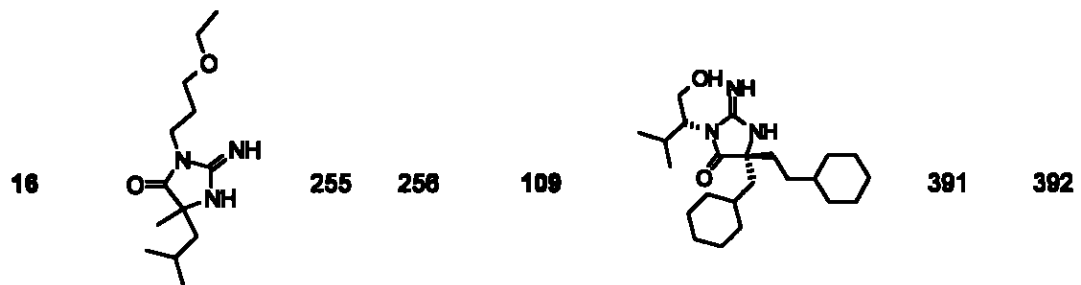
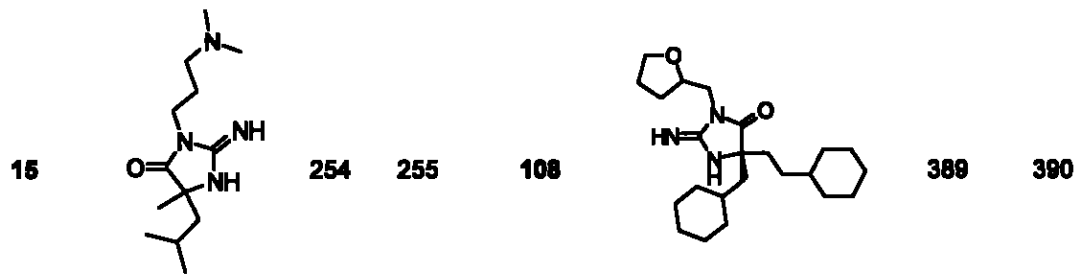
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3		225	226	96		369	370
4		225	226	97		374	375

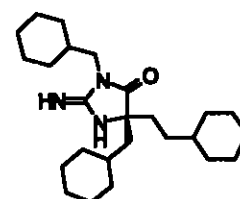
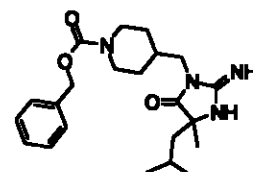
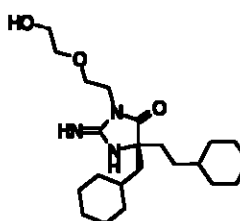
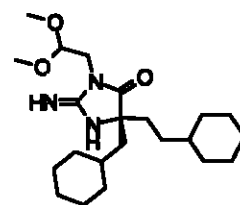
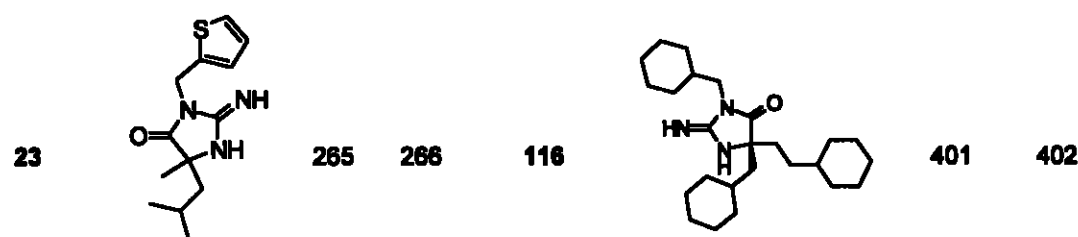
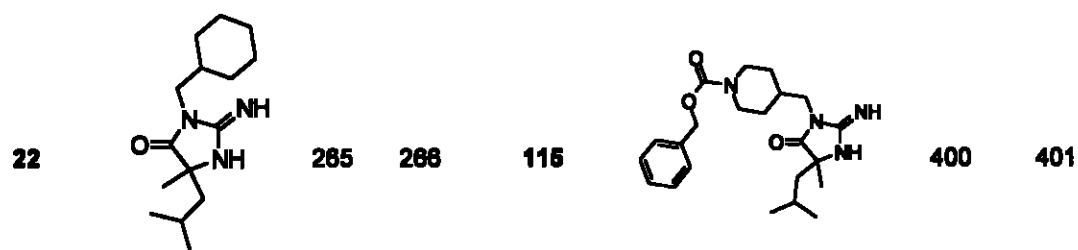
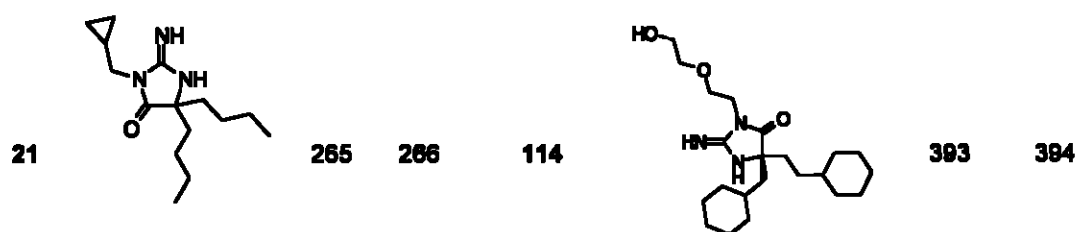
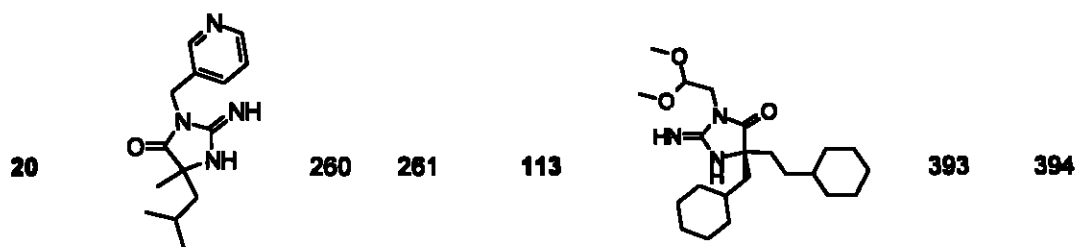
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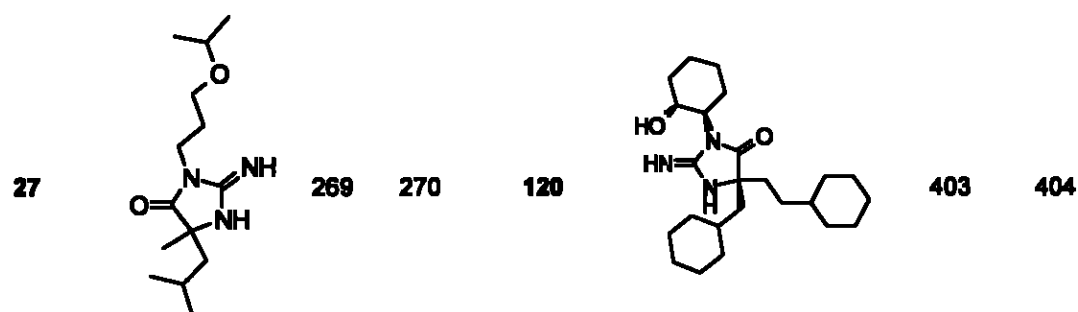
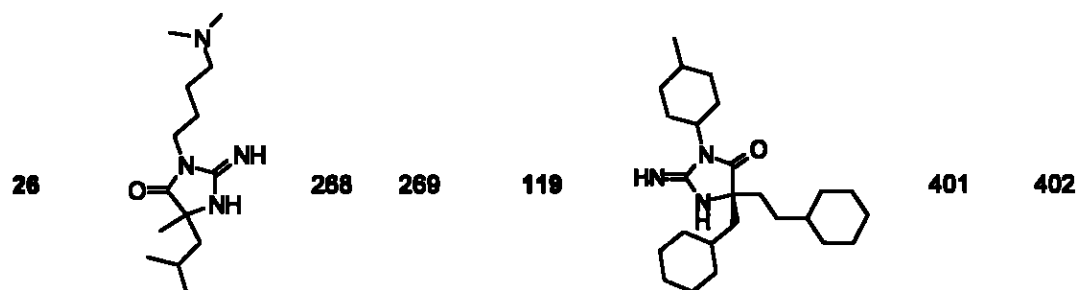
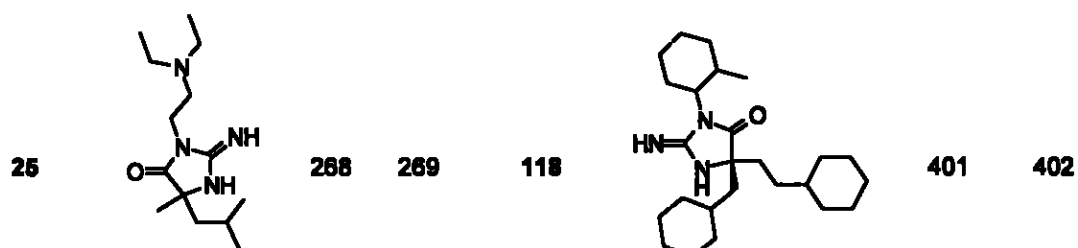




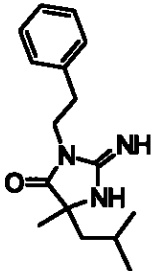
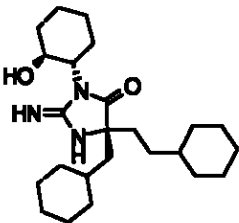
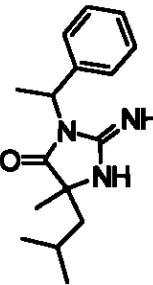
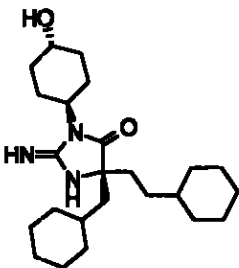
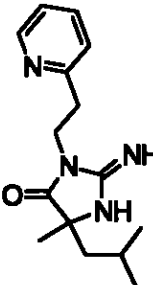
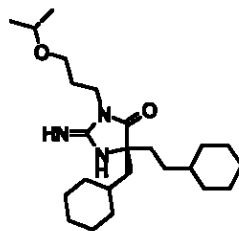
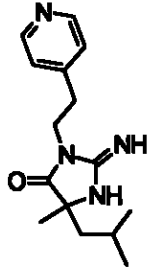
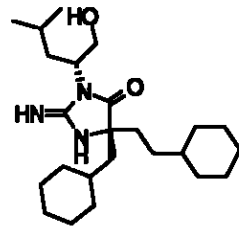
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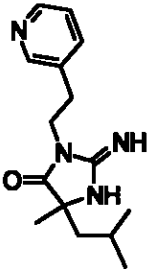
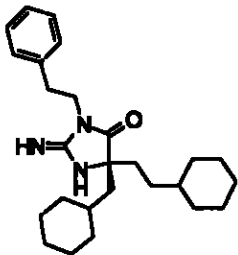
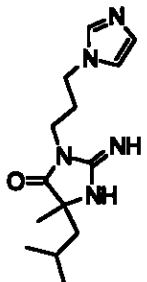
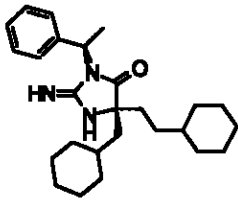
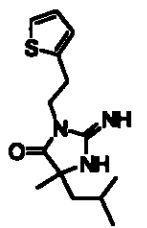
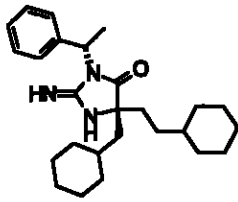
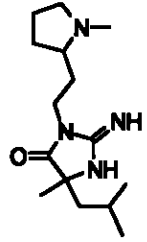
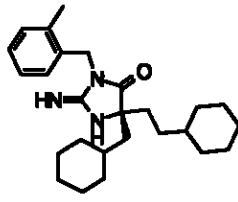




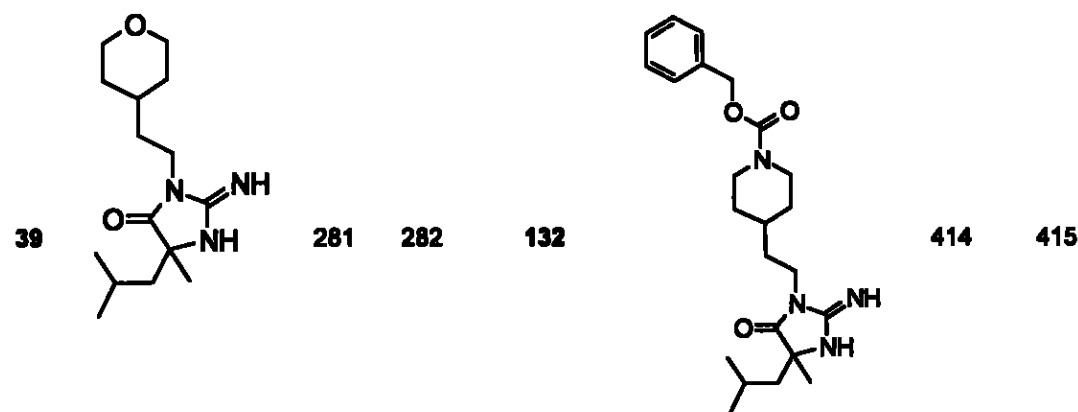
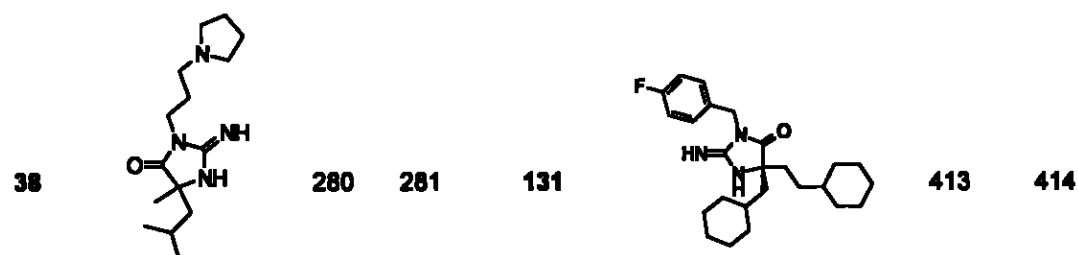
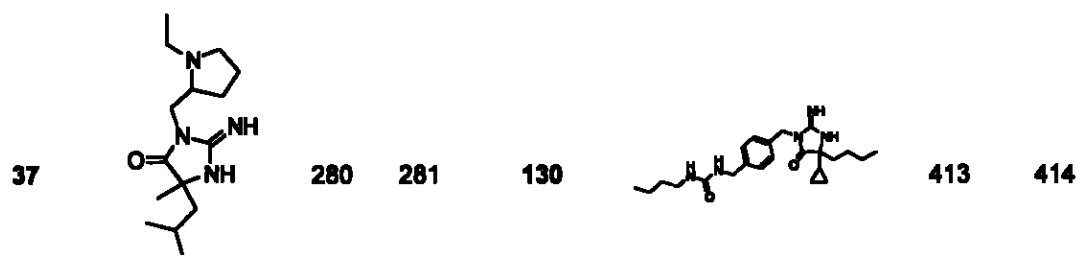
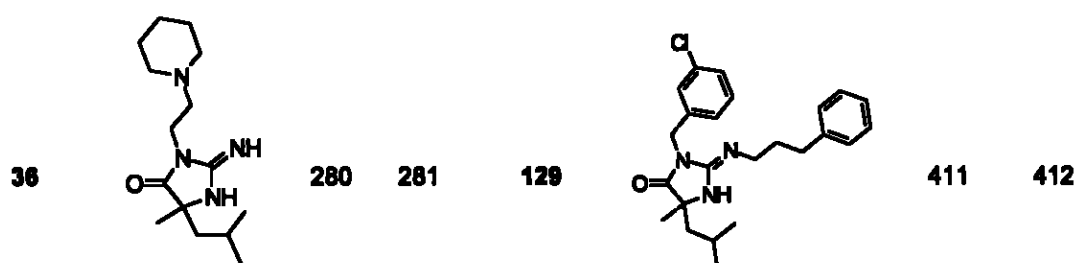
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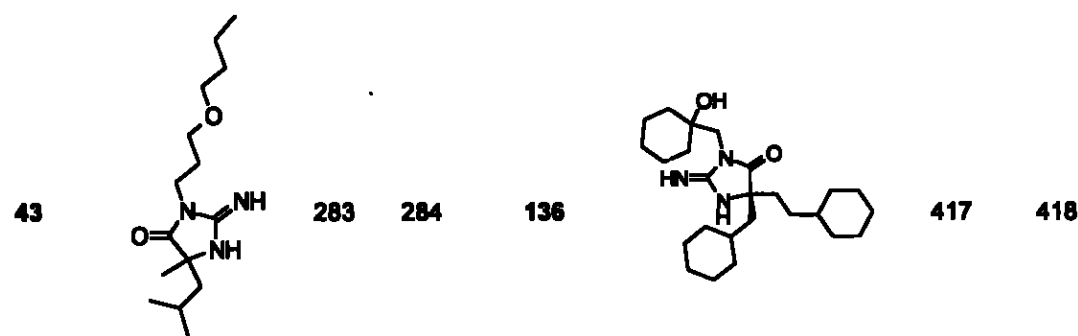
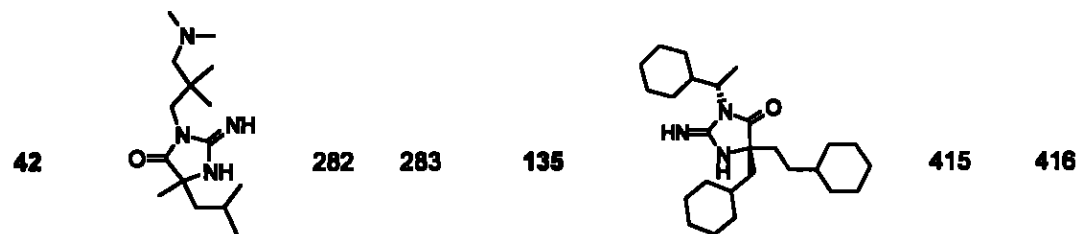
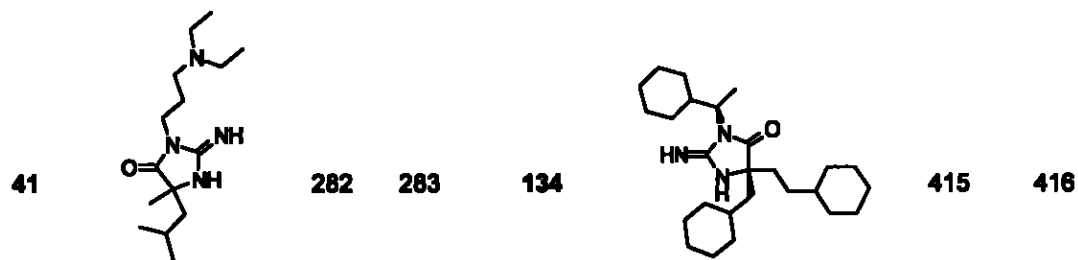
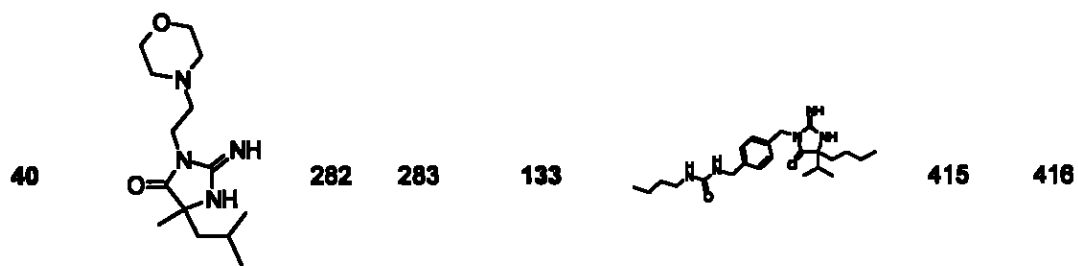
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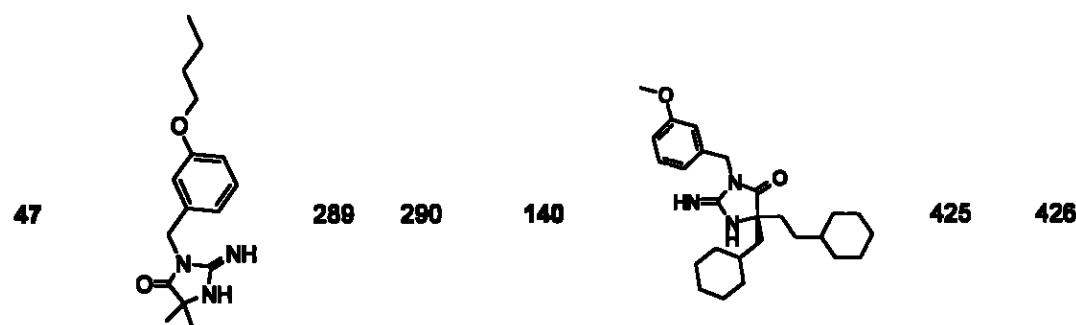
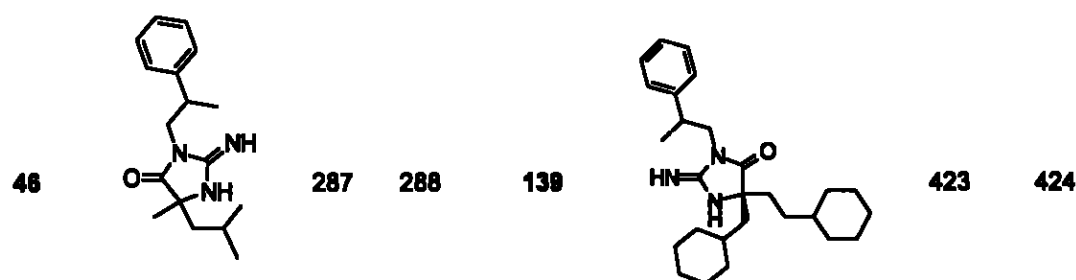
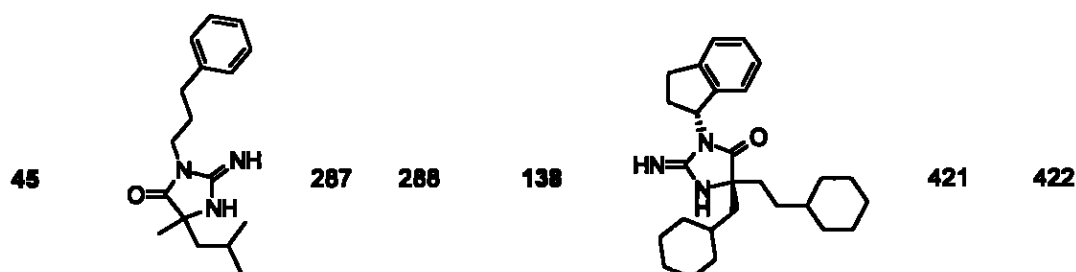
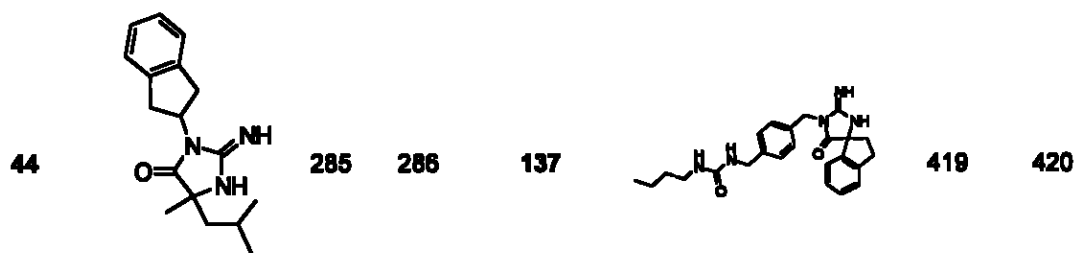
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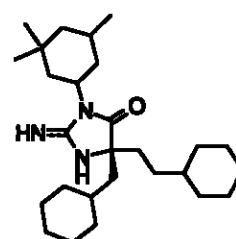
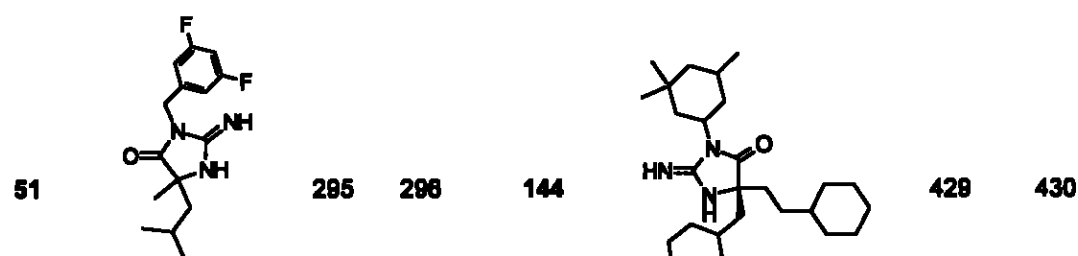
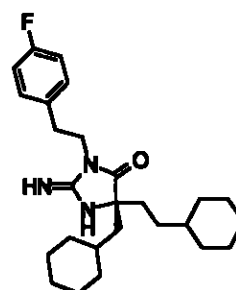
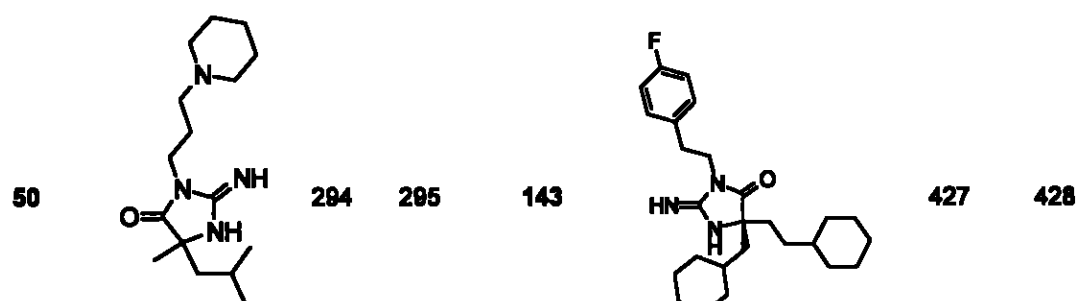
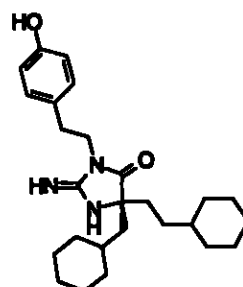
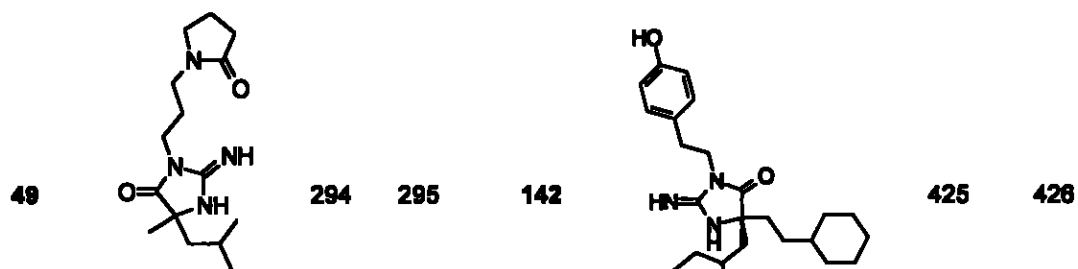
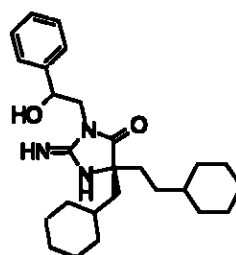
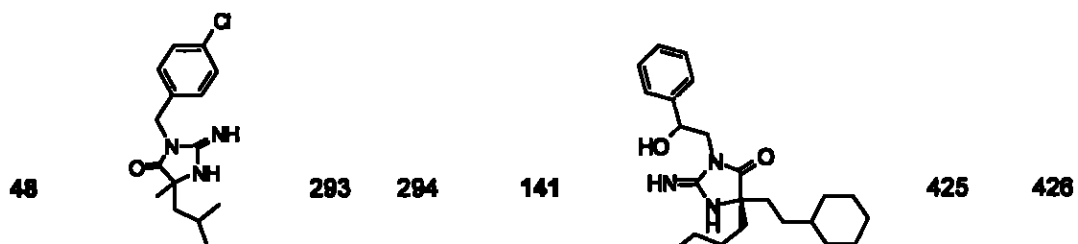
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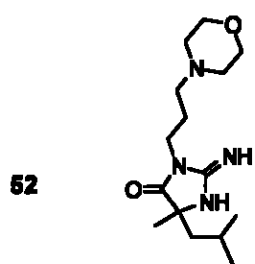
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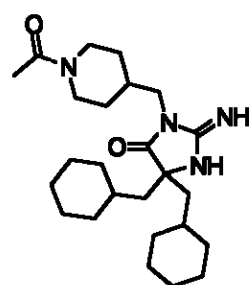
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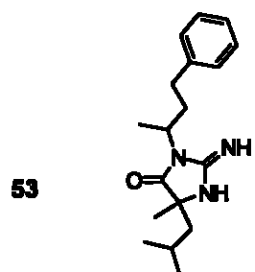
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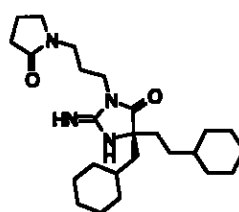
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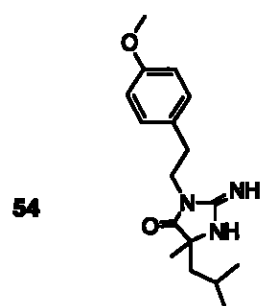
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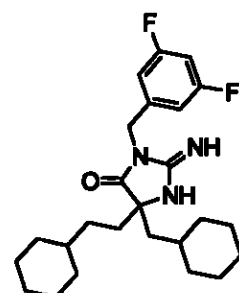
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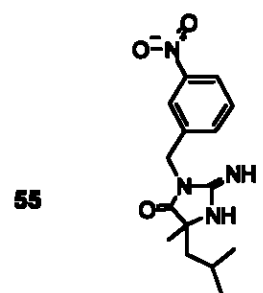
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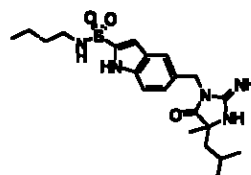
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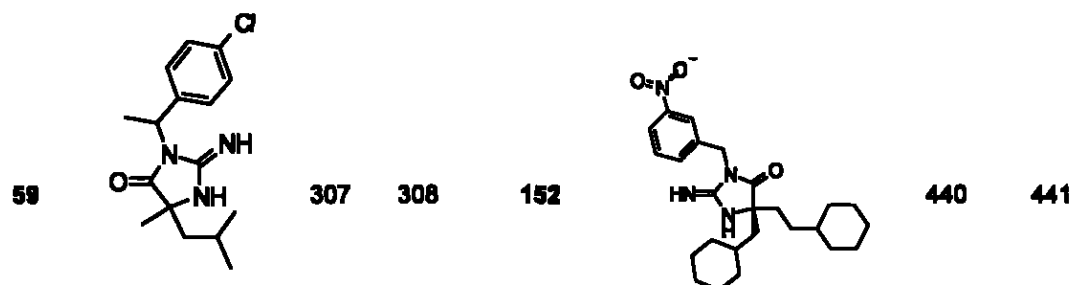
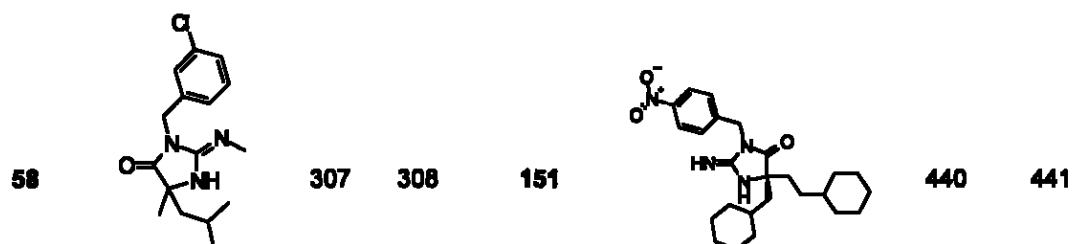
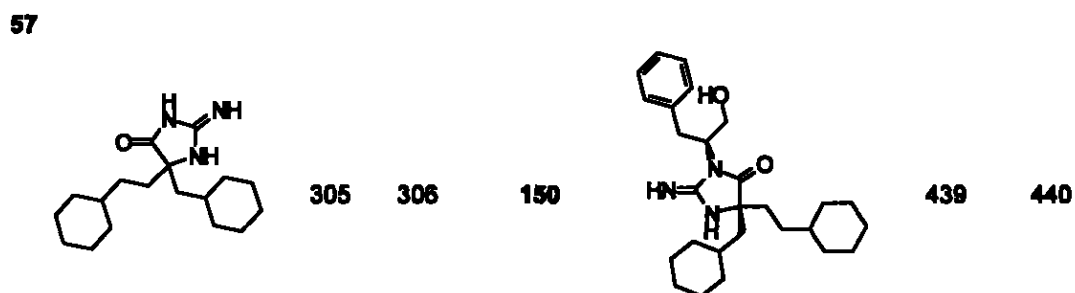
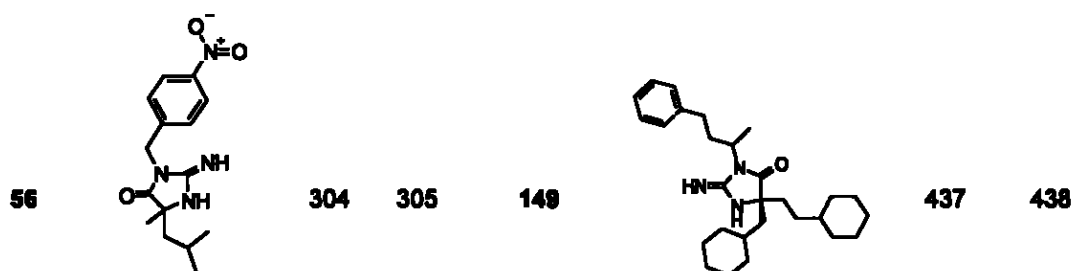
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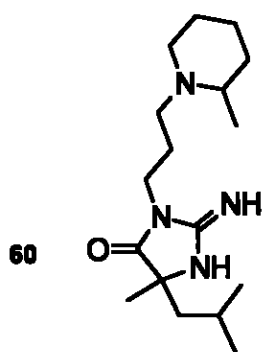


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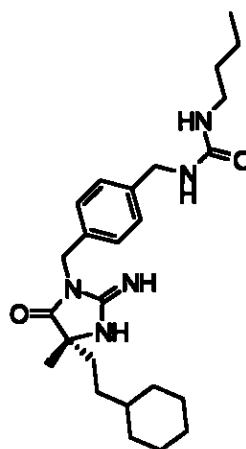
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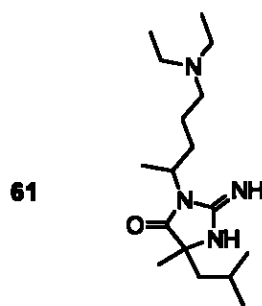
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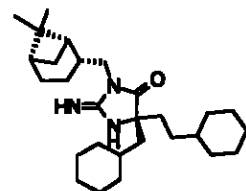
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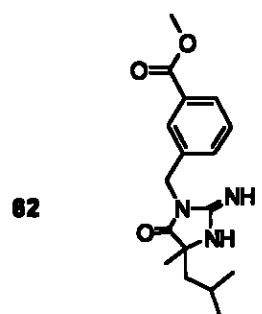
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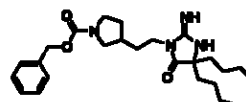
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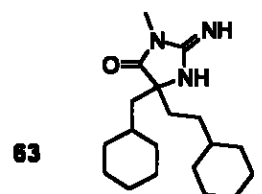
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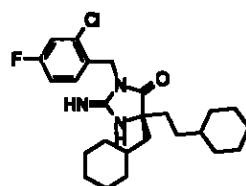
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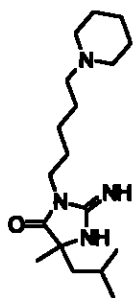


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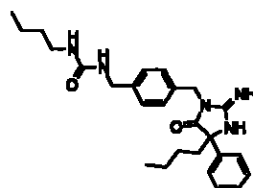
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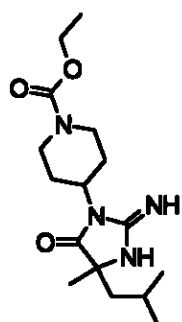
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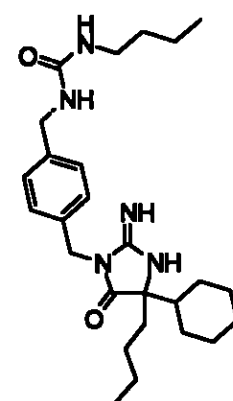
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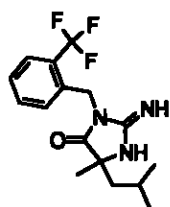
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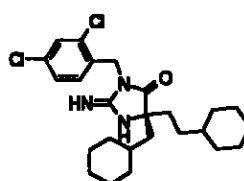
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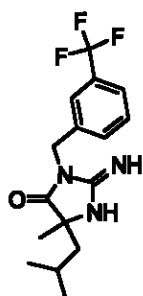
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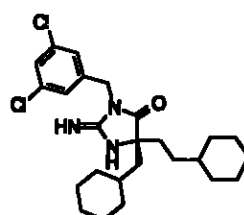
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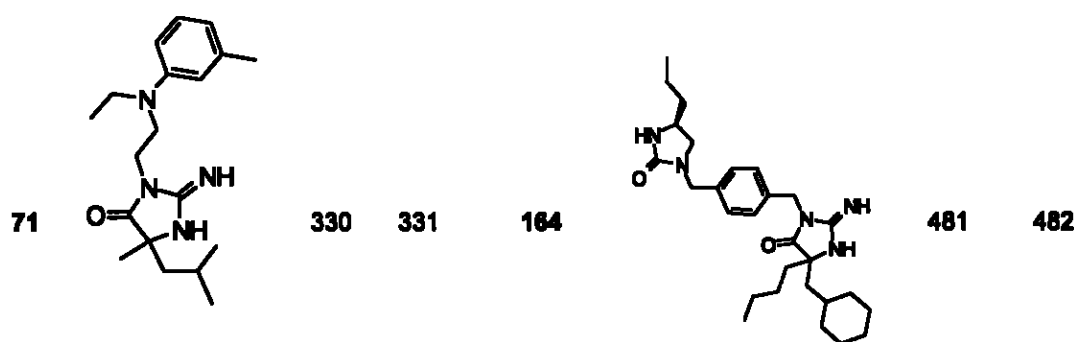
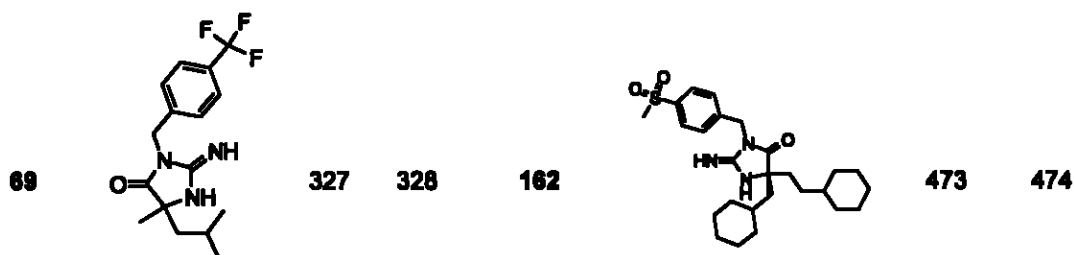
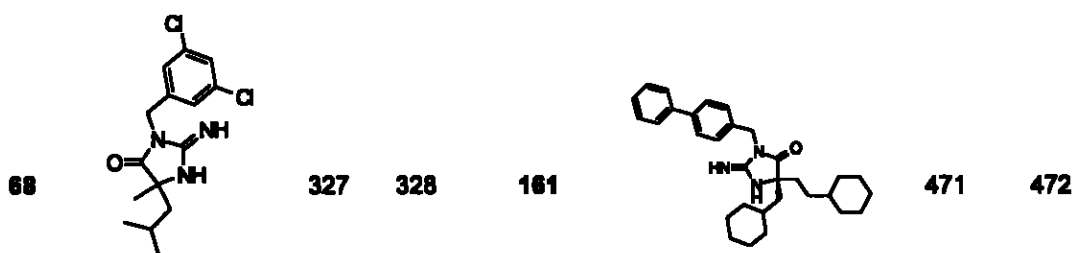
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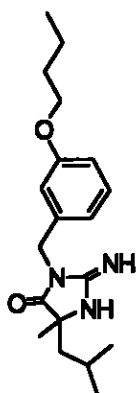
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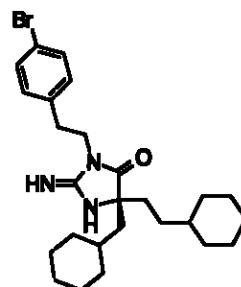
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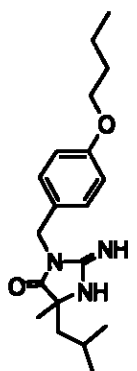
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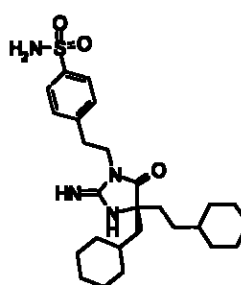
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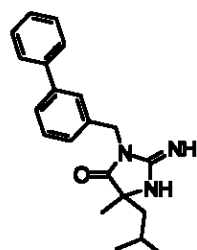
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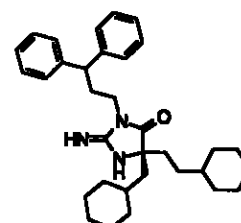
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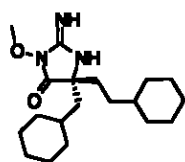


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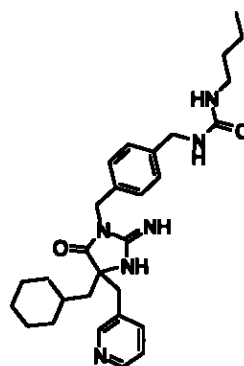
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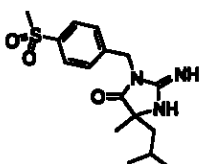
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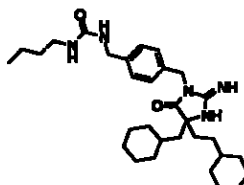
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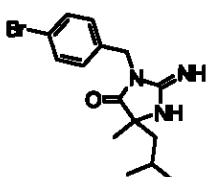
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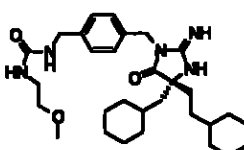
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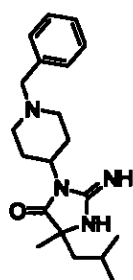
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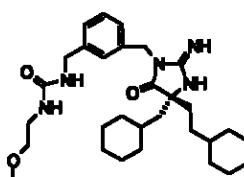
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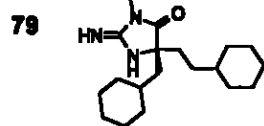
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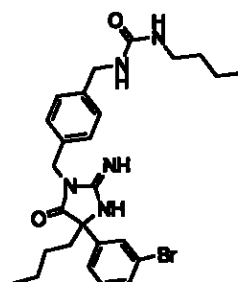
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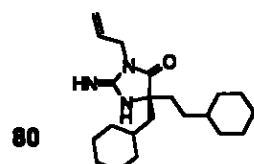


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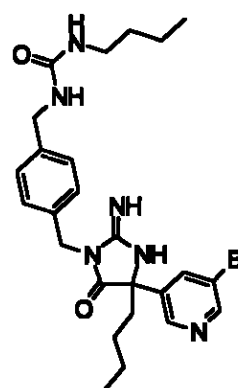


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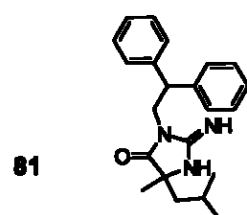


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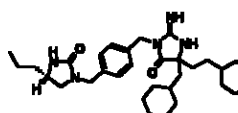


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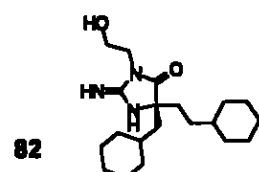


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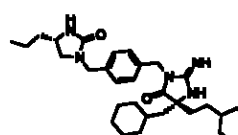


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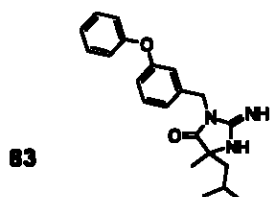
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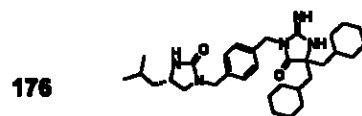


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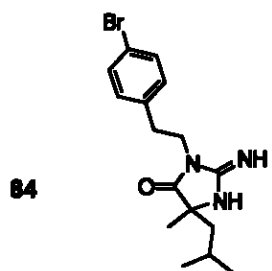
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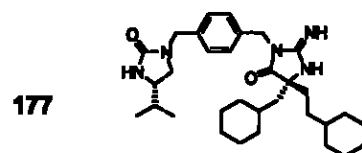
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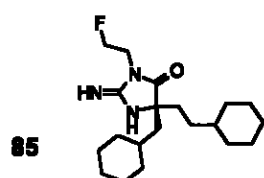
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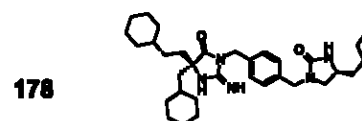
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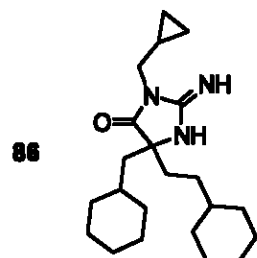
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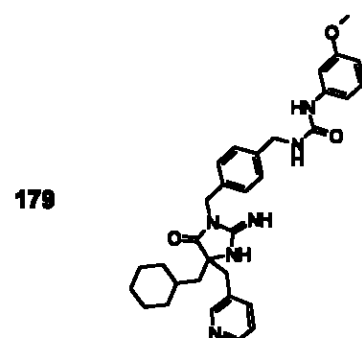
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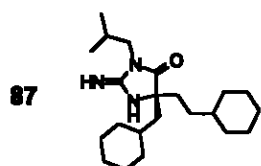


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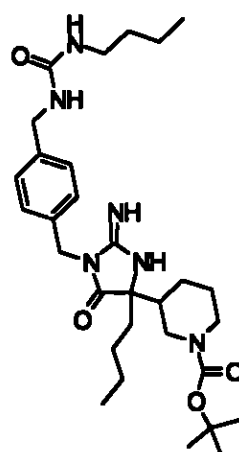
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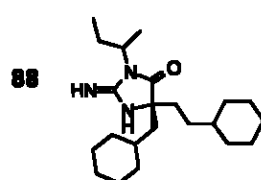
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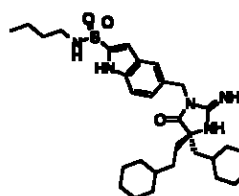
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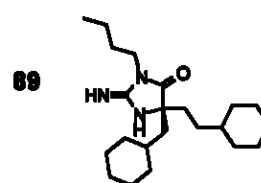
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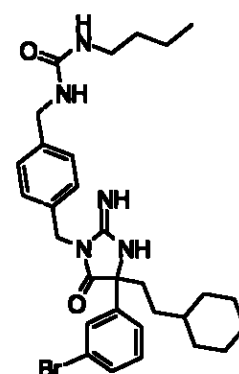
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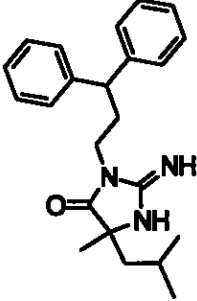
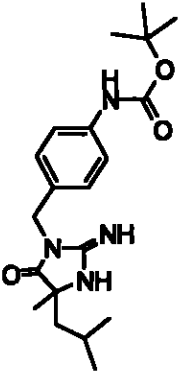
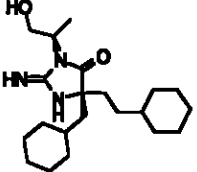
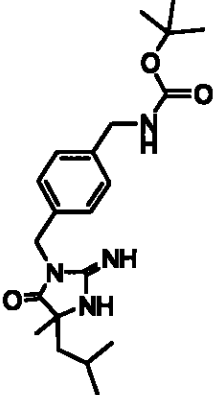
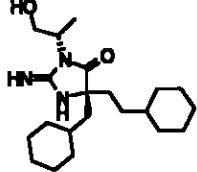
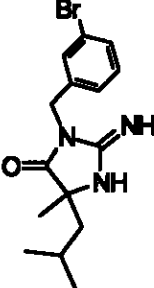
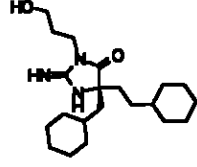
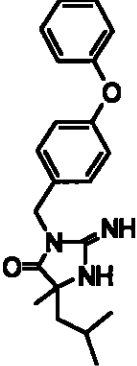
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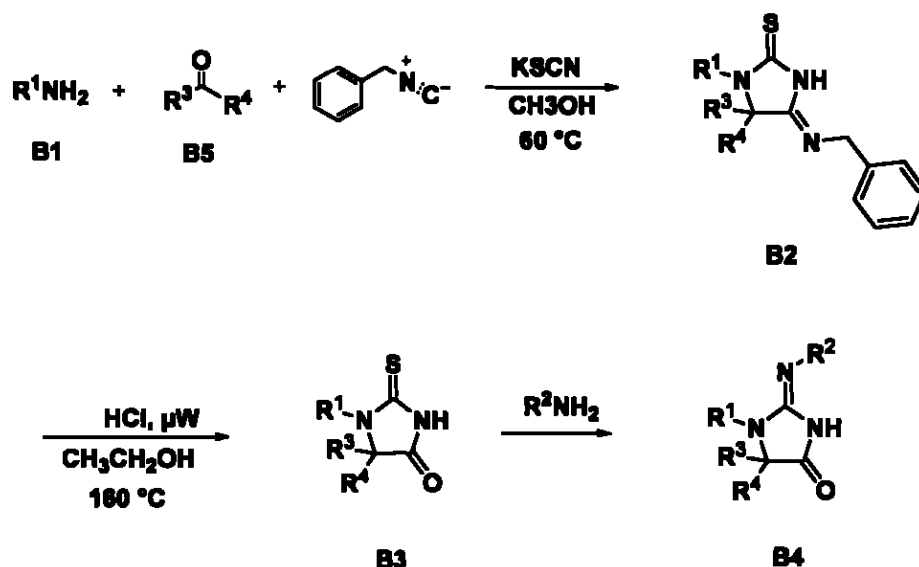
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90		363	364	183		374	NA
91		363	364	184		388	NA
92		363	364	185		337	NMR
93		363	364	186		351	NMR

Método B



Se usó un procedimiento modificado de la literatura (Ugi, I. *Angew. Chem.* 1962, 74 9-22).

Método B, Etapa 1:

A una solución de B1 (sal de HCl, $\text{R}^1 = 3\text{-clorofenetilo}$) (1,1 g, 5,73 mmoles) en CH_3OH anhidro (15 mL) se le agregó tiocianato de potasio (0,56 g, 5,73 mmoles). La mezcla de reacción se calentó a 60°C durante 1 hora. La suspensión se filtró y el filtrado se agregó a B5 ($\text{R}^3 = \text{Me}$, $\text{R}^4 = \text{t-Bu}$) (0,72 mL, 5,73 mmoles) e isocianuro de bencilo (0,77 mL, 6,3 mmoles). La mezcla se agitó durante la noche antes de concentrar la solución y el residuo se purificó por cromatografía evaporativa eluyendo con acetato de etilo en hexano para proporcionar 0,28 g of B2 ($\text{R}^3 = \text{CH}_3$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, y $\text{R}^1 = 3\text{-Clorofenetilo}$).

Método B, Etapa 2:

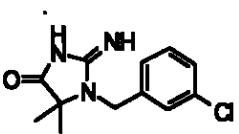
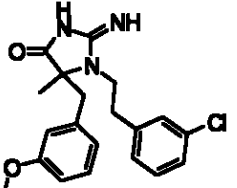
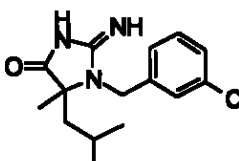
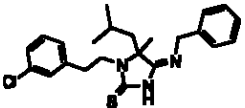
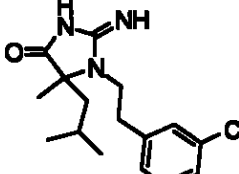
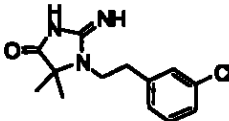
Una solución de HCl concentrado al 40% en $\text{CH}_3\text{CH}_2\text{OH}$ se agregó a B2 ($\text{R}^3 = \text{CH}_3$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, y $\text{R}^1 = 3\text{-Clorofenetilo}$) y la solución se calentó en un microondas a 160°C durante 30 minutos. La solución se concentró y se purificó por HPLC preparativa de fase inversa eluyendo con un gradiente de $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (con 0,1% de ácido fórmico) para proporcionar B3 ($\text{R}^3 = \text{CH}_3$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$, y $\text{R}^1 = 3\text{-Clorofenetilo}$).

475
487

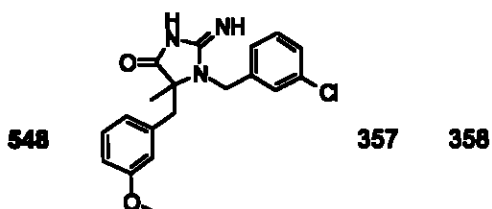
Método B, Etapa 3:

Se preparó el compuesto **B4** ($R^2 = H$, $R_3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, y $R^1 = 3\text{-Clorofenetilo}$) a partir de **B3** ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, y $R^1 = 3\text{-Clorofenetilo}$) seguido de un procedimiento similar al Método A, Etapa 3. NMR(CD_3OD): δ 8,1, br, 1H; δ 7,35, s, 1H; δ 7,25, m, 3H; δ 3,6, m, 1H; δ 3,4, m, 1 H; δ 3,0, m, 1H; δ 2,8, m, 1 H; δ 1,75, m, 1H; δ 1,6, m, 1H; δ 1,35, m, 1H; δ 1,2 s, 3H; δ 0,8, m, 6H. ES_LCMS (m/e): 308,1

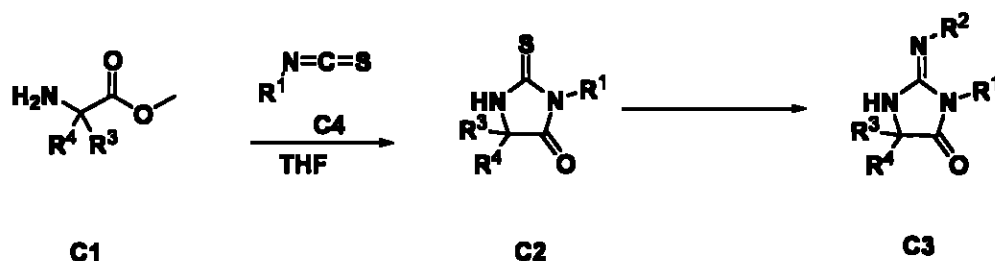
Se prepararon los siguientes compuestos usando métodos similares

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
545		251	252	549		371	372
546		293	294	550		413	
547		307	308	551		285	

476
1289



Método C



Método C, Etapa 1:

Una solución de **C1** ($R^3 = R^4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) (50 mg, 0,25 mmoles) y **C4** ($R^1 = 3\text{-clorofenilo}$) (38 μL , 0,26 mmoles) se refluxó durante la noche. Se agregaron resina de trisamina (2 eq) y resina de isocianato de poliestireno (2 eq) y la mezcla se agitó. Después de 3 horas la suspensión se filtró y la resina se lavó con CH_2Cl_2 (3x) y CH_3OH (3x). El filtrado se concentró para proporcionar **C2** ($R^1 = 3\text{-Cl-C}_6\text{H}_4$, $R^3 = R^4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) (60 mg, 68%).

Método C, Etapa 2:

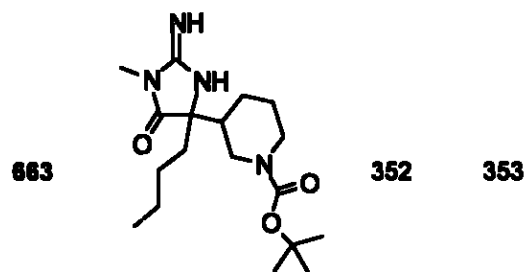
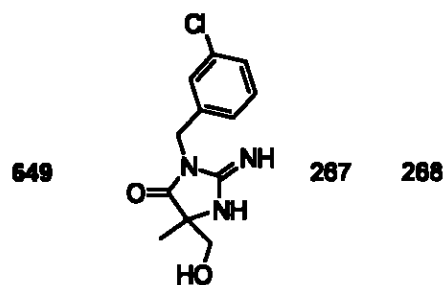
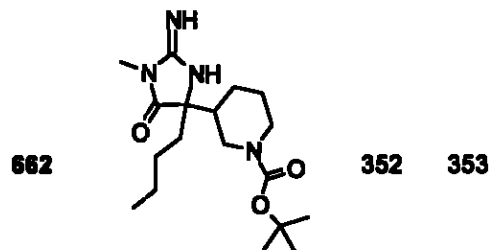
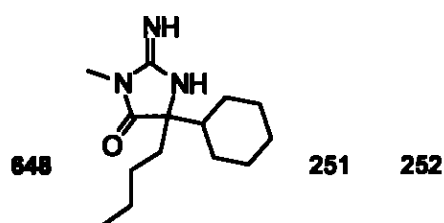
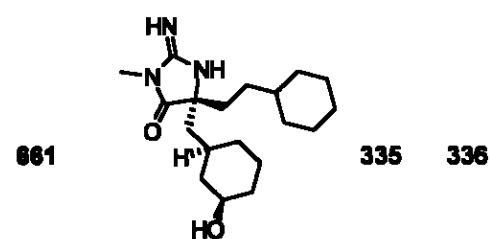
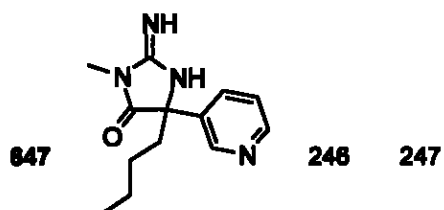
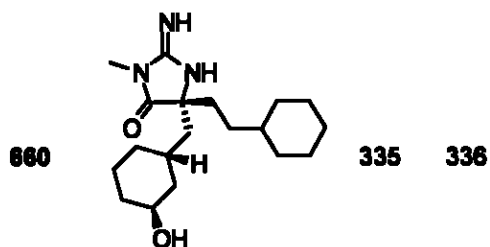
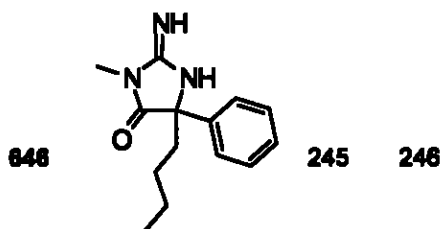
Se preparó el compuesto **C3** ($R^1 = 3\text{-Cl-C}_6\text{H}_4$, $R^2 = \text{H}$, $R^3 = R^4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) a partir de **C2** ($R^1 = 3\text{-Cl-C}_6\text{H}_4$, $R^3 = R^4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) seguido de un procedimiento similar al Método A, Etapa 3. NMR(CDCl_3): δ 7,4, m, 2H; δ 7,2, m, 2H; δ 5,0, s, 2H; δ 1,7, m, 4H; δ 1,1, m, 8H; δ 0,7, m, 6H. ES-LCMS (m/e): 336,1.

Se prepararon los compuestos siguientes usando métodos similares.

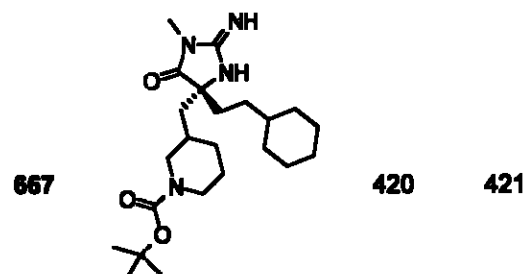
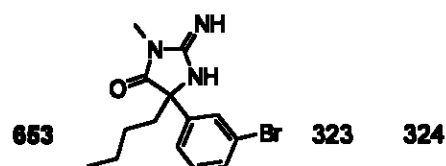
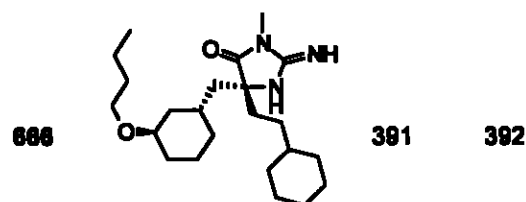
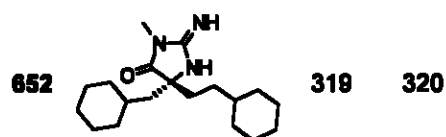
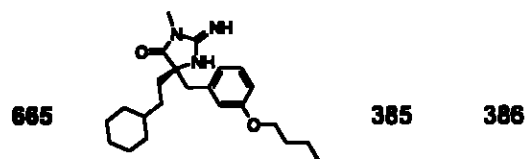
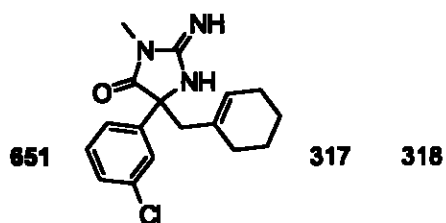
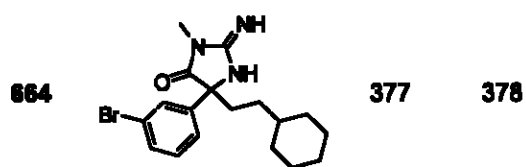
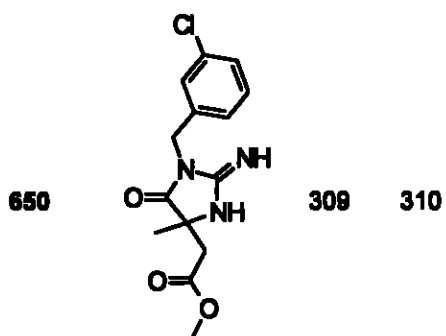
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645		239	240	659		335	336

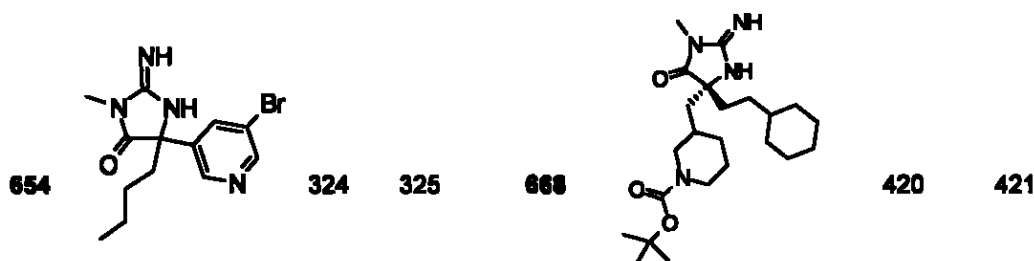
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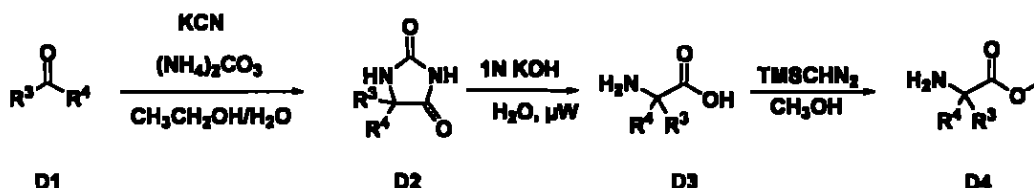
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Método D



Método D, Etapa 1:

Una mezcla de D1 ($R^3 = R^4 = \text{CH}_2\text{C}_6\text{H}_5$) (20 g), cianuro de potasio (40 g) y carbonato de amonio (15 g) en etanol (100 mL) y H_2O (200 mL) se calentaron en un frasco sellado a 130°C durante la noche para proporcionar 25 g of D2 ($R^3 = R^4 = \text{CH}_2\text{C}_6\text{H}_5$) después de filtración seguida de lavado con agua.

Método D, Etapa 2:

Se agregó una solución de KOH 2N (3eq) a D2 ($R^3 = R^4 = \text{CH}_2\text{C}_6\text{H}_5$) (1 eq) y se irradió y a través de microondas a 185°C durante 3 horas seguido de adición de HCl concentrado a la solución hasta que se obtuvo un pH = 2–3. El sólido se filtró y lavó con agua para proporcionar D3 ($R^3 = R^4 = \text{CH}_2\text{C}_6\text{H}_5$).

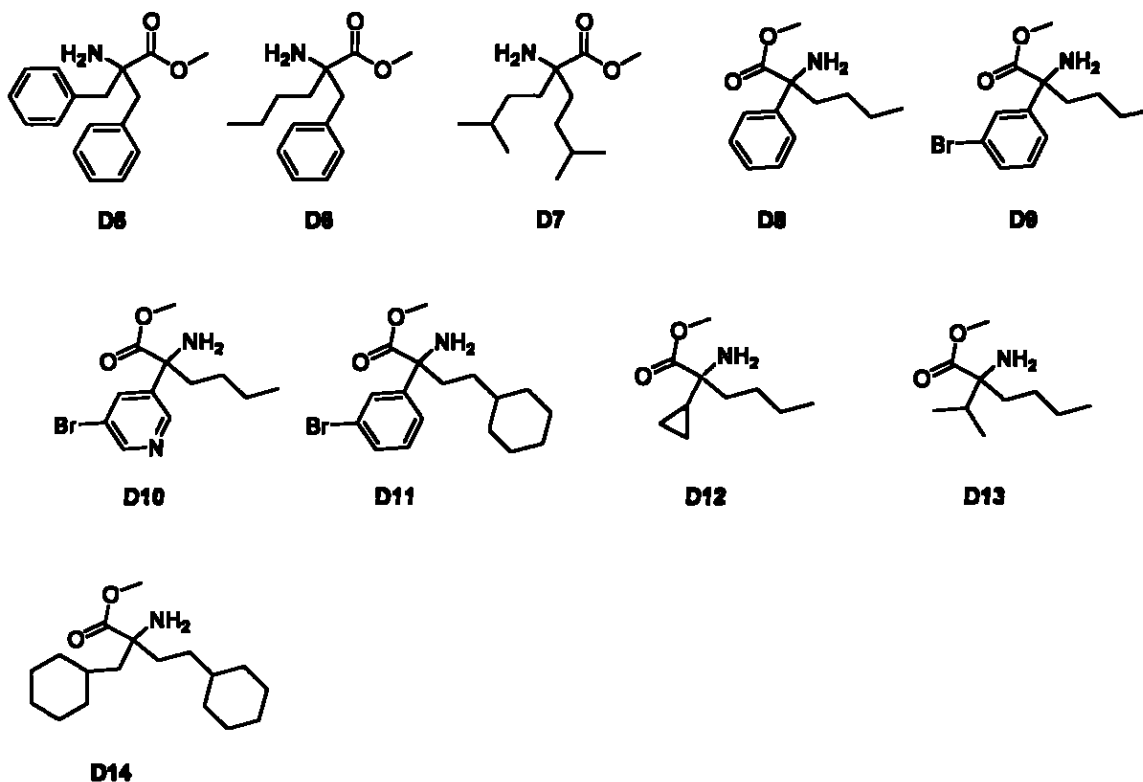
Método D, Etapa 3:

Se agregó una solución de trimetilsilildiazometano en hexano (2 N) (2 eq) por goteo a una solución de D3 ($R^3 = R^4 = \text{CH}_2\text{C}_6\text{H}_5$) (1 eq) en CH_3OH anhidro (30 mL). Después de 1 hora, se agregaron 2 equivalentes adicionales de trimetilsilildiazometano en hexano (2 N) y la reacción se agitó durante 20 minutos antes de concentrarla. El residuo se disolvió en una solución de HCl 0,2N (25 mL) y se lavó con éter (3x). Se agregó una solución saturada de Na_2CO_3 a la fase acuosa hasta que el pH de la solución fue básico. La solución se extrajo con acetato de etilo (3x). Se combinaron los extractos orgánicos, se

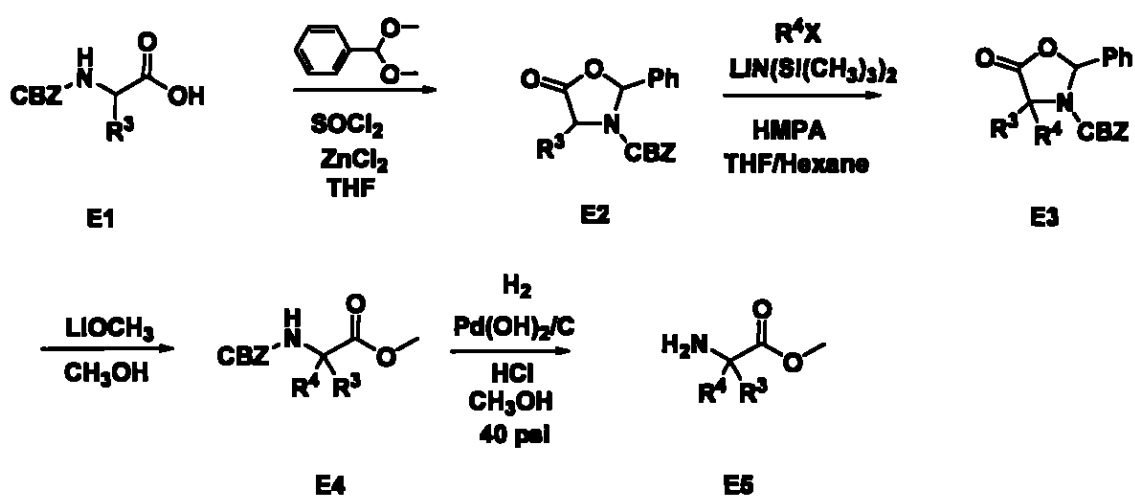
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493

secaron sobre Na_2SO_4 , y se concentraron para proporcionar D4 ($\text{R}^3 = \text{R}^4 = \text{CH}_2\text{C}_6\text{H}_5$).

Se prepararon los siguientes amino ésteres usando un método similar.



Método E



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Método E, Etapa 1:

Se agregó por goteo cloruro de tionilo (0,47, 6,38 mmoles) a una solución de E1 ($R^3 = CH_2CH_2C_6H_5$) (2 g, 6,38 mmoles) y dimetil acetal de benzaldehído (0,96 mL, 6,38 mmoles) en THF anhidro 0°C bajo N_2 , después de 5 minutos se agregó $ZnCl_2$ (0,87 g, 6,38 mmoles) y la mezcla de reacción se agitó a 0°C. Después de 3 horas se agregaron una cantidad adicional de $ZnCl_2$ (0,18 g, 1,28 mmoles) y cloruro de tionilo (0,1 mL, 1,28 mmoles) durante 1 hora a 0°C. La mezcla de reacción se vertió en una suspensión agitada de hielo/ H_2O . La mezcla se agitó ocasionalmente hasta que fundió el hielo. Se extrajo la solución acuosa con éter (3x). Los extractores orgánicos combinados se lavaron con H_2O (3x), una solución acuosa saturada de $NaHCO_3$ (1x), y H_2O (2x). La solución orgánica se secó sobre Na_2SO_4 , se filtró y concentró. El material crudo se purificó a través de cromatografía evaporativa eluyendo con acetato de etilo en hexano para proporcionar el compuesto E2 ($R^3 = CH_2CH_2C_6H_5$).

Método E, Etapa 2:

Se agregó por goteo una solución de hexametildisilazido de litio en hexano (1,0 M, 1,65 mL, 1,64 mmoles) a una solución de E2 ($R^3 = CH_2CH_2C_6H_5$) (600 mg, 1,49 mmoles) y HMPA (0,85 mL) en THF (6,5 mL) enfriada a -78°C bajo N_2 . Después de 15 minutos, se agregó por goteo yoduro de isobutilo (0,52 mL, 4,48 mmoles) y la mezcla de reacción se agitó a -78°C durante 3 horas. La reacción se calentó a -65°C, se agitó durante 2 horas y se calentó a temperatura ambiente durante la noche. La solución de reacción se vertió en una mezcla de $NaHCO_3$ saturado (aq)/éter/hielo. La capa acuosa se extrajo con éter (3x). Los extractos orgánicos se combinaron y lavaron con salmuera (2x). La solución orgánica se secó sobre Na_2SO_4 , se filtró y concentró. El material crudo se purificó por cromatografía evaporativa eluyendo con acetato de etilo en hexano para proporcionar el compuesto E3 ($R^3 = CH_2CH_2C_6H_5$, $R^4 = CH_2CH(CH_3)_2$).

Método E, Etapa 3:

Se agregó una solución de metóxido de litio (1N en CH_3OH) (0,36 mL, 0,36 mmoles) al compuesto E3 ($R^3 = CH_2CH_2C_6H_5$, $R^4 = CH_2CH(CH_3)_2$). La mezcla de reacción se agitó a temperatura ambiente durante 50 minutos. Se agregaron 0,55 eq adicionales de metóxido de litio. Después de 2,5 horas, se

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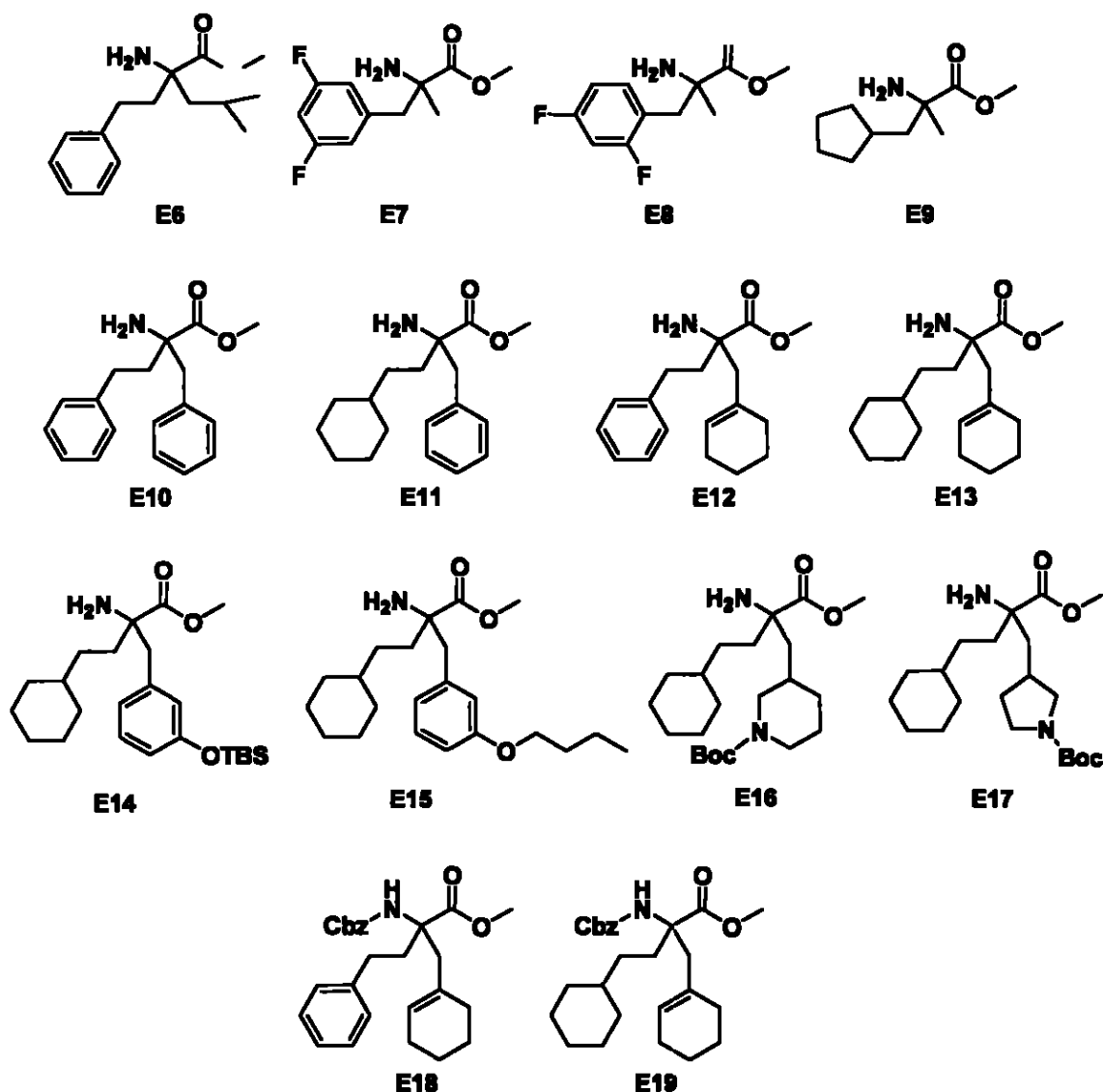
agregó una solución acuosa saturada de NaHSO_3 (0,75 mL) y acetato de litio (3 mL), a la mezcla de reacción y se agitó durante 15 minutos. La suspensión se filtró. El sólido blanco resultante se lavó con una solución acuosa saturada de NaHSO_3 (1x) y acetato de etilo (1x). La fase acuosa del filtrado se separó y se extrajo con acetato de etilo (2x). Los extractos orgánicos se combinaron y lavaron con una solución acuosa saturada de NaHSO_3 (8x). La solución orgánica se secó sobre Na_2SO_4 , se filtró y se concentró para proporcionar E4 ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (109 mg, 87%).

Método E, Etapa 4:

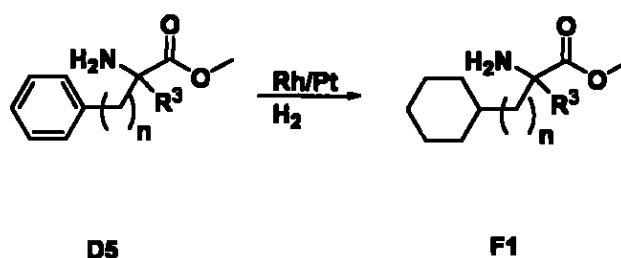
A una solución de E4 ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (109 mg, 0,28 mmoles) en CH_3OH (4 mL) se le agregó HCl 1N (0,28 mL, 0,28 mmoles) y 20% de hidróxido de paladio sobre carbón (22 mg). La mezcla de reacción se hidrogenó a 275 kPa (40 psi). Después de 2,5 horas, la reacción se filtró y el catalizador se lavó con CH_3OH (3x). El filtrado se concentró para proporcionar E5 ($\text{R}^3 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $\text{R}^4 = \text{CH}_2\text{CH}(\text{CH}_3)_2$) (78 mg, 96%).

Se prepararon los siguientes aminoésteres usando un método similar.

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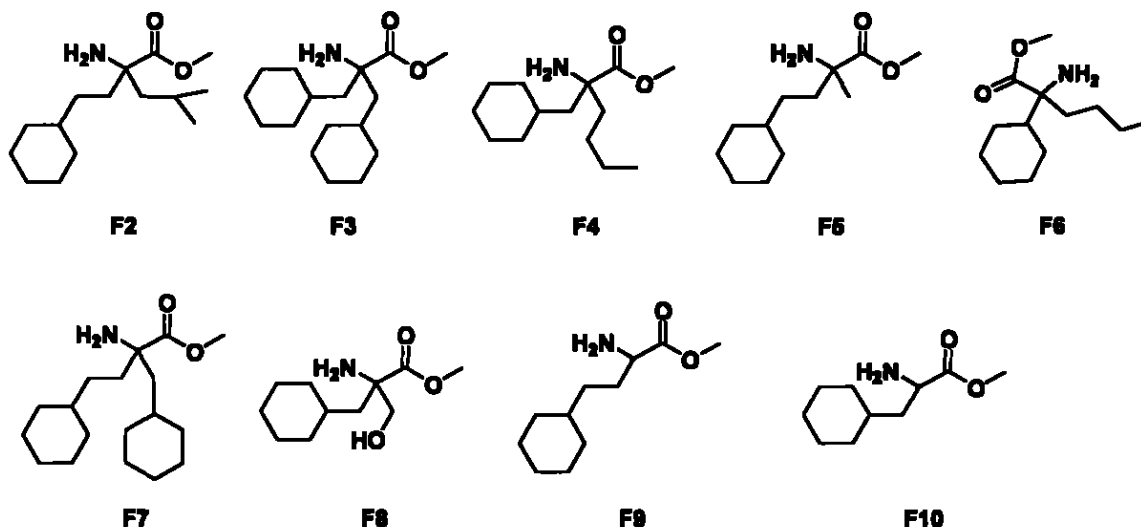


Método F

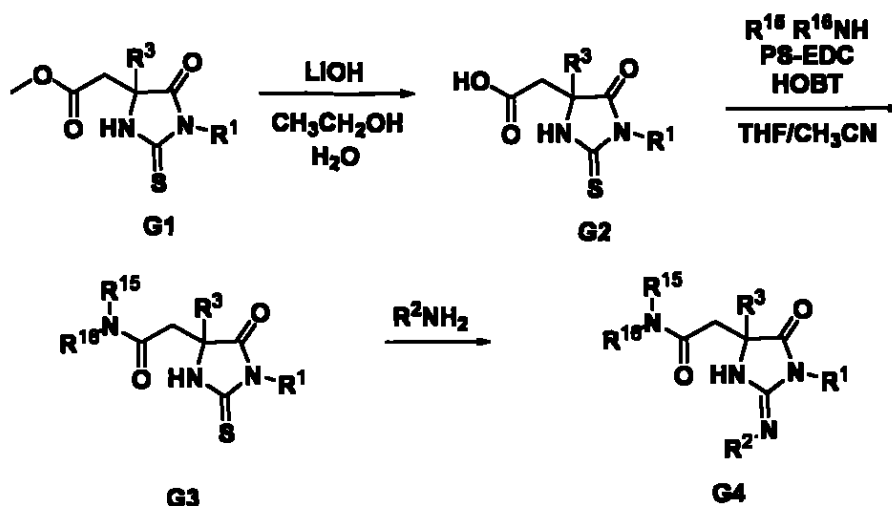


Se hidrogenó una solución de 500 mL de metanol de 20 g de D5 (R³ = bencilo, n = 1) con 1,5 eq de HCl, con 1 g de Rh/C (5% p/p) y 2 g de Pt/C (5% p/p) a 413 kPa (60 psi) durante 2 días. El sólido se filtró y se lavó con un exceso de metanol. La solución combinada se evaporó para proporcionar 20 g de F1 (R³ = ciclohexilmetilo, n = 1) como sal de HCl.

Los siguientes amino ésteres son ejemplos preparados usando métodos similares.



Método G



Método G, Etapa 1:

A una solución de G1 ($\text{R}^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$ y $\text{R}^3 = \text{CH}_3$) (400 mg, 1,23 mmoles, generada siguiendo un procedimiento similar al Método C, Etapa 1) en etanol (5 mL) se le agregó monohidrato de hidróxido de litio (100 mg, 2,45 mmoles) en H_2O (0,5 mL). Después de 2,5 horas, se agregó otra porción de monohidrato de hidróxido de litio (100 mg, 2,45 mmoles). Después de 5,5 horas, se diluyó la mezcla de reacción con H_2O (15 mL) y se extrajo con éter (2x). Se

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agregó una solución de 30% de HCl a la fase acuosa hasta que su pH = 1 a 2. La solución se saturó con NaCl y se extrajo con acetato de etilo (3x). La solución orgánica se secó sobre Na₂SO₄, se filtró y se concentró para proporcionar G2 (R¹ = CH₂(3-ClC₆H₄) y R³ = CH₃) (357 mg, 93%).

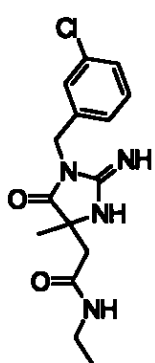
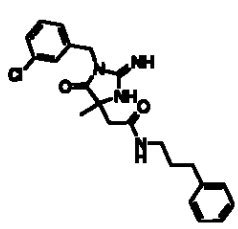
Método G, Etapa 2:

Se agregó una solución de bencilamina (1,2 eq) a G2 (R¹ = CH₂(3-ClC₆H₄) y R³ = CH₃) (1 eq), HOBT (1,5 eq) y resina de poliestireno EDC (94 mg, 1,53 mmoles/g, 3eq) en 1:1 THF:CH₃CN (1 mL). La mezcla de reacción se agitó durante la noche a temperatura ambiente. Se agregaron resina de trisamina (85 mg, 3,38 mmoles/g, 6 eq) y resina de isocianato (100 mg, 1,47 mmoles/g, 3 eq). Después de 6 horas, la suspensión se filtró y el filtrado se concentró para proporcionar G3 (R¹ = CH₂(3-ClC₆H₄), R³ = CH₃, R¹⁵ = CH₂C₆H₅ y R¹⁶ = H).

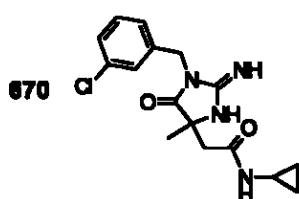
Método G, Etapa 3:

Se preparó el compuesto G4 (R¹ = CH₂(3-ClC₆H₄), R² = H, R₃ = CH₃, R¹⁵ = CH₂C₆H₅ y R¹⁶ = H) a partir de G3 (R¹ = CH₂(3-ClC₆H₄), R³ = CH₃, R¹⁵ = CH₂C₆H₅ y R¹⁶ = H) seguido de un procedimiento similar al Método A, Etapa 3,

Se prepararon los siguientes compuestos usando métodos similares.

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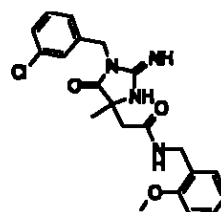
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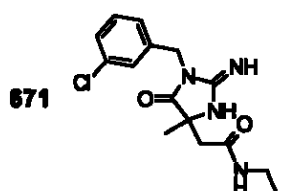
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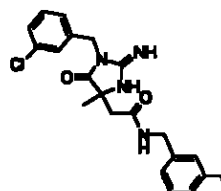
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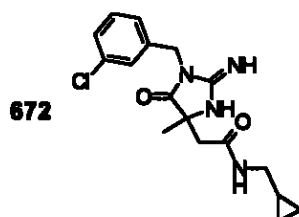
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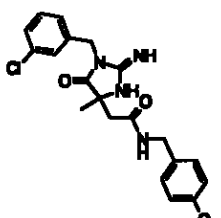
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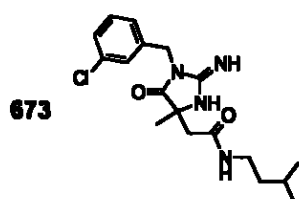
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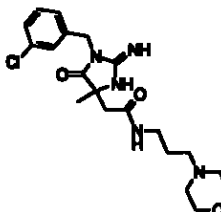
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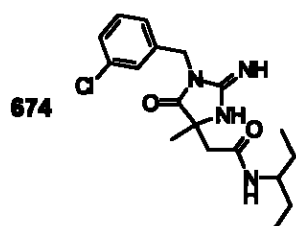
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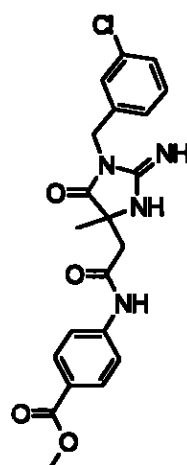
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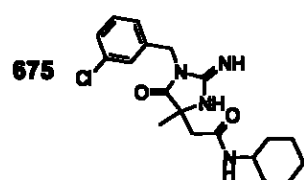
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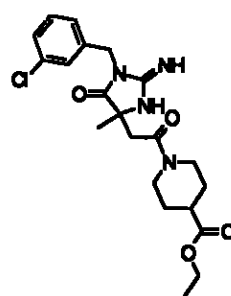
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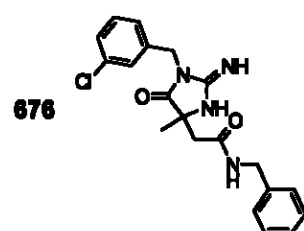
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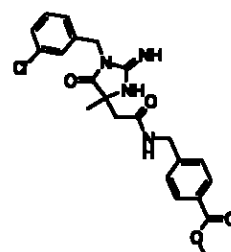
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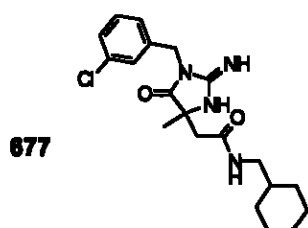
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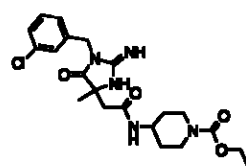
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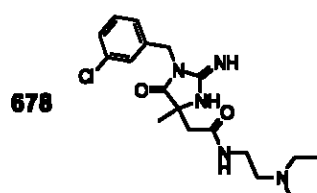
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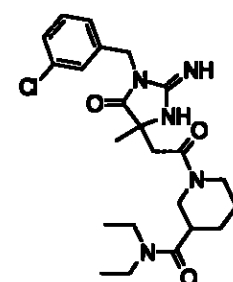
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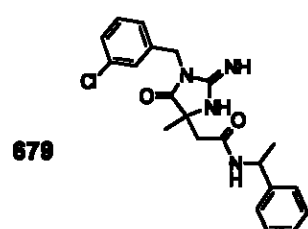
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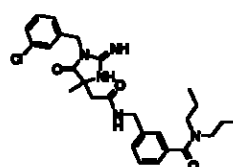
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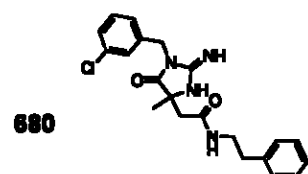
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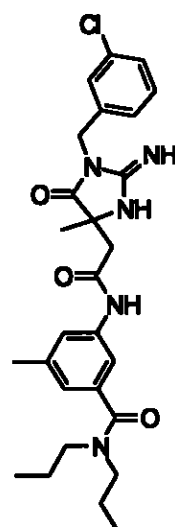
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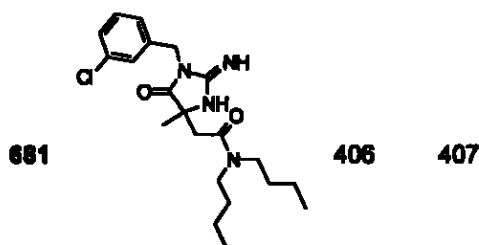
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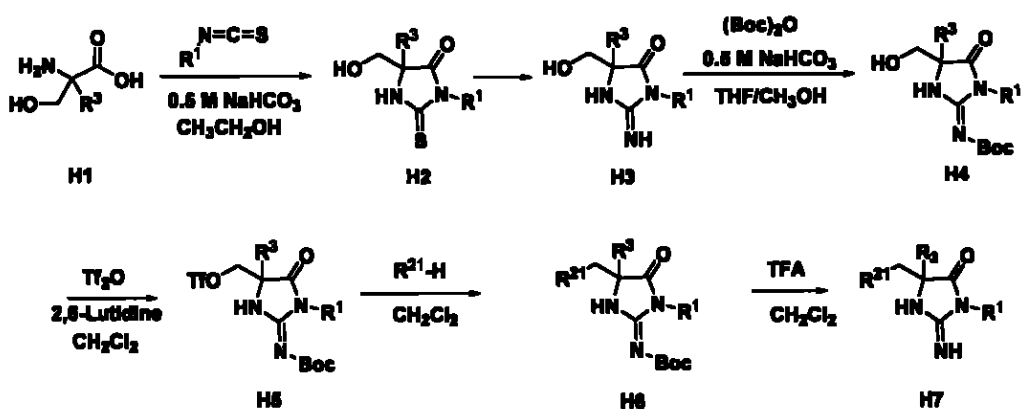


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Método H



Método H, Etapa 1:

A una solución de H1 ($R^3 = CH_3$) (5 g, 39 mmoles) en una mezcla de 1:1 de 0,5 M $NaHCO_3$: CH_3CH_2OH se le agregó R^1 -NCS (R^1 =3-clorobencilo) (11,5 mL, 78 mmoles). La mezcla de reacción se calentó a $50^\circ C$ durante la noche. La reacción se enfrió y diluyó con agua. La fase acuosa se extrajo con acetato de etilo (5x). Los extractos orgánicos se combinaron, se lavaron con agua (2x) y se secaron sobre Na_2SO_4 . La solución se filtró y el solvente se extrajo para proporcionar un pequeño volumen de solución. Se agregó hexano y la suspensión resultante se filtró para proporcionar 6,8 g de un sólido H2 ($R^3 = CH_3$, $R^1 = CH_2(3-ClC_6H_4)$) (61%).

Método H, Etapa 2:

Se sintetizó el compuesto H3 ($R^3 = CH_3$, $R^1 = CH_2(3-ClC_6H_4)$) a partir de H2 ($R^3 = CH_3$, $R^1 = CH_2(3-ClC_6H_4)$) seguido de un procedimiento similar al Método A, Etapa 3,

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~~303~~

Método H, Etapa 3:

A una solución de H3 crudo ($R^3 = CH_3$, $R^1 = CH_2(3-ClC_6H_4)$) (14 mmoles) en una mezcla de 1:3 de $CH_3OH:THF$ se le agregó $NaHCO_3$ 0,5M en H_2O (28 mL, 14 mmoles) y dicarbonato de di-*ter*-butilo (3,69 g, 16,9 mmoles). La reacción se agitó a temperatura ambiente durante 2,5 horas y luego se almacenó a $-10^\circ C$ durante la noche. La reacción se diluyó con salmuera y se extrajo con acetato de etilo (4x). Los extractos orgánicos se combinaron y lavaron con salmuera (1x). La solución orgánica se secó sobre Na_2SO_4 , se filtró y concentró. El material crudo se purificó por cromatografía evaporativa eluyendo con acetato de etilo en hexano para proporcionar 1,5 g of H4 ($R^1 = CH_2(3-ClC_6H_4)$ y $R^3 = CH_3$).

Método H, Etapa 4:

Se agregó por goteo una solución de anhídrido trifílico (128 μL , 0,76 mmoles) en CH_2Cl_2 (5 mL) a una solución de H4 ($R^1 = CH_2(3-ClC_6H_4)$ y $R^3 = CH_3$) (200 mg, 0,55 mmoles) y 2,6-lutidina (176 μL , 2,18 mmoles) a $-30^\circ C$. La mezcla de reacción se agitó durante 1,5 horas. Se agregó agua (10 mL) a $-20^\circ C$ y se extrajo el baño de hielo. La reacción se agitó hasta que alcanzó $0^\circ C$. La capa orgánica se separó, se secó sobre Na_2SO_4 , se filtró y concentró para proporcionar 310 mg de H5 ($R^1 = CH_2(3-ClC_6H_4)$ y $R^3 = CH_3$).

Método H, Etapa 5:

Una solución de H5 crudo ($R^1 = CH_2(3-ClC_6H_4)$ y $R^3 = CH_3$) (0,11 mmoles) y amoníaco 7N en metanol ($R^{21}-H = NH_2-H$) (10 eq) se agitó durante la noche a temperatura ambiente. La solución de reacción se concentró. El material crudo se purificó usando HPLC preparativa de fase inversa eluyendo con un gradiente CH_3CN/H_2O con 0,1% de ácido fórmico para proporcionar H6 ($R^1 = CH_2(3-ClC_6H_4)$, $R^3 = CH_3$, $R^{21} = NH_2$).

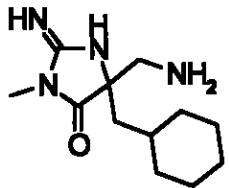
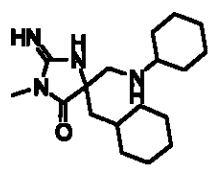
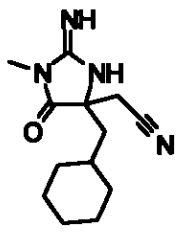
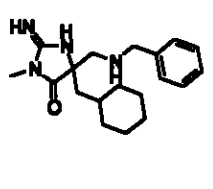
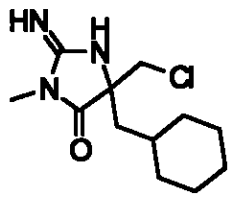
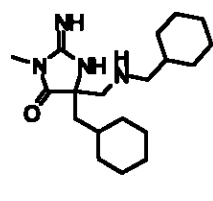
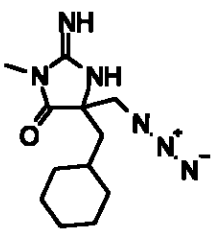
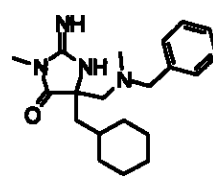
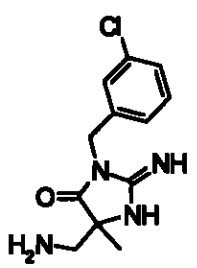
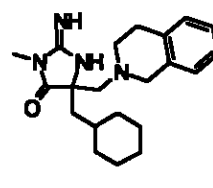
Método H, Etapa 6:

Se agregó una solución de ácido trifluoracético al 50% en CH_2Cl_2 (2 mL) a H6 ($R^1 = CH_2(3-ClC_6H_4)$, $R^3 = CH_3$, $R^{21} = NH_2$). Después de 40 minutos el solvente se evaporó y el residuo se purificó por HPLC/LCMS preparativa eluyendo con un gradiente de CH_3CN/H_2O para proporcionar H7 ($R^1 = CH_2(3-$

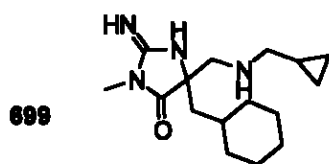
492
50A

ClC_6H_4), $\text{R}_3 = \text{CH}_3$, $\text{R}^{21} = \text{NH}_2$). RMN (CDCl_3), δ 7,45, m, 3H; δ 7,35, m, 1H; δ 4,9, m, 2H; δ 3,5, m, 2H; δ 1,65, s, 3H. ES_LCMS (m/e) 267,07.

Se prepararon los compuestos siguientes usando métodos similares.

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
694		238	239	702		320	321
695		248	249	703		328	329
696		257	258	704		334	335
697		264	265	705		342	343
698		266	267	706		354	355

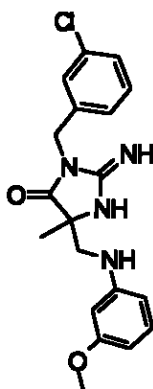
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282

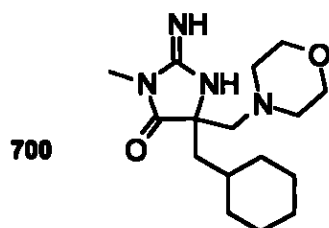
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707



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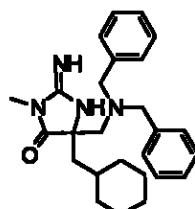
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308

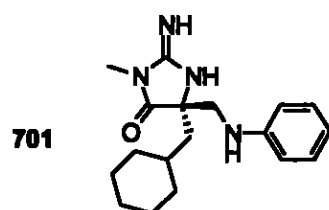
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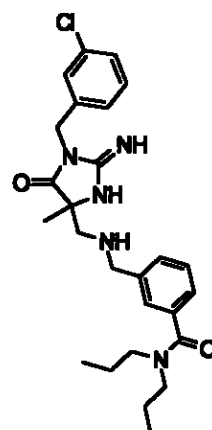
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314

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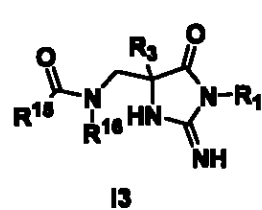
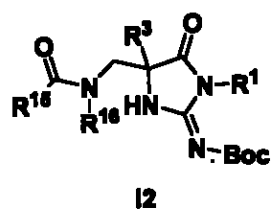
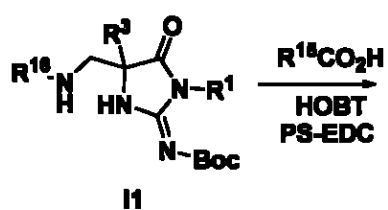
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483

484

Método I



494
508

Método I, Etapa 1:

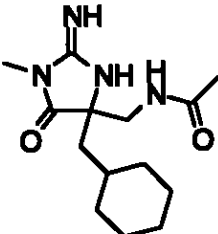
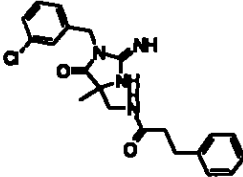
Se agregó resina de dietilaminometil poliestireno (5 eq) a una solución de la sal de formiato de I1 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$ y $R^{16}=\text{H}$) en CH_2Cl_2 y la suspensión se agitó. Después de 15 minutos la mezcla se filtró y la resina se lavó con CH_2Cl_2 (4x). El filtrado se concentró para proporcionar la base libre I1 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$ y $R^{16}=\text{H}$).

Se agregó una solución de $R^{18}\text{COOH}$ ($R^{18}=\text{fenetilo}$) (1,3 eq) a una mezcla de resina EDC (41 mg, 1,53 mmoles/g, 3eq), HOBT (1,5 eq), y la base libre de I1 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$ y $R^{16}=\text{H}$) (0,021 mmoles) en 1:1 $\text{CH}_3\text{CN}:\text{THF}$. La suspensión se agitó durante la noche. Se agregó resina de isocianato de poliestireno (45 mg, 3 eq), resina de trisamina de poliestireno (40 mg, 6 eq) y una mezcla de 1:1 de $\text{CH}_3\text{CN}:\text{THF}$ (0,5 mL). La mezcla se agitó durante 6 horas. La suspensión se filtró y el filtrado se concentró para proporcionar I2 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{16}=\text{H}$ y $R^{15} = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$).

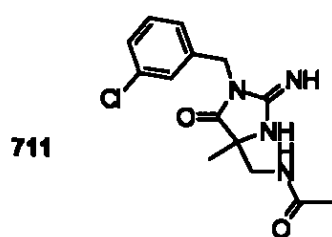
Método I, Etapa 2:

Se preparó I3 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{16}=\text{H}$ y $R^{15} = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$) a partir de I2 ($R^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $R^3 = \text{CH}_3$, $R^{16}=\text{H}$ y $R^{15} = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$) usando un método similar al método H etapa 6.

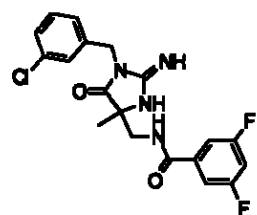
Se prepararon los siguientes compuestos usando un método similar.

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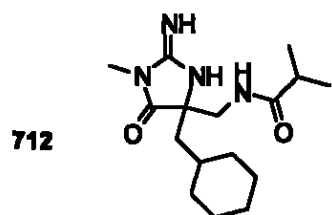
995
507



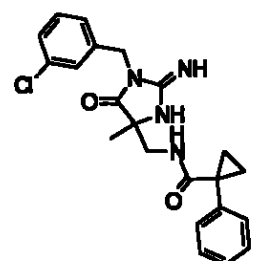
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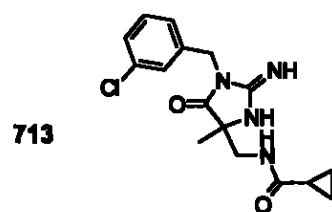
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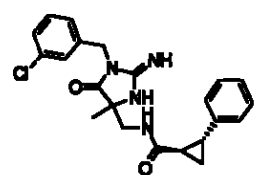
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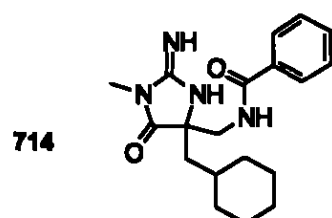
410 11



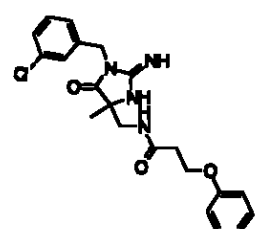
334 335 721



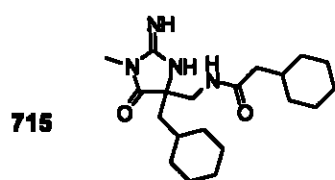
410 11



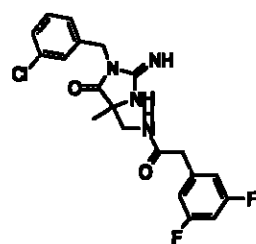
342 343 722



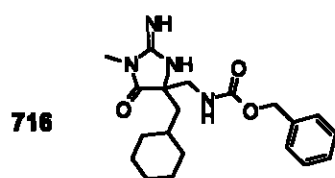
414 15



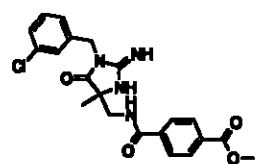
362 363 723



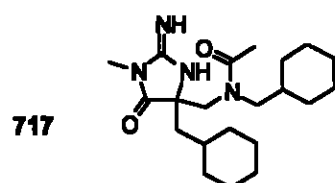
420 21



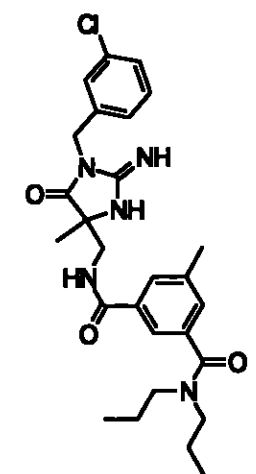
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428 29

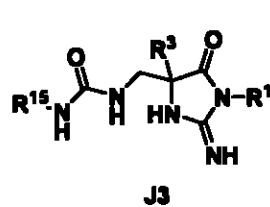
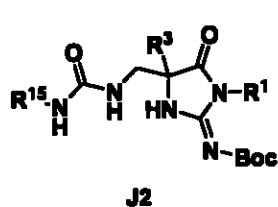
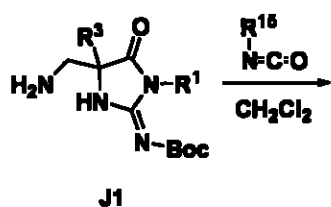


376 377 725



511 12

Método J



497
~~509~~

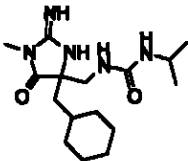
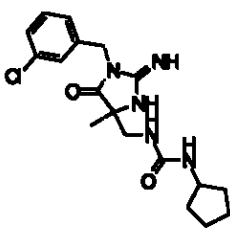
Método J, Etapa 1:

Se agregó resina de dietilaminometil poliestireno (5 eq) a una solución de J1 (sal de TFA, $R^1 = CH_2(3-ClC_6H_4)$ y $R^3 = CH_3$) en CH_2Cl_2 y la suspensión se agitó. Después de 15 minutos, la mezcla se filtró y la resina se lavó con CH_2Cl_2 (4x). El filtrado se concentró para proporcionar la base libre. Una solución de $R^{15}NCO$ ($R^{15} =$ butilo) (2 eq) en CH_2Cl_2 se agregó a la base libre de J1 ($R^1 = CH_2(3-ClC_6H_4)$ y $R^3 = CH_3$) (0,021 mmoles) en 1:1 $CH_3CN:THF$. La suspensión se agitó durante la noche. Se agregaron resina de isocianato de poliestireno (45 mg, 3 eq), resina de trisamina de poliestireno (40 mg, 6 eq) y una mezcla de 1:1 de $CH_3CN:THF$ (0,5 mL). La mezcla se agitó durante 6 horas. La suspensión se filtró y el filtrado se concentró para proporcionar J2 ($R^1 = CH_2(3-ClC_6H_4)$, $R^3 = CH_3$, y $R^{15} = CH_2CH_2CH_2CH_3$).

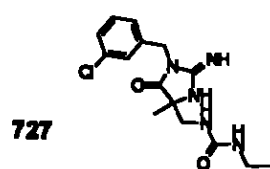
Método J, Etapa 2:

Se preparó el compuesto J3 ($R^1 = CH_2(3-ClC_6H_4)$, $R^3 = CH_3$, y $R^{15} = CH_2CH_2CH_2CH_3$) a partir de J2 ($R^1 = CH_2(3-ClC_6H_4)$, $R^3 = CH_3$, y $R^{15} = CH_2CH_2CH_2CH_3$) siguiendo el procedimiento descrito en el Método H, Etapa 2.

Se prepararon los compuestos siguientes usando un método similar.

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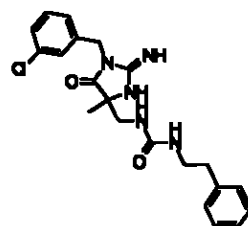
498
510



337

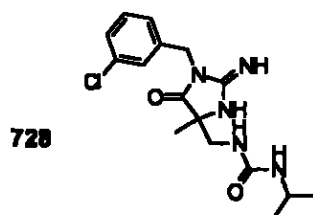
338

732



413

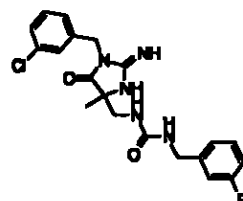
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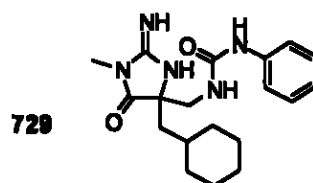
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733



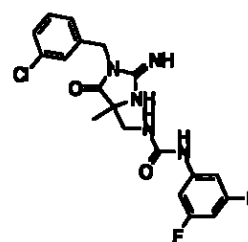
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418



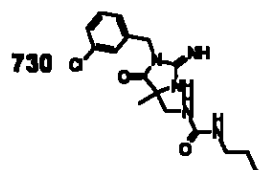
358

734



421

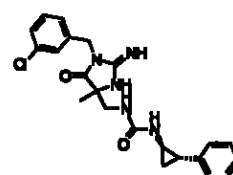
422



365

366

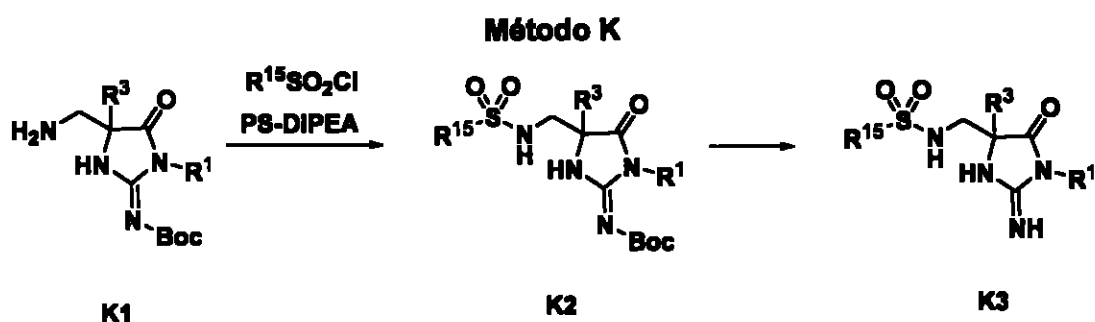
735



425

426

499
511



Método K, Etapa 1:

Se agregó una solución de $\text{R}^{15}\text{SO}_2\text{Cl}$ ($\text{R}^{15}=\text{Propil}$)(1,5 eq) a una suspensión de resina de diisopropiletilamina de poliestireno (18 mg, 3,45 mmoles/g, 3 eq) y se preparó la base libre de K1 usando el método H ($\text{R}^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$ y $\text{R}^3 = \text{CH}_3$) (0,021 mmoles) en 1:1 $\text{CH}_3\text{CN}:\text{THF}$. La suspensión se agitó durante la noche. Se agregó resina de isocianato de poliestireno (45 mg, 3 eq), resina de trisamina de poliestireno (40 mg, 6 eq) y una mezcla 1:1 de $\text{CH}_3\text{CN}:\text{THF}$ (0,5 mL). La mezcla se agitó durante 6 horas. La suspensión se filtró y el filtrado se concentró para proporcionar K2 ($\text{R}^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $\text{R}^3 = \text{CH}_3$, y $\text{R}^{15} = \text{CH}_2\text{CH}_2\text{CH}_3$).

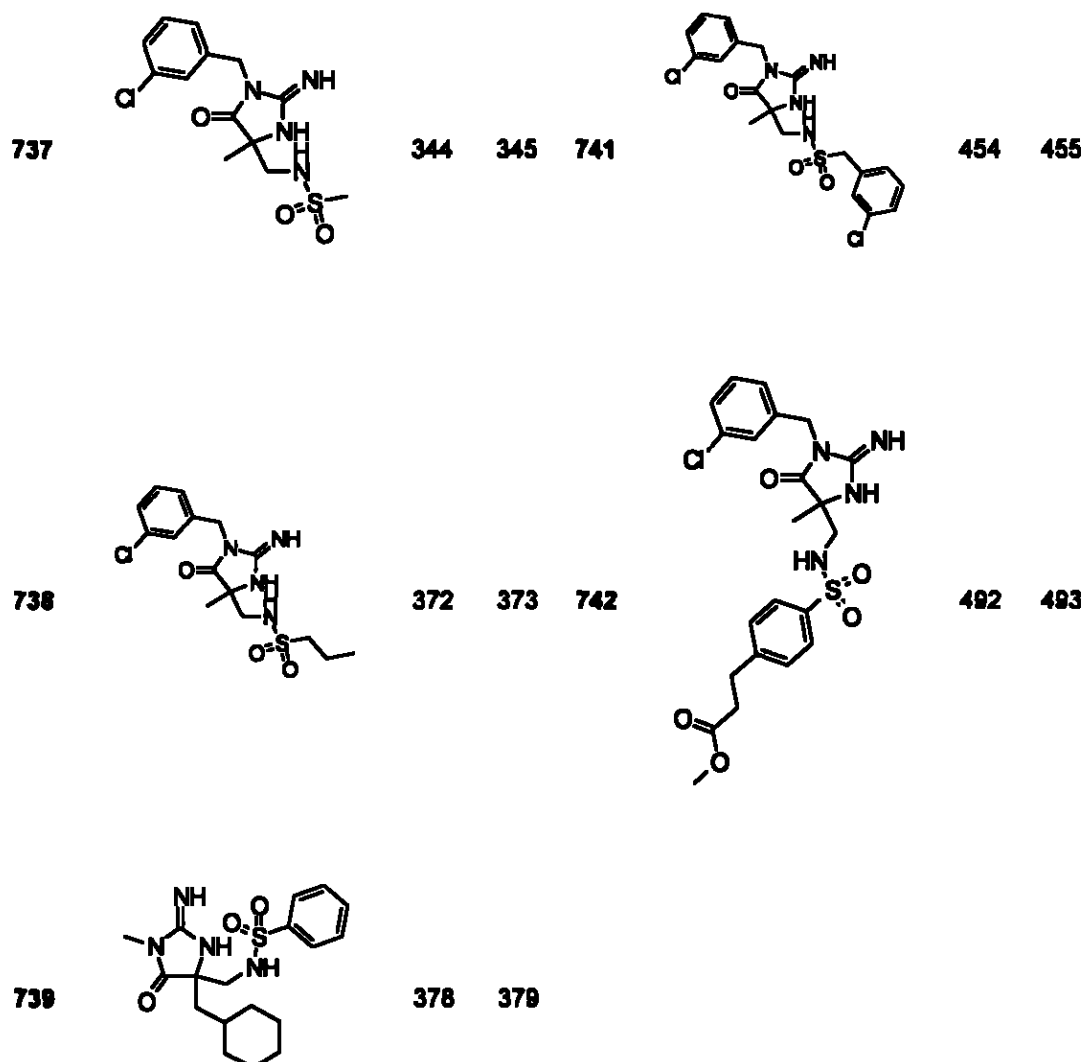
Método K, Etapa 2:

Se preparó el compuesto K3 ($\text{R}^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $\text{R}^3 = \text{CH}_3$, y $\text{R}^{15} = \text{CH}_2\text{CH}_2\text{CH}_3$) a partir de K2 ($\text{R}^1 = \text{CH}_2(3\text{-ClC}_6\text{H}_4)$, $\text{R}^3 = \text{CH}_3$, y $\text{R}^{15} = \text{CH}_2\text{CH}_2\text{CH}_3$) siguiendo el procedimiento descrito en el Método H, Etapa 6.

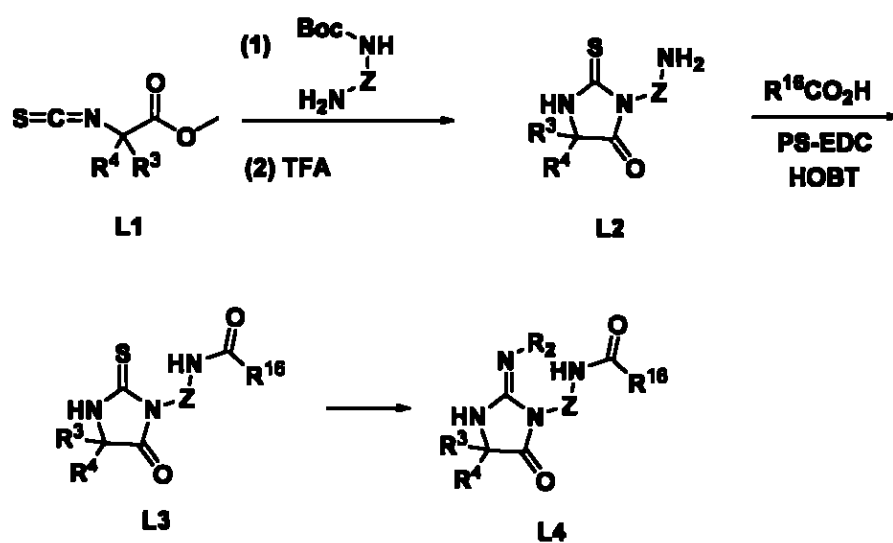
Se prepararon los compuestos siguientes usando un método similar.

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
736		318	317	740		442	443

500
552



Método L



501
SB

(En el esquema, $-Z-NH-C(O)R^{18}$ - es equivalente a R^1 sustituido con R^{21} , o R^1 sustituido con alquilo- R^{22} , donde R^{21} y R^{22} son $-N(R^{15})C(O)R^{18}$ y R^{15} es H, y donde Z es alquileo-arileno opcionalmente sustituido, alquileo-arileno-alquileo, alquileo-heteroarileno, alquileo-heteroarileno-alquileo, alquileo-cicloalquileo, alquileo-cicloalquileo-alquileo, alquileo-heterocicloalquileo, alquileo-heterocicloalquileo-alquileo, arileno, heteroarileno, cicloalquileo o heterocicloalquileo)

Método L, Etapa 1:

Una solución de L1 ($R^3 = CH_3$ y $R^4 = CH_2CH(CH_3)_2$) (1 eq) y Z = -para-metilen-bencilo) (1.05 eq) en CH_2Cl_2 se agitó a temperatura ambiente. La solución de reacción se concentró y se purificó por cromatografía evaporativa. El material se trató con 50% de ácido trifluoracético en CH_2Cl_2 durante 30 min. La solución se concentró. El residuo se disolvió en HCl 1 N (10 mL) y se lavó con éter (2x). Se agregó una solución saturada de Na_2CO_3 en H_2O a la fase acuosa hasta que la solución se basificó. La solución se extrajo con CH_2Cl_2 (3x). Los extractos de CH_2Cl_2 se combinaron se secaron sobre Na_2SO_4 , se filtraron y se concentraron para proporcionar L2 ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para- $(CH_2)C_6H_4(CH_2)-$).

Método L, Etapa 2:

Se preparó el compuesto L3 ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para- $(CH_2)C_6H_4(CH_2)-$, $R^{18} = CH_2CH_2CH_2CH_3$) a partir de L2 ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para- $(CH_2)C_6H_4(CH_2)-$) seguido del procedimiento descrito en Método I, Etapa 1.

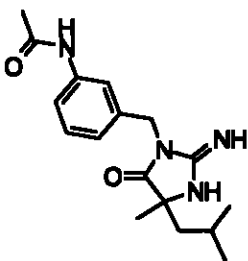
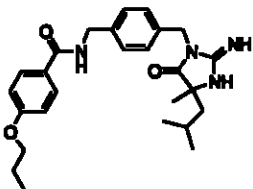
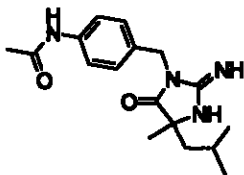
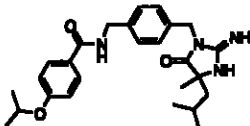
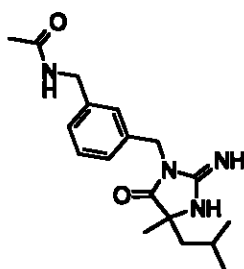
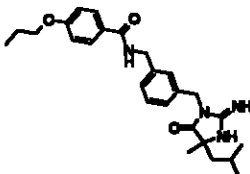
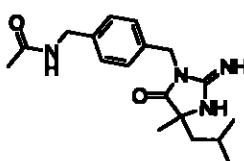
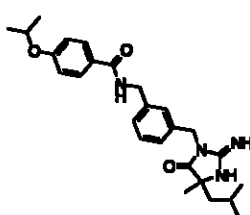
Método L, Etapa 3:

Se preparó el compuesto L4 ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para- $(CH_2)C_6H_4(CH_2)-$, $R^1 = CH_2CH_2CH_2CH_3$) a partir ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para- $(CH_2)C_6H_4(CH_2)-$, $R^{18} = CH_2CH_2CH_2CH_3$) seguido del procedimiento descrito en Método A, Etapa 3.

Se prepararon los compuestos siguientes usando un método similar.

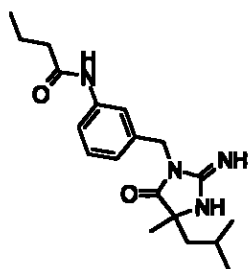
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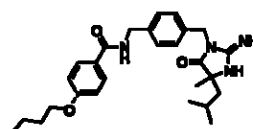
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744		316	317	762		450	451
745		330	331	763		450	451
746		330	331	764		450	451

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518

747

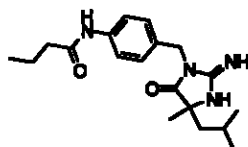


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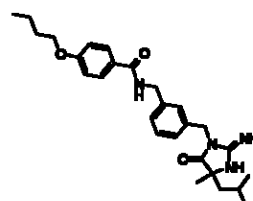


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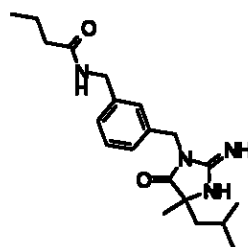


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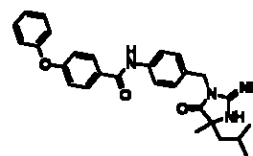


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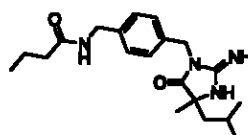


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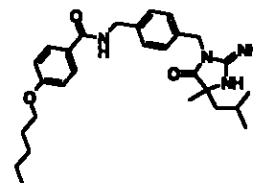


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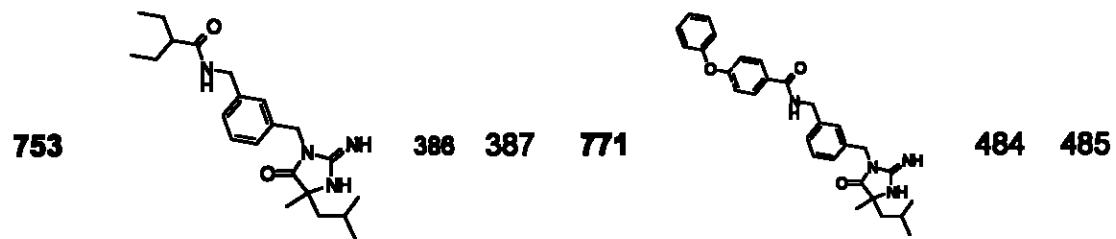
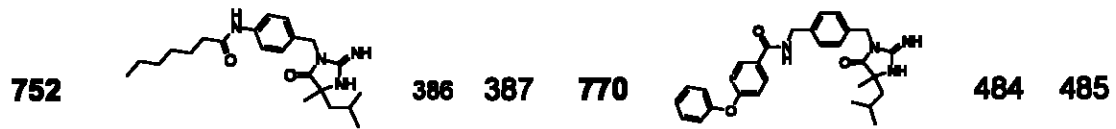
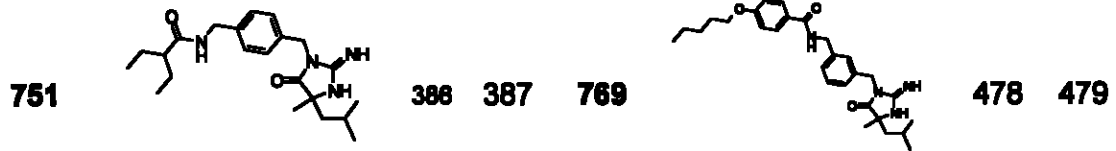


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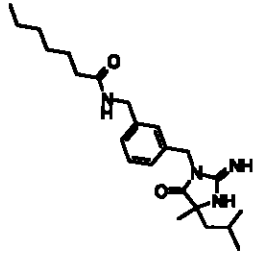
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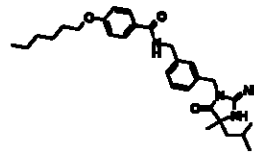


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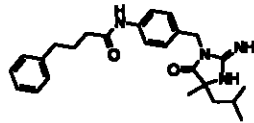


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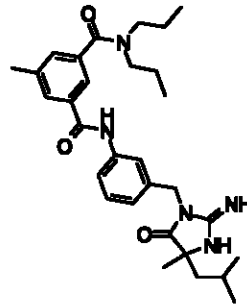


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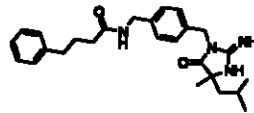


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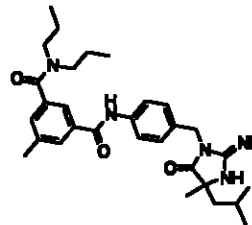


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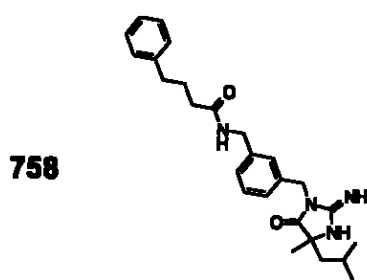
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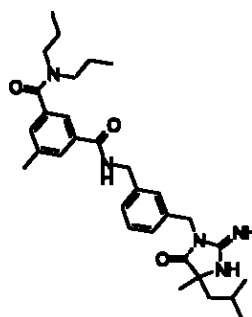
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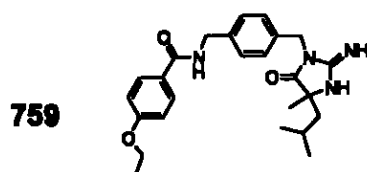
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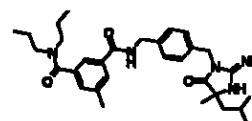
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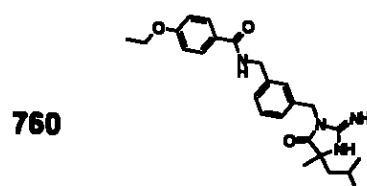
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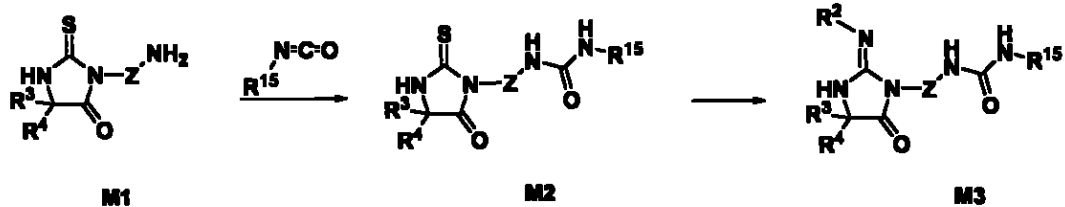


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Método M



(En el esquema, $-Z-NH-C(O)-NHR^{15}$ - es equivalente a R^1 sustituido con R^{21} , o R^1 sustituido con alquilo- R^{22} , donde R^{21} y R^{22} son $-N(R^{16})-C(O)-NHR^{15}$ y

507

519

R^{16} es H, y donde Z es alquileo-arileno, alquileo-arileno-alquileo, alquileo-heteroarileno, alquileo-heteroarileno-alquileo, alquileo-cicloalquileo, alquileo-cicloalquileo-alquileo, alquileo-heterocicloalquileo, alquileo-heterocicloalquileo-alquileo, arileno, heteroarileno, cicloalquileo o heterocicloalquileo opcionalmente sustituido)

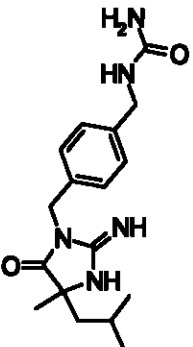
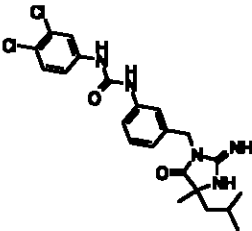
Método M, Etapa 1:

Se preparó el compuesto **M2** ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para-(CH₂)C₆H₄(CH₂)-, $R^{15} = 3,4$ -difluorfenilo a partir de **M1** ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para-(CH₂)C₆H₄(CH₂)-) siguiendo el procedimiento descrito en el Método J, Etapa 1.

Método M, Etapa 2:

Se preparó el compuesto **M3** ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para-(CH₂)C₆H₄(CH₂)-, $R^{15} = 3,4$ -difluorfenilo) a partir de **M2** ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para-(CH₂)C₆H₄(CH₂)-, $R^{15} = 3,4$ -difluorfenilo) siguiendo el procedimiento descrito en el Método A, Etapa 3. RMN (CD₃OD) δ 7,45, m, 1H; δ 7,26, m, 4H; 7,24, m, 1H; δ 6,96, m, 1H; δ 4,8, m; δ 4,3, s, 2H; δ 1,69, m, 2H; δ 1,44, m, 1H; δ 1,37, s, 3H; δ 0,8, m, 3H; δ 0,63, m, 3H. ES_LCMS (m/e) 430,27.

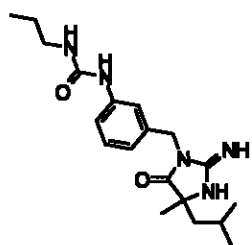
Se prepararon los siguientes compuestos usando un método similar.

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508

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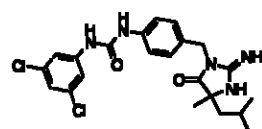
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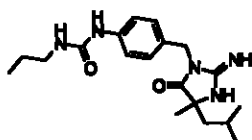
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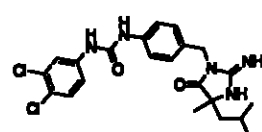
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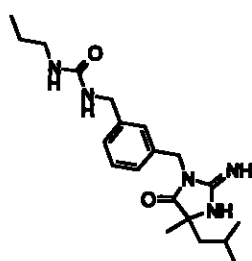
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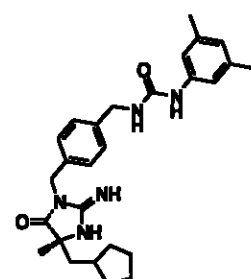
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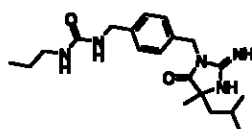
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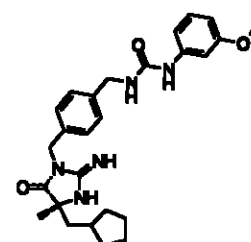
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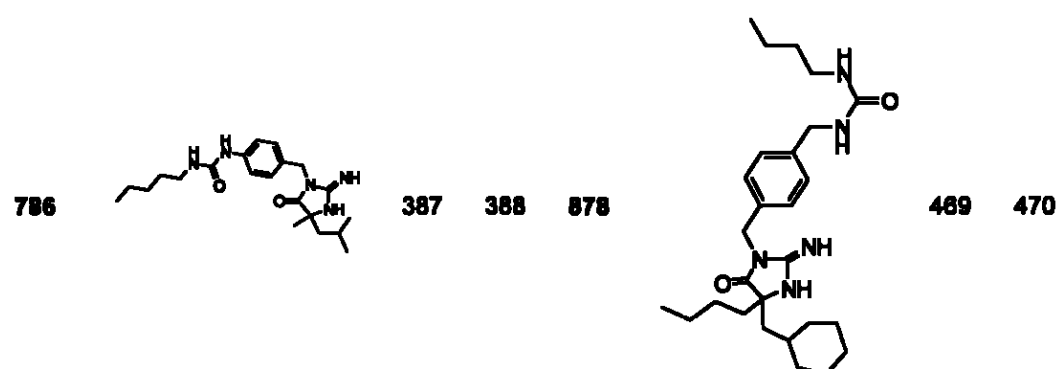
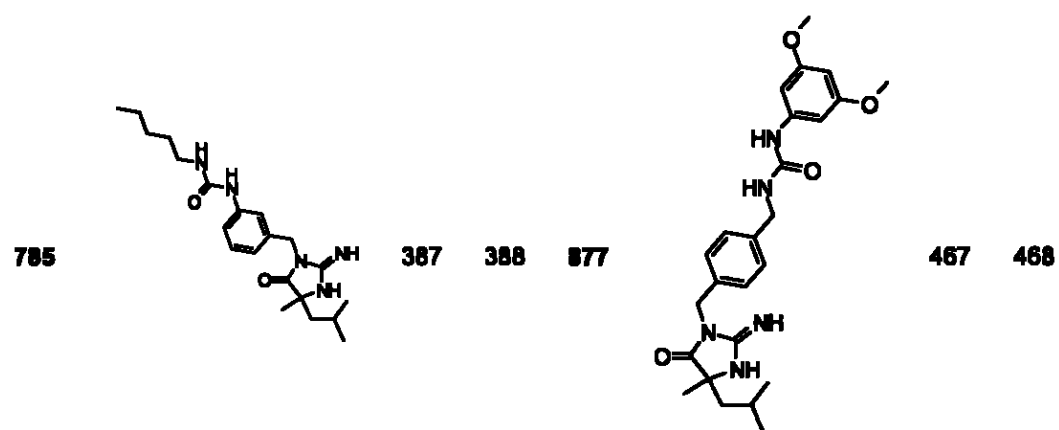
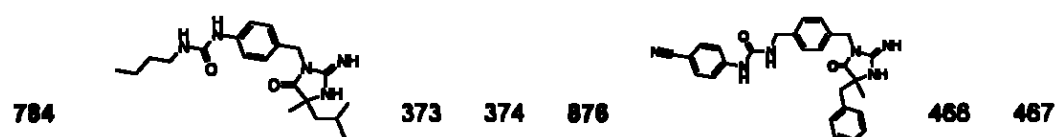
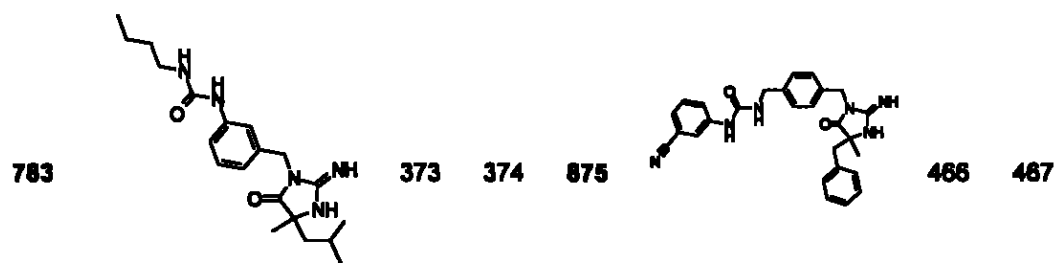
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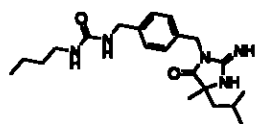


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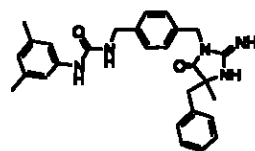
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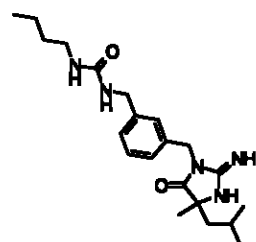
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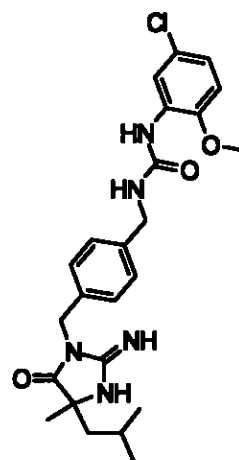
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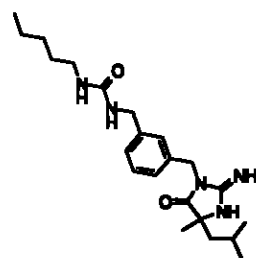
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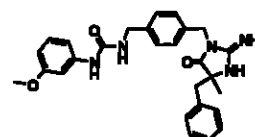
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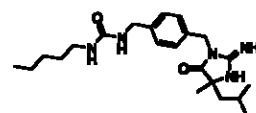
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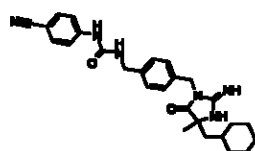
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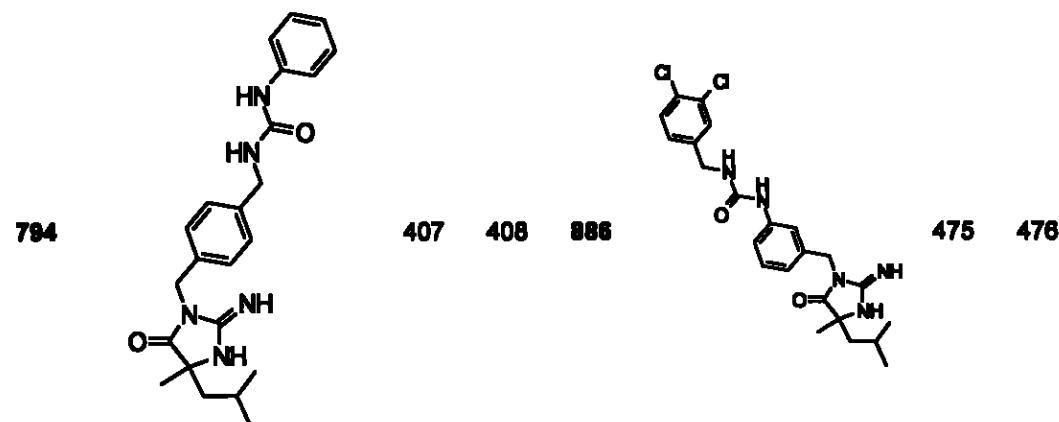
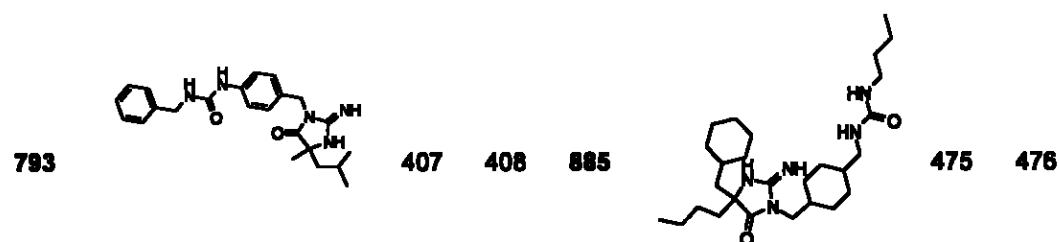
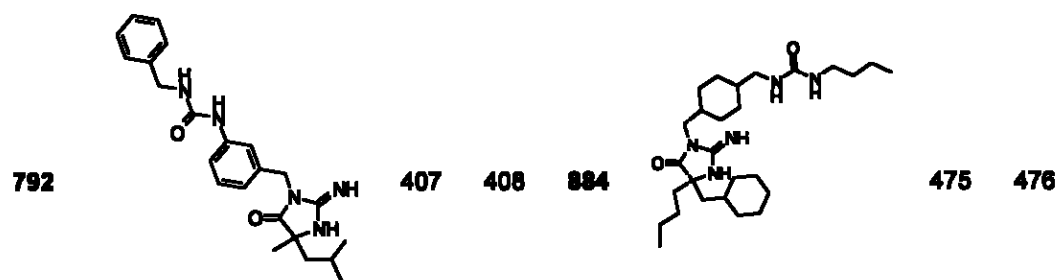
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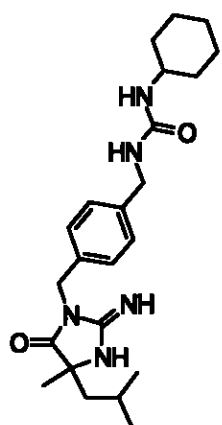
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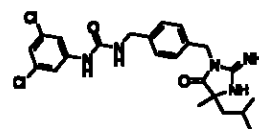
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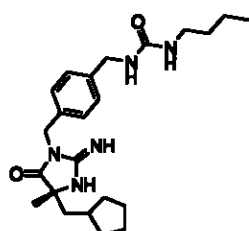
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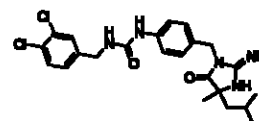
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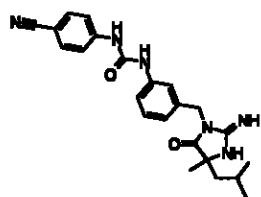
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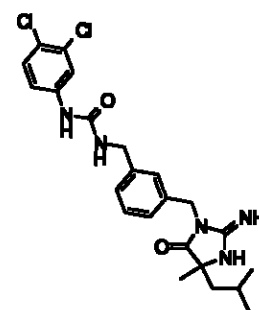
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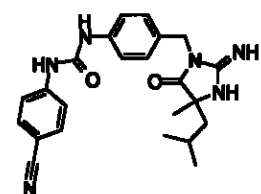
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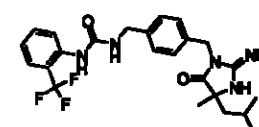
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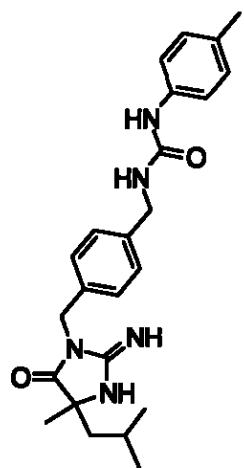


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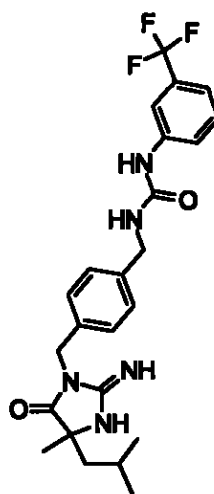
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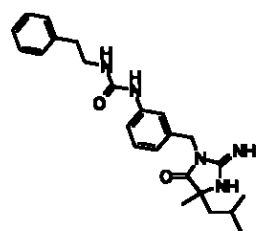
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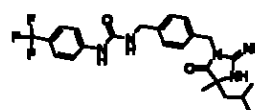
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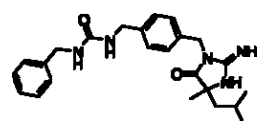
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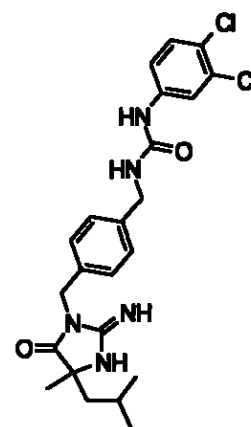
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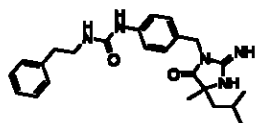
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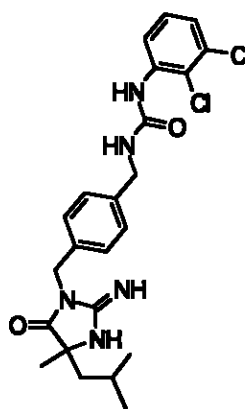
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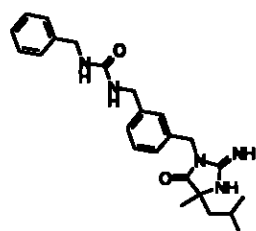
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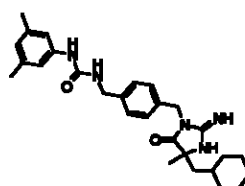
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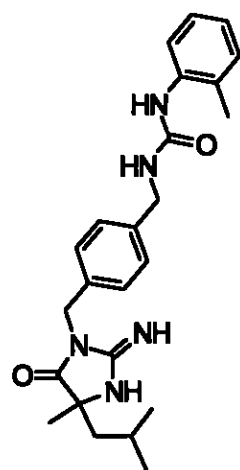
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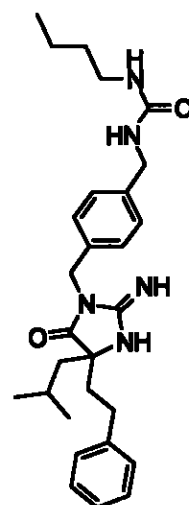
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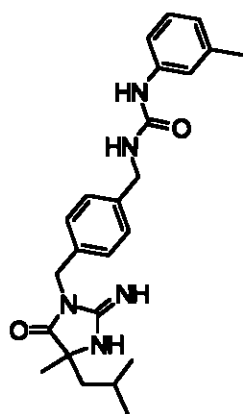
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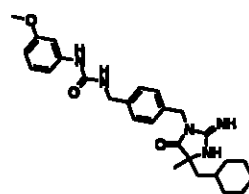
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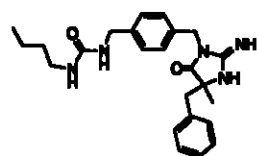
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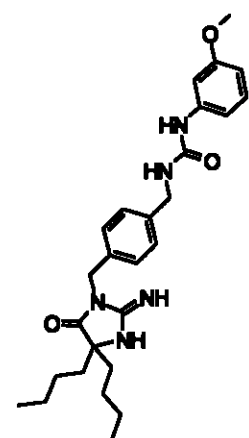
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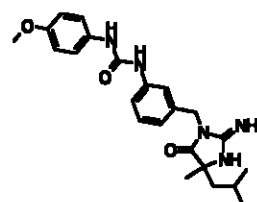
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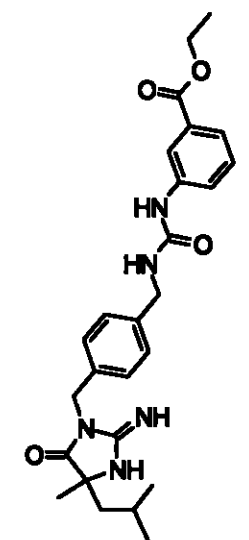
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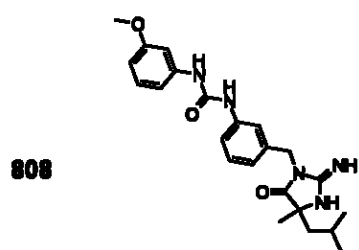
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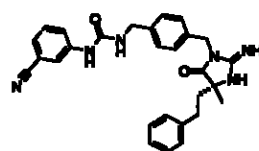
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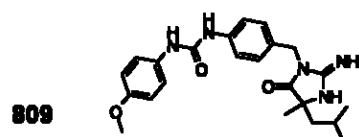
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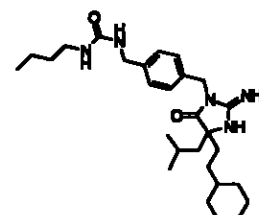
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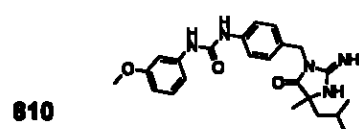
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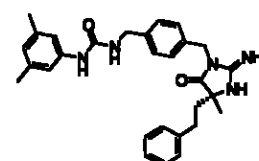
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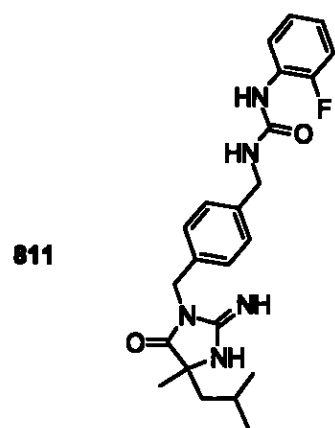
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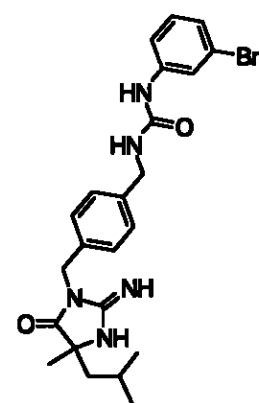
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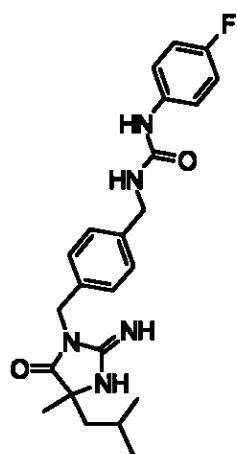
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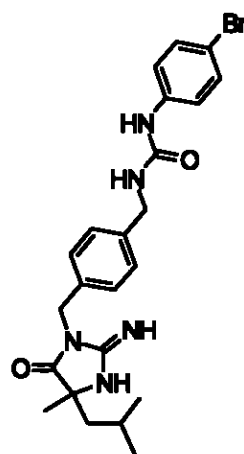
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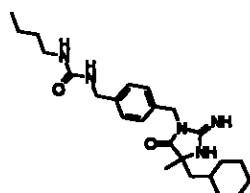


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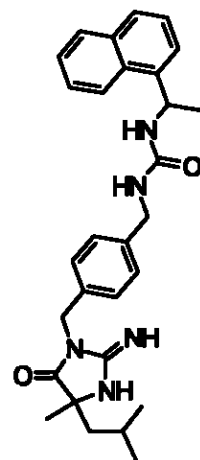


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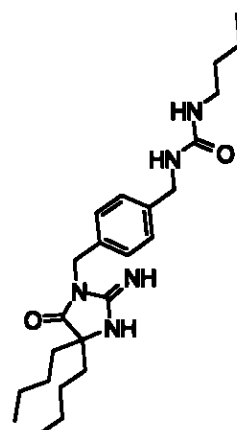


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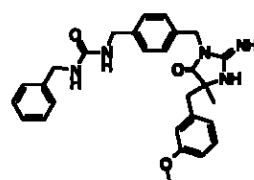


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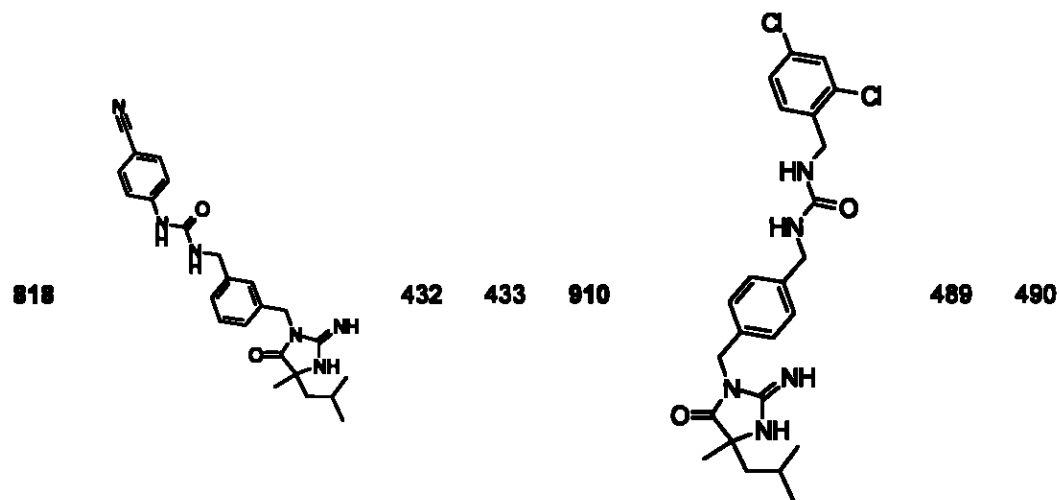
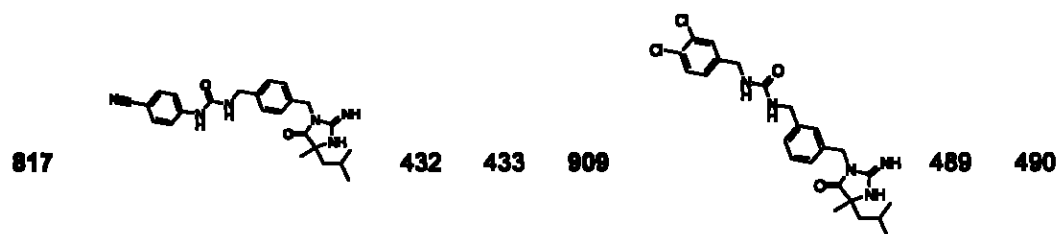
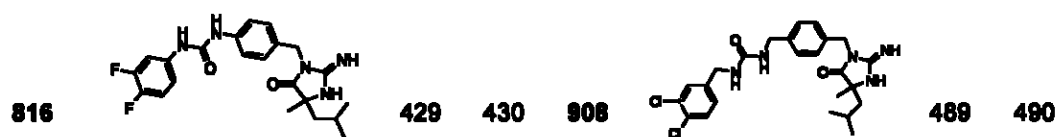
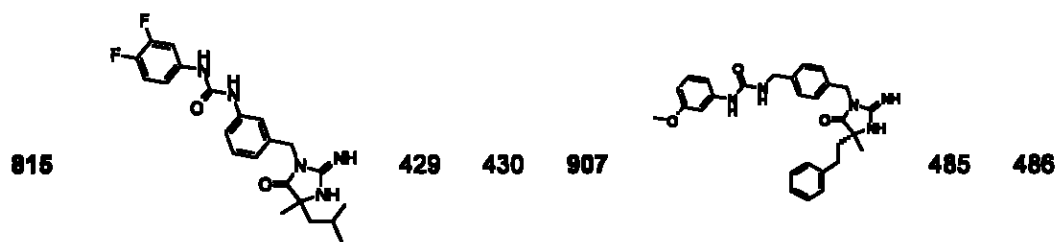


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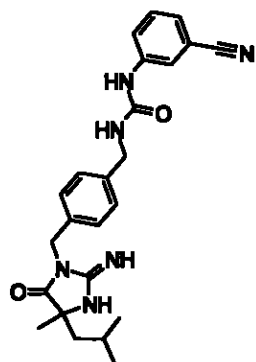


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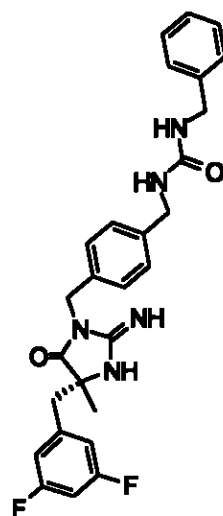
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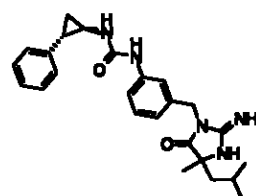
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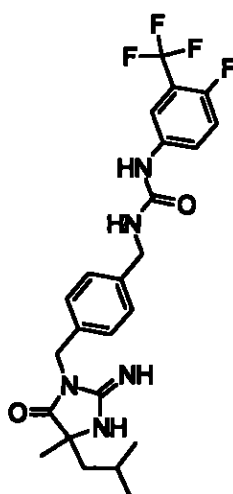
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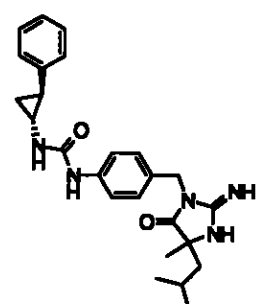
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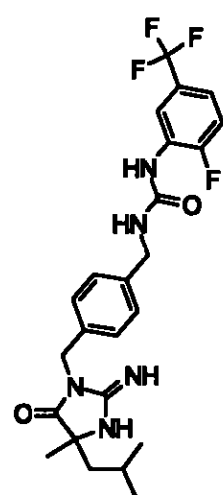
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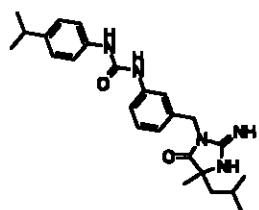


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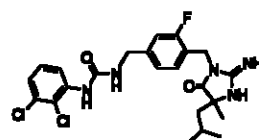
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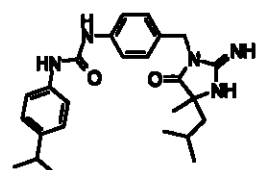
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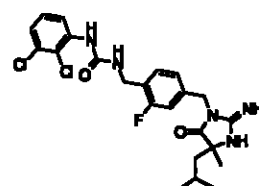
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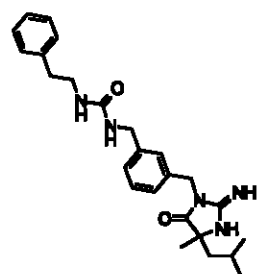
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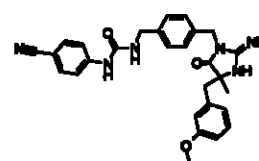
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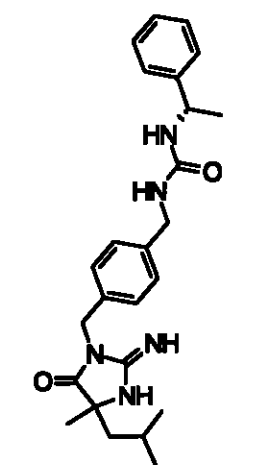
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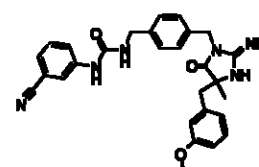
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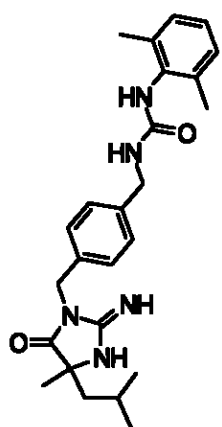


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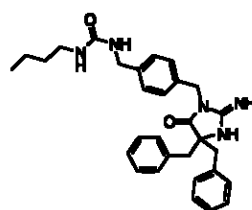
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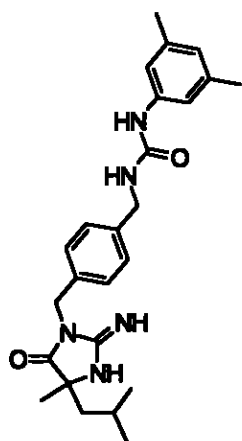
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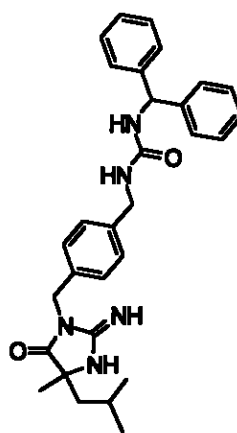
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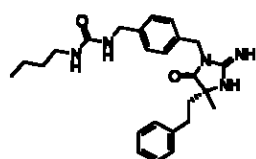
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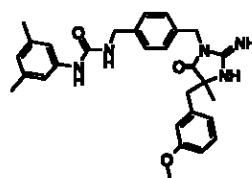
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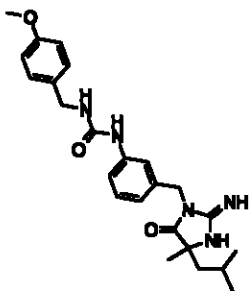


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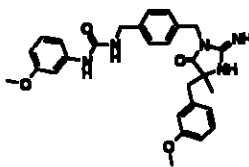
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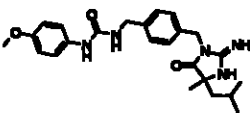
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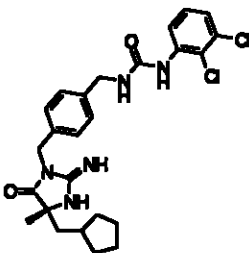
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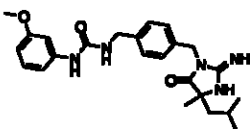
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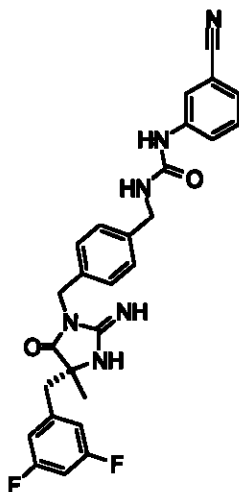
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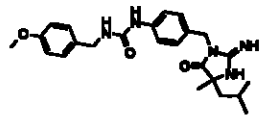


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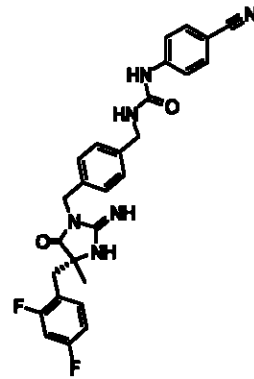
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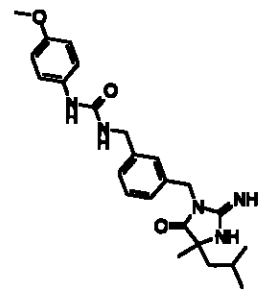
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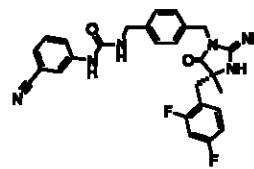
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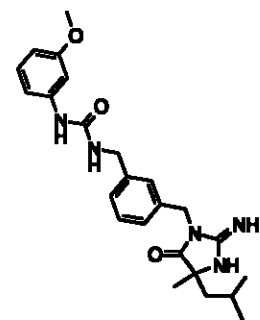
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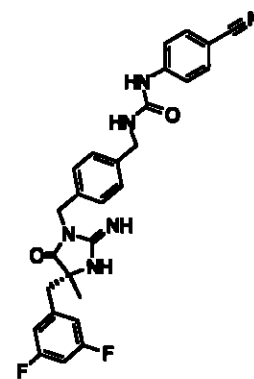
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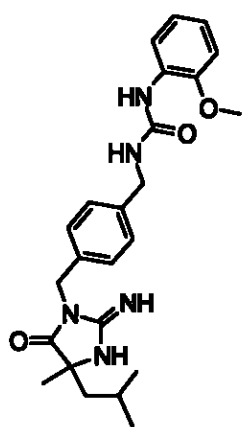


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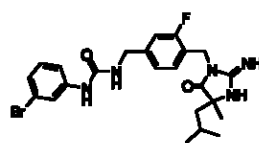
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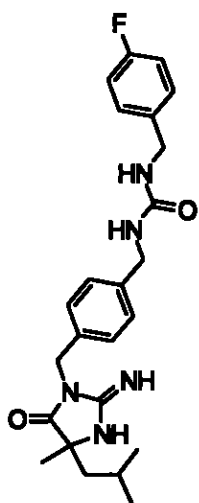
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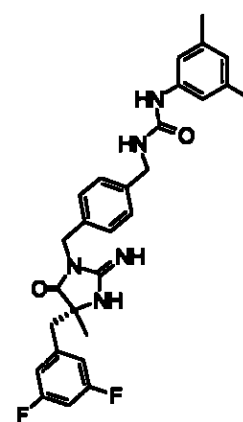
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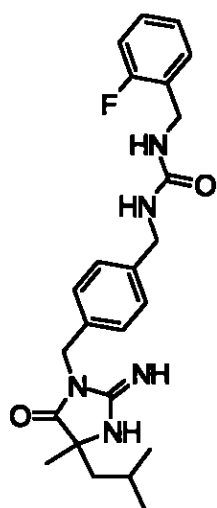
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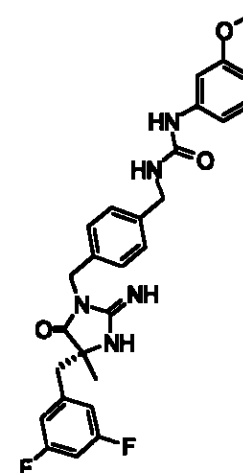
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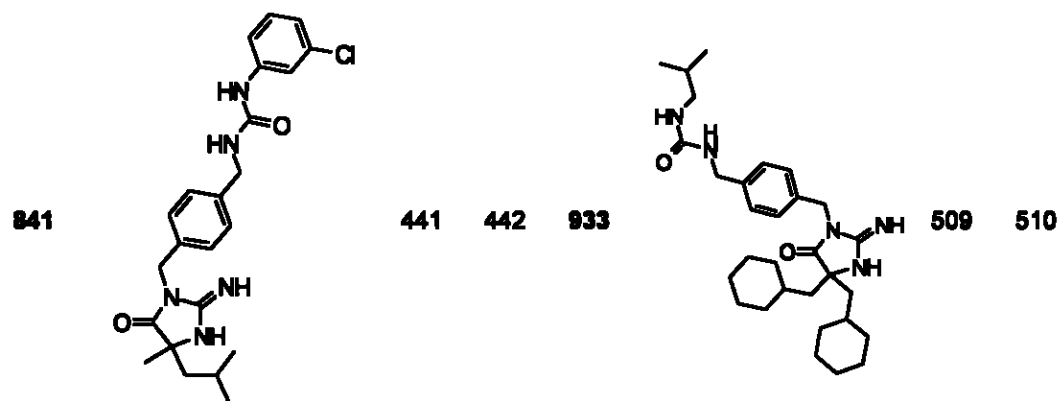
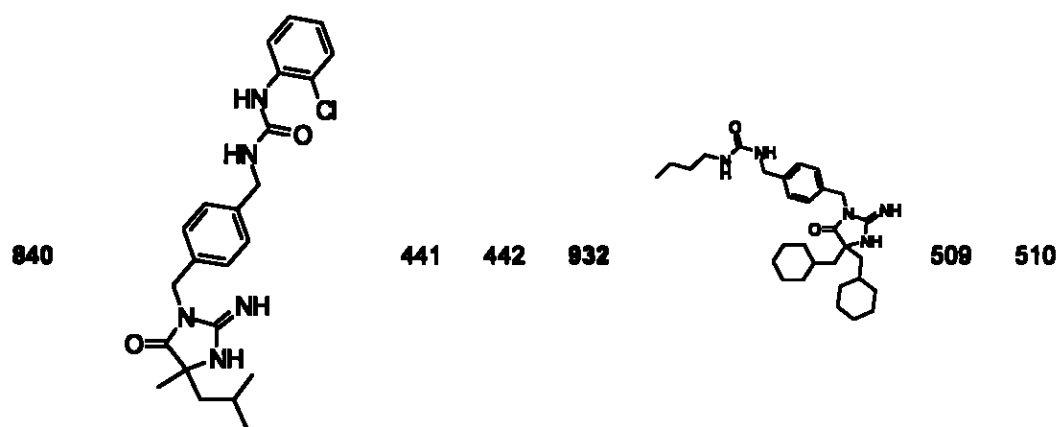
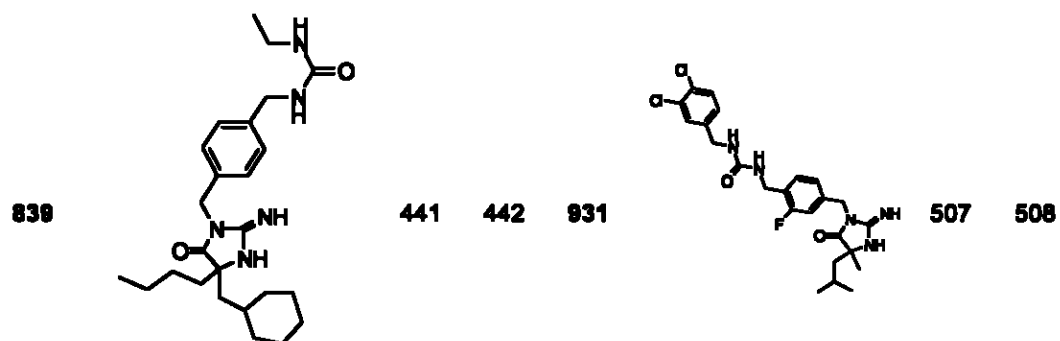
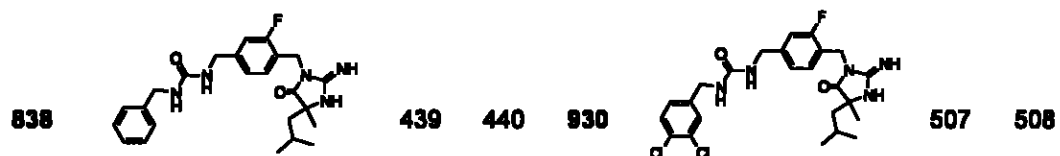
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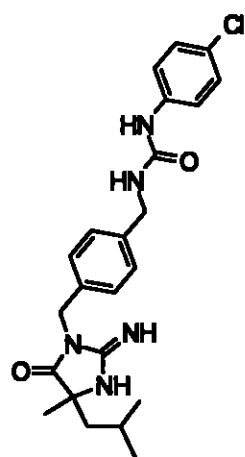
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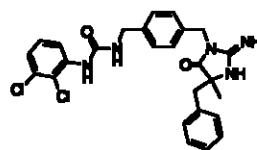
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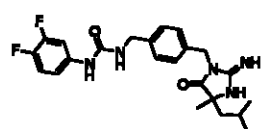
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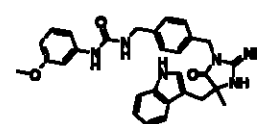
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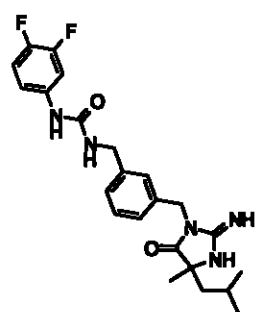
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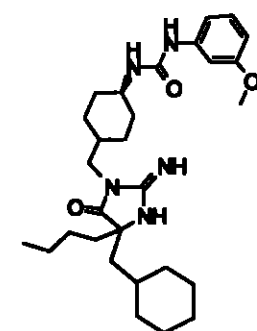
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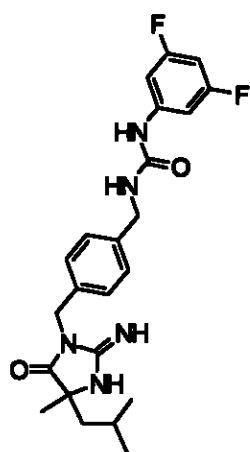


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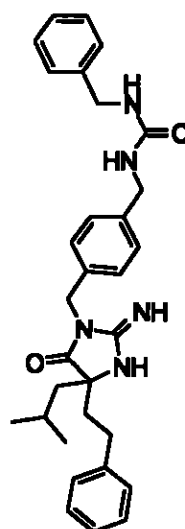
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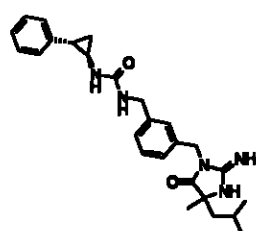
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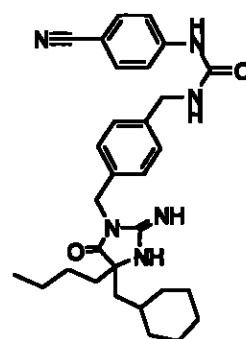
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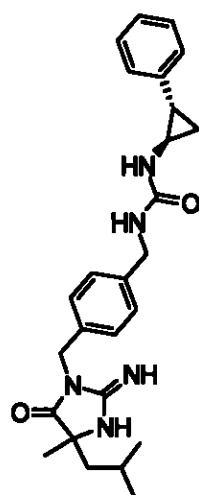
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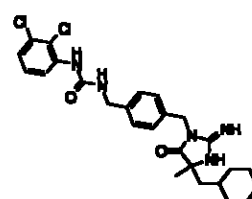
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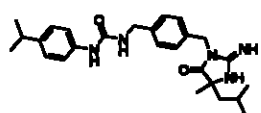


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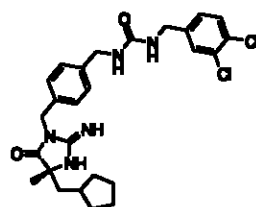
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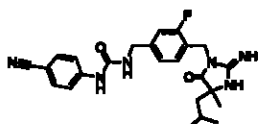
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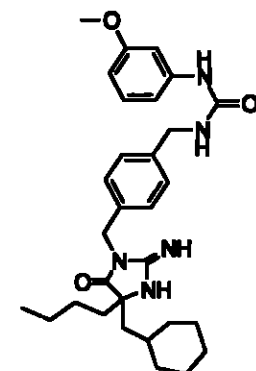
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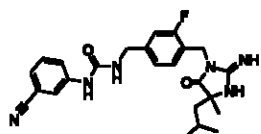
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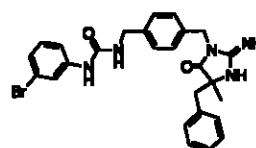
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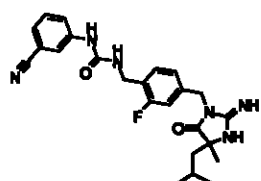
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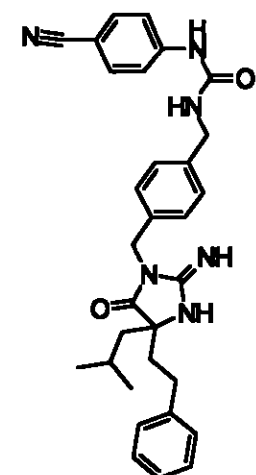
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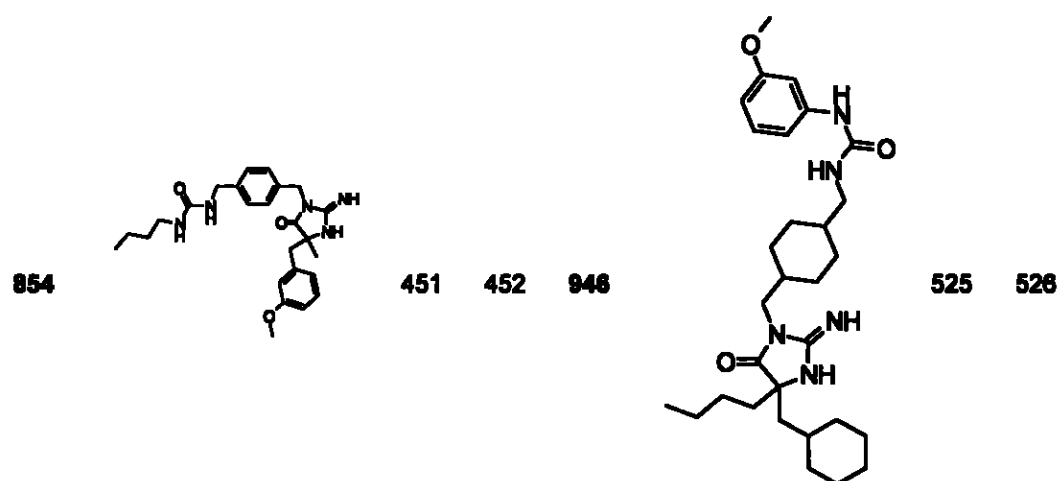
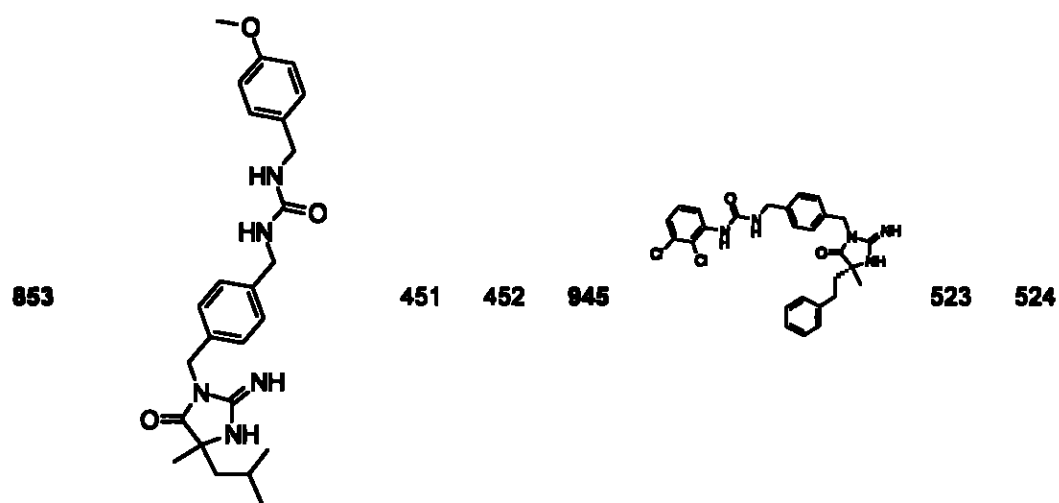
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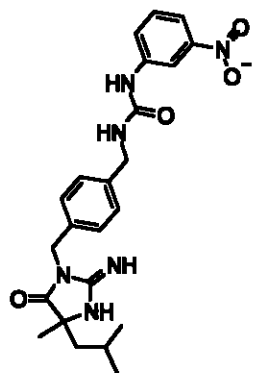
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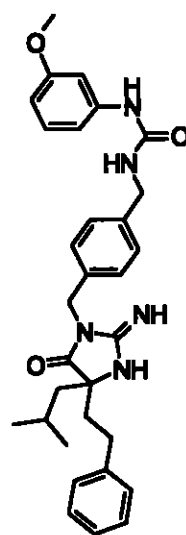
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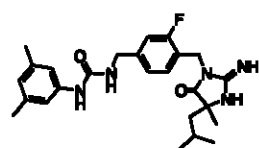
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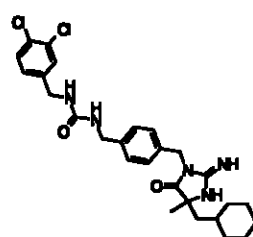
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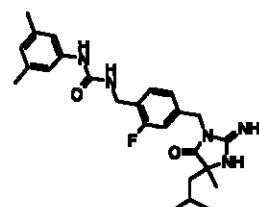
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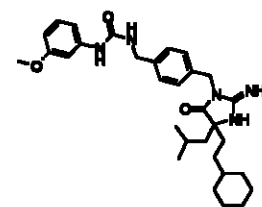
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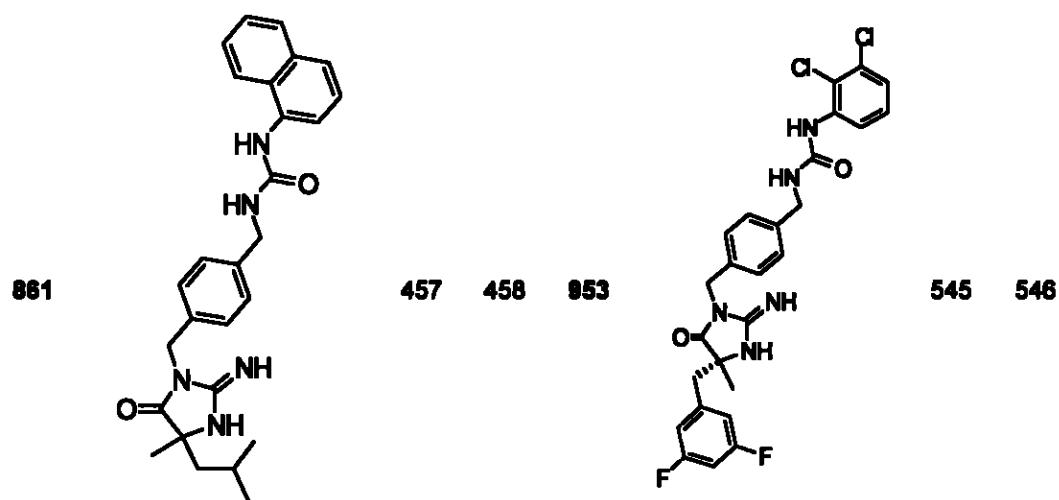
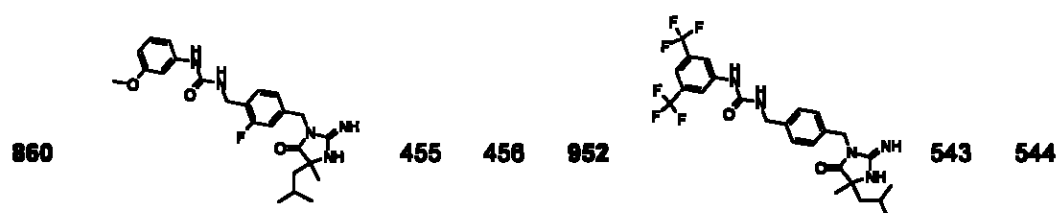
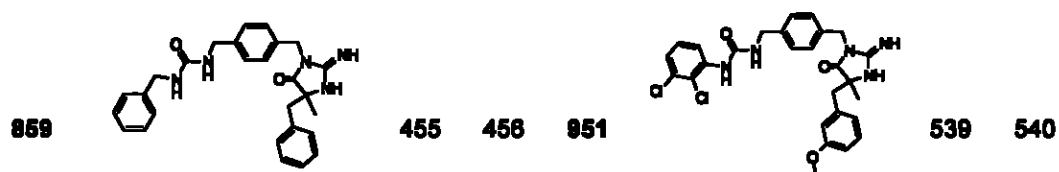
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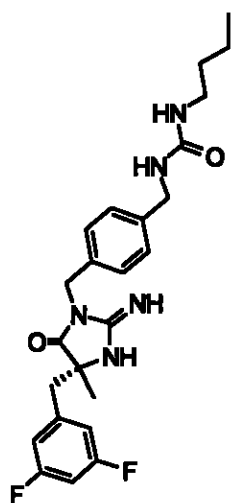
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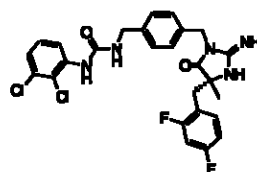
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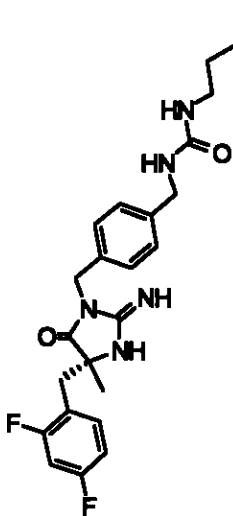
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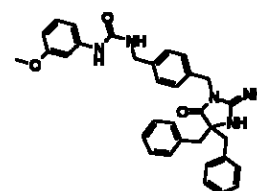
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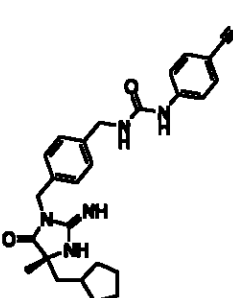
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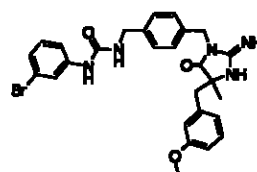
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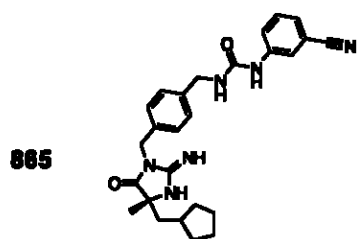
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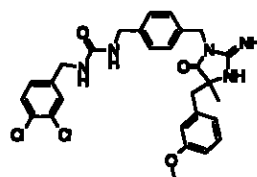
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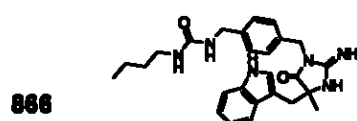
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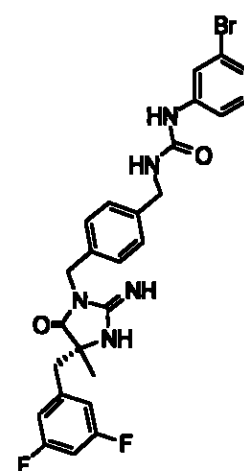
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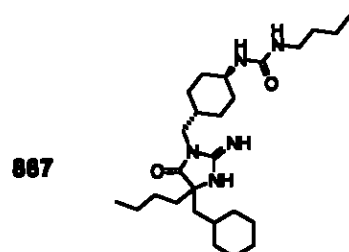
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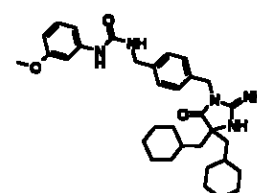
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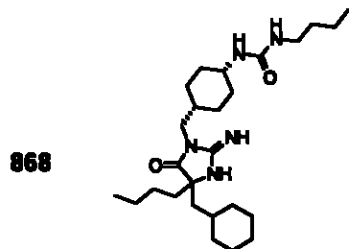


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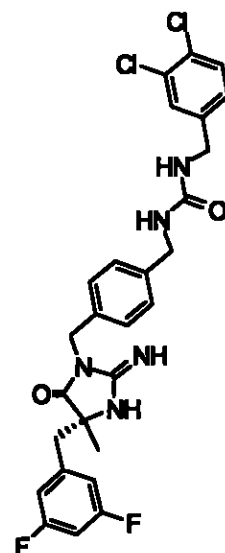


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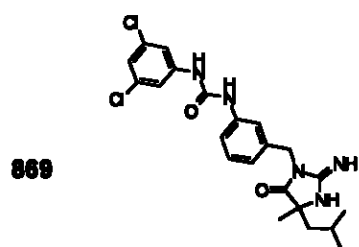
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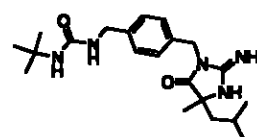
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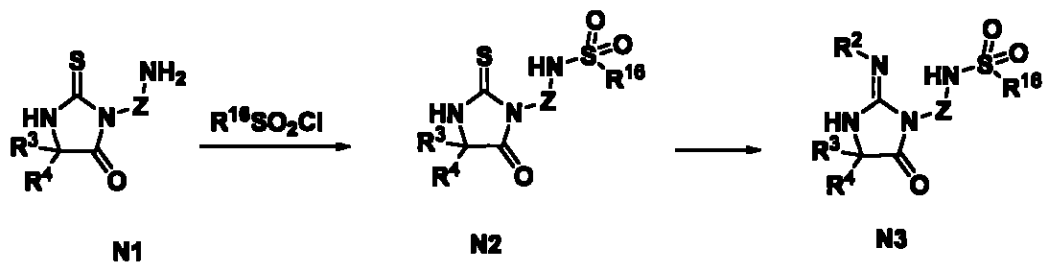


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Método N



(En el esquema, $-\text{Z}-\text{NH}-\text{S}(\text{O})_2\text{R}^{16}$ - es equivalente a R^1 sustituido con R^{21} , o R^1 sustituido con alquilo- R^{22} , donde R^{21} y R^{22} son $-\text{N}(\text{R}^{16})-\text{C}(\text{O})-\text{NHR}^{15}$ y R^{16} es H, y donde Z es alquileo-arileno, alquileo-arileno-alquileo, alquileo-heteroarileno, alquileo-heteroarileno-alquileo, alquileo-cicloalquileo, alquileo-cicloalquileo-alquileo, alquileo-heterocicloalquileo, alquileo-

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heterocicloalquileo-alquileo, arileno, heteroarileno, cicloalquileo o heterocicloalquileo opcionalmente sustituido).

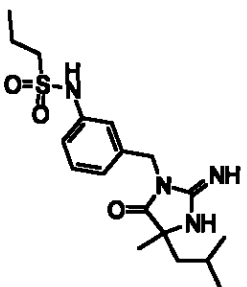
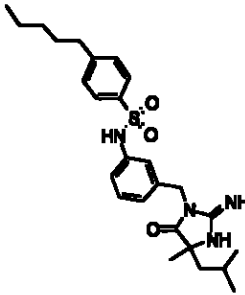
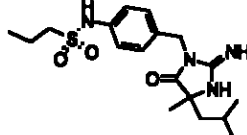
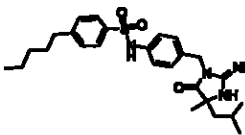
Método N, Etapa 1:

Se preparó el compuesto N2 ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para-(CH_2) C_6H_4 (CH_2)-, $R^{16} = CH_2CH(CH_3)_2$) a partir de N1 ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para-(CH_2) C_6H_4 (CH_2)-) siguiendo el procedimiento descrito en el Método K, Etapa 1.

Método N, Etapa 2:

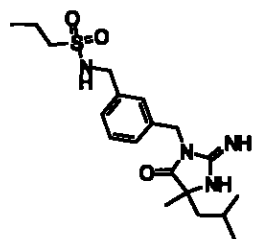
Se preparó el compuesto N3 ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para-(CH_2) C_6H_4 (CH_2)-, $R^{16} = CH_2CH(CH_3)_2$) a partir de N2 ($R^3 = CH_3$, $R^4 = CH_2CH(CH_3)_2$, Z = para-(CH_2) C_6H_4 (CH_2)-, $R^{16} = CH_2CH(CH_3)_2$) siguiendo el procedimiento descrito en el Método A, Etapa 3.

Se prepararon los compuestos siguientes usando métodos similares.

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963		380	381	968		484	485

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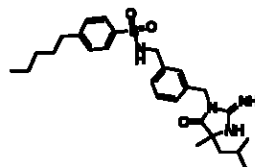
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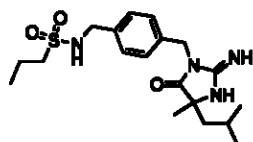
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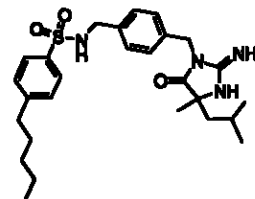
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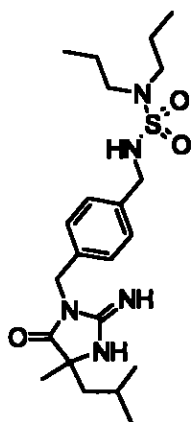
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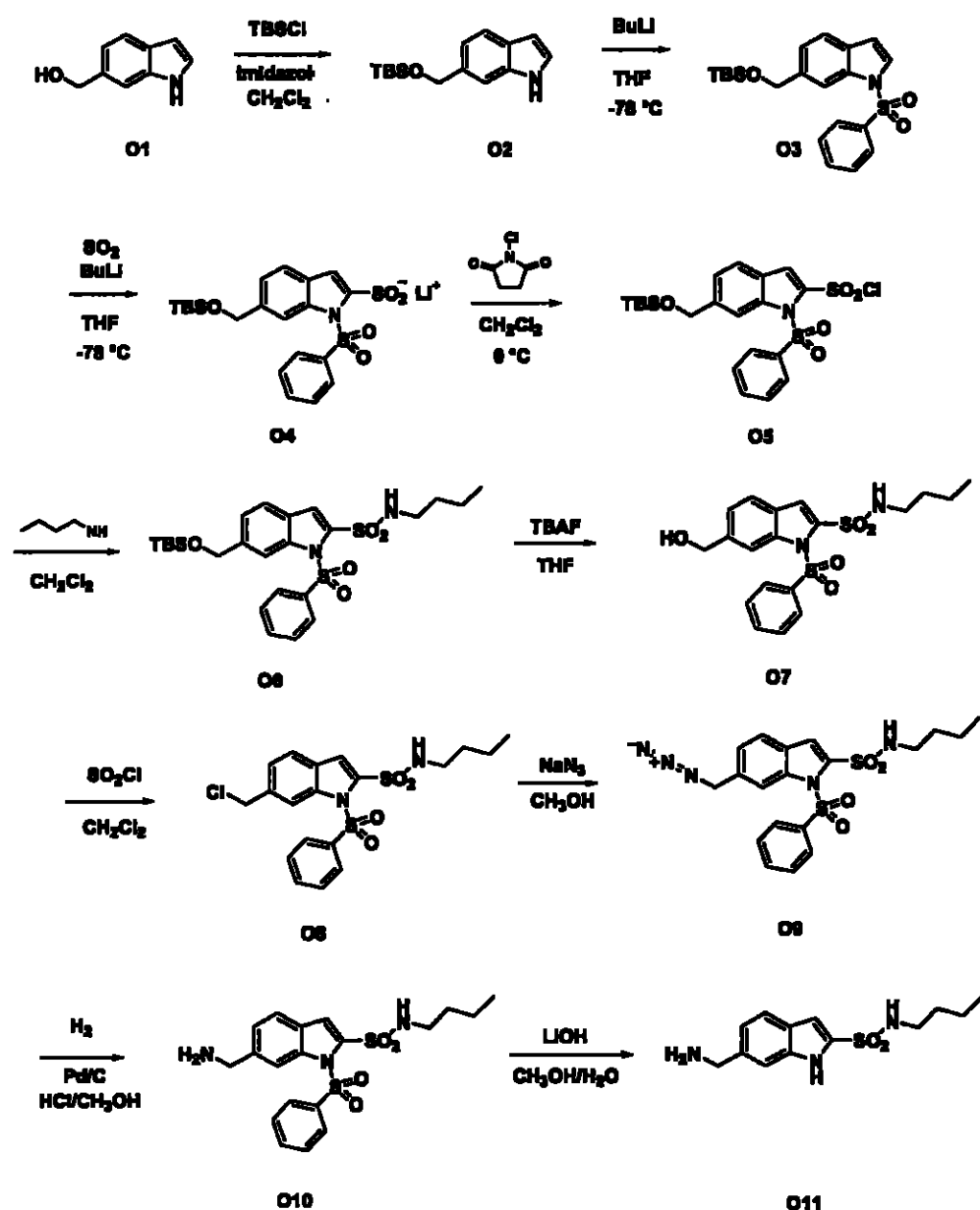


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Método



Método O, Etapa 1:

Una solución de indol-6-metanol (400 mg, 2,72 mmoles), cloruro de ter-butildimetilsililo (816 mg, 5,41 mmoles) y imidazol (740 mg, 10,9 mmoles) en CH_2Cl_2 se agitó a temperatura ambiente durante la noche antes de evaporarse el solvente y el residuo se cromatografió usando acetato de etilo/hexano para proporcionar el producto O2.

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Método O, Etapa 2:

A una solución de O2 (200 mg, 0,77 mmoles) en THF (10 mL) a -78 °C se le agregó butil litio (1,2 eq). La solución se agitó a -78°C durante 5 minutos y luego se calentó a temperatura ambiente. La mezcla de reacción se enfrió a -78°C y se agregó cloruro *p*-toluensulfonilo. La solución se calentó a temperatura ambiente y se agitó durante la noche. La reacción se apagó con una solución acuosa saturada de K₂CO₃, se extrajo con acetato de etilo y CH₂Cl₂. El material crudo se purificó por cromatografía evaporativa usando acetato de etilo/hexano para proporcionar 360 mg de O3.

Método O, Etapa 3:

Se agregó una solución de butil litio (1,2 eq) a una solución de O3 (340 mg, 0,829 mmoles) en THF (20 mL). La mezcla de reacción se agitó durante 15 minutos a -78°C y luego se hizo burbujear dióxido de azufre a través de la solución durante 15 minutos. Se agregó hexano (100 mL) a la mezcla de reacción. La mezcla de reacción se evaporó para proporcionar O4 que se usó para la etapa siguiente sin purificación adicional.

Método O, Etapa 4:

A una solución de O4 (0,829 mmol) en CH₂Cl₂ enfriada a 0°C se le agregó N-clorosuccinimida (220 mg, 1,66 mmoles). Después de 2 horas de agitación, la solución se filtró a través de un tapón de Celite. El filtrado se concentró para proporcionar O5.

Método O, Etapa 5:

A una solución de O5 en piridina anhidra (3 mL) se le agregó butil amina (100 µL). La reacción se agitó a temperatura ambiente durante 4 días. La mezcla de reacción se dividió entre HCl 1 N y CH₂Cl₂. La capa orgánica se separó y lavó con HCl 1 N (3x). La solución orgánica se secó sobre Na₂SO₄, se filtró y concentró. El material crudo se purificó a través de cromatografía evaporativa usando acetato de etilo/hexano para proporcionar O6.

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Método O, Etapa 6:

A Una solución de O6 (70 mg) en THF se le agregó TBAF. La reacción se agitó a temperatura ambiente antes de cromatografiar la mezcla de reacción usando acetato de etilo/hexano para proporcionar 50 mg de O7 (95%).

Método O, Etapa 7:

A una solución de O7 (50 mg) en CH₂Cl₂ (5 mL) se le agregó cloruro de tionilo (1 mL) la reacción se agitó durante 5 minutos y luego se evaporó para proporcionar O8.

Método O, Etapa 8:

A una solución de O8 en CH₃OH (5 mL) se le agregó azido de sodio (50 mg). La solución se agitó a temperatura ambiente durante la noche y se evaporó en solvente. El residuo se cromatografió usando acetato de etilo/hexano para proporcionar O9 después de la purificación.

Método O, Etapa 9:

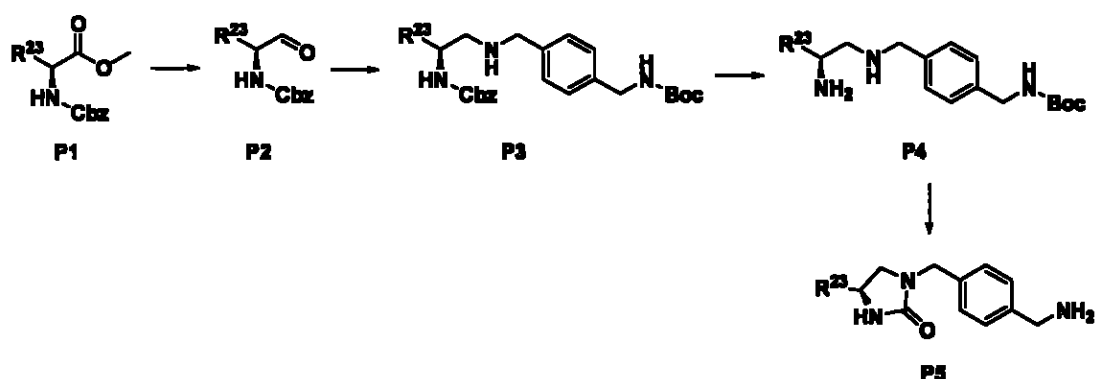
A una suspensión de O9 (70 mg) en CH₃OH se le agregó 1 eq de HCl (acuoso) y paladio sobre carbón. La mezcla de reacción se hidrogenó bajo 1 atmósfera durante 20 minutos para proporcionar 90 mg del producto O10 crudo.

Método O, Etapa 10:

Una solución de hidróxido de litio (30 mg) en H₂O se agregó a una solución de O10 (40 mg) en CH₃OH (3 mL). La reacción se agitó a temperatura ambiente durante 2 horas y se agregó una porción adicional de LiOH (40 mg) y la solución se agitó durante 2 más. El solvente se evaporó y el residuo se cromatografió usando acetato de etilo/hexano para proporcionar O11.

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Método P



Método P, Etapa 1:

Una solución de 300 mL de THF de 100 g de P1 ($R^{23}=n\text{-Pr}$) se agregó a una suspensión de 38 g de LAH en 2 L de THF anhidro a 0°C . La mezcla de reacción se agitó a temperatura ambiente durante 1 hora antes de agregar 30 ml de H_2O , 90 ml de NaOH al 15% a 0°C . La mezcla se agitó a temperatura ambiente durante una hora antes de agregar Na_2SO_4 (anh), la mezcla se filtró, y la solución se evaporó para proporcionar un producto que se secó bajo vacío durante la noche. Este producto se disolvió en 600 ml de DCM y la solución se agregó a una solución de cloruro de oxalilo (37.3 ml) y DMSO (60,8 ml) en 1.4 L de DCM a -78°C durante 40 minutos antes de agregar diisopropiletilamina (299 ml) a -78°C . La reacción se dejó llevar a -10°C . La reacción se apagó con 1 L de H_2O a -10°C y la mezcla se extrajo con DCM. Después de remoción del solvente se obtuvo P2 ($R^{23}=\text{Pr}$, 106 g). El material crudo se usó para la etapa siguiente sin purificación.

Método P, Etapa 2:

A una solución de 1,5 L DCM de P2 ($R^{23}=\text{Pr}$, 106 g) se la agregó p-Boc-aminometilbencilamina (1,1 eq) y triacetoxiborohidruro de sodio (1,1 eq) y la reacción se agitó a temperatura ambiente durante la noche. La reacción se apagó con H_2O y el contenido se extrajo con DCM. Después remoción de los solventes, el residuo se cromatografió usando una columna de gel de sílice eluida con 3% de MeOH en DCM para dar 42,5 g de P3 ($R^{23}=\text{Pr}$).

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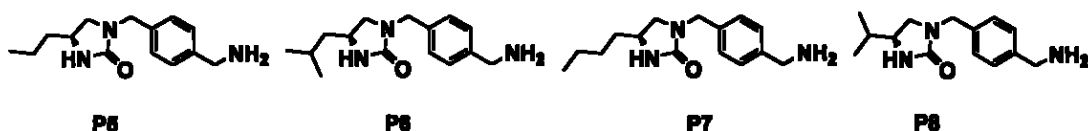
Método P, Etapa 3:

Una solución de 10 ml de MeOH de P3 ($R^{23}=Pr$, 110 mg) se hidrogenó usando Pd/C (5%, 11 mg) a 1 atm de hidrógeno para proporcionar el producto P4 ($R^{23}=Pr$) después de remoción del solvente y el catalizador.

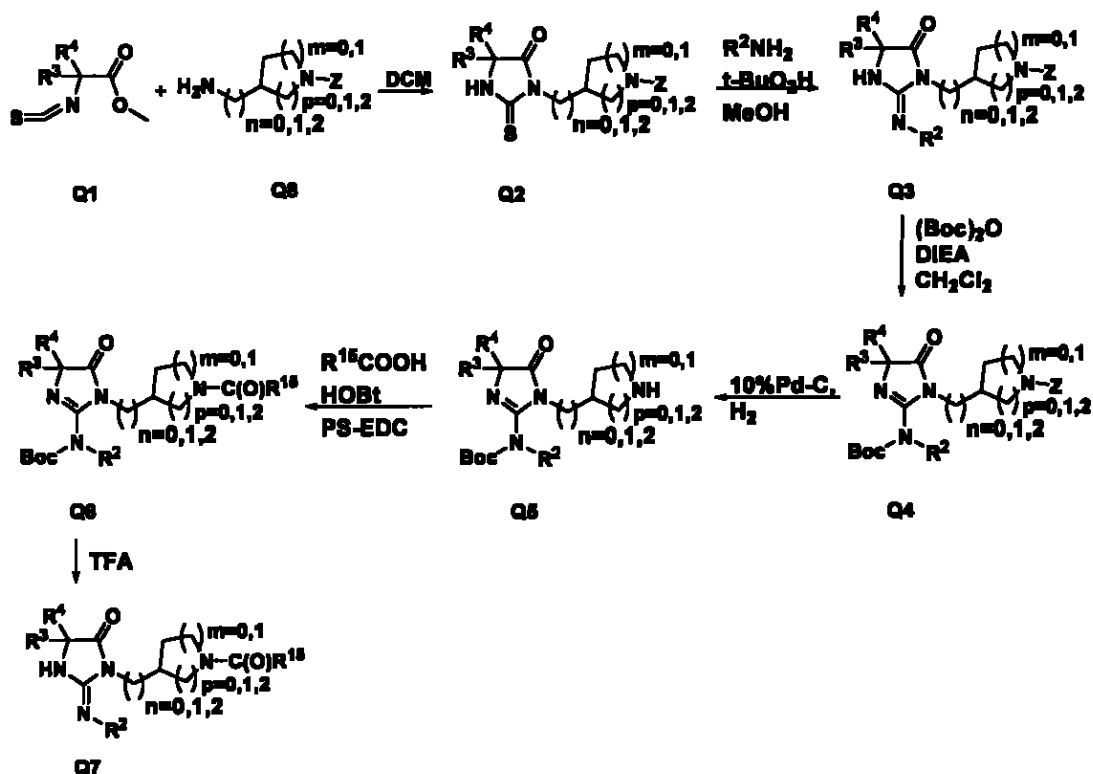
Método P, Etapa 4:

A una solución de 10 ml de DCM de P4 a 0°C ($R_{23}=Pr$) se le agregó trifosgeno (1,2 eq) y trietilamina (2,4 eq) y la solución se agitó a 0°C durante 2 horas antes de extraer la reacción con DCM/H₂O. Después de remoción del solvente, el residuo se cromatografió usando una columna de gel de sílice eluida con EtOAc/Hexano para proporcionar un sólido blanco que se trató con HCl 2N en dioxano durante 2 horas. Después de remoción del solvente, se obtuvo el compuesto P5 ($R^{23}=Pr$) en forma de un sólido blanco (80 mg).

Se sintetizaron los compuestos siguientes usando métodos similares.



Método Q



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Método Q, Etapa 1

Se agitaron durante 42 horas, a temperatura ambiente, **Q1** ($R^3=Me$; $R^4=iBu$) (1.00 g) y **Q8** ($n=1$, $p=2$, $m=1$) (1.24 g) en diclorometano (30 mL). Esta mezcla se concentró al vacío para proporcionar un aceite de color ámbar el cual se purificó sobre una columna de gel de sílice (200 mL) eluida con acetato de etilo/hexano para proporcionar **Q2** ($n=1$, $p=2$, $m=1$, $R^3=Me$; $R^4=iBu$), en forma de un aceite incoloro (1,59 g).

Método Q, Etapa 2

Se preparó el compuesto **Q3** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) a partir de **Q2** ($n=1$, $p=2$, $m=1$, $R^3=Me$; $R^4=iBu$) usando un método similar al método A Etapa 3.

Método Q, Etapa 3

Se trató el compuesto **Q3** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) (1.37 g) en diclorometano anhidro (25 mL) con dicarbonato de di-*ter*-butilo (0,68 g, 1,1 equiv.) y diisopropiletilamina (0,66 mL, 1,1 equiv.). La solución resultante se agitó a temperatura ambiente durante 20 horas antes de diluirla con diclorometano y se lavó con ácido clorhídrico 1N. La solución de diclorometano seca se concentró al vacío para proporcionar una película incolora (1,32 g) la cual se purificó sobre una columna de gel de sílice (125 mL) y se eluyó con hexano:acetato de etilo para proporcionar un compuesto **Q4** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=i-Bu$) en forma de una espuma blanca (0,74 g).

Método Q, Etapa 4

Se hidrogenó el compuesto **Q4** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) (0,540 g) en EtOH absoluto (20 mL) con 10% Pd/C (0,400 g) a 1 atmósfera durante 2 horas. La mezcla de reacción se filtró y el filtrado se concentró al vacío para proporcionar **Q5** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) en forma de un aceite incoloro (0,35 g).

Método Q, Etapa 5

El compuesto **Q5** ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) (0,012 g) y HOBt (0,005 g) disuelto en acetonitrilo (0,8 mL) y tetrahidrofurano (0,25 mL) se

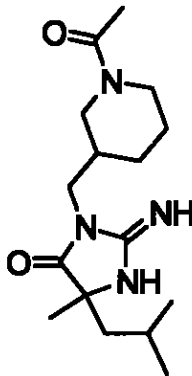
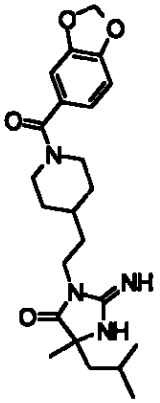
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trató con resina EDC (0,080 g, 3 eq., 1,53 mmoles/g) en un receptáculo de una placa microtituladora mediante adición de una solución de dicloroetano 1M, R¹⁵-COOH (40uL, 1,25 eq.). Después de tapar el receptáculo y agitarlo durante 18 horas, la mezcla se filtró y la resina se lavó con acetonitrilo (0,5 mL). La solución combinada se trató con resina de Trisamina (0,050 g, 6 eq., 4,23 mmoles/g) y resina de Isocianato (0,067 g, 3 eq., 1,53 mmoles/g) durante 18 horas antes de filtrar la solución y el solvente se extrajo al vacio para proporcionar Q6 (n=1, p=2, m=1, R²=H, R³=Me; R⁴=ⁱBu, R¹⁵=Me).

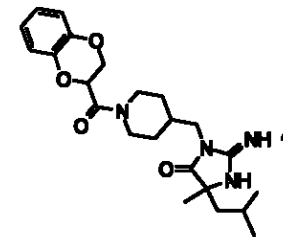
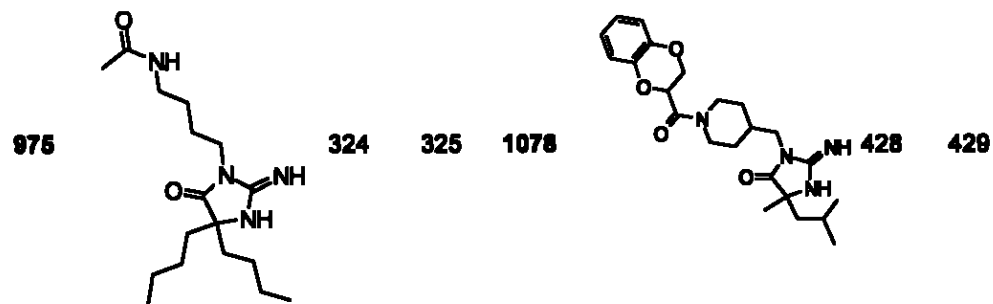
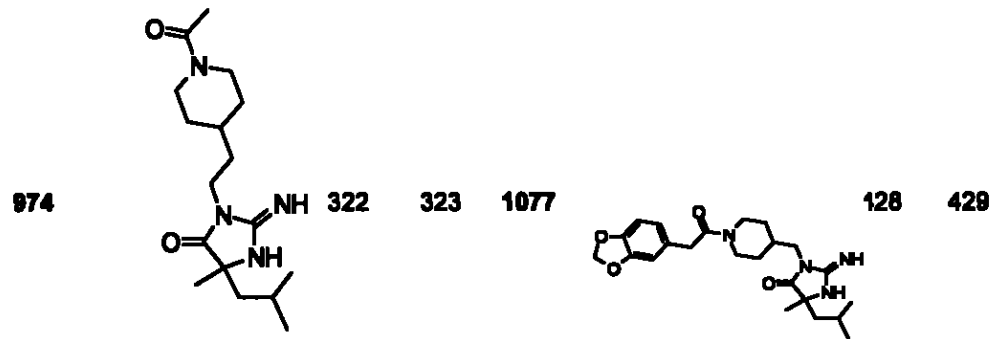
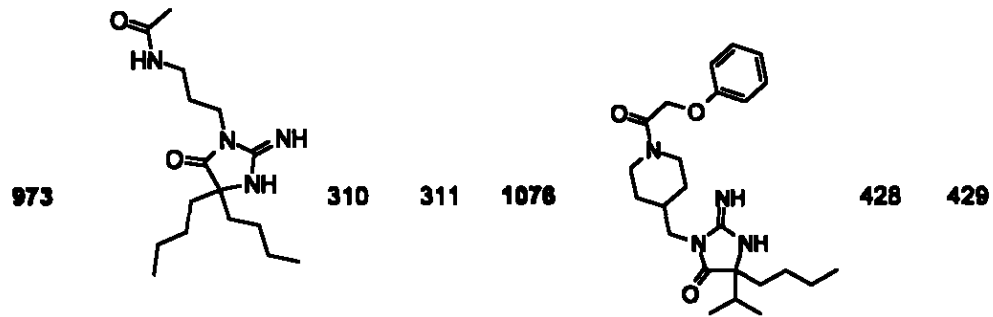
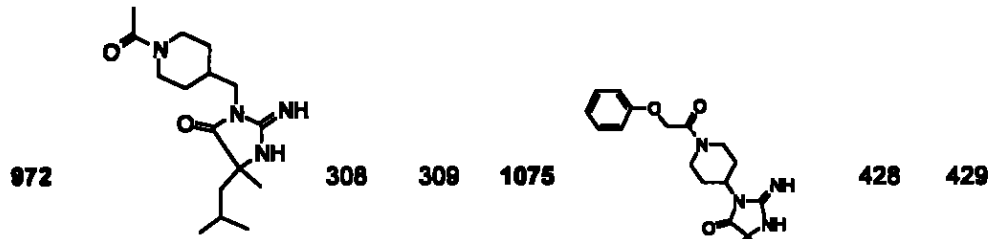
Método Q, Etapa 6.

Se mezcló una solución de diclorometano (1.0 mL) de Q6 (n=1, p=2, m=1, R²=H, R³=Me; R⁴=ⁱBu, R¹⁵=Me) con ácido trifluoracético (1,0 mL) y la solución se agitó durante 2 horas antes de concentrarla. Se agregó éter dietílico (0,5 mL) y luego se concentró al vacío para proporcionar un residuo el cual se purificó sobre una unidad de LCMS para proporcionar Q7 (n=1, p=2, m=1, R²=H, R³=Me; R⁴=ⁱBu, R¹⁵=Me). RMN (CDCl₃): δ 8,38, br, 2H; δ 4,56, m, 1H; δ 3,79, m, 1H; δ 3,57, m, 2H; δ 2,99, m, 1H; δ 2,48, m, 1H; δ 2,04, s, 3H; δ 1,95, m, 1H; δ 1,5-1,8, m, 5H; δ 1,5, s, 3H; 1,25, m, 2H; δ 0,95, m, 3H; δ 0,85, m, 3H. ES_LCMS (m/e) 309.17.

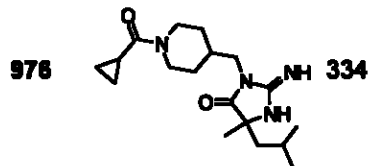
Se prepararon los siguientes compuestos usando métodos similares.

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971		308	309	1074		428	429

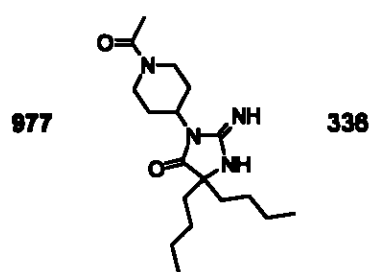
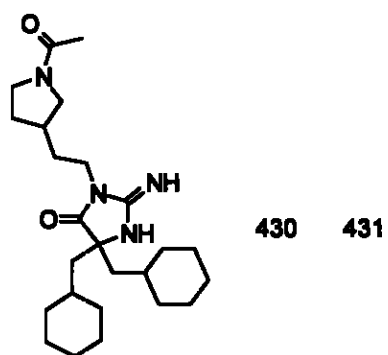
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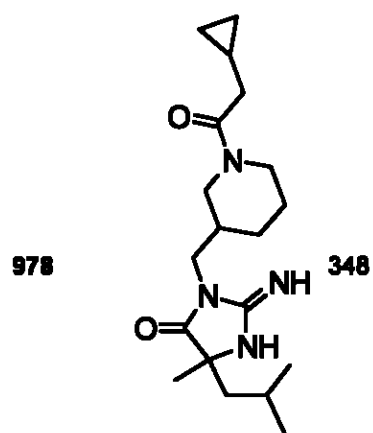
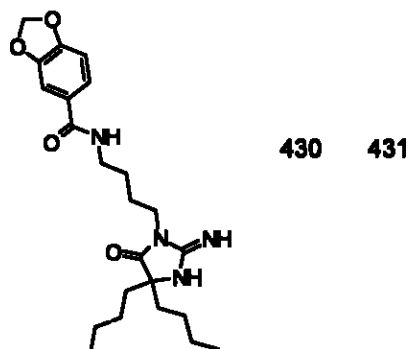
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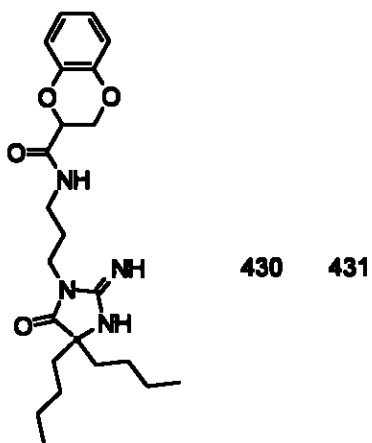
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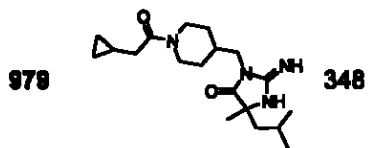
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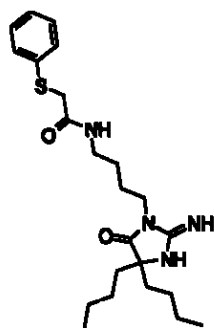
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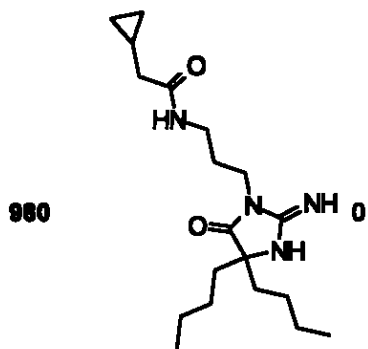
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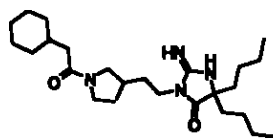


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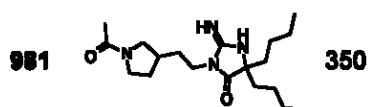
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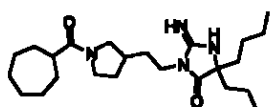


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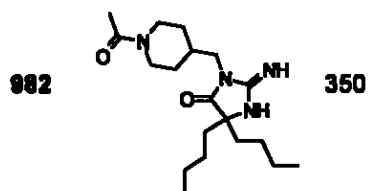
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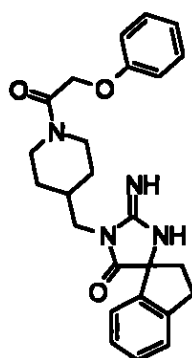
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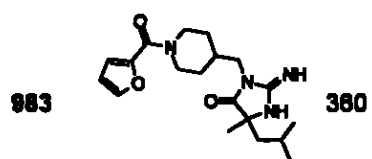


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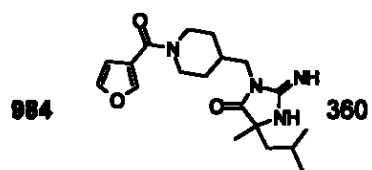
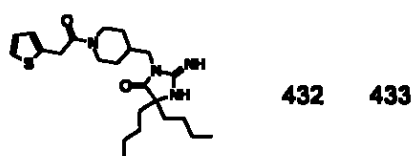
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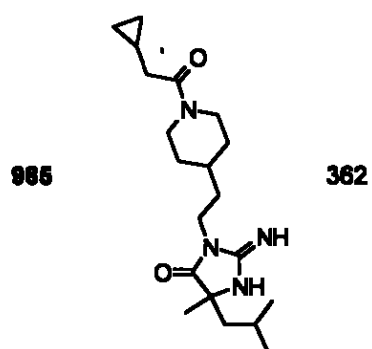
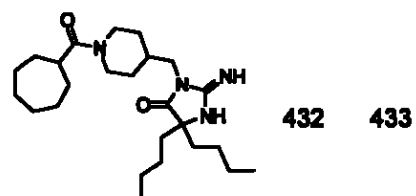
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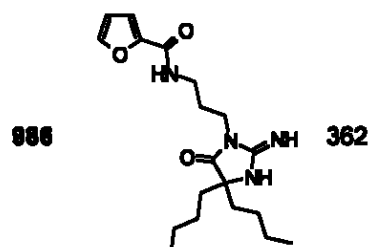
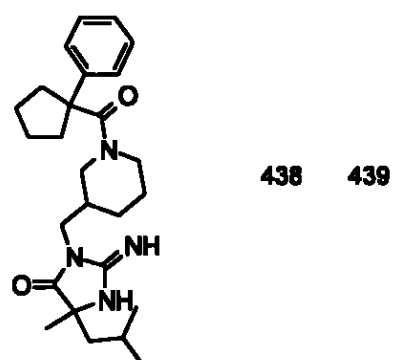
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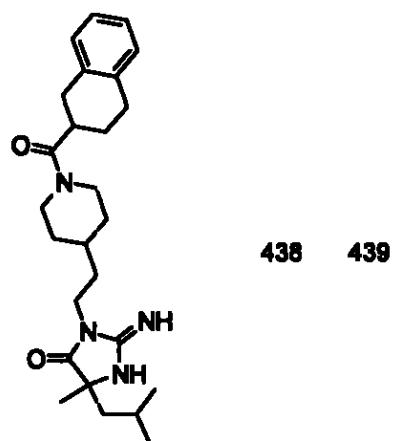
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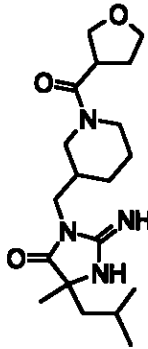


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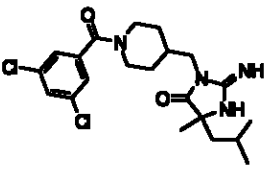
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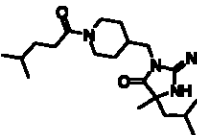
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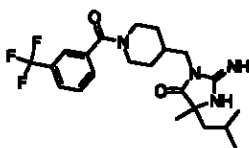
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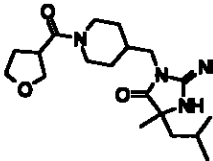
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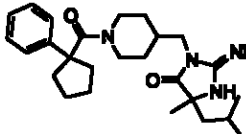
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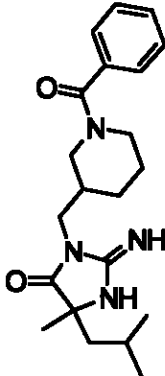
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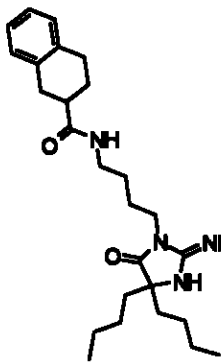
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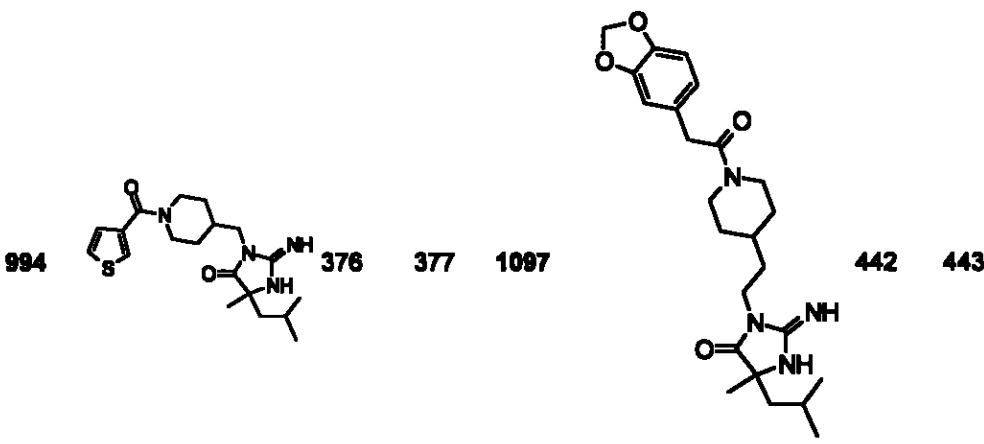
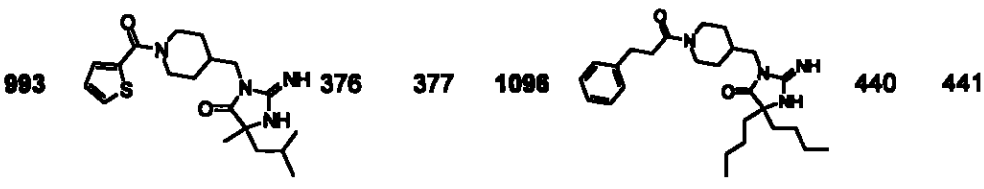
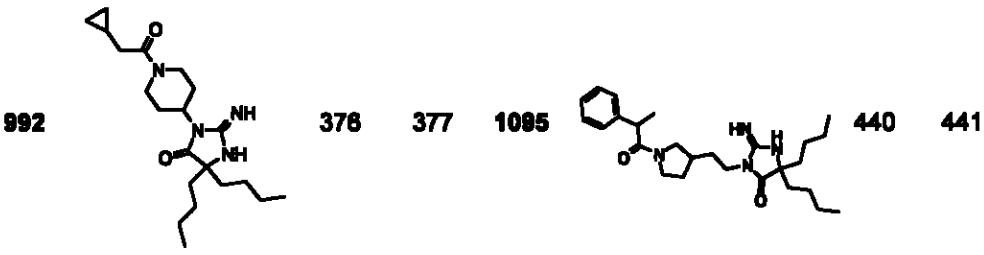
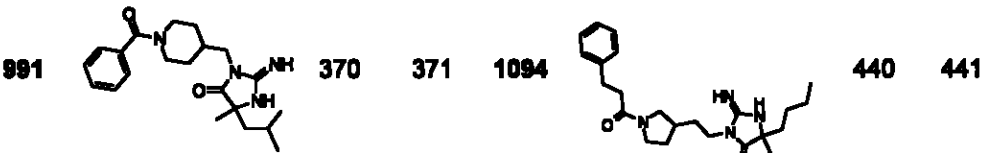
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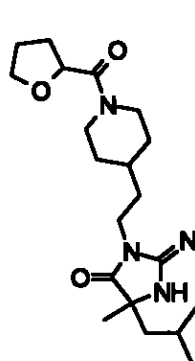
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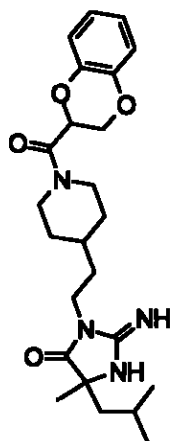
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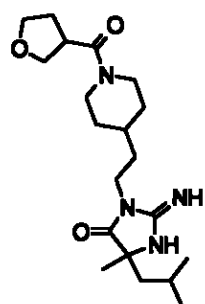
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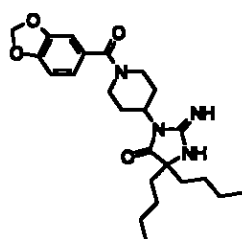
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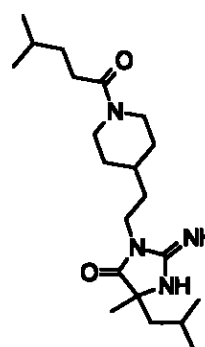
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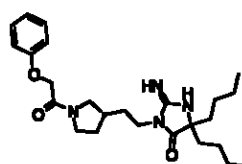
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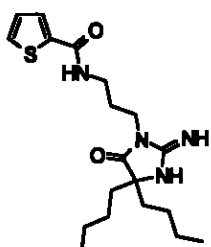
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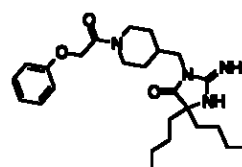
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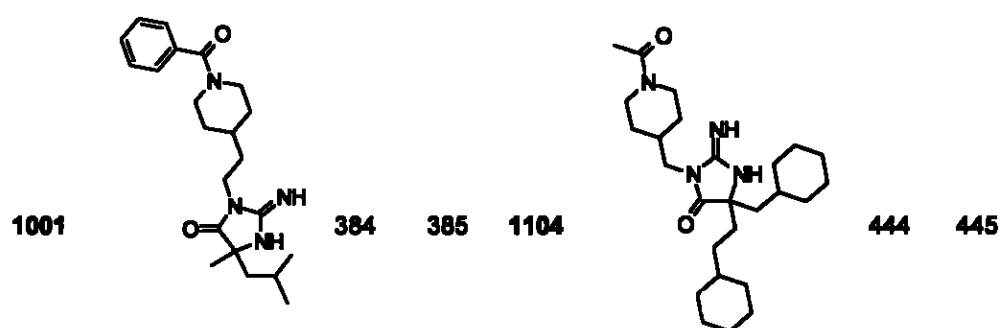
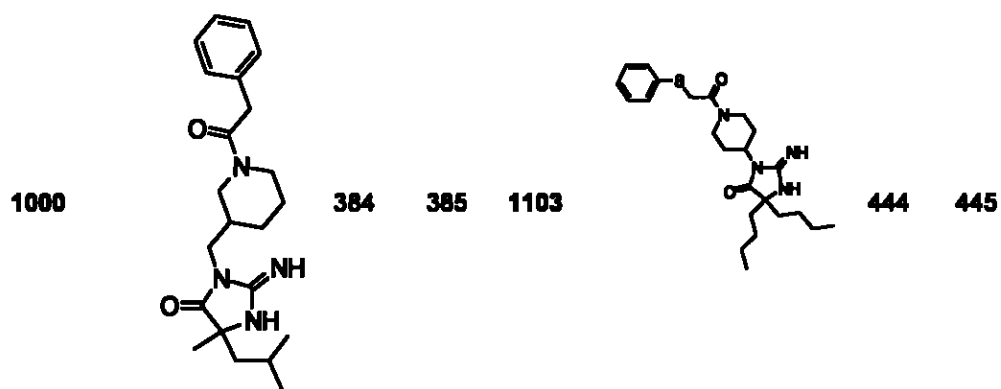
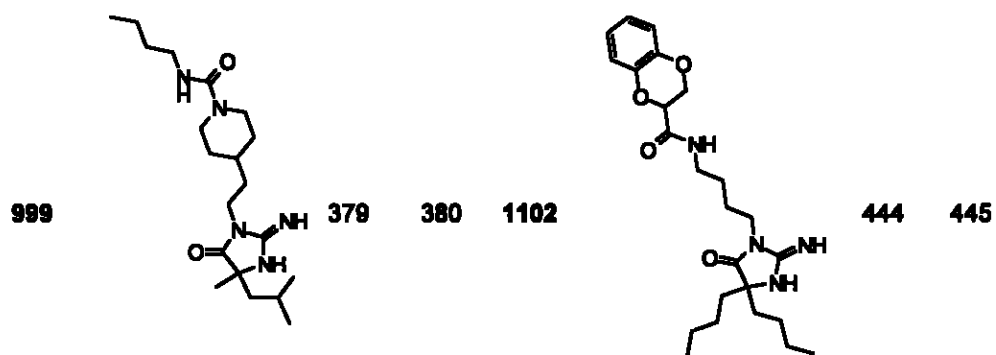
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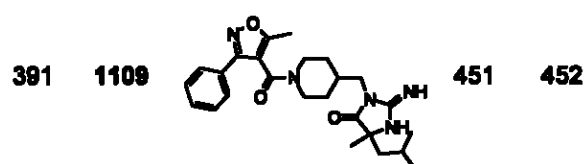
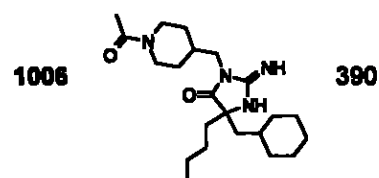
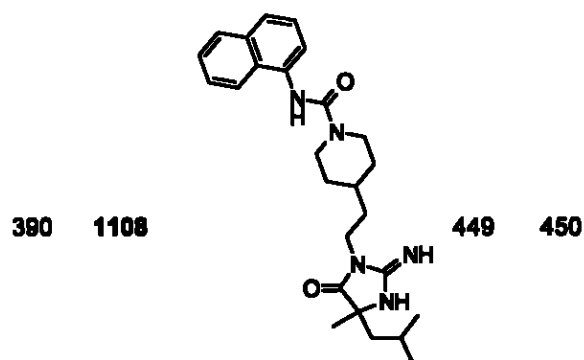
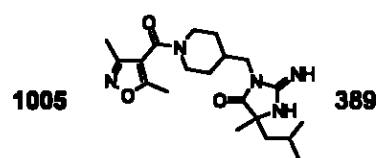
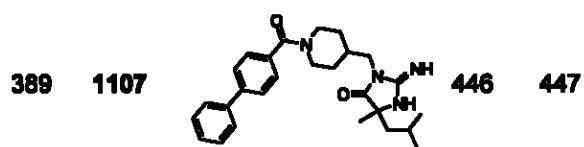
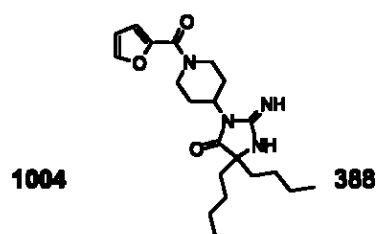
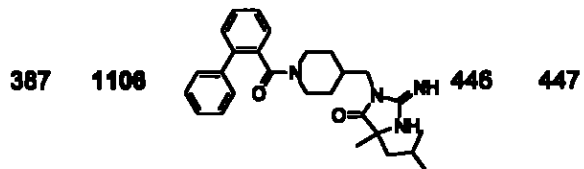
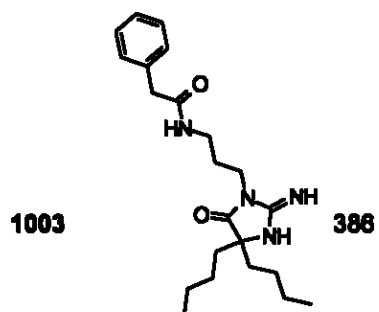
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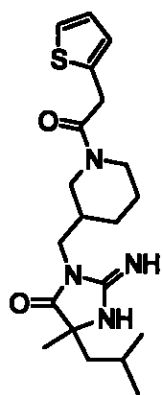
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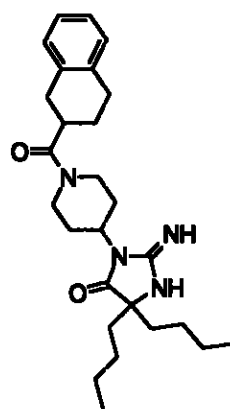
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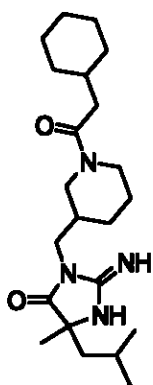
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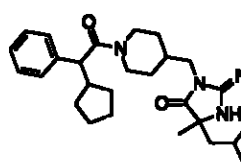
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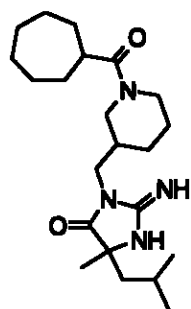
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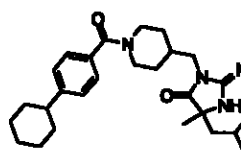
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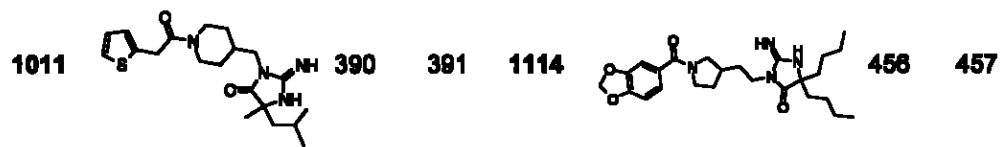
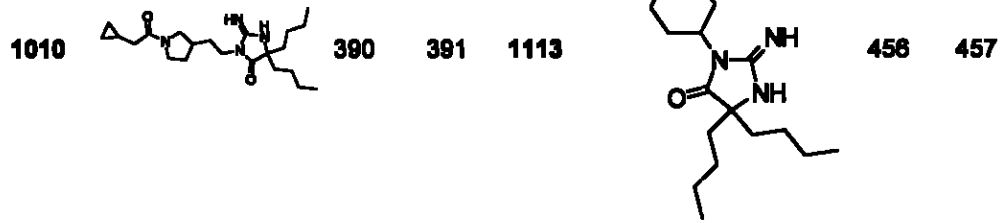
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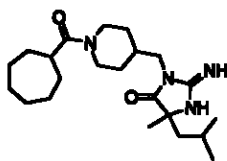
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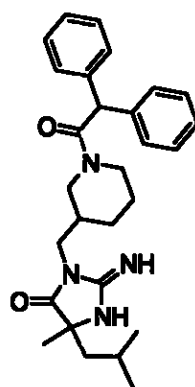
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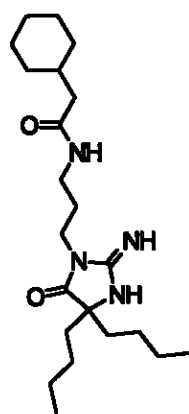
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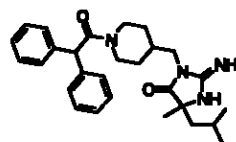
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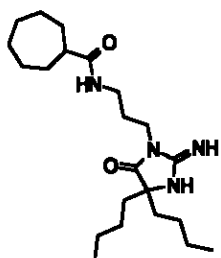
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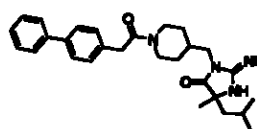
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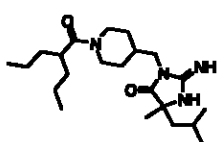
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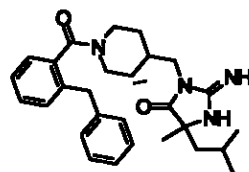
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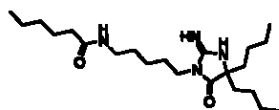
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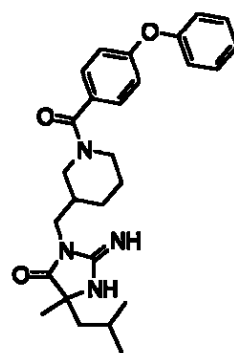
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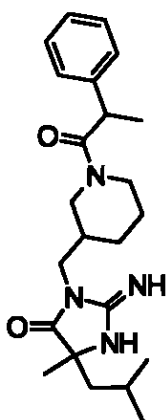
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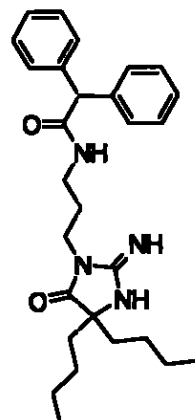
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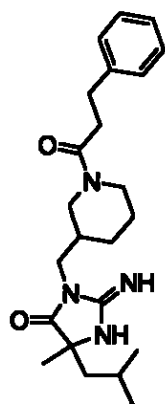
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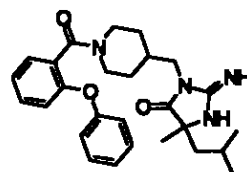
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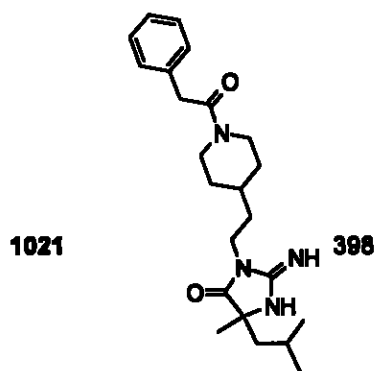
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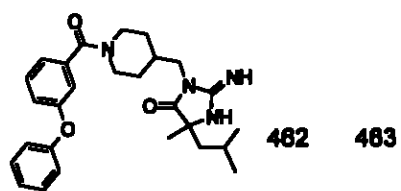
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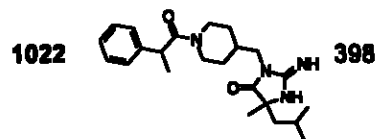


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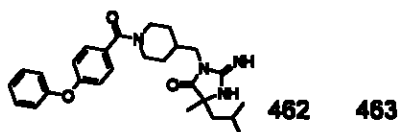


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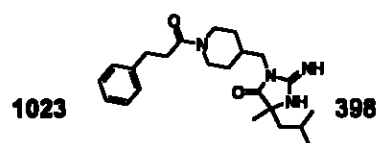


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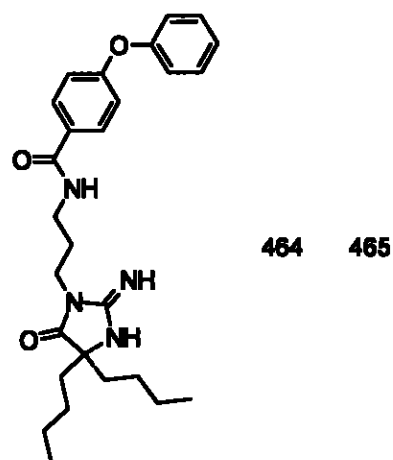


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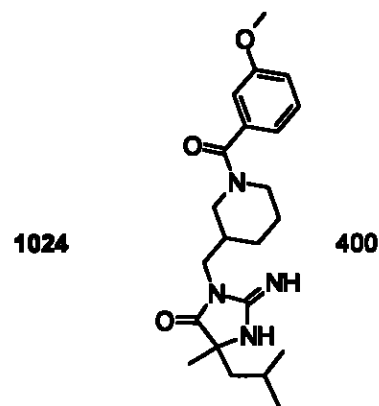


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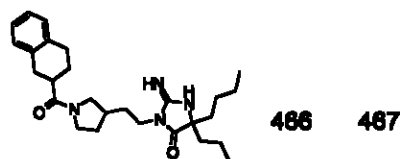


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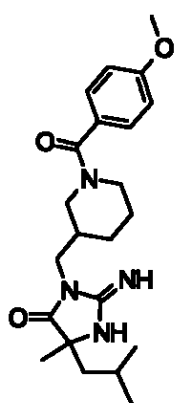
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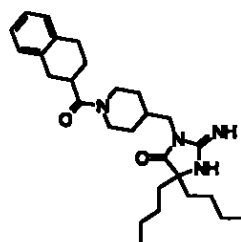
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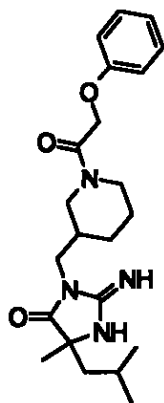
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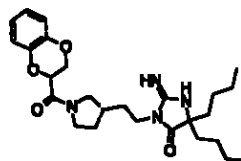
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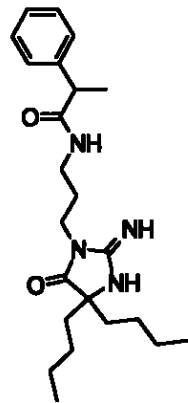
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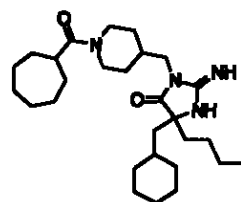
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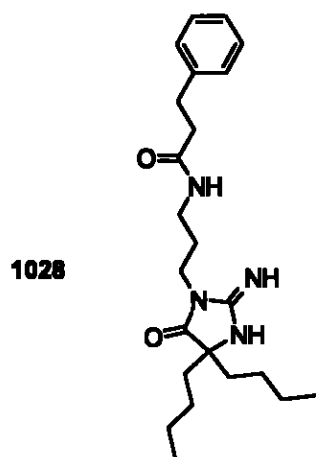
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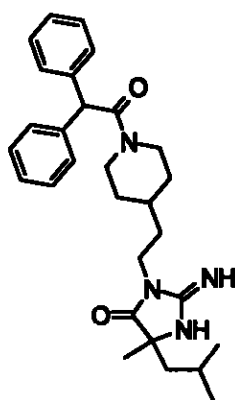
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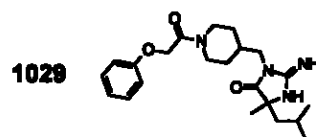
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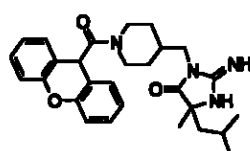
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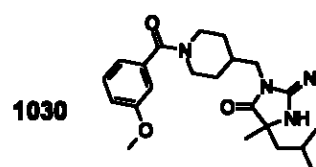
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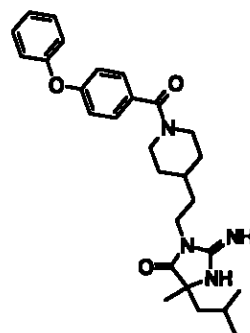
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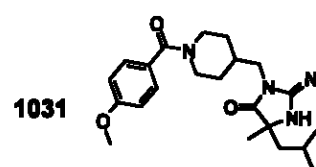
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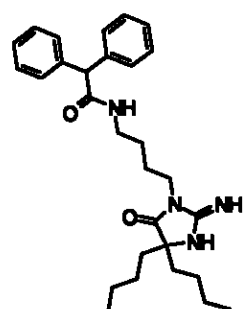
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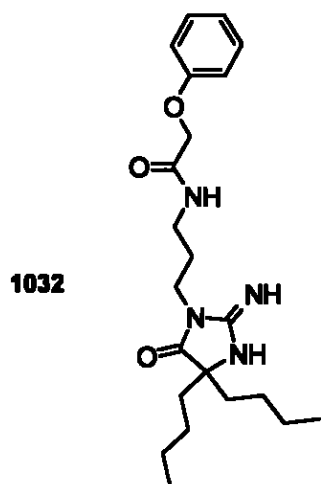
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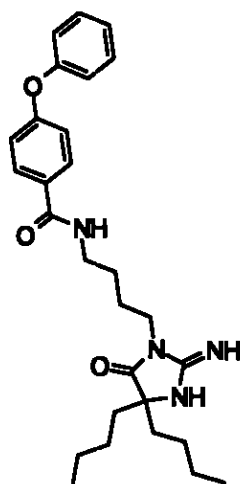
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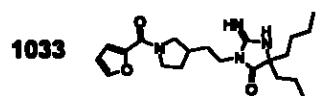
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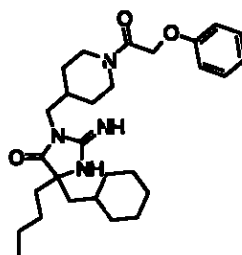
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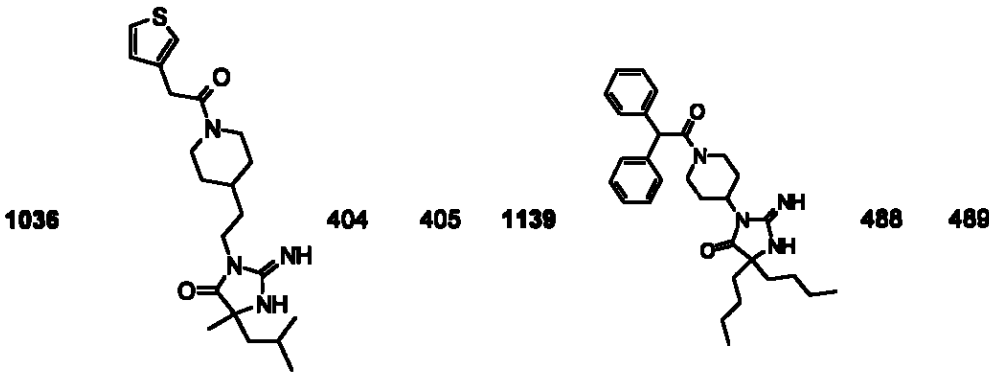
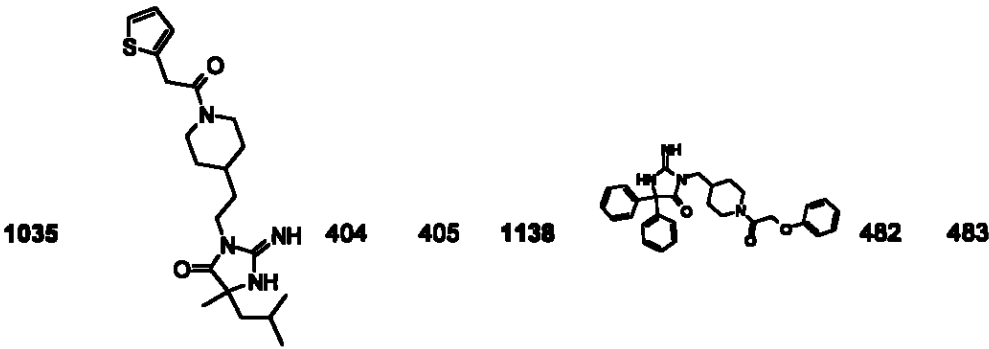
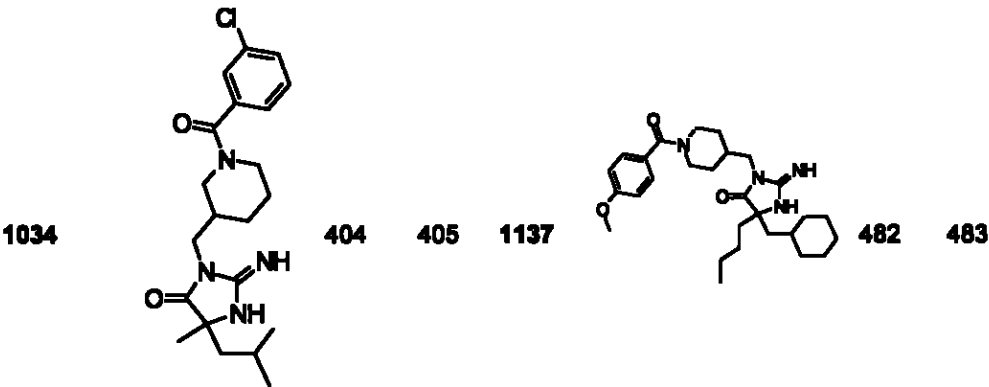


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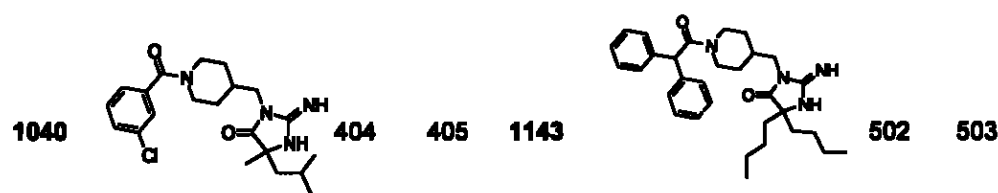
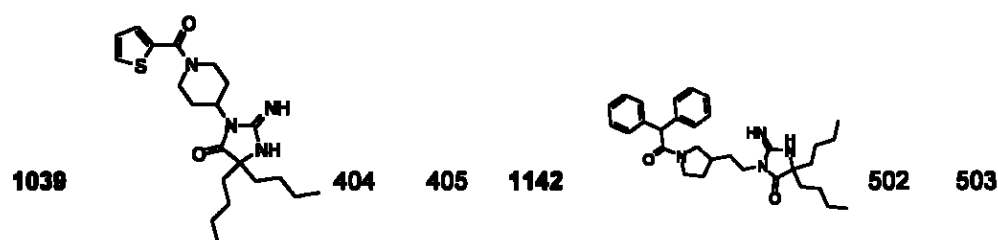
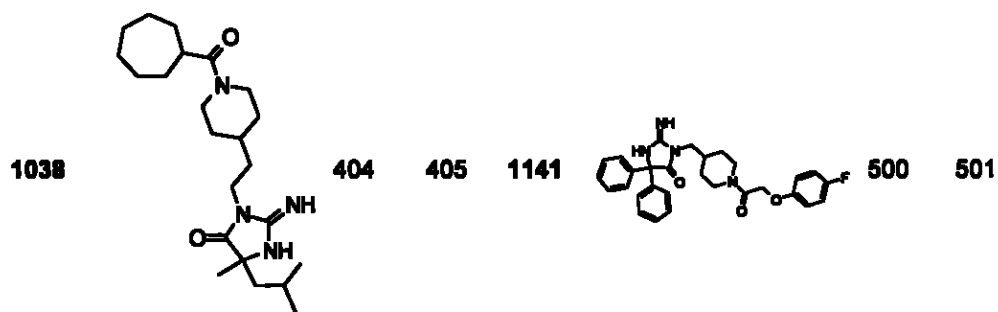
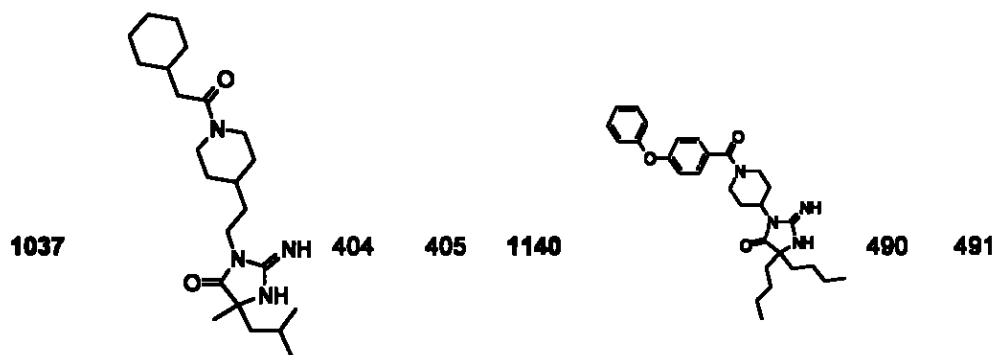


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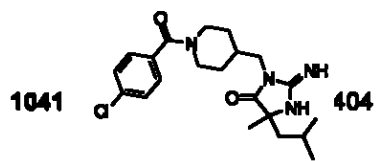
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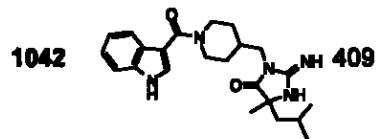
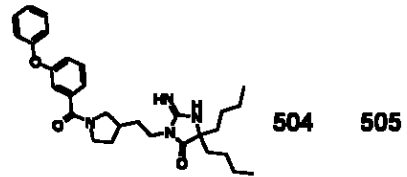
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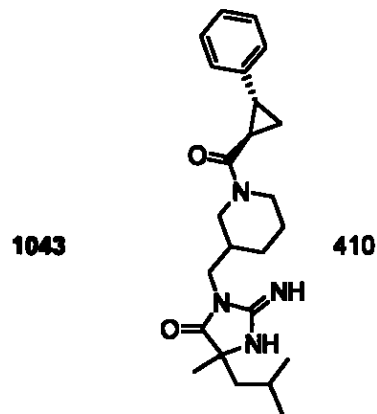
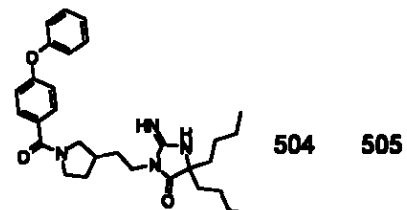
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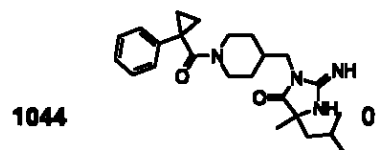
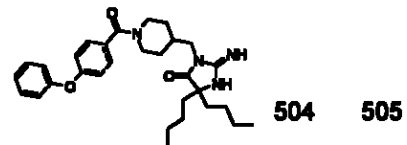
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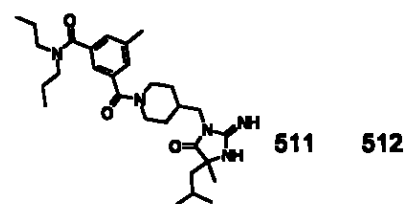
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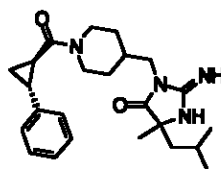


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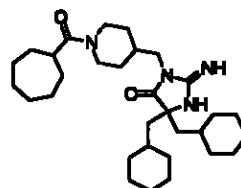
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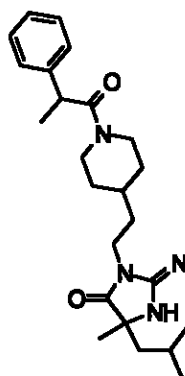
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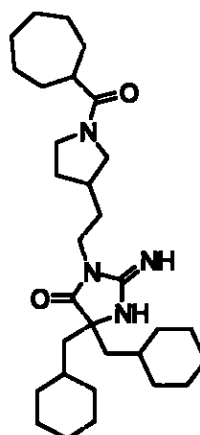
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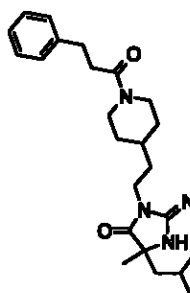
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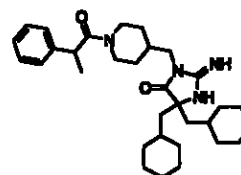
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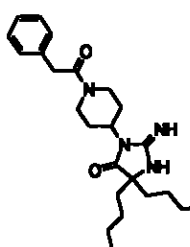
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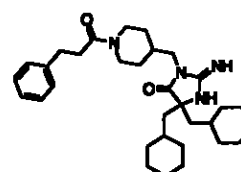
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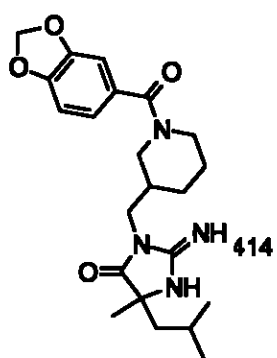


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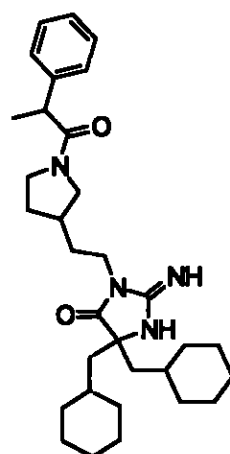
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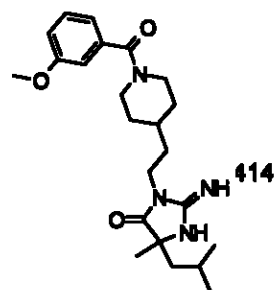
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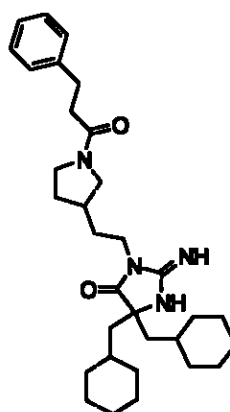
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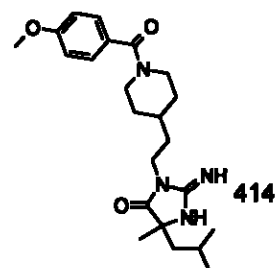
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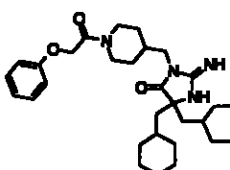
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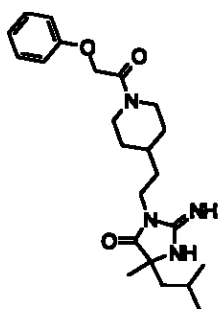


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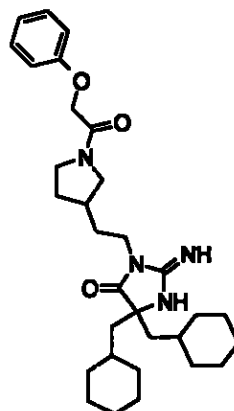
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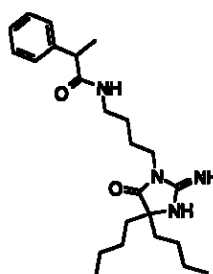
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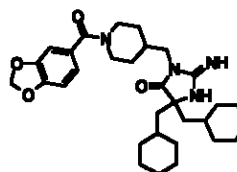
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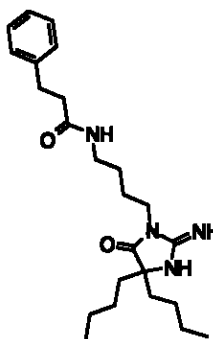
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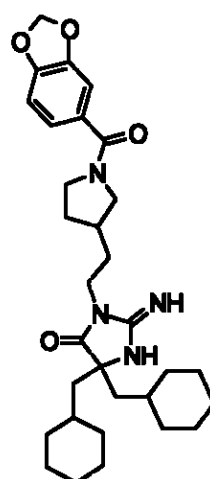
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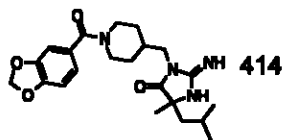


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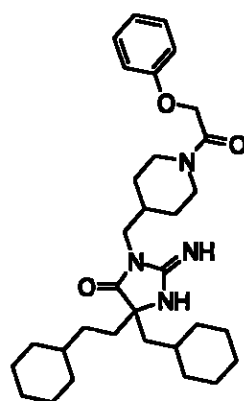
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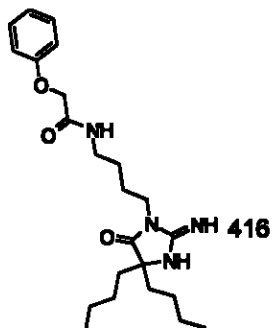
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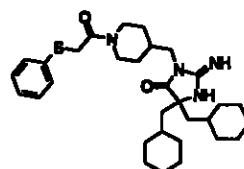
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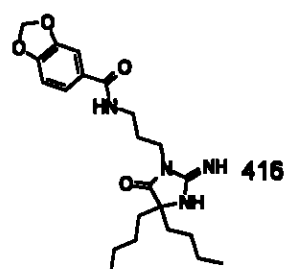
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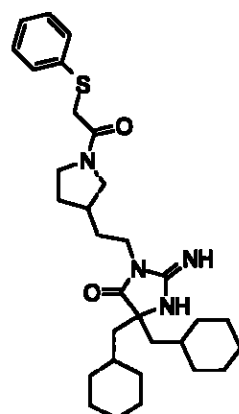
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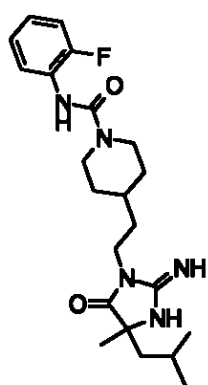


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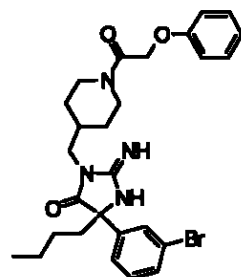
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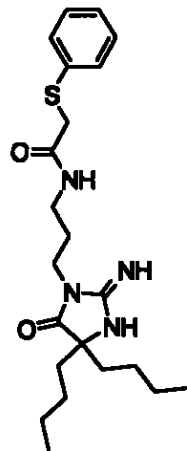
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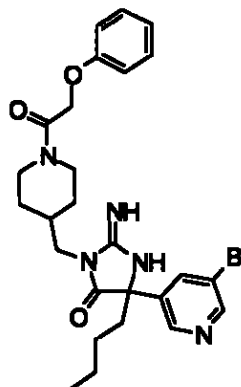
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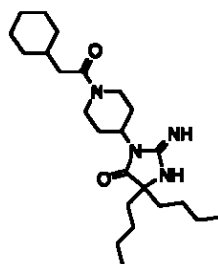
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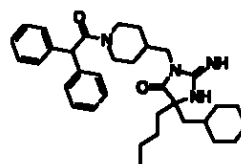
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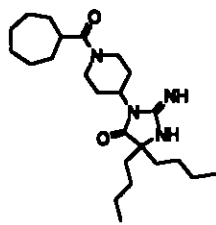


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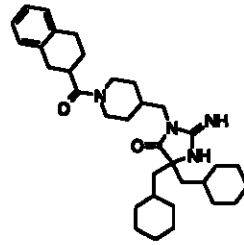
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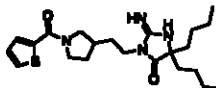
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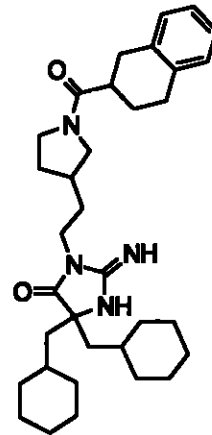
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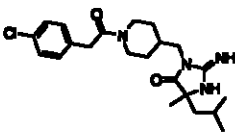
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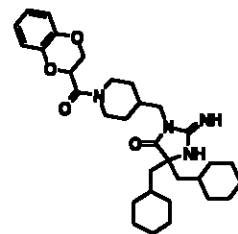
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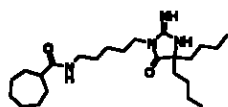


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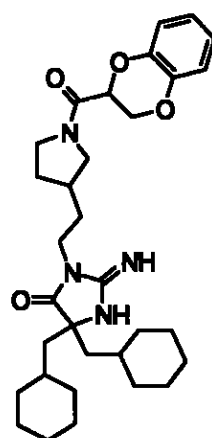
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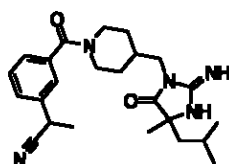
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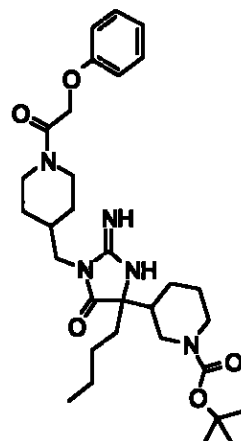
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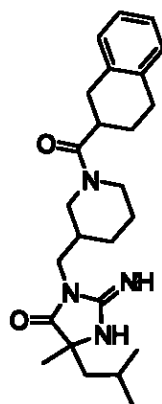
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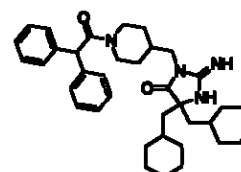
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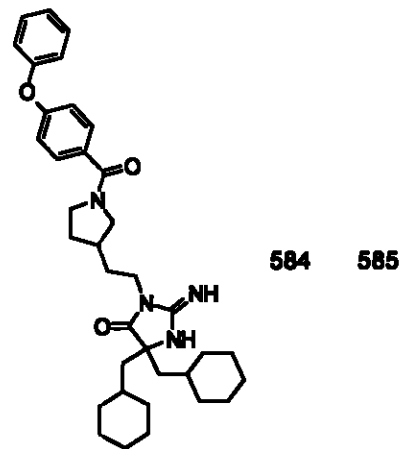
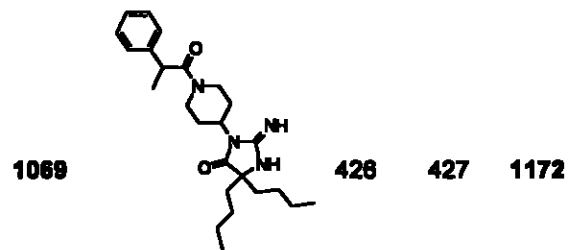
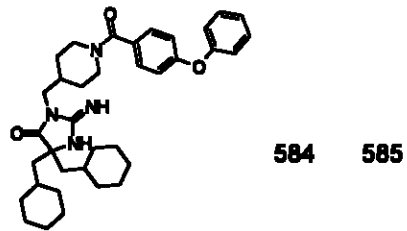
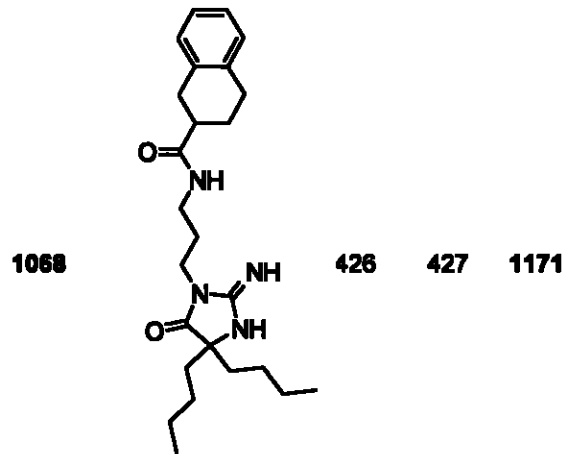
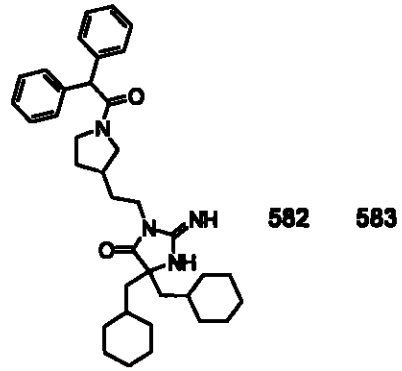
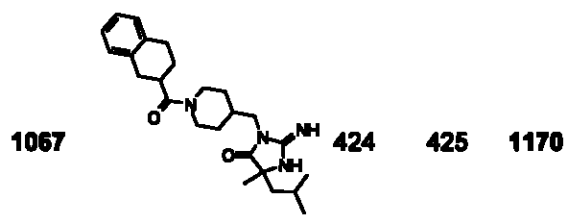
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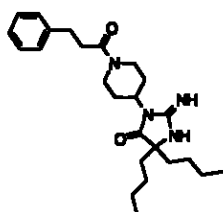
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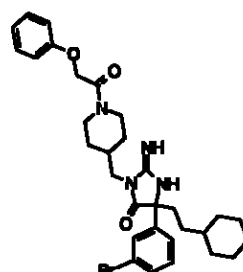
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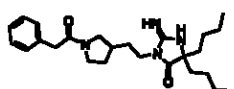
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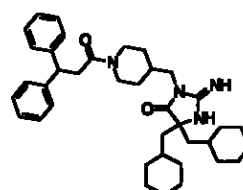
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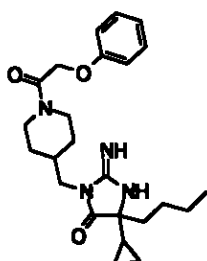
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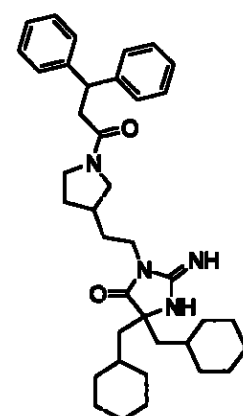
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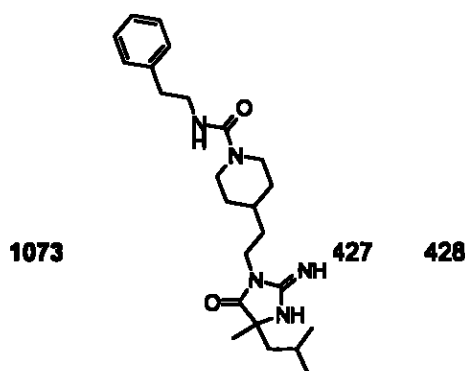


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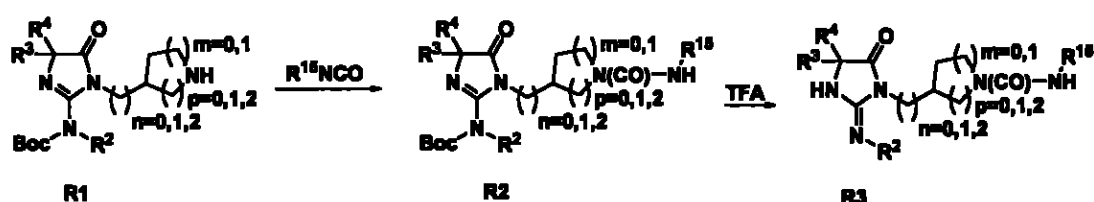
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584



Método R



Método R, Etapa 1.

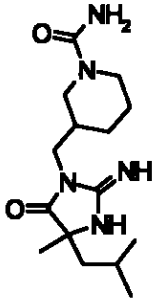
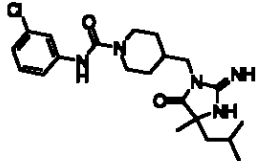
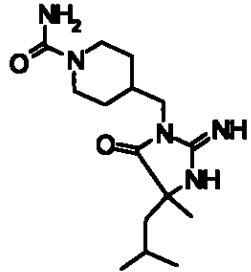
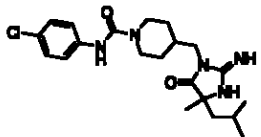
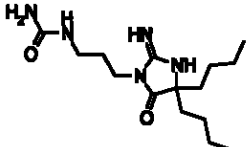
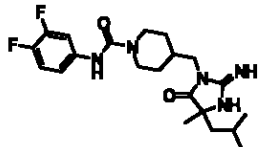
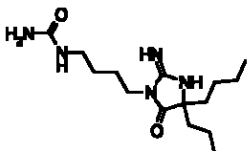
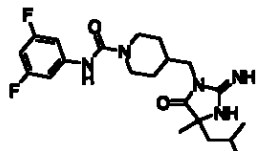
Una solución de R^1 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=^iBu$) (0,010 g) en acetonitrilo (0,85 mL) y dicloroetano (0,15 mL) dentro de un receptáculo de una placa microtituladora, seguido de adición de 0,12 ml de una solución de fenilisocianato 0,5M en dicloroetano. El receptáculo se selló y la placa se agitó durante 20 horas antes de filtrar la mezcla y el sólido se lavó con acetonitrilo (0,5 ml). La solución combinada se trató con una resina de Trisamina (0,050 g, 6 eq., 4,23 mmoles/g) y una resina de Isocianato (0,067 g, 3 eq., 1,53 mmoles/g) y la mezcla se agitó durante 18 horas. La mezcla se filtró y la solución se evaporó para proporcionar R2 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=^iBu$ y $R^{15}=Ph$).

Método R, Etapa 2.

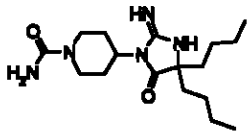
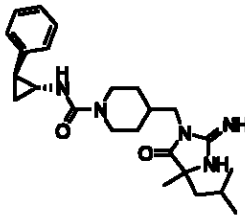
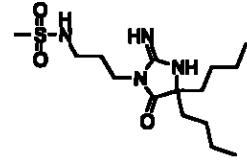
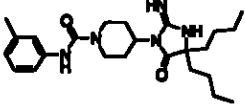
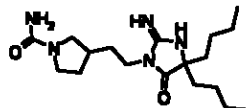
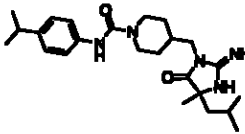
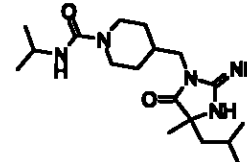
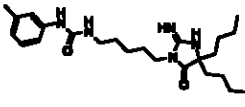
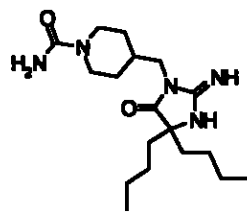
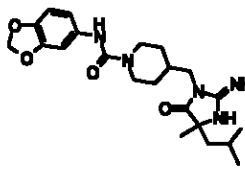
Se usó un procedimiento similar al Método Q, Etapa 6 para la transformación de R2 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=^iBu$ y $R^{15}=Ph$) a R3 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=^iBu$ y $R^{15}=Ph$).

Se prepararon los compuestos siguientes usando métodos similares.

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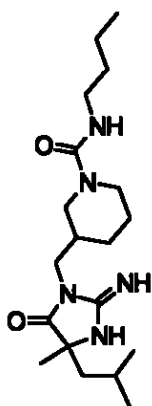
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1178		311	312	1217		421	422
1179		325	326	1218		421	422

575
~~583~~

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1181		346	347	1220		427	428
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1183		351	352	1222		429	430
1184		351	352	1223		429	430

576
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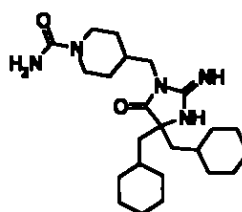
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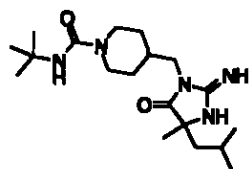
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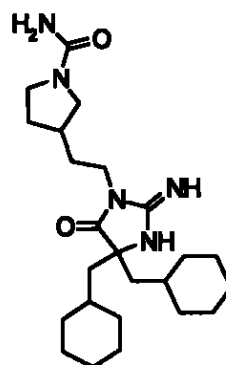
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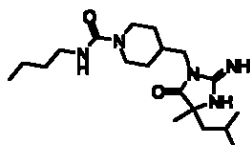
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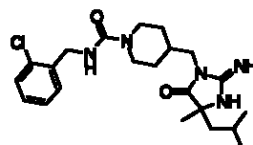
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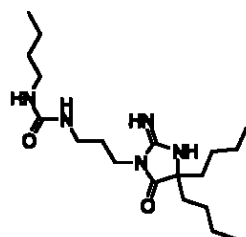
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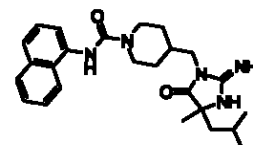
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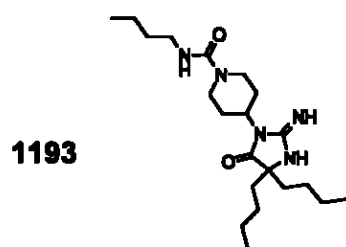
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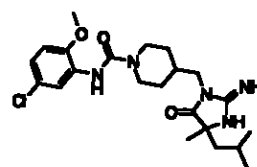
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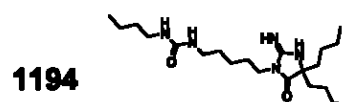
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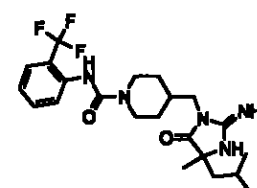
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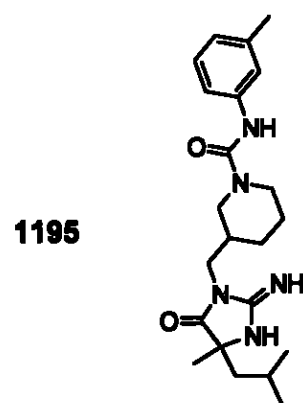
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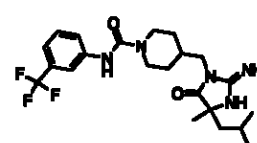
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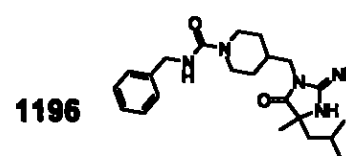
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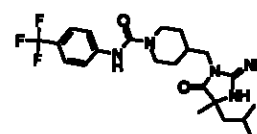
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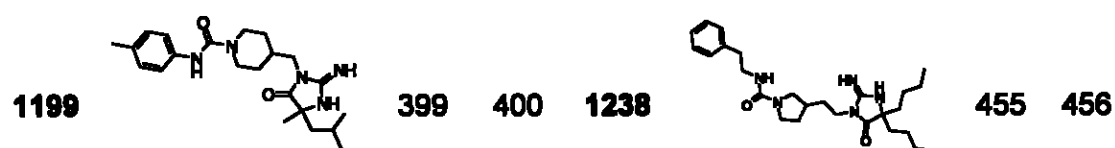
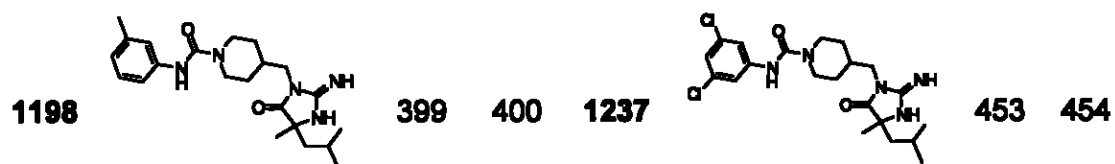
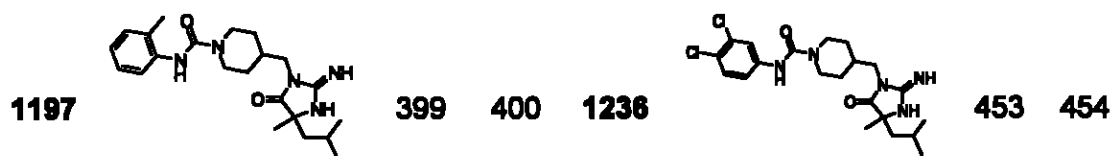
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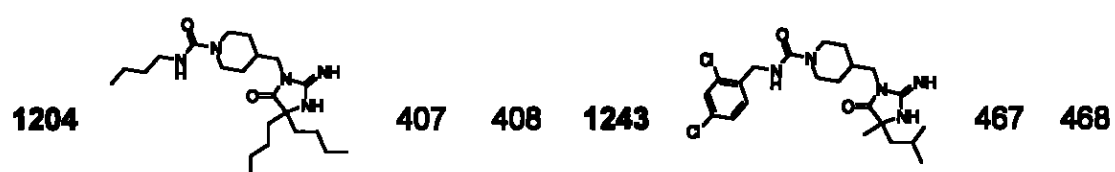
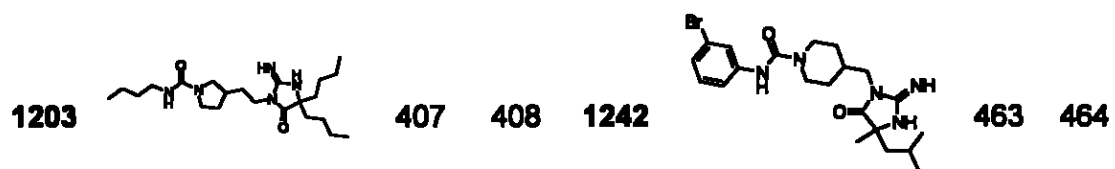
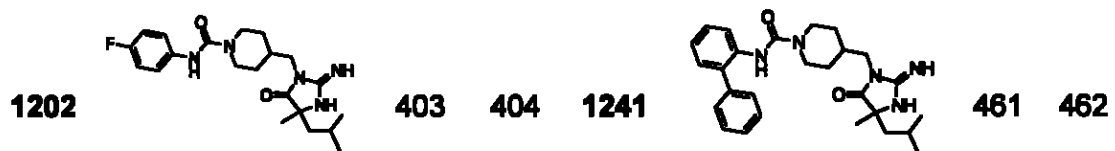
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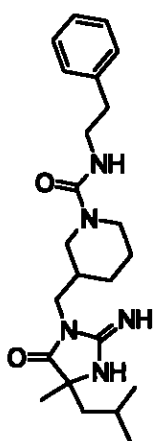


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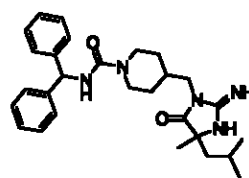
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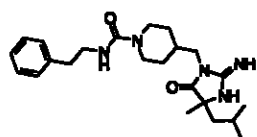
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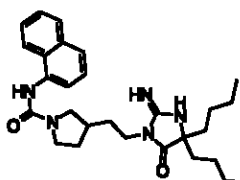
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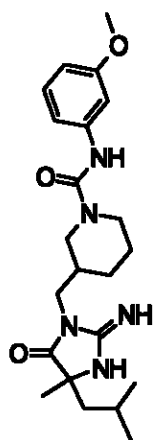
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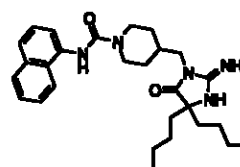
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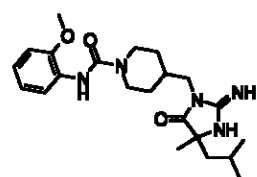
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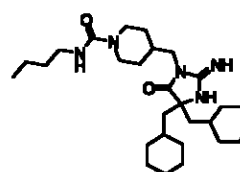
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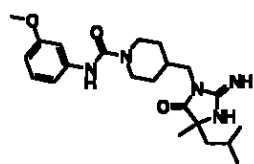


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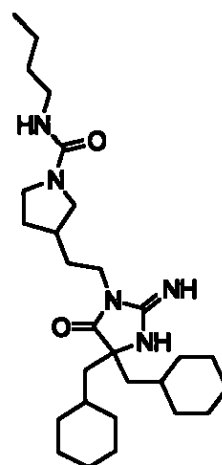
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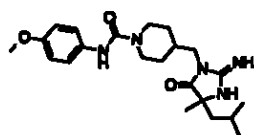
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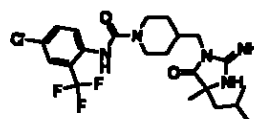
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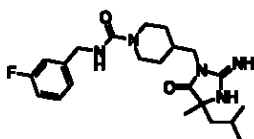
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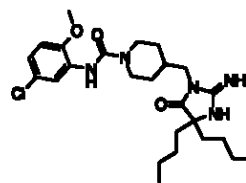
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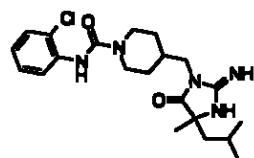
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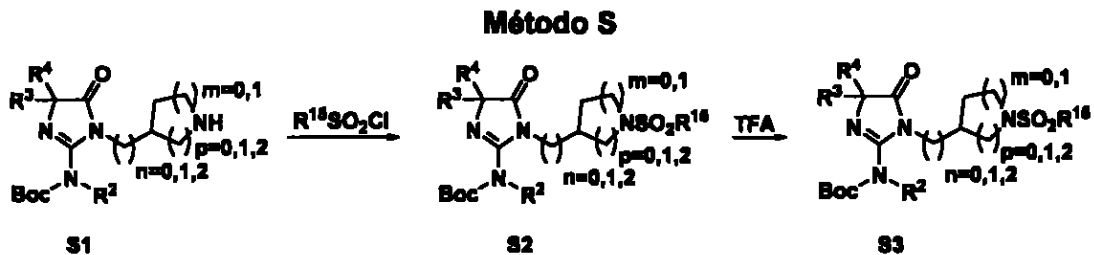
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Método S, Etapa 1.

Una solución de **S1** ($n=1$, $p=2$, $m=1$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{Me}$; $\text{R}^4=\text{iBu}$) (0,010 g) en acetonitrilo (0,85 mL) y dicloroetano (0,15 mL) se colocó dentro de una placa microtituladora seguido de adición de resina DIPEA-MP (0,030 g, 4 eq) y cloruro de fenilsulfonilo en dioxano (1M, 45 μL , 0,045 mmol. El receptáculo se tapó y se agitó durante 18 horas antes de filtrarlo y el residuo se lavó con acetonitrilo (0,5 mL). La solución combinada se trató con resina de Trisamina (0,040 g, 6 eq., 4,23 mmoles/g) y resina de Isocianato (0,060 g, 3 equiv., 1,53 mmoles/g) y se agitó durante 18 horas antes de filtrar la mezcla y el solvente se extrajo para proporcionar **S2** ($n=1$, $p=2$, $m=1$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{Me}$; $\text{R}^4=\text{iBu}$ y $\text{R}^{15}=\text{Ph}$).

Método S, Etapa 2.

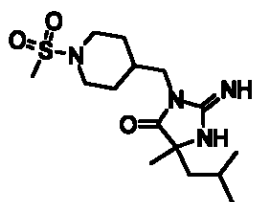
Se usó un procedimiento similar al Método Q, Etapa 6 para la transformación de **S2** a **S3** ($n=1$, $p=2$, $m=1$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{Me}$; $\text{R}^4=\text{iBu}$ y $\text{R}^{15}=\text{Ph}$).

Se prepararon los siguientes compuestos usando métodos similares.

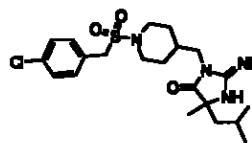
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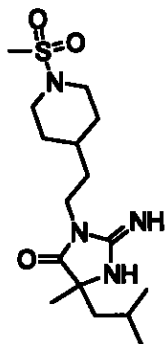


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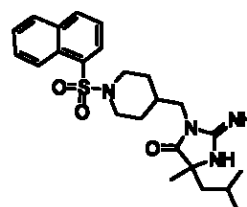


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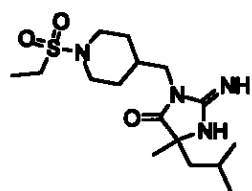


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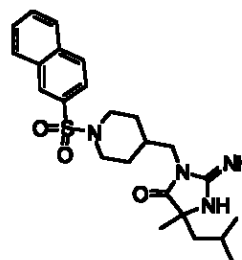


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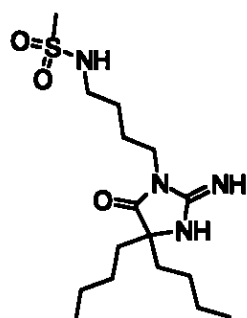


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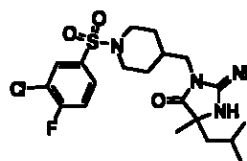


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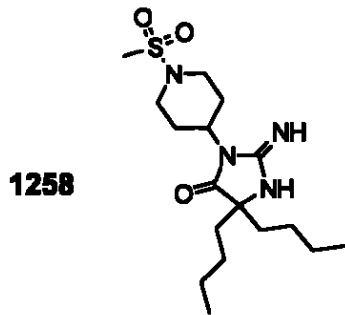


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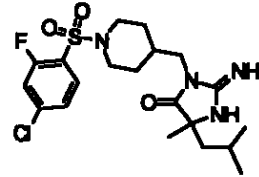


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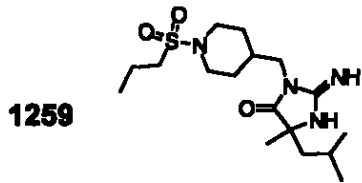
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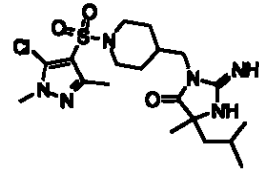
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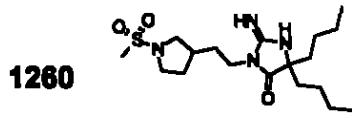
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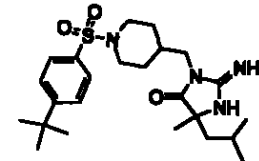
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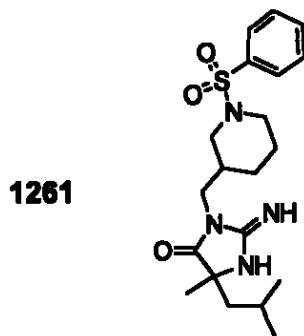
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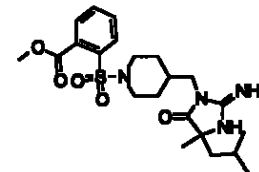
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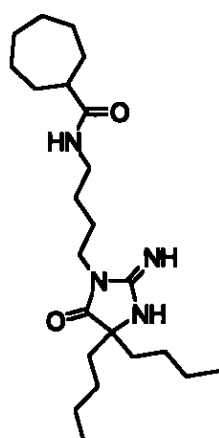


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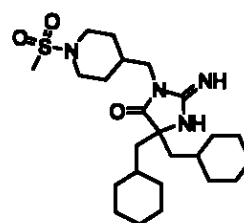
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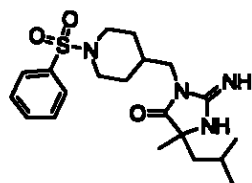


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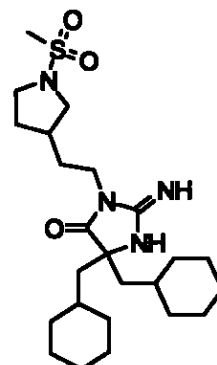


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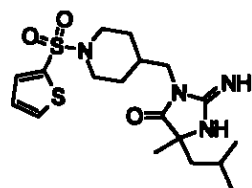


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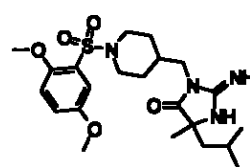


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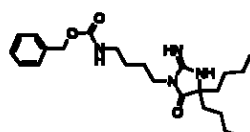


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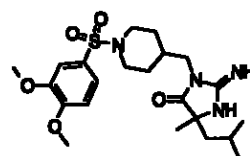


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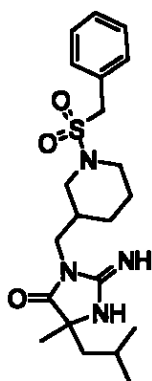
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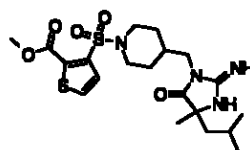
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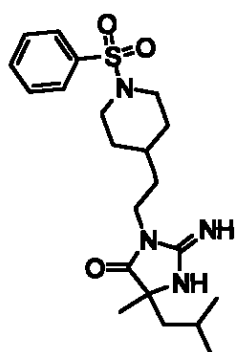


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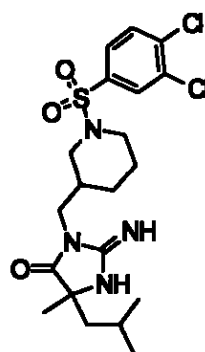


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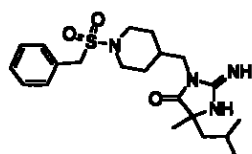


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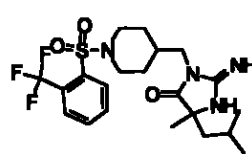


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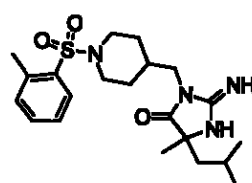


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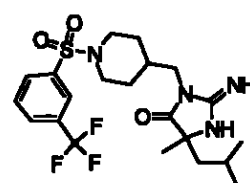


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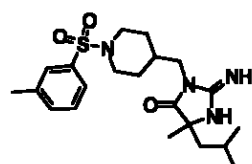


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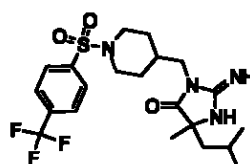


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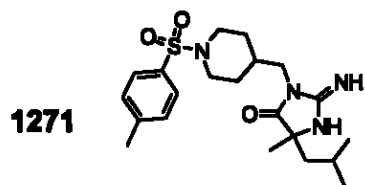


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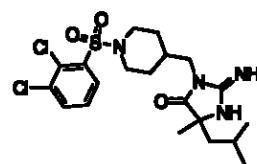


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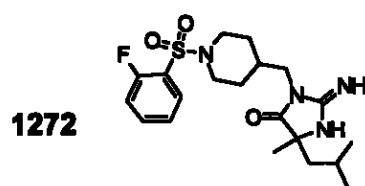
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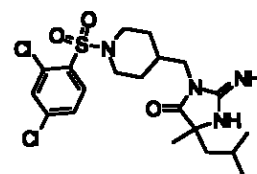
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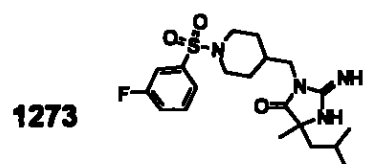
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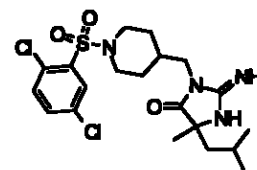
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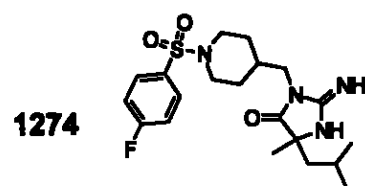
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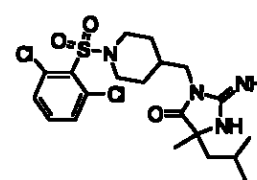
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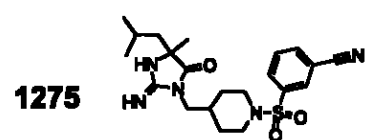
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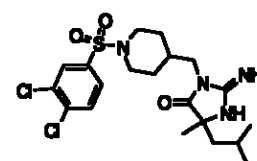
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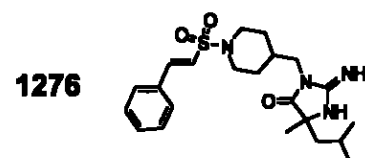
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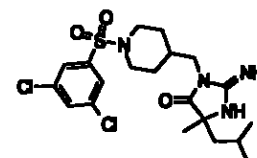
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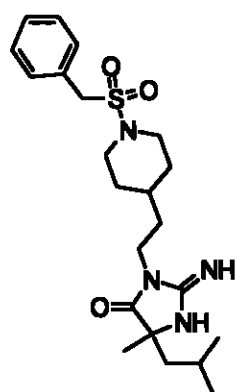
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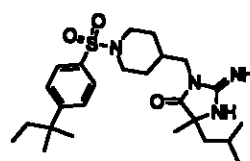
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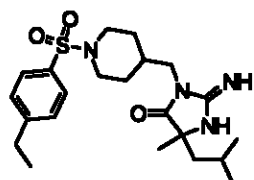


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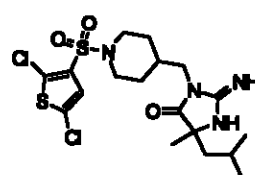


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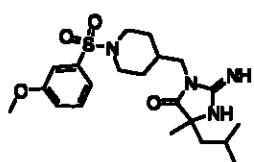


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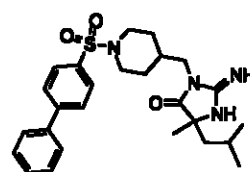


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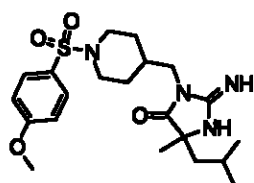


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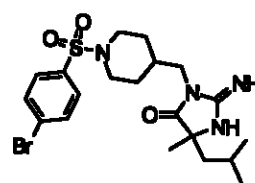


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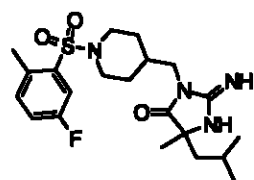


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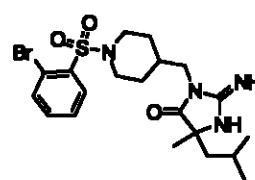


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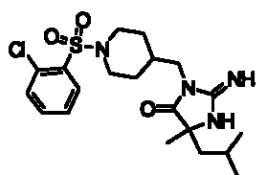


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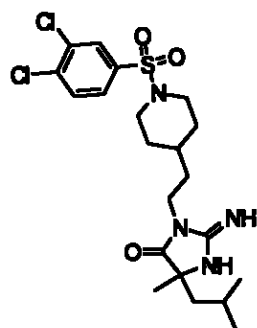
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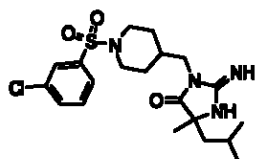


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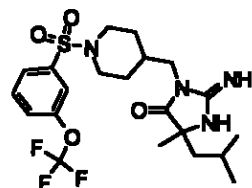


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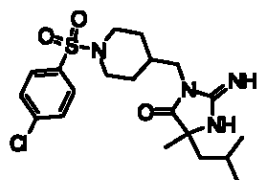


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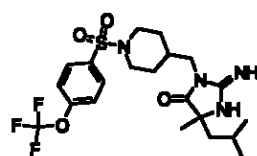


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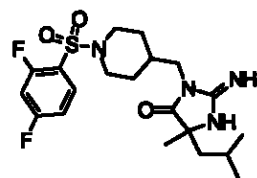


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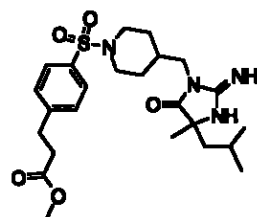


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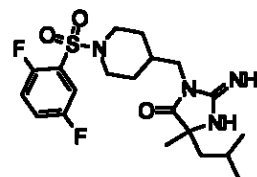


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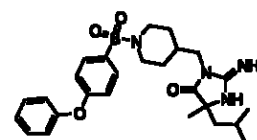


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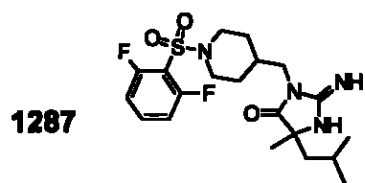
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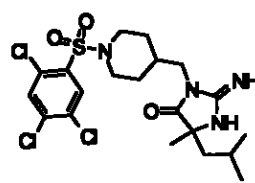
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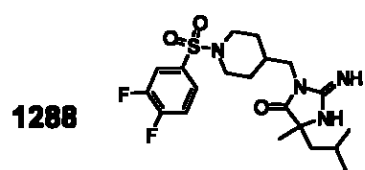
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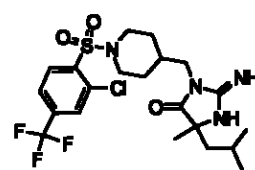
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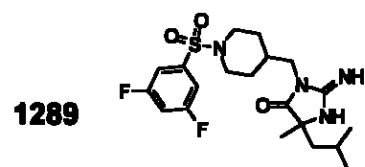
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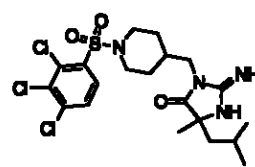
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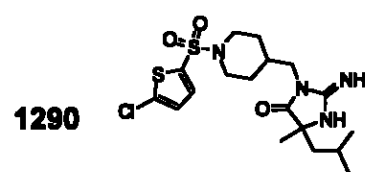
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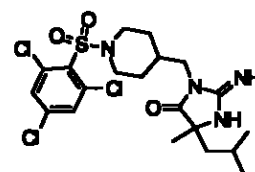
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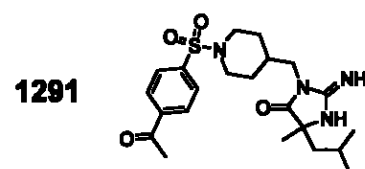
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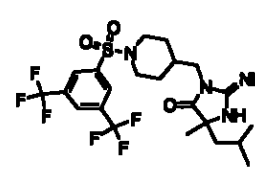
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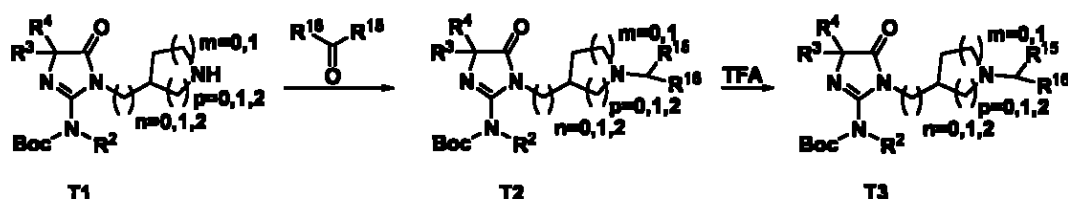
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542 543



Método T



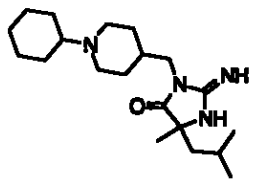
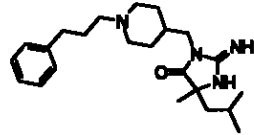
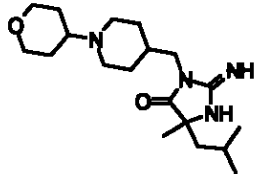
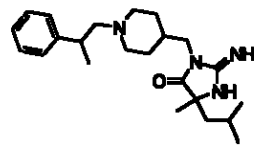
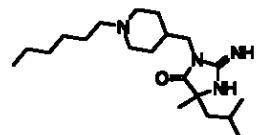
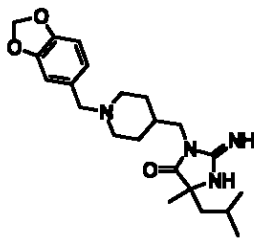
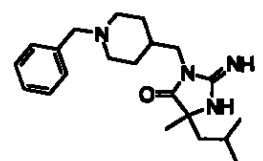
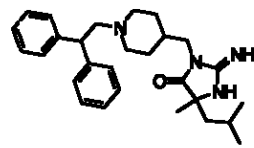
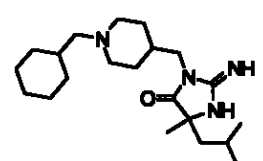
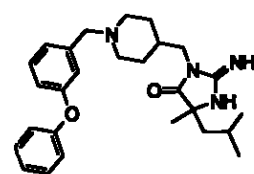
Método T, Etapa 1.

A un receptáculo de una placa microtituladora que contenía 1 ml de solución T1 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$) en DCM (0.010 g) y $R^{15}C(O)R^{16}$ (5 equiv, $R^{15}=H$, $R^{16}=Ph$) se le agregó cianoborohidruro de sodio en dicloroetano (14,3 mg / mL, 2 equiv.). El receptáculo se tapó y se agitó durante 20 horas antes de agregar MP-TsOH (100 mg, 1,29 mmoles/g) al receptáculo, seguido de resina de MP-TsOH (50 mg) después 2 h. Después de agitar la mezcla durante 1 hora más, la mezcla se filtró y la resina se lavó con dicloroetano (1 mL) (3 X), luego con MeOH (1 mL) (2 X). La resina se trató con amoníaco 7N en MeOH (1 mL) durante 30 min (2X) seguido de filtración y evaporación del solvente para proporcionar T2 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$ y $R^{15}=Ph$ y $R^{16}=H$).

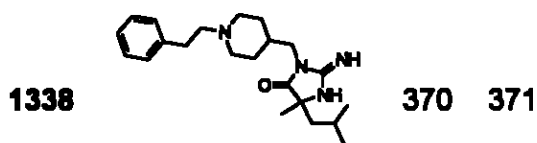
Método T, Etapa 2.

Se usó un procedimiento similar al Método Q, Etapa 6 para la transformación de T2 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$ y $R^{15}=Ph$ y $R^{16}=H$) a T3 ($n=1$, $p=2$, $m=1$, $R^2=H$, $R^3=Me$; $R^4=iBu$ y $R^{15}=Ph$ y $R^{16}=H$).

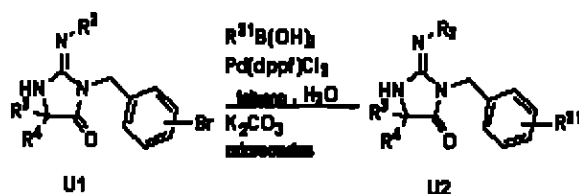
Se prepararon los compuestos siguientes usando métodos similares.

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
1333		348	349	1339		384	385
1334		350	351	1340		384	385
1335		350	351	1341		400	401
1336		356	357	1342		446	447
1337		362	363	1343		448	449

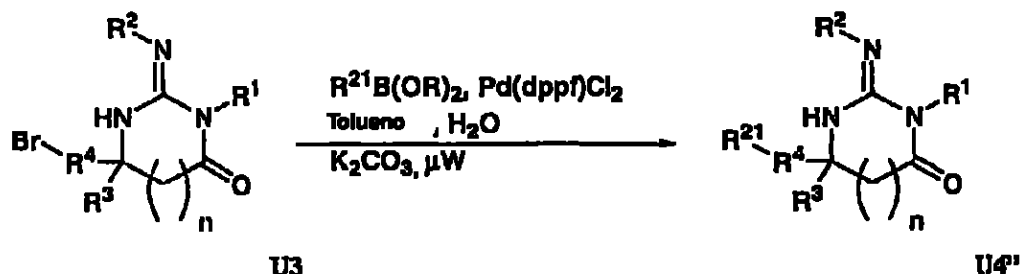
594
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Método U



Alternativamente, se puede usar un método sintético similar para la generación de otros tipos de compuestos, es decir,

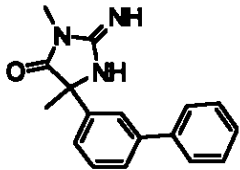
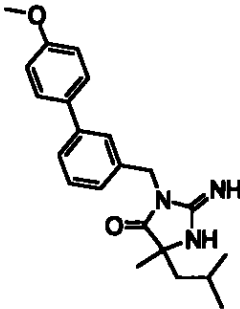
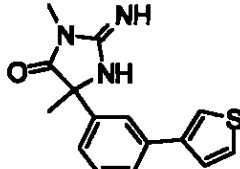
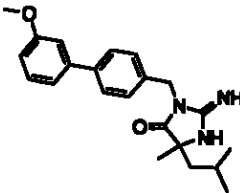
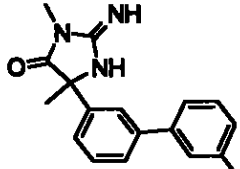
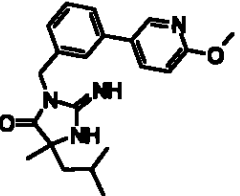
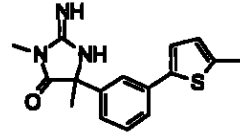
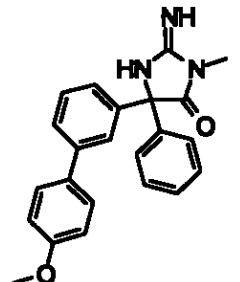


En un frasco para microondas se cargó U1 ($R^2 = H$; $R^3 = i\text{-Bu}$, $R^4 = \text{Me}$) (0,025 g) en tolueno (4 mL), carbonato de potasio (0,035 g), Pd(dppf)Cl_2 (0,020 g) agua (0,02 mL) y se introdujeron $\text{R}^{21}\text{B(OH)}_2$ ($\text{R}^{21} = m\text{-Metoxifenilo}$) (3 eq.). El frasco se colocó en un microondas durante 10 minutos a 150°C . La mezcla de reacción se diluyó con diclorometano y se extrajo con NaOH 2,5N. Se concentró la solución de diclorometano seca (MgSO_4) al vacío para proporcionar un residuo de color castaño, el cual se purificó mediante un sistema RP Prep LCMS para proporcionar el producto U2 ($R^2 = H$; $R^3 = i\text{Bu}$; $R^4 = \text{Me}$; $\text{R}^{21} = m\text{-metoxifenilo}$).

Se prepararon los compuestos siguientes usando métodos similares.

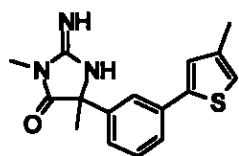
595

604

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
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1345		285	286	1382		365	366
1346		293	294	1383		366	367
1347		299	300	1384		371	372

596
603

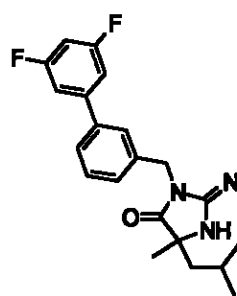
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299

300

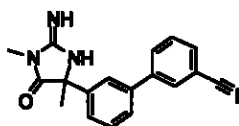
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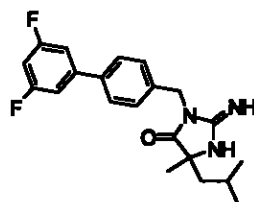
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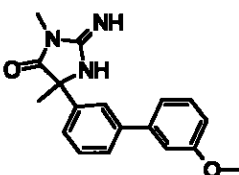
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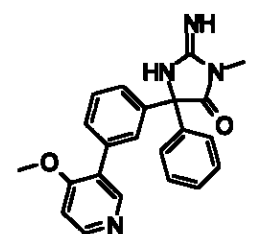
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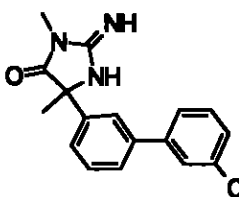
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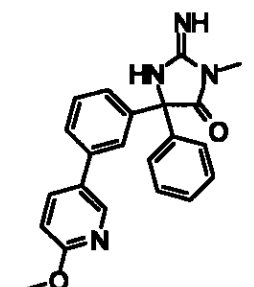
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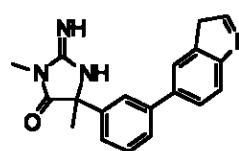
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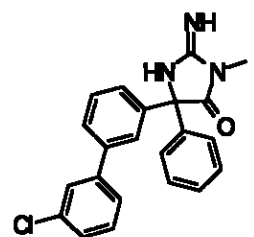
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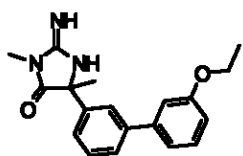


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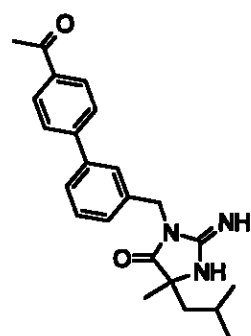
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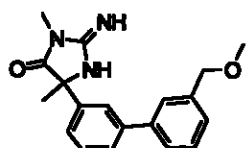
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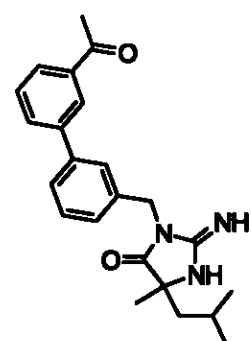
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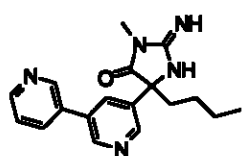
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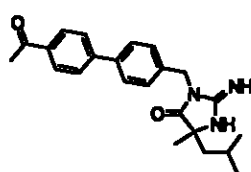
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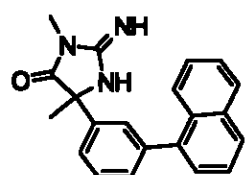
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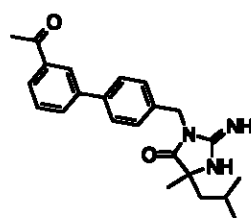
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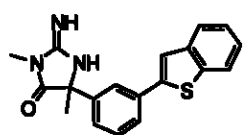


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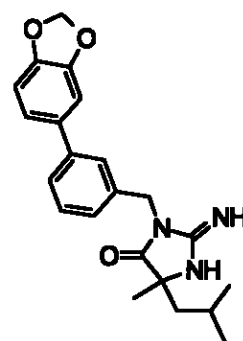
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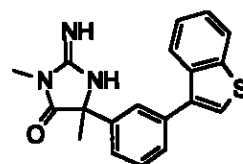
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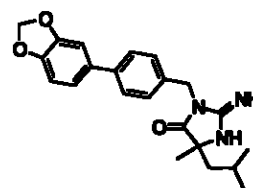
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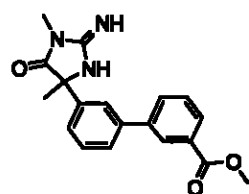
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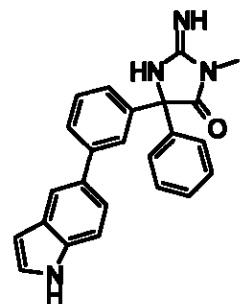
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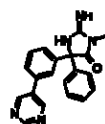
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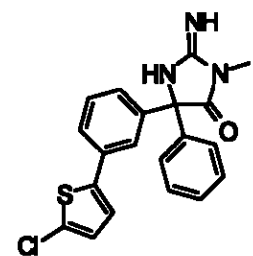
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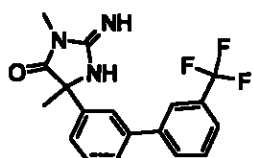


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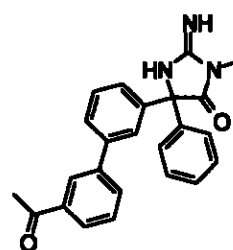
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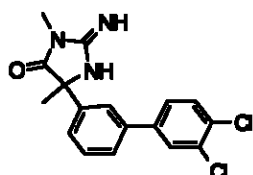
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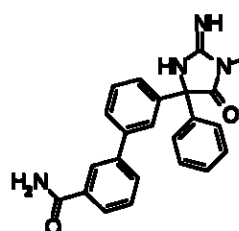
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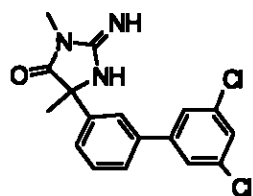
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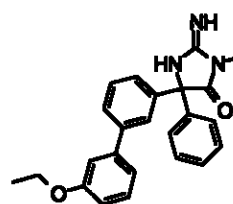
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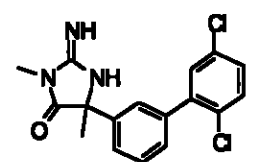
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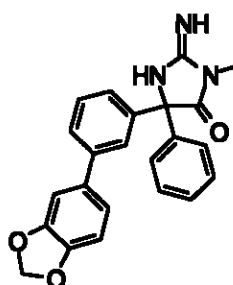
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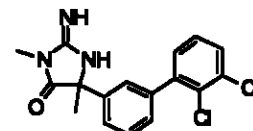
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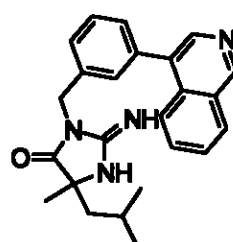
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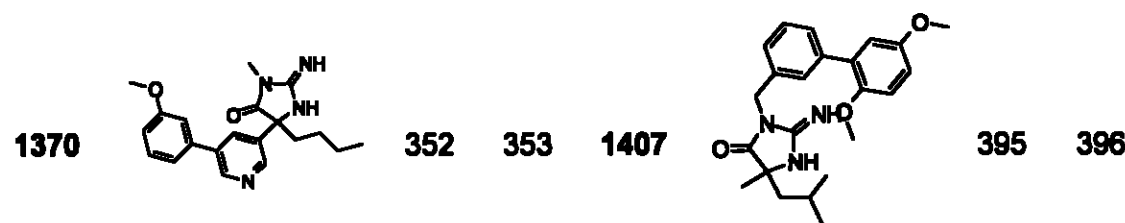
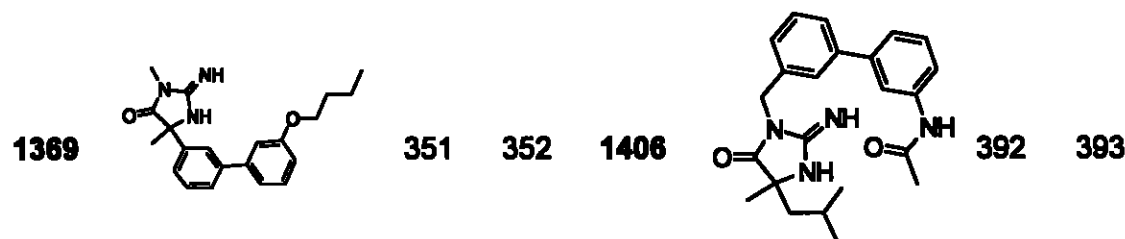
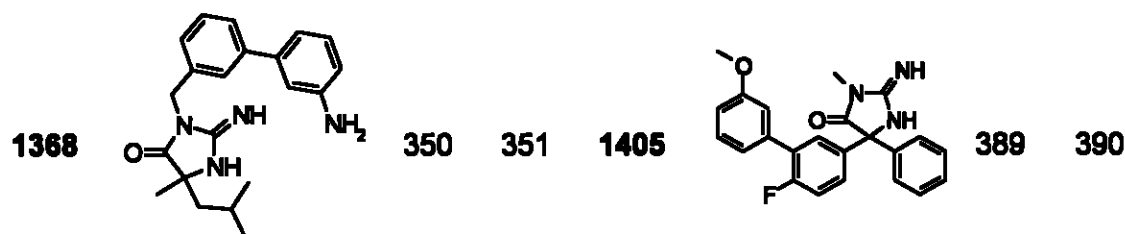
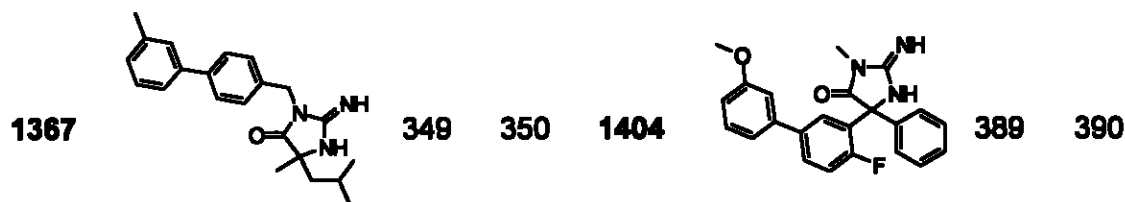
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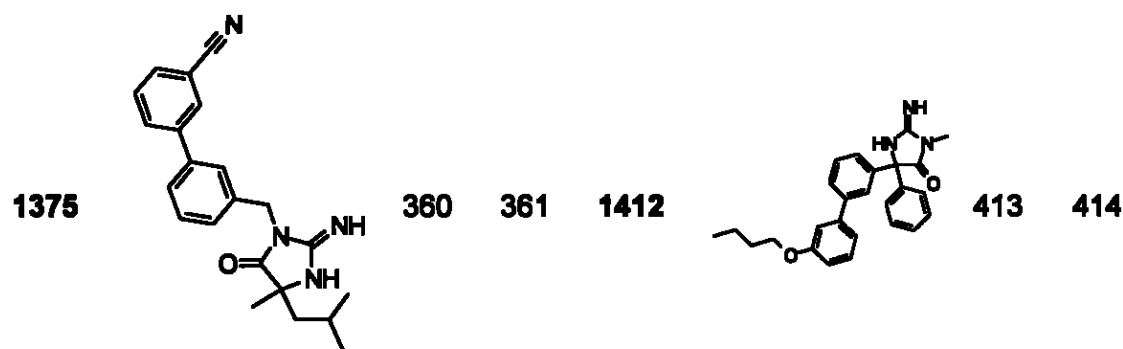
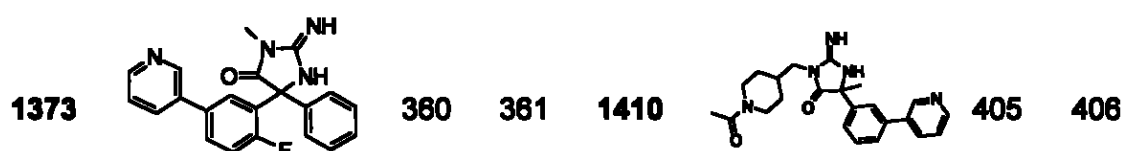
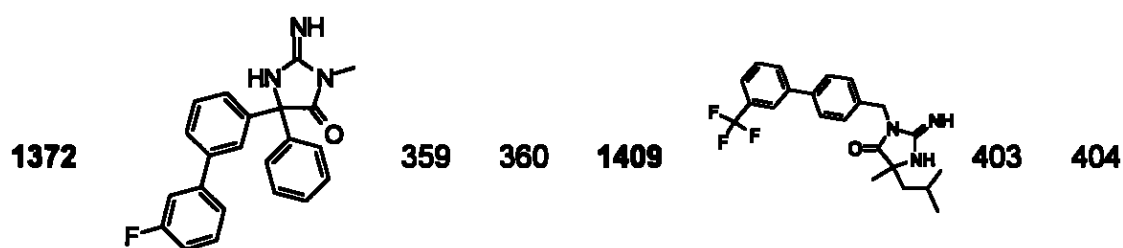
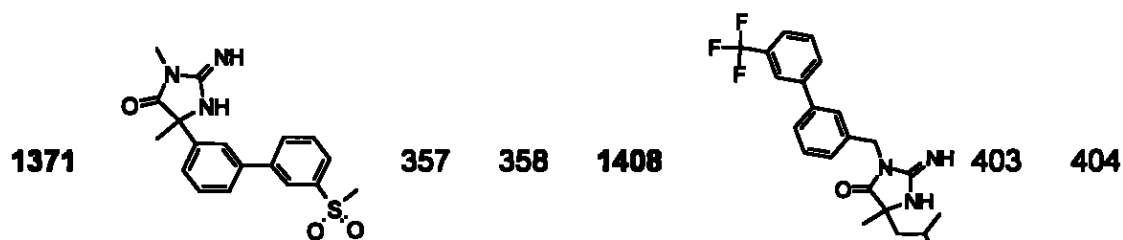
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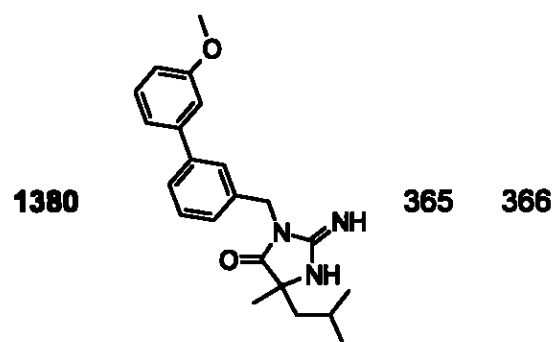
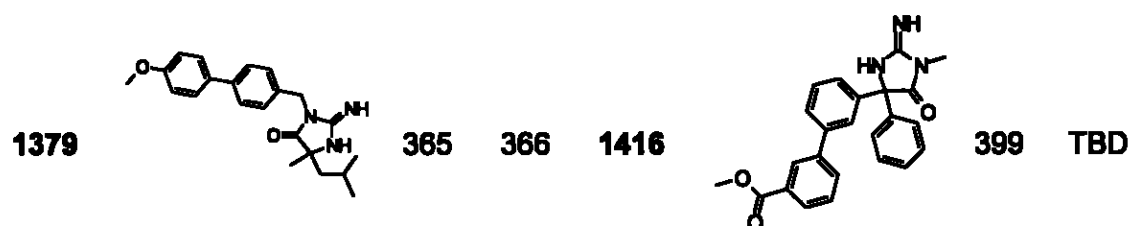
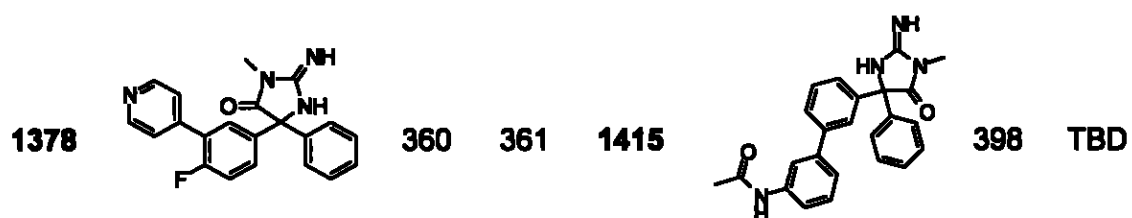
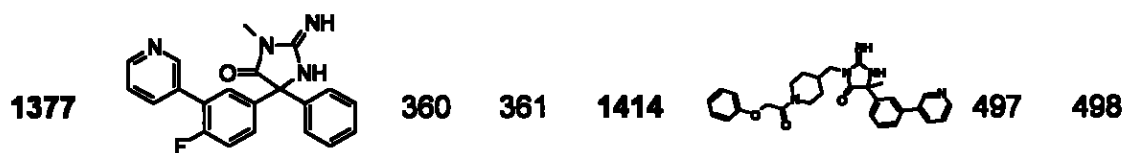
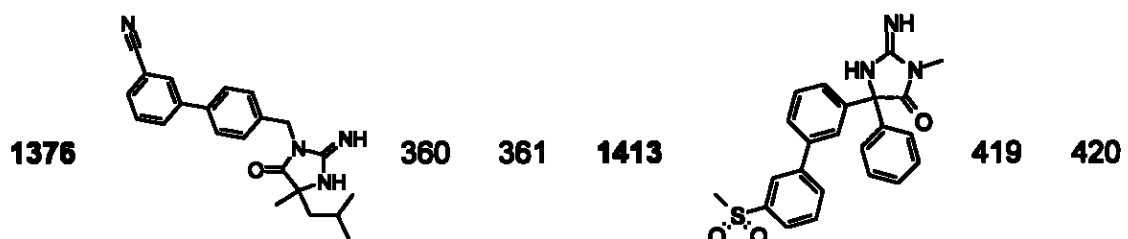
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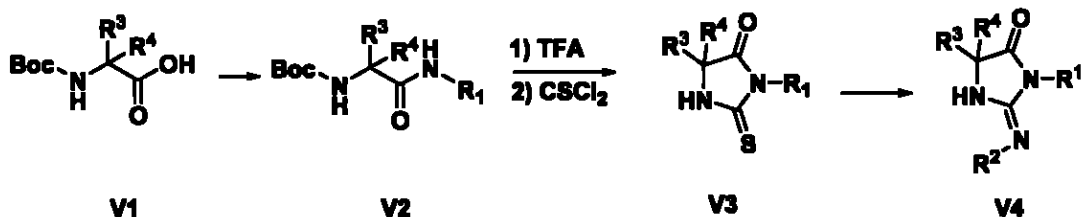


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Método V



Método V, Etapa 1:

Se mezcló el compuesto **V1** ($\text{R}^3 = \text{R}^4 = \text{Me}$) (14,76 mmoles), EDCI (14,76 mmoles), HOAt (14,76 mmoles), y DIEA (14,76 mmoles) con 36 ml de DCM. Esta mezcla se agitó a temperatura ambiente durante 15 minutos antes de agregar 3-clorobencilamina. Después de agitar la solución de reacción a temperatura ambiente durante la noche, se lavó con carbonato de sodio (3X), agua, HCl 1N (4 X), y bicarbonato de sodio acuoso y se secó sobre sulfato de sodio anhidro. El solvente se evaporó y el residuo se purificó sobre una columna evaporativa para proporcionar un producto de amida **V2** ($\text{R}^1 = 3\text{-clorobencilo}$; $\text{R}^3 = \text{R}^4 = \text{Me}$).

Método V, Etapa 2

Se disolvió el compuesto **V2** ($\text{R}^1 = 3\text{-clorobencilo}$; $\text{R}^3 = \text{R}^4 = \text{Me}$) (8,33 mmoles) en 35 ml de DCM anhidro, y se enfrió a 0-5°C. Se agregó por goteo Tiofosgeno (9,16 mmoles) en 10 ml de DCM bajo N_2 seguido de adición de DIEA (11,96 mmoles). La solución se agitó en un baño de hielo durante 0,5 horas antes de lavar la mezcla de reacción con bicarbonato de sodio saturado (3 X), salmuera, y se secó sobre sulfato de sodio anhidro. El solvente se evaporó y el residuo se purificó sobre columna evaporativa usando acetato de etilo/hexano para proporcionar la tihidantoina **V3** ($\text{R}^1 = 3\text{-clorobencilo}$; $\text{R}^3 = \text{R}^4 = \text{Me}$).

Método V, Etapa 3:

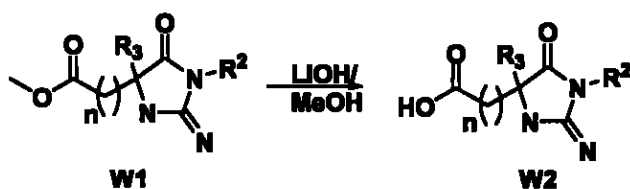
Se trató la tihidantoina **V3** ($\text{R}^1 = 3\text{-clorobencilo}$; $\text{R}^3 = \text{R}^4 = \text{Me}$) con hidroperóxido de t-butilo e hidróxido de amonio en MeOH a temperatura ambiente durante 48 horas para proporcionar el compuesto **V4** ($\text{R}^1 = 3\text{-clorobencilo}$; $\text{R}^2 = \text{H}$; $\text{R}^3 = \text{R}^4 = \text{Me}$).

Se prepararon los compuestos siguientes usando métodos similares.

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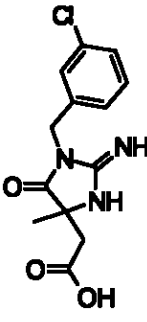
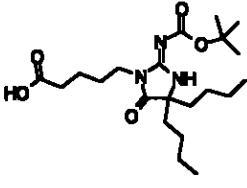
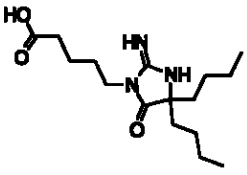
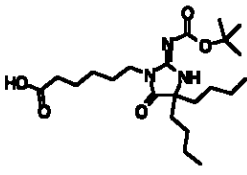
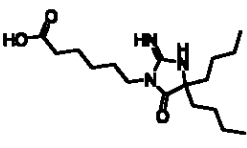
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1418		265	268	1421		357	358
1419		293	294	1422		371	372

Método W

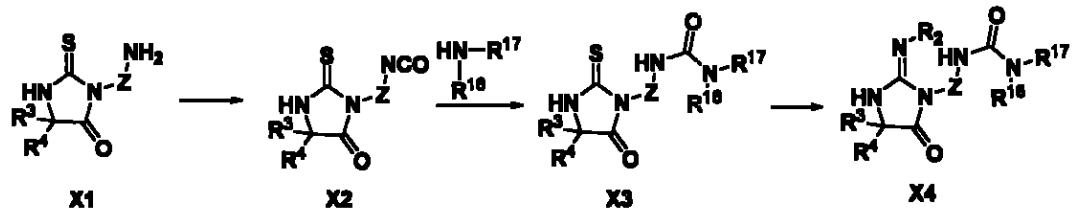


El Compuesto se W1 obtenido usando el Método A ($n=1$, $R^2=m\text{-Cl-Bn}$, $R^3=\text{Me}$) se hidrolizó a W2 ($n=1$, $R^2=m\text{-Cl-Bn}$, $R^3=\text{Me}$) usando dos equivalentes de LiOH en MeOH.

Se sintetizaron los compuestos siguientes de manera similar:

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
1423		295	296	1426		411	412
1424		311	312	1427		425	426
1425		325	326				

Método X



(En el esquema, $-\text{Z}-\text{NH}-\text{C}(\text{O})-\text{N}(\text{R}^{16})(\text{R}^{17})$ - es equivalente a R^1 sustituido con R^{21} , o R^1 sustituido con alquilo- R^{22} , donde R^{21} y R^{22} son $-\text{NH}-\text{C}(\text{O})-\text{N}(\text{R}^{16})(\text{R}^{17})$ y R^{15} es H, y donde Z es alquileno-arileno, alquileno-arileno-alquileno, alquileno-heteroarileno, alquileno-heteroarileno-alquileno, alquileno-cicloalquileno, alquileno-cicloalquileno-alquileno, alquileno-heterocicloalquileno,

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alquileno-heterocicloalquileno-alquileno, arileno, heteroarileno, cicloalquileno o heterocicloalquileno opcionalmente sustituidos).

Método X, Etapa 1:

A una mezcla de la amina **X1** obtenida usando el método L ($R^3 = \text{Me}$; $R^4 = \text{i-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) (10 mg) en DCM y NaHCO_3 sat. (1:1 en volumen) se le agregó trifosgeno (0,33 eq) a temperatura ambiente. La solución se agitó vigorosamente durante 40 minutos antes de separar la capa orgánica y se secó sobre Na_2SO_4 anhidro. La solución orgánica se evaporó para proporcionar el compuesto **X2** ($R^3 = \text{Me}$; $R^4 = \text{i-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$).

Método X, Etapa 2:

Se preparó el compuesto **X3** ($R^{15} = \text{H}$; $R^{16} = \text{ciclopropilmetilo}$; $R^3 = \text{Me}$; $R^4 = \text{i-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) a partir de **X2** ($R^3 = \text{Me}$; $R^4 = \text{i-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) usando el método similar al método M, etapa 1.

Método X, Etapa 3:

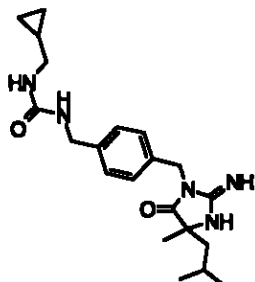
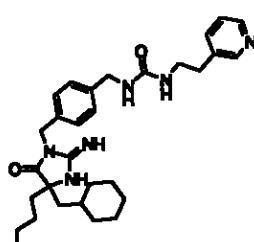
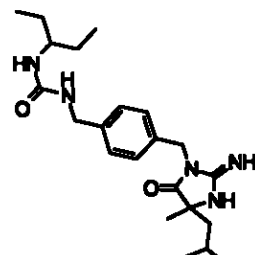
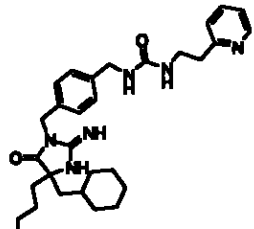
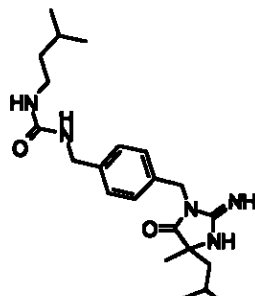
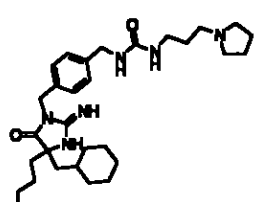
Se preparó el compuesto **X4** ($R^{16} = \text{H}$; $R^{17} = \text{ciclopropilmetilo}$; $R^2 = \text{H}$; $R^3 = \text{Me}$; $R^4 = \text{i-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) a partir de **X3** ($R^{16} = \text{H}$; $R^{17} = \text{ciclopropilmetilo}$; $R^2 = \text{H}$; $R^3 = \text{Me}$; $R^4 = \text{i-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) usando el método similar al método A Etapa 3. RMN (CD_3OD): δ 7,25, s, 4H; δ 4,8, m, 2H; δ 4,25, s, 2H; δ 2,9, m, 2H; δ 1,68, m, 2H; δ 1,44, m, 1H; δ 1,36, s, 3H; δ 0,9, m, 1H; δ 0,82, m, 3H; δ 0,66, m, 3H; δ 0,4, m, 2H; δ 0,12, m, 2H. ES_LCEM (m/e) 386,1.

Se prepararon los siguientes compuestos usando un método similar.



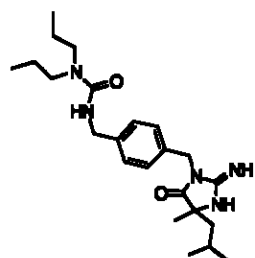
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#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
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1429		401	402	1444		518	519
1430		401	402	1445		524	525

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617

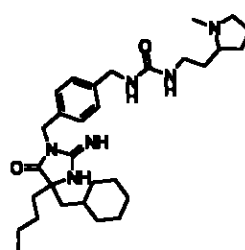
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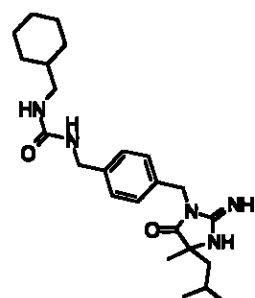
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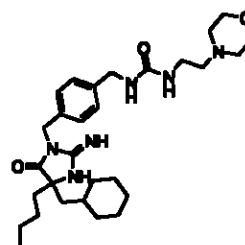
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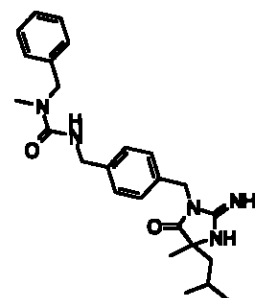
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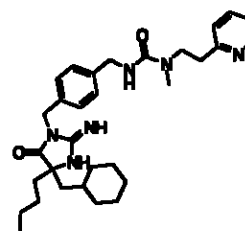
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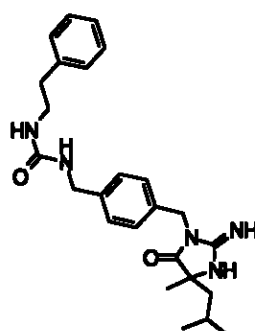
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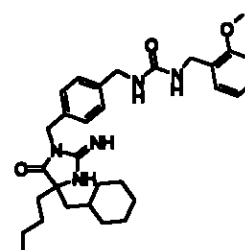
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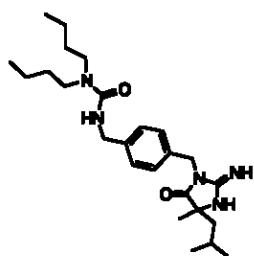


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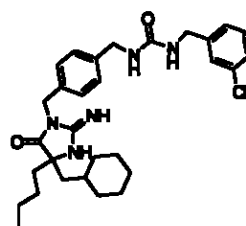
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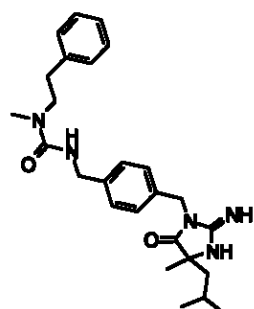
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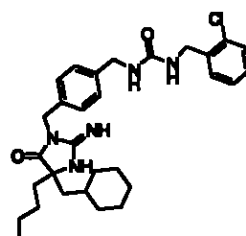
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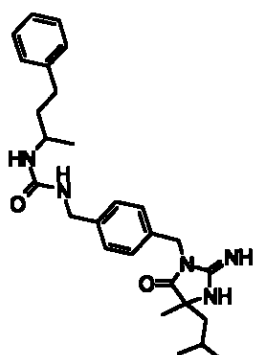
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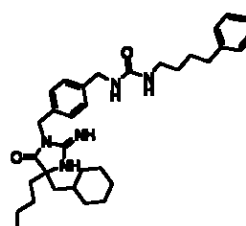
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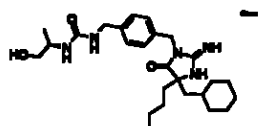
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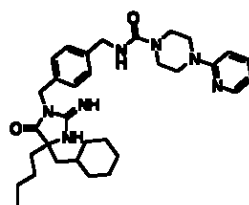
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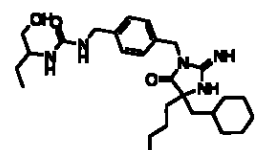
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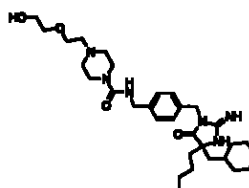
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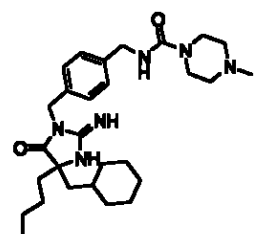
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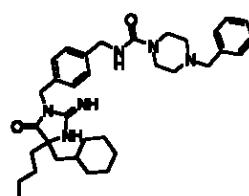
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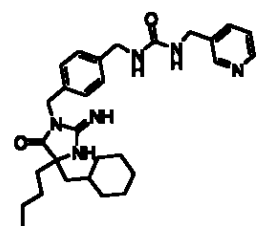
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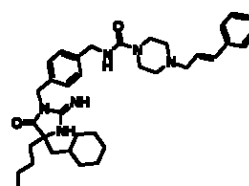
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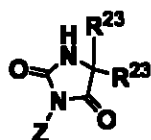


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Método Y



(En el esquema,

Método Y, Etapa 1:

La mezcla de reacción del compuesto Y1 obtenida a partir del Método L ($R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) (0,1639 mmol), Y2 ($R^{23} = \text{H}$; $R^{23} = \text{Pr}$) (0,1967 mmol), resina PS-EDC (0,4917 mmol) y HOBT (0,2459 mmol) en 3,5 ml de una mezcla de THF, MeCN y DMF (1:1:0,3) se agitó durante la noche a temperatura ambiente antes de agregar 6 eq de PS-resina trisamina, 3 eq de PS-resina de isocianato. Después de 6 horas la mezcla de reacción se filtró y la resina se lavó con THF, DCM y MeOH. El filtrado combinado se evaporó y el producto crudo se trató con 40% de TFA en DCM durante 40 minutos antes de

evaporar el solvente y el residuo se purificó sobre un sistema de RP HPLC para proporcionar el producto Y3 ($R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $R^{23} = \text{H}$; $R^{23} = \text{Pr}$).

Método Y, Etapa 2:

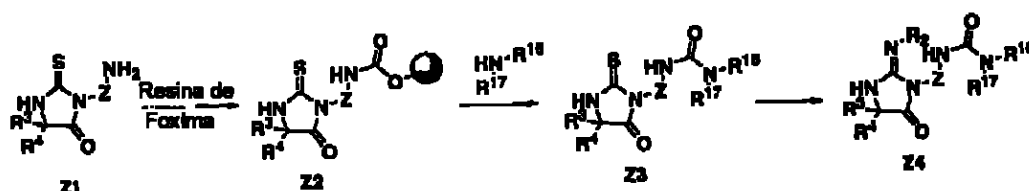
La solución de reacción de Y3 ($R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $R^{23} = \text{H}$; $R^{23} = \text{Pr}$) (0,030 mmol), carbonil diimidazol (0,032 mmol), y DIEA (0,09 mmol) en 0,5 ml de DCM se agitó durante el fin de semana a temperatura ambiente. Luego se purificó el producto crudo sobre una columna inversa para proporcionar el producto de tiohidantoina el cual se convirtió a Y4 ($R^2 = \text{H}$; $R^3 = \text{Me}$; $R^4 = i\text{-Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $R^{23} = \text{H}$; $R^{23} = \text{Pr}$).

Se prepararon los compuestos siguientes usando un método similar.

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
1457		413	414	1459		427	428
1458		413	414				

613
622

Método Z



(En el esquema, $-Z-NH-C(O)-N(R^{16})(R^{17})$ - es equivalente a R^1 sustituido con R^{21} , o R^1 sustituido con alquilo- R^{22} , donde R^{21} y R^{22} son $-N(R^{15})-C(O)-N(R^{16})(R^{17})$ y R^{15} es H, y donde Z es alquileno-arileno, alquileno-arileno-alquileno, alquileno-heteroarileno, alquileno-heteroarileno-alquileno, alquileno-cicloalquileno, alquileno-cicloalquileno-alquileno, alquileno-heterocicloalquileno, alquileno-heterocicloalquileno-alquileno, arileno, heteroarileno, cicloalquileno o heterocicloalquileno opcionalmente sustituidos).

Método Z, Etapa 1:

A la solución de la resina Phoxime™ (1,23 mmol/g) en DCM se le agregó la amina Z1 obtenida en el método L ($R^3 = \text{Me}$; $R^4 = \text{'Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$) (2 eq). La mezcla se agitó durante la noche antes de filtrar la resina y se lavó con DCM, MeOH, THF (3 ciclos), y luego DCM (x2), y se secó al vacío para obtener la resina Z2 ($R^3 = \text{Me}$; $R^4 = \text{'Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$).

Método Z, Etapa 2:

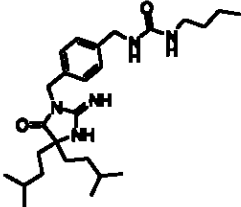
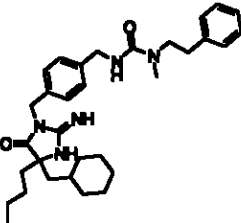
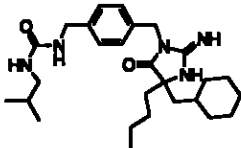
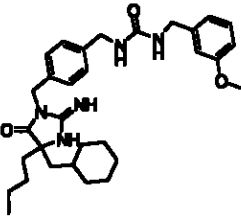
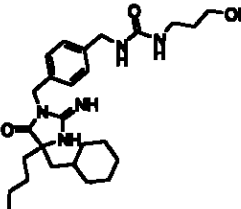
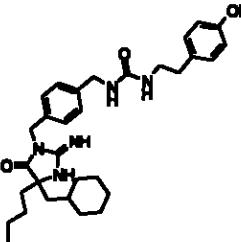
A la resina Z2 ($R^3 = \text{Me}$; $R^4 = \text{'Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$), hinchada en DCM, en tolueno se le agregó N-metilbencilamina (4 eq). La mezcla se calentó a 80-90°C durante la noche antes de agregar la resina MP-TSOH (1,3 mmol/g, 12 eq). La mezcla se agitó durante 1,5 horas, la solución se filtró y la resina se lavó con DCM y MeOH. La solución orgánica combinada se concentró al vacío para obtener Z3 ($R^3 = \text{Me}$; $R^4 = \text{'Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$; $R^{16} = \text{Me}$; $R^{17} = \text{Bn}$).

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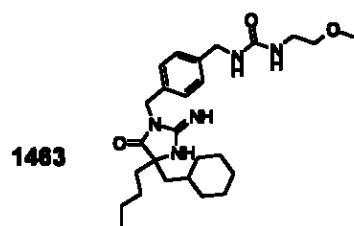
Método Z, Etapa 3:

Se generó el compuesto **Z4** ($R^3 = \text{Me}$; $R^4 = \text{'Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$, $R^{16} = \text{Me}$; $R^{17} = \text{Bn}$) a partir de **Z3** ($R^3 = \text{Me}$; $R^4 = \text{'Bu}$; $Z = \text{para}-(\text{CH}_2)\text{C}_6\text{H}_4(\text{CH}_2)-$; $R^{16} = \text{Me}$; $R^{17} = \text{Bn}$) usando un método similar al Método A etapa 3.

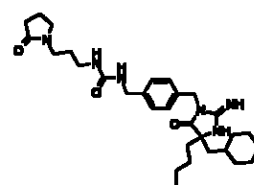
Se prepararon los compuestos siguientes usando un método similar.

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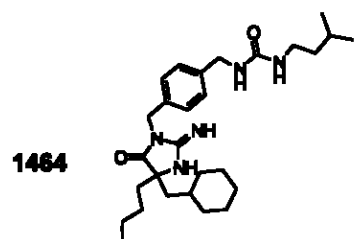
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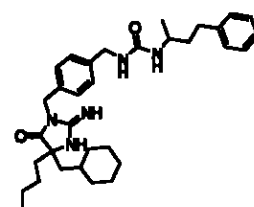
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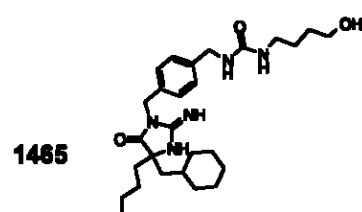
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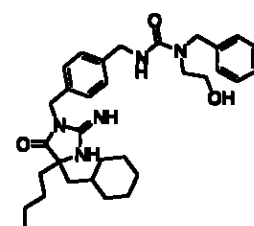
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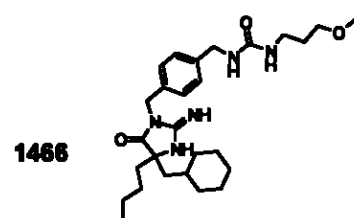
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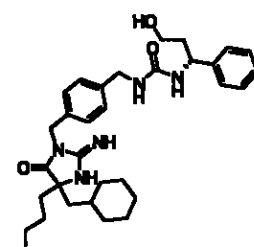
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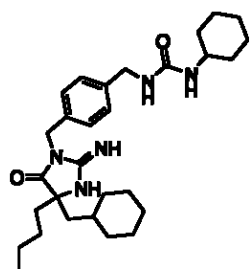
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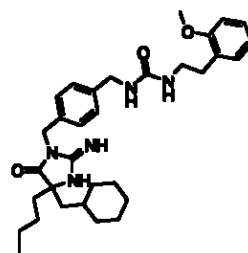
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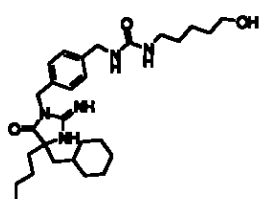
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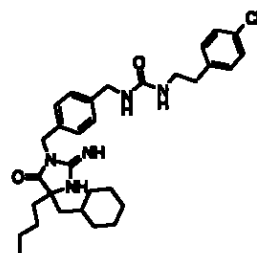
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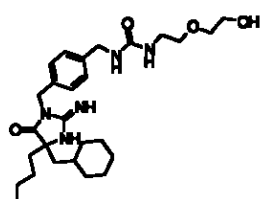
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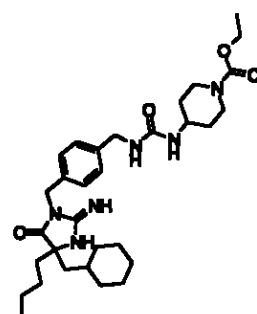
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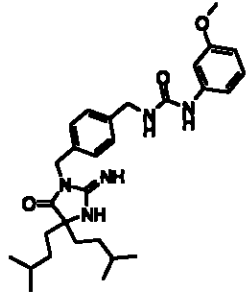


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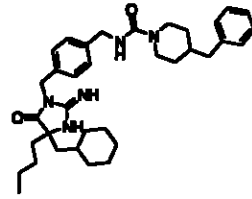
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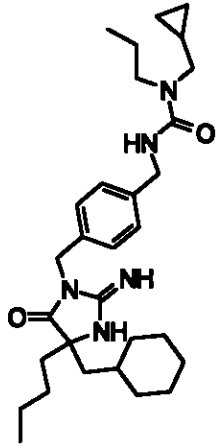
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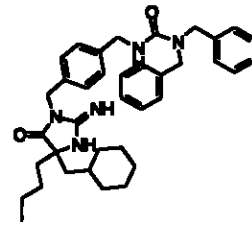
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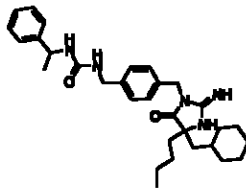
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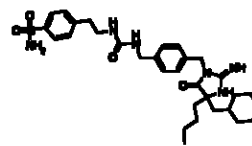
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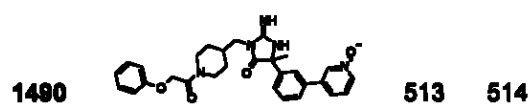
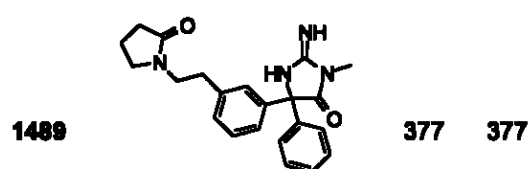
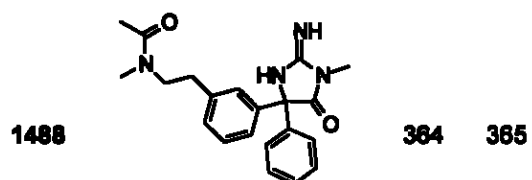
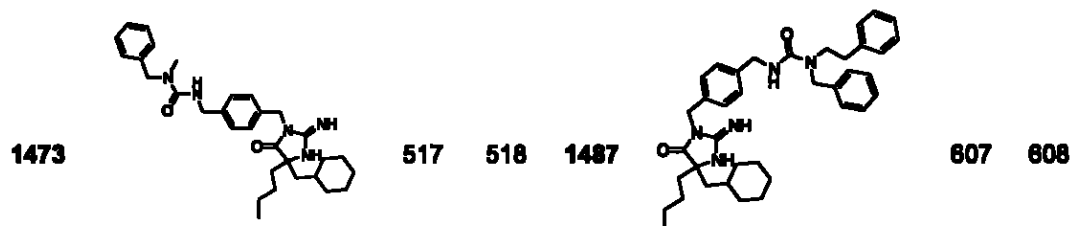
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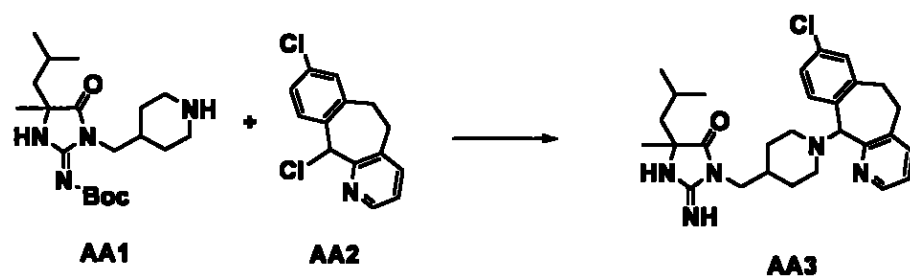
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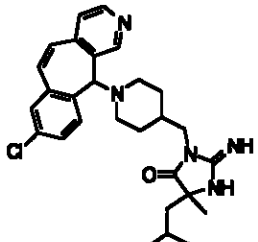
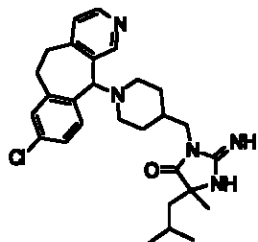
Método AA



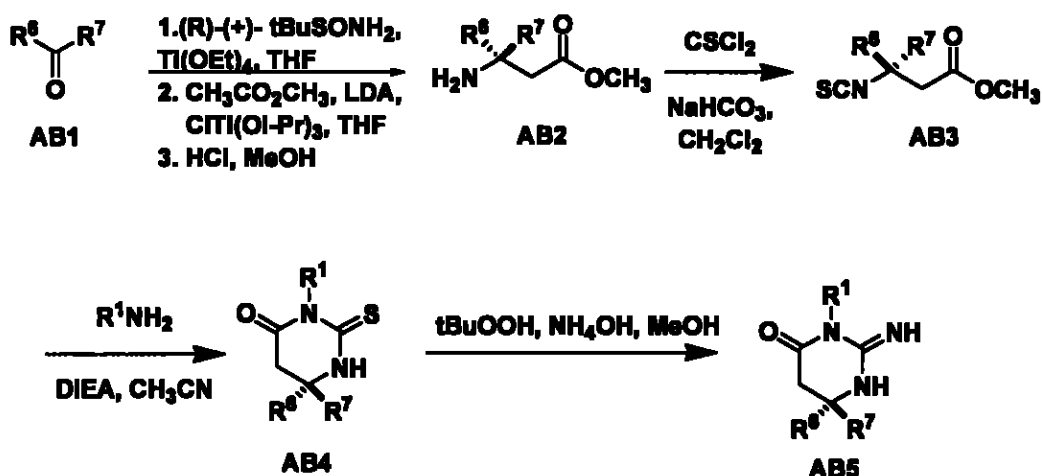
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620

Se hizo reaccionar 8,11-dicloro-6,11-dihidro-5H-benzo[5,6]ciclohepta[1,2-b]piridina (AA2) (18 mg) con AA1, obtenida en el método Q, y diisopropiletilamina (14 uL) en acetonitrilo (2,5 mL). La mezcla resultante se calentó a 65°C durante 18 horas. La mezcla de reacción se colocó en una placa preparativa de gel de sílice y se eluyó con hexano: acetato de etilo 3:1 para proporcionar el producto deseado el cual se trató con 40% de TFA. La evaporación del solvente seguida de purificación proporcionó el compuesto AA3.

Se prepararon los siguientes compuestos usando un método similar.

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
187		491	492	188		493	494

Método AB



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Método AB, Etapa 1:

A una solución de (R)-(+)-2-metil-2-propan sulfonamida (1,0 g, 8,3 mmoles, 1 eq) y AB1 (R^6 =Ph, R^7 = n-Bu) (3 mL, 9,1 mmoles, 1,1 eq) en THF anhidro (30 mL) a temperatura ambiente se le agregó $Ti(OEt)_4$ (7 mL, 17 mmoles, 2 eq). La mezcla se calentó a 70°C durante 24 horas. Después de enfriar a temperatura ambiente, la mezcla se vertió en 30 mL de salmuera bajo agitación vigorosa. La suspensión resultante se filtró a través de una almohadilla de Celite y el sólido se lavó con EtOAc (2 x 20 mL). El filtrado se lavó con salmuera (30 mL), se secó (Na_2SO_4), y se concentró al vacío. El residuo se cromatografió sobre sílice eluyendo con hexano/ Et_2O (5:1) para proporcionar 1,9 g (85%) de (R)-2-metil-N-(1-fenilpentiliden)propan-2-sulfinamida. ^1H RMN ($CDCl_3$, 300 MHz): δ 7,91 (m, 2H), 7,52-7,37 (m, 3H), 3,27 (m, 1H), 3,15 (m, 1H), 1,73-1,61 (m, 2H), 1,47-1,38 (m, 2H), 1,31 (s, 9H), 0,95 (m, 3H). EM(ESI): MH^+ = 265,9. HPLC t_R = 7,24, 7,58 min (E/Z = 5,5:1).

A una solución de acetato de metilo (0,6 mL, 6,9 mmoles, 2 eq) en THF (5 mL), LDA (2M en heptano/THF, se agregaron por goteo 3,4 mL, 6,9 mmoles, 2 eq) a través de una jeringa a -78°C. Después de agitar a -78°C durante 30 minutos, se agregó por goteo una solución de $CITi(Oi-Pr)_3$ (1,8 mL, 7,6 mmoles, 2,2 eq) en THF (5 mL). Después de agitar durante 30 minutos más se agregó por goteo una solución de (R)-2-metil-N-(1-fenilpentiliden)propan-2-sulfinamida (0,9 g, 3,4 mmoles, 1 eq) en THF (2 mL) a través de una jeringa. La mezcla se agitó a -78°C durante 3 horas y la TLC mostró que no quedaba material de partida. Se agregó una solución acuosa saturada NH_4Cl (10 eq) y la suspensión se calentó a temperatura ambiente. La mezcla se diluyó con H_2O (50 mL) y se agitó durante 10 minutos. Luego la mezcla se dividió entre H_2O (50 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (3 x 50 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron para proporcionar 1,1 g de un aceite de color castaño. La cromatografía sobre gel de sílice usando 50% de EtOAc/hexanos como eluyente proporcionó 0,8 g (76%) 3-((R)-2-metilpropan-2-ilsulfinamido)-3-fenilheptanoato de metilo en forma de un aceite de color amarillo. ^1H RMN ($CDCl_3$, 300 MHz): δ 7,15-7,07 (m, 5H), 3,35 (s, 1H), 3,19 (dd, J =16, 5,6Hz, 1H), 3,01 (dd, J =15,8, 5,5Hz, 1H), 2,07 (m, 2H), 1,71 (m, 2H), 1,35-1,26 (m, 4H), 1,17

621
630

(s, 9H), 0,89 (m, 3H). EM(ESI): MH^+ = 339,9. HPLC t_R = 7,50, 7,6 min (E/Z = 1,5:1)

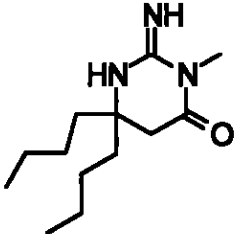
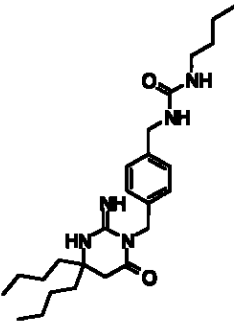
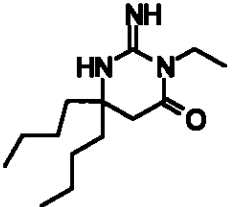
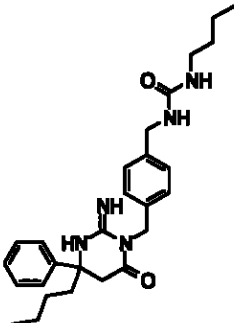
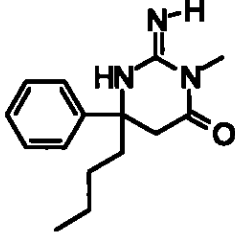
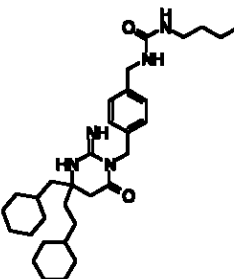
A una solución de 3-((R)-2-metilpropan-2-ilsulfinamido)-3-fenilheptanoato de metilo (0,4 g, 1,1 mmoles) en 12 mL de MeOH se le agregaron 16 mL de HCl 4N/dioxano. Después de agitar durante 30 minutos, se extrajeron los volátiles al vacío. El residuo se re-disolvió en MeOH (6 mL), se agitó durante 5 minutos y se evaporó nuevamente para proporcionar 0,30 g (97%) de AB2 (R^6 =Ph, R^7 = n-Bu) en forma de un sólido de color amarillo. $^1\text{HRMN}$ (CDCl_3 , 300 MHz): δ 9,01 (br s, 2H), 7,37-7,12 (m, 5H), 3,64 (m, 1H), 3,54 (s, 3H), 3,31 (m, 1H), 2,09 (m, 2H), 1,8 (m, 2H), 1,1 (m, 4H), 1,07 (s, 9H), 0,7 (m, 3H). EM(ESI): MH^+ = 235,9. HPLC t_R = 4,72 min.

Método AB, Etapa 2:

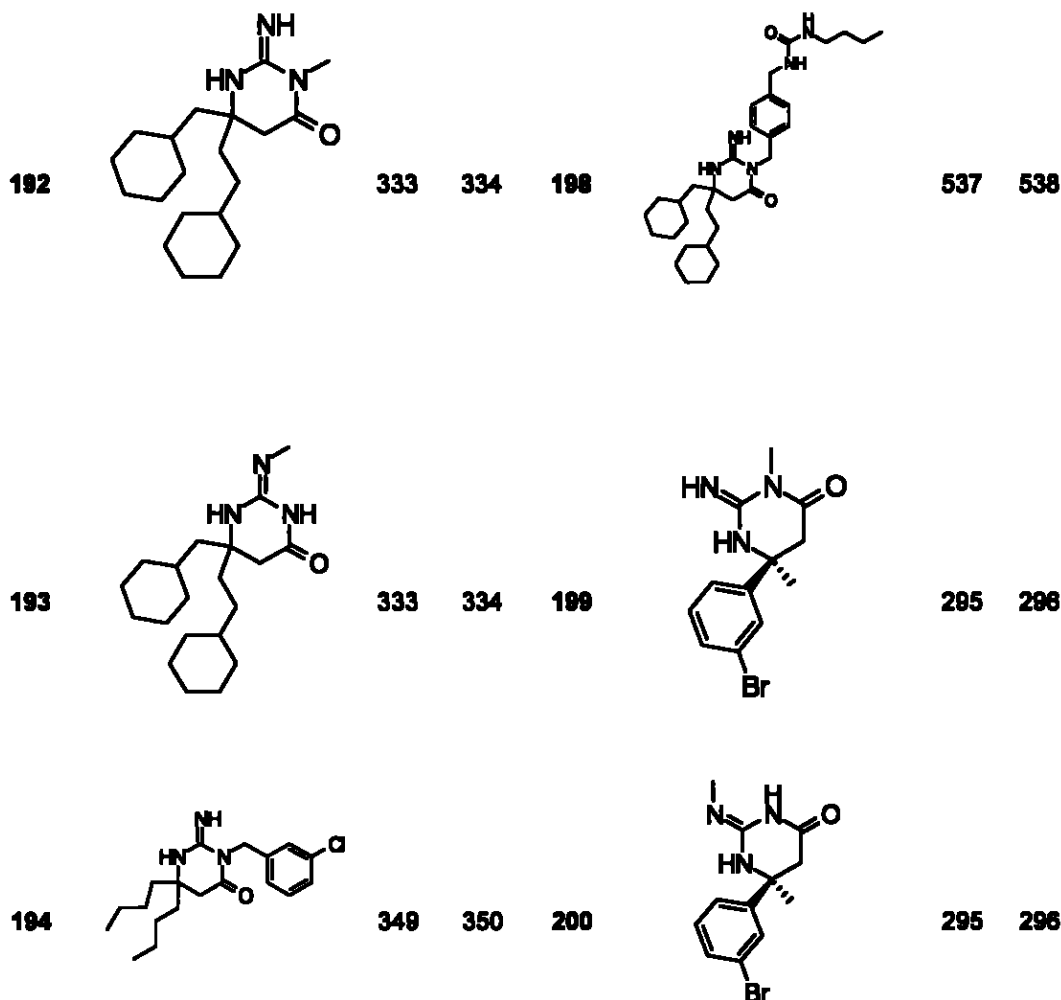
El tratamiento del compuesto AB2 (R^6 =Ph, R^7 =n-butilo) con tiofosgeno en CH_2Cl_2 en presencia de NaHCO_3 acuoso a 0°C genera el isotiocianato AB3 (R^6 =Ph, R^7 =n-butilo) el cual se convirtió al producto final usando un método similar al Método A Etapa 2 y al Método A Etapa 3 para proporcionar el producto AB5 (R^6 =Ph, R^7 =n-butilo, R^1 =Me). $^1\text{HRMN}$ (CDCl_3 , 300 MHz): δ 10,4 (br s, 1H), 7,25-7,11 (m, 5H), 3,23 (dd, J = 16, 5,6 Hz, 1H), 3,03 (s, 3H), 2,8 (dd, J = 15,8, 5,5 Hz, 1H), 2,49 (s, 1H), 1,78 (m, 2H), 1,1-1,0 (m, 4H), 0,99 (m, 3H). EM(ESI): MH^+ = 260,2. HPLC t_R = 5,09 min.

Se sintetizaron los compuestos siguientes usando métodos similares.

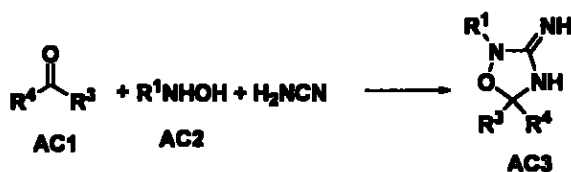
622
637

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
189		239	240	195		443	444
190		253	254	196		463	464
191		259	260	197		537	538

613
632



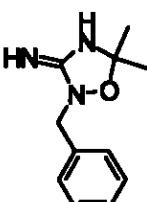
Método AC



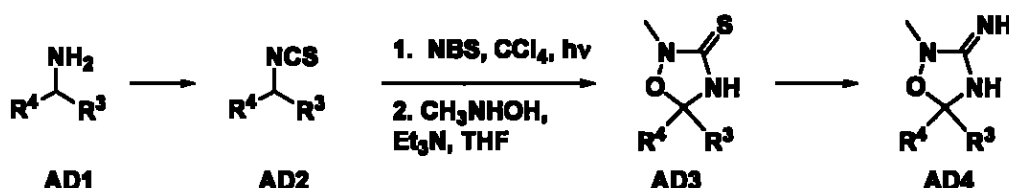
Se adaptó la síntesis a partir de un procedimiento de Hull, R. *et al*, *J. Chem. Soc.* 1963, 6028-6033. De este modo, a una solución de AC2 (R¹=bencilo) (0,72 g, 5,9 mmoles) en AC1 (R⁴=Me, R³=Me) (1,4 mL) se le agregó una solución acuosa al 50% de cianamida (0,31 mL, 8,0 mmoles). La reacción se calentó con agitación a reflujo (~40°C) durante 0,5 horas, y luego se enfrió a 25°C y se agitó durante 16 horas adicionales. Los volátiles se extrajeron al vacío y el residuo se dividió entre éter y H₂O. La capa orgánica se secó sobre

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Na₂SO₄, se filtró y se removieron los volátiles al vacío. El residuo se purificó por cromatografía en columna usando 5-10% de CH₃OH/CH₂Cl₂ como eluyente seguido de HPLC preparativa de fase inversa para proporcionar 0,15 g (8,0%) AC3 (R¹=bencilo, R⁴=Me y R³=Me) en forma de un sólido blanco. ¹H RMN (CH₃OH, 300 MHz): δ 7,35-7,33 (m, 5H), 4,71 (s, 2H), 1,46 (s, 6H); ¹³C RMN (CDCl₃, 75 MHz) δ 157,8, 135,6, 129,1, 128,5, 127,9, 104,2, 59,6, 28,8. EM (ESI) m/e 206,1 (M+H)⁺.

#	Estructura	PM	Obs. m/e
201		205	206

Método AD



Método AD, Etapa 1:

Se preparó AD2 (R³=Ph, R⁴=^tbutilo) a partir de AD1 usando un método similar al Método AB, etapa 2.

Método AD, Etapa 2:

La síntesis se adaptó de un procedimiento de Hussein, A. Q. *et al*, *Chem. Ber.* 1979, 112, 1948-1955. Por lo tanto, a una mezcla de AD2 (R³=Ph, R⁴=^t-butilo) (0,56 g, 2,7 mmoles) y trozos bajo ebullición en CCl₄ (25 mL) se le agregó *N*-bromosuccinimida (0,49 g, 2,7 mmoles). La mezcla se irradió con una fuente lumínica de 200 vatios durante 1 hora. La reacción se enfrió, el sólido se separó por filtración y los volátiles se extrajeron al vacío. La cromatografía sobre gel de

625
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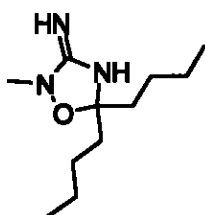
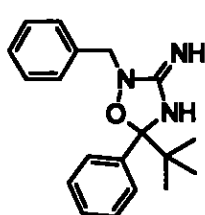
silice, eluyendo con 5% de EtOAc/hexano proporcionó 0,57 g (73%) de 1-(1-bromo-1-isotiocianato-2,2-dimetilpropil)benceno en forma de un polvo de color beige. ^1H RMN (CDCl_3 , 300 MHz): δ 7,63-7,61 (m, 2H), 7,37-7,26 (m, 3H), 1,17 (s, 9H); ^{13}C RMN (CDCl_3 , 75 MHz): δ 139,1, 129,0, 128,9, 128,6, 127,5, 91,2, 45,6, 26,6. EM (ESI) m/e 284,9 ($\text{M}+\text{H}$) $^+$.

A una solución de 1-(1-bromo-1-isotiocianato-2,2-dimetilpropil)benceno (0,13 g, 0,47 mmol) y la sal de clorhidrato de *N*-metilhidroxilamina (0,047 g, 0,57 mmol) en THF (3 mL) se le agregó trietilamina (0,18 mL, 1,32 mmoles). La mezcla se agitó a 25°C durante 16 horas, se filtró y los volátiles se extrajeron al vacío. El residuo se purificó por cromatografía en columna usando $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ como eluyente para proporcionar 0,050 g (42%) de AD3 ($\text{R}^3=\text{Ph}$, $\text{R}^4=\text{ter-Butilo}$) en forma de un sólido vítreo. ^1H RMN (CDCl_3 , 300 MHz): δ 7,35-7,26 (m, 5H), 3,38 (s, 3H), 1,0 (s, 9H); EM (ESI) m/e 251,1 ($\text{M}+\text{H}$) $^+$.

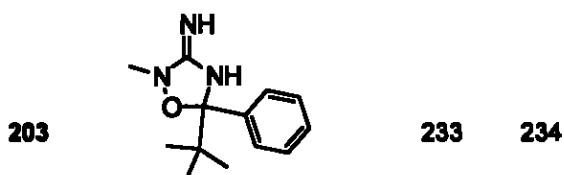
Método AD, Etapa 3:

A una solución de AD3 ($\text{R}^3=\text{Ph}$, $\text{R}^4=\text{ter-Butilo}$) (0,065 g, 0,26 mmol) en CH_3OH (5 mL) a 0°C se le agregó una solución de amoníaco acuoso (2 mL) seguido de una solución acuosa al 70% de hidróperóxido de *t*-butilo (2 mL). La reacción se dejó calentar a 25°C y se agitó durante 16 horas. Se extrajeron los volátiles y el residuo se purificó por HPLC de fase inversa para proporcionar 2,0 mg (2,2%) de AD4 ($\text{R}^3=\text{Ph}$, $\text{R}^4=\text{ter-Butilo}$) en forma de un aceite incoloro. ^1H RMN (CDCl_3 , 300 MHz) δ 7,47-7,43 (m, 2H), 7,39-7,35 (m, 3H), 3,23 (s, 3H), 1,0 (s, 9H); EM (ESI) m/e 234,2 ($\text{M}+\text{H}$) $^+$.

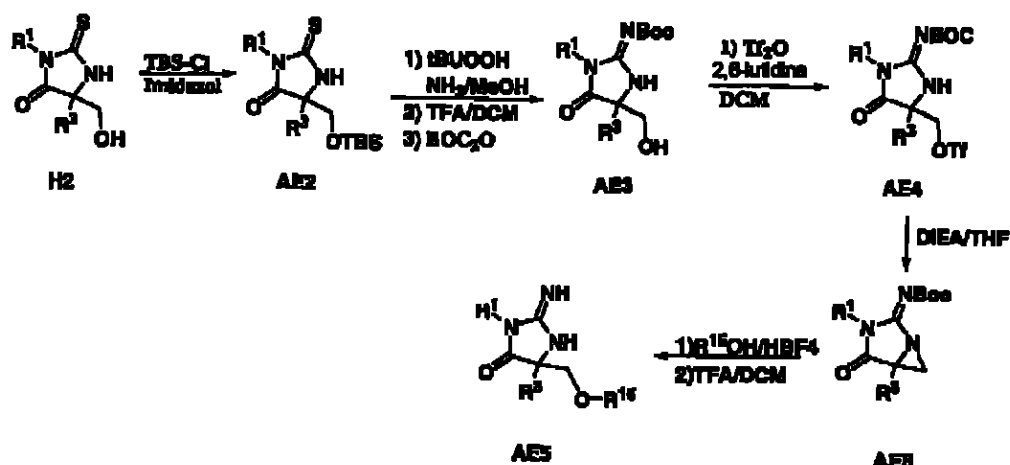
Se sintetizaron los compuestos siguientes usando métodos similares.

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
202		213	214	204		309	310

626
635



Método AE



Método AE, Etapa 1:

Se agregaron TBDEM-Cl (5,3 g, 35,19 mmoles) e imidazol (2,4 g, 35,19 mmoles) a una suspensión de H2 ($R^1=\text{Me}$, $R^3=\text{ciclohexilmetilo}$) (8,2 g, 31,99 mmoles) en 220 ml de DCM. La mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró, y el filtrado se diluyó con 1200 ml de EtOAc. La fase orgánica se lavó con NaHCO_3 saturado 3X y salmuera 3X, y se secó sobre Na_2SO_4 anhidro para proporcionar 12 g de AE2 ($R^1=\text{Me}$, $R^3=\text{ciclohexilmetilo}$), el cual se usó para la etapa siguiente sin purificación adicional.

Método AE, Etapa 2:

AE2 ($R^1=\text{Me}$, $R^3=\text{ciclohexilmetilo}$; 12 gramos crudo) se convirtió a iminohidantoina usando condiciones similares al Método A Etapa 3, que subsiguientemente se trató con 75% de TFA en DCM a temperatura ambiente durante 24 horas. El solvente se evaporó al vacío para proporcionar 13,6 g de un

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producto que se hizo reaccionar con anhídrido Boc para proporcionar 5,8 g de AE3 ($R^1=Me$, $R^3=ciclohexilmetilo$) después de purificación en columna.

Método AE, Etapa 3:

Se obtuvo AE4 ($R^1=Me$, $R^3=ciclohexilmetilo$) (8,2 g) a partir de AE3 (5,8 g) de acuerdo con la etapa 4 del método H.

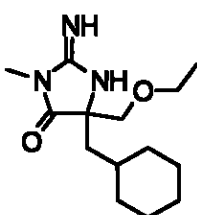
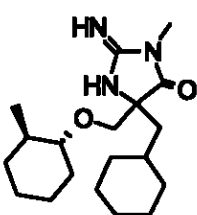
Método AE, Etapa 4:

A una solución de AE4 ($R^1=Me$, $R^3=ciclohexilmetilo$) (3,95 g, 8,38 mmoles) en THF anhidro (98 mL) se le agregó diisopropiletilamina (7 mL, 40 mmoles). La reacción se agitó bajo N_2 (gas) a temperatura ambiente. Después de 5,5 horas, la reacción se concentró y el material crudo se purificó a través de cromatografía evaporativa eluyendo con un gradiente de 0 a 75% de acetato de etilo en hexano para proporcionar AE5 ($R^1=Me$, $R^3=ciclohexilmetilo$) (2,48 g, 92%).

Método AE, Etapa 4:

A una solución de $R^{15}OH$ ($R^{15}=ciclobutilo$) (10 μ l) y HBF_4 (1 equiv) en cloruro de metileno anhidro (0,5 mL) se le agregó una solución de AE5 ($R^1=Me$, $R^3=ciclohexilmetilo$) (20 mg, 0,062 mmol) en cloruro de metileno (0,5 mL). La reacción se agitó durante la noche a temperatura ambiente. Se agregó ácido trifluoracético (1 mL) a la mezcla de reacción y la solución se agitó durante 1 hora a temperatura ambiente. La reacción se concentró y el material crudo se purificó por cromatografía preparativa de fase inversa HPLC/EM eluyendo con un gradiente de 7 minutos de 5 a 95% de CH_3CN en H_2O con 0,1% de ácido fórmico para proporcionar AE5 ($R^1=Me$, $R^3=ciclohexilmetilo$, $R^{15}=ciclobutilo$).

Los compuestos siguientes se sintetizaron usando un método similar:

#	Estructura	PM	Obs. m/e	#	Estructur	PM	Obs. m/e
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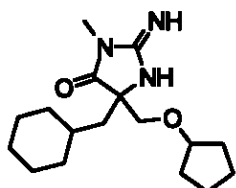
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206		293	294	227		335	336
207		295	296	228		335	336
208		295	296	229		335	336
209		295	296	230		335	336
210		295	296	231		335	336
211		305	306	232		335	336

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~~638~~

212



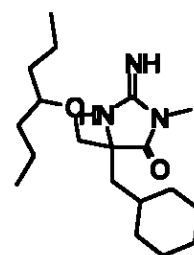
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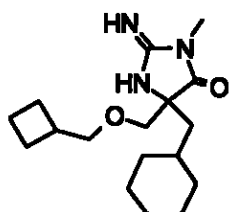
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213



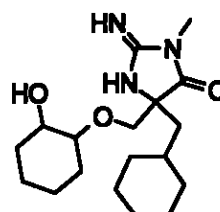
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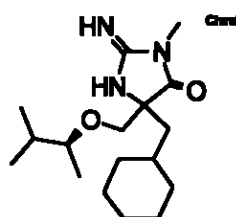
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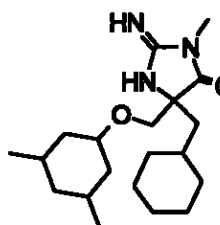
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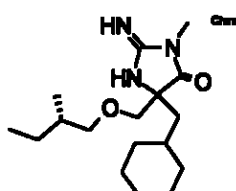
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215



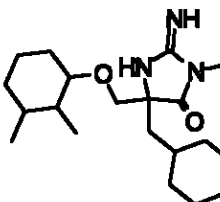
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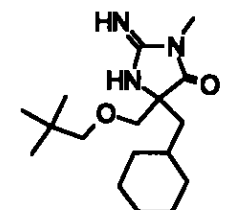
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216



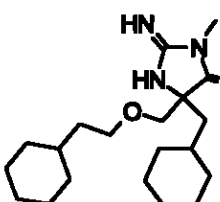
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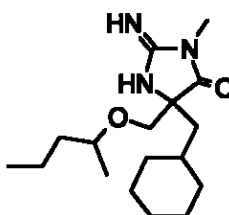
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217



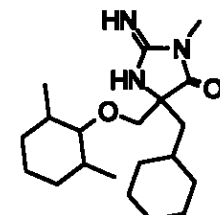
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238

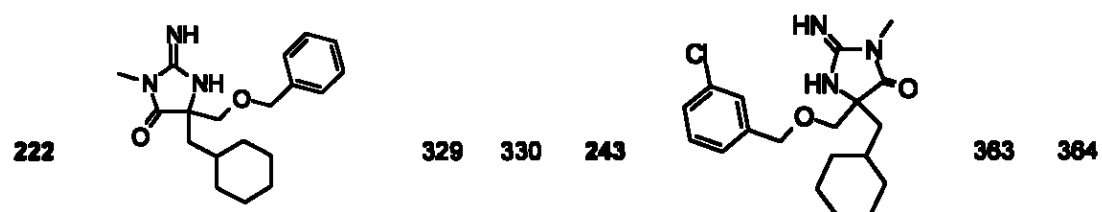
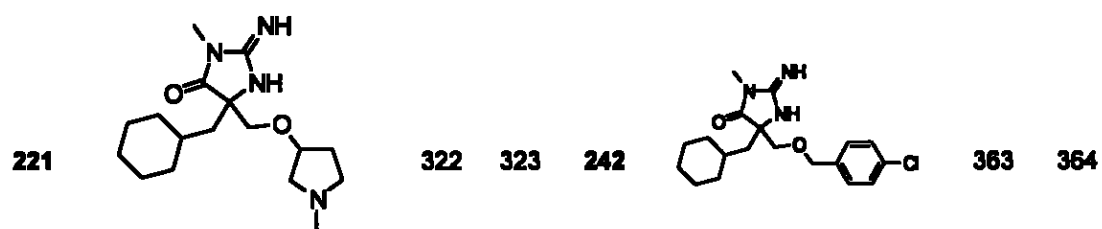
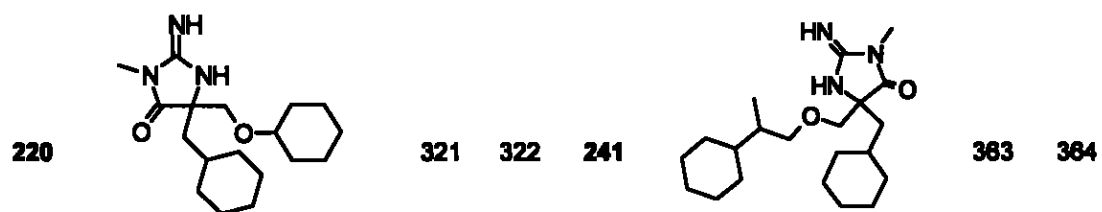
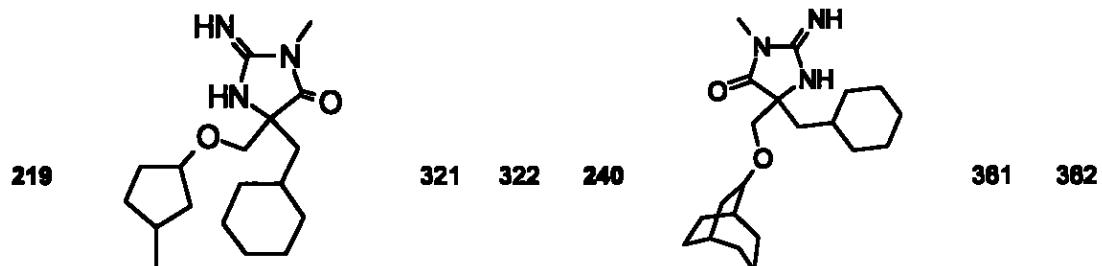
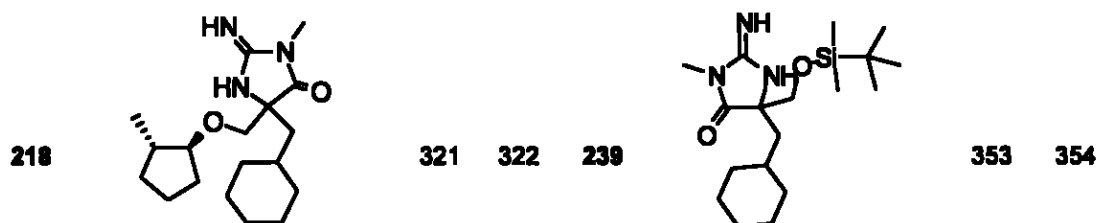
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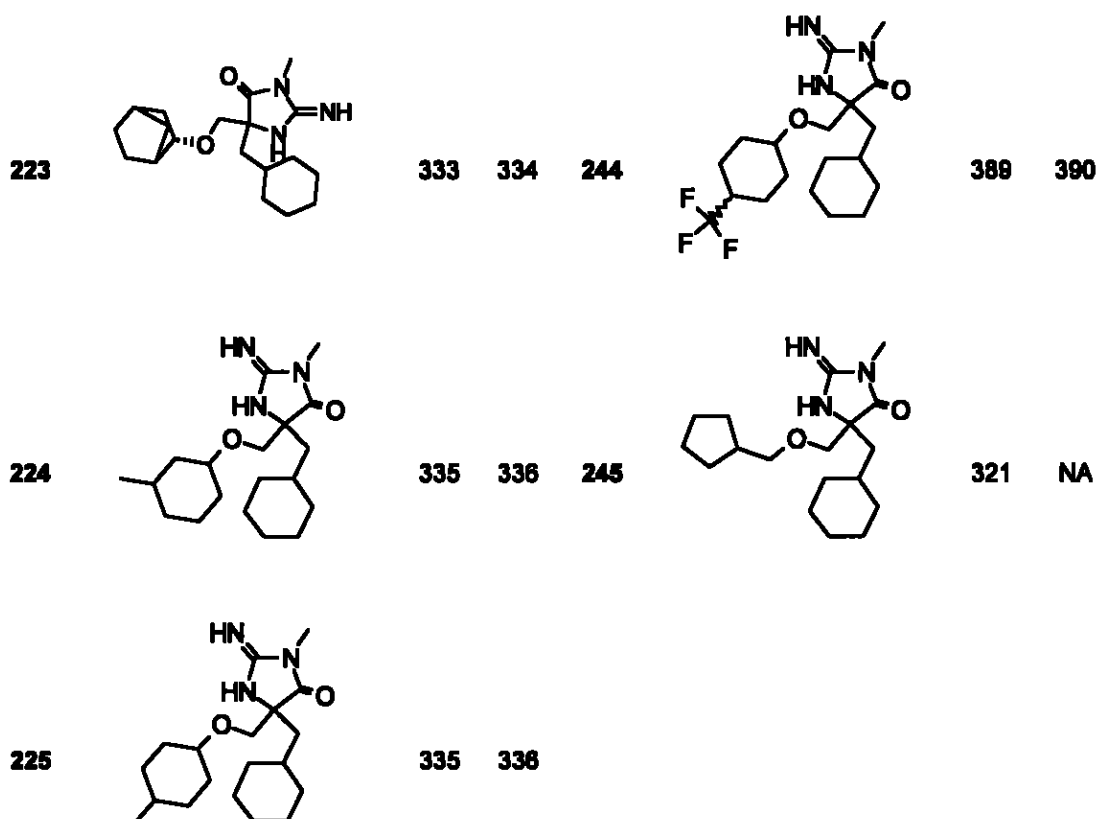


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640



Método AF

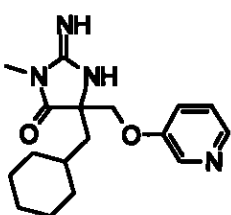
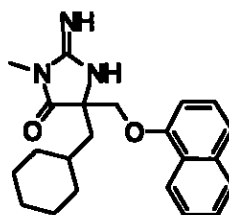
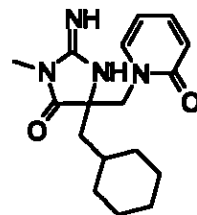
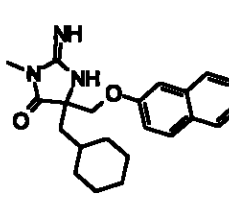
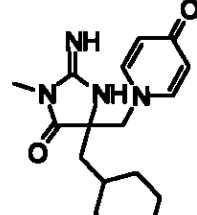
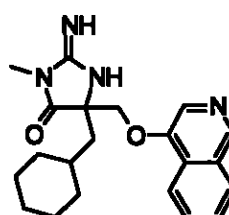
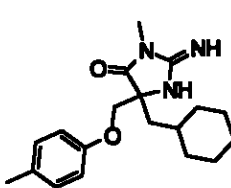
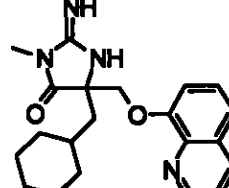


A una solución de tBuOK (9,5 mg, 0,0848 mmol) en 0,5 ml de THF anhidro se agregó ArOH (Ar=m-clorofenilo)(13 µl, 0,1273 mmol) en 0,5 ml de THF anhidro seguido de adición de AE4 (R¹=Me, R³=ciclohexilmetilo) (20 mg, 0,0424 mmol) en 0,5 ml de THF anhidro. La mezcla de reacción se agitó a temperatura ambiente durante 2 días antes de diluirla con 1 ml de MeCN, se trató con 100 mg de resina MP-TsOH y 100 mg de resina Amberlyst A26. La resina se extrajo por filtración y el filtrado se evaporó para proporcionar un producto que se trató con 50% de TFA durante 1 hora. Después de evaporación de TFA al vacío, el residuo se disolvió en 2 ml de MeCN, y se trató con 100 mg

632
641

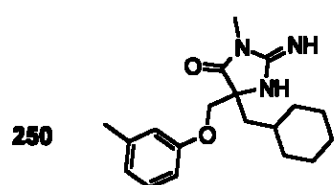
de resina MP-TsOH. La resina se lavó cuidadosamente con THF, MeCN y MeOH, y luego se trató con NH₃ 2M en MeOH para proporcionar AF2 (R¹=Me, R³=ciclohexilmetilo y R¹⁵=3-clorofenilo).

Se sintetizaron los compuestos siguientes usando un método similar:

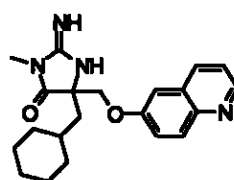
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247		316	317	310		365	366
248		316	317	311		366	367
249		329	330	312		366	367

633

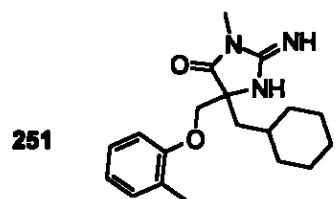
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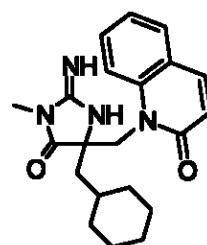
329 330 313



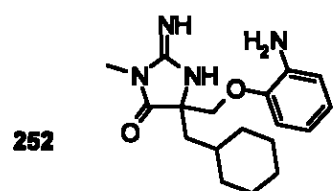
366 367



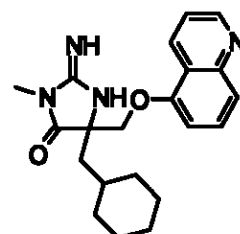
329 330 314



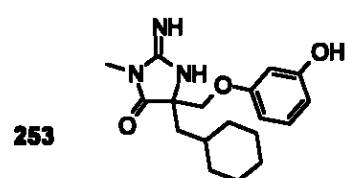
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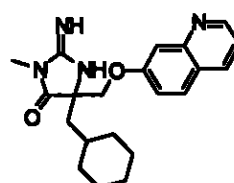
330 331 315



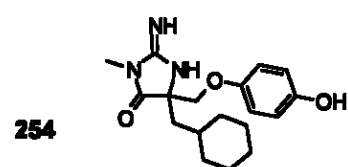
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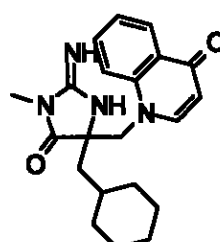
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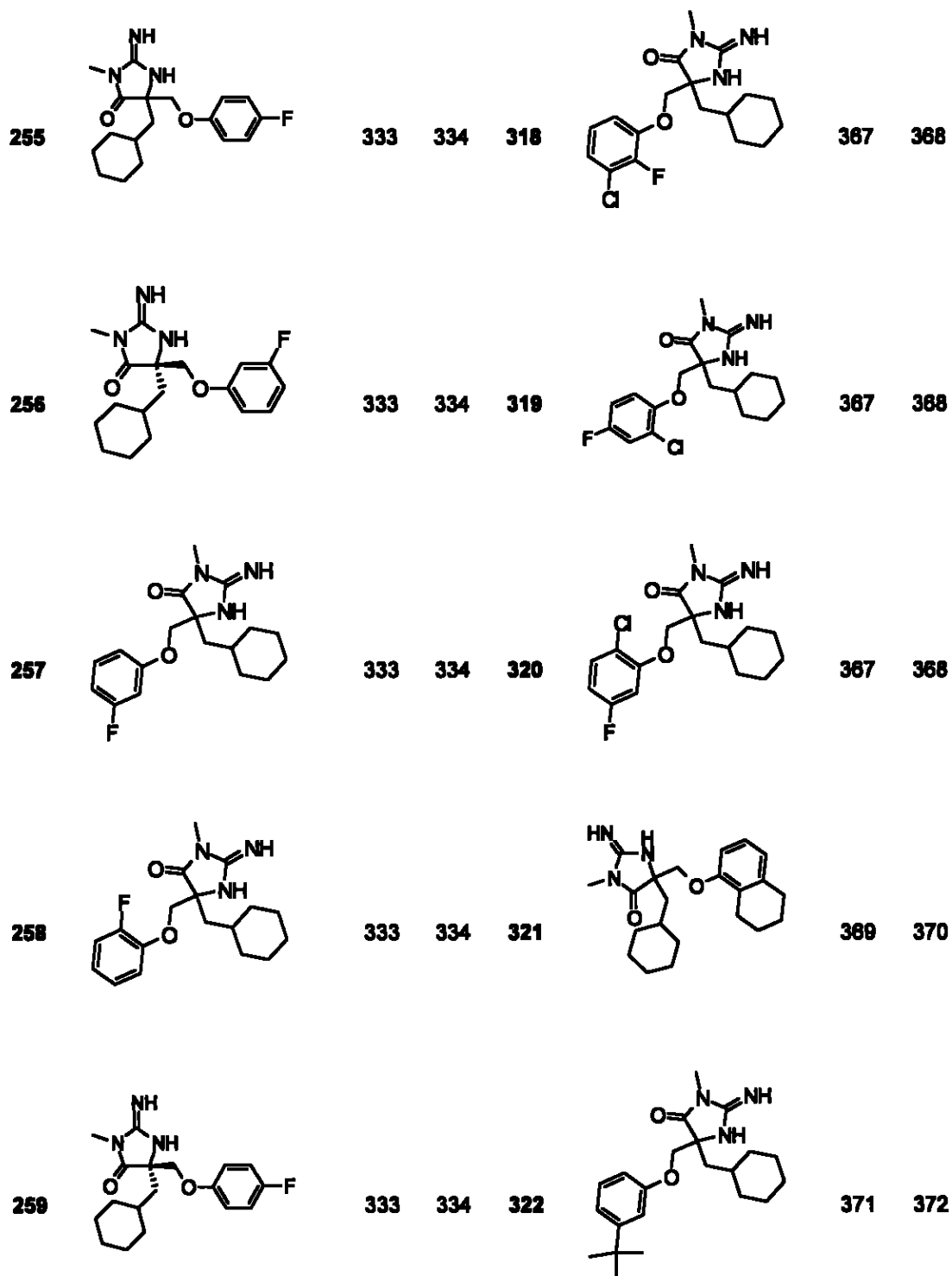


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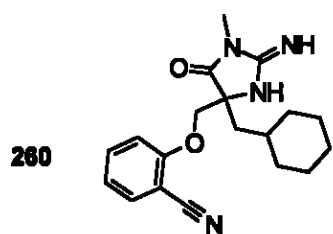


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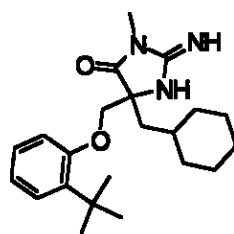
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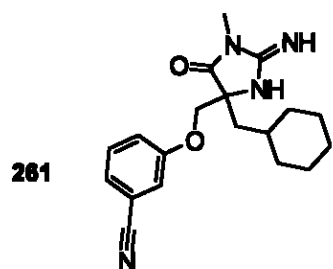
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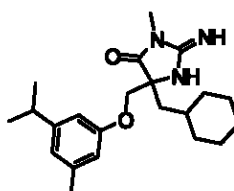
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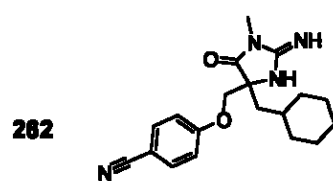
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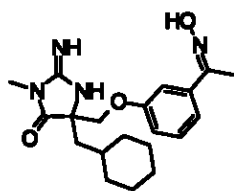
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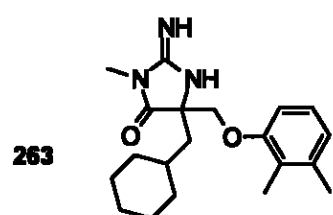
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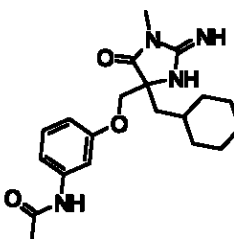
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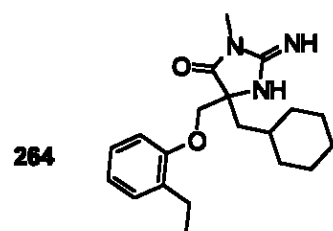
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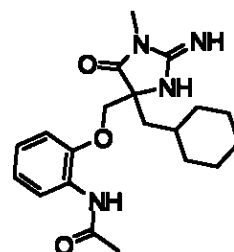
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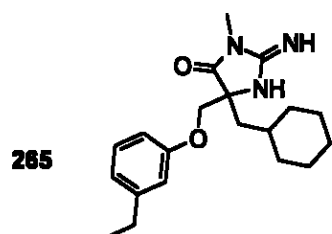


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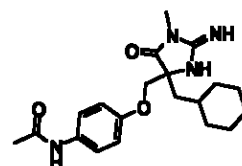


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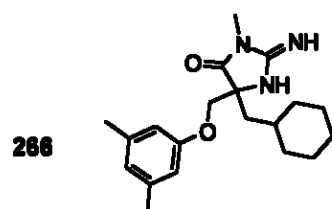
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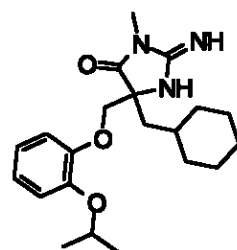
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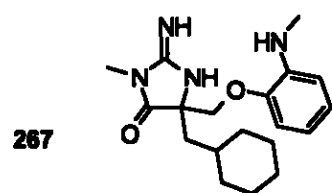
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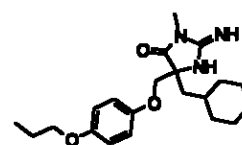
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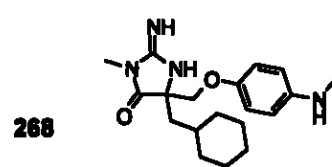
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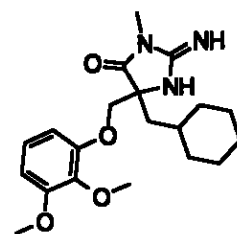
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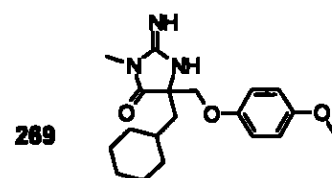
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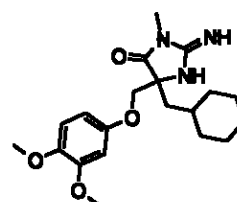
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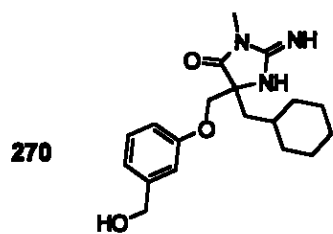
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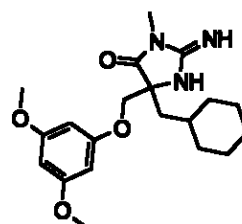
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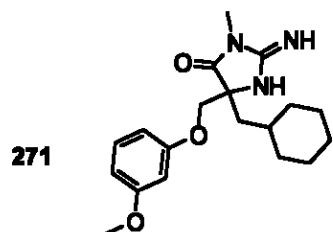
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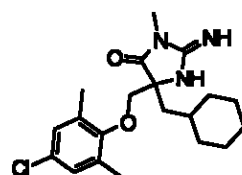
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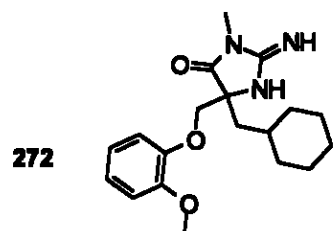
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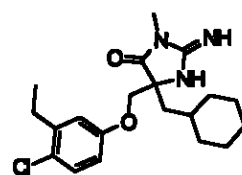
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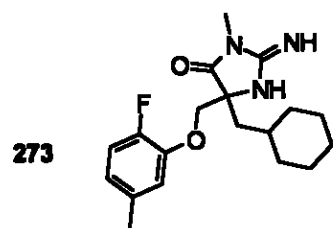
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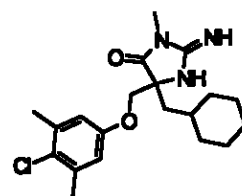
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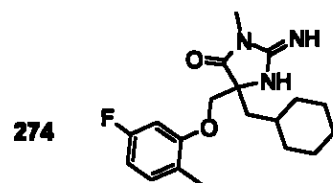
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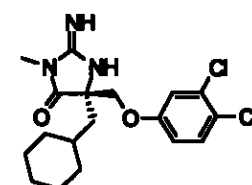
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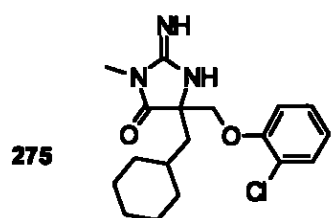
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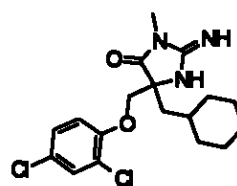
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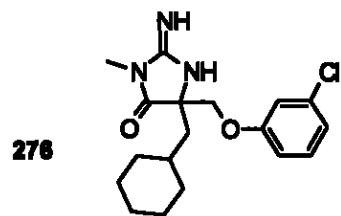
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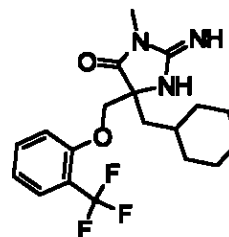
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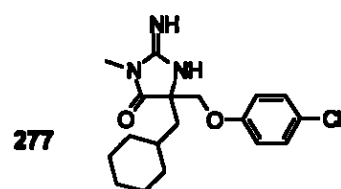
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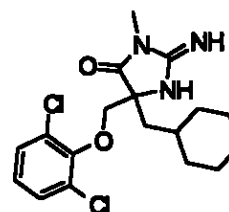
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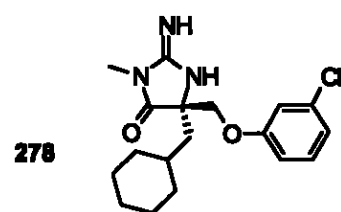
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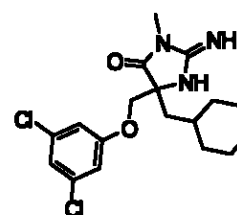
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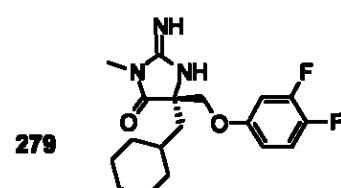
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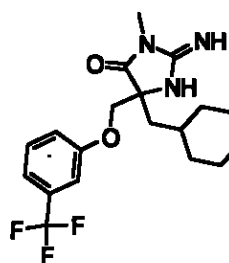
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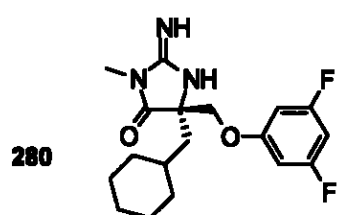
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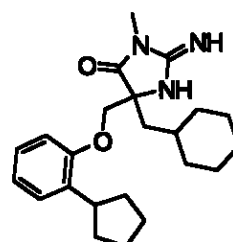
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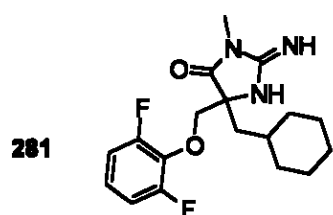
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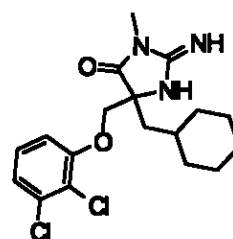
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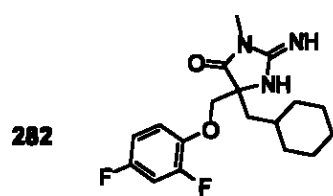
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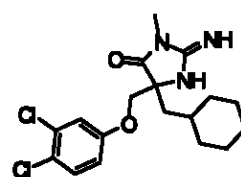
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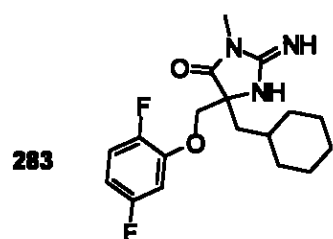
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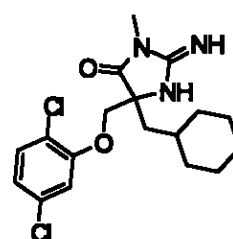
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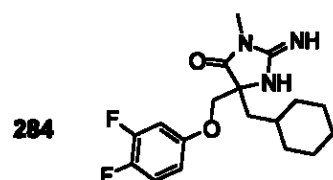
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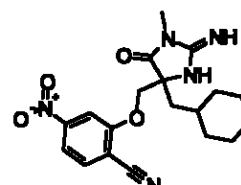
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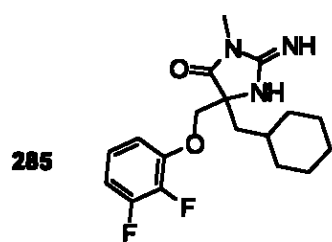
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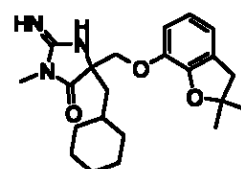
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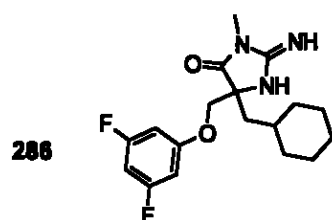
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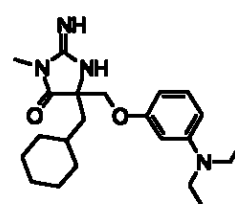
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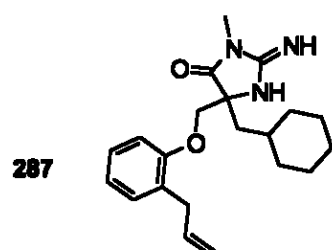
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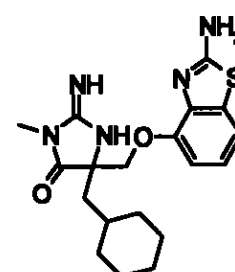
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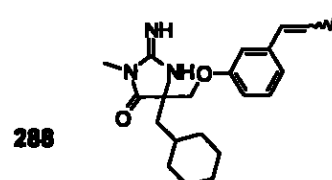
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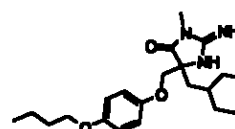
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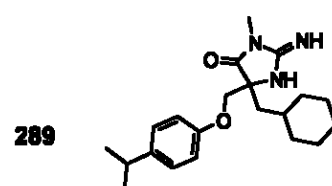
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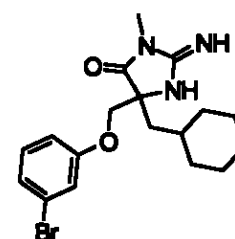
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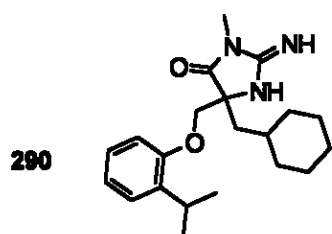


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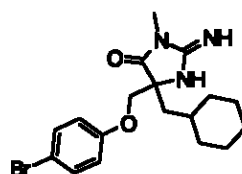


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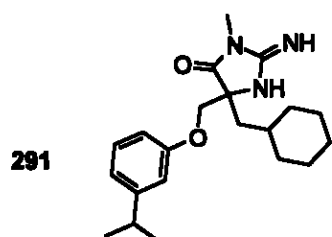
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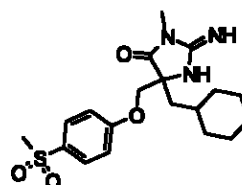
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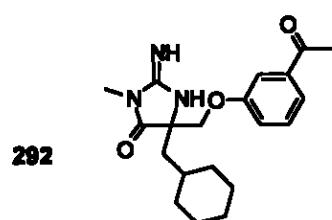
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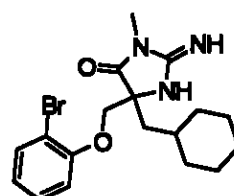
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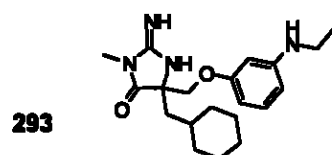
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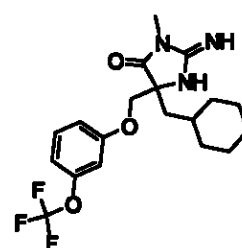
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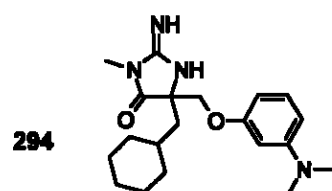
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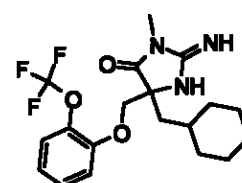
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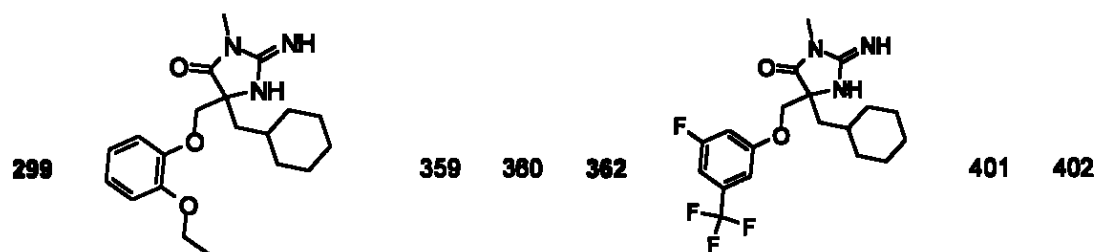
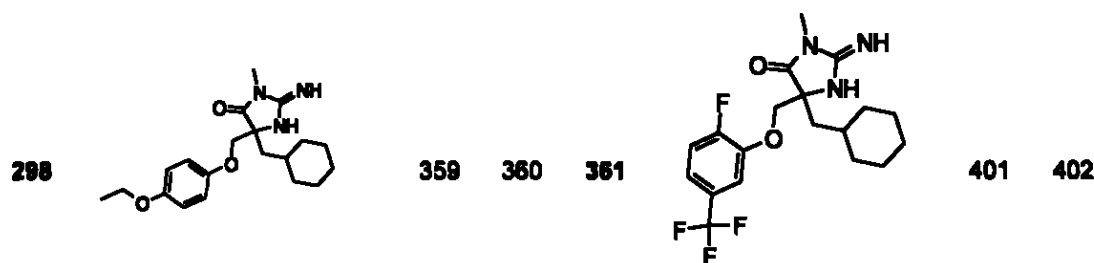
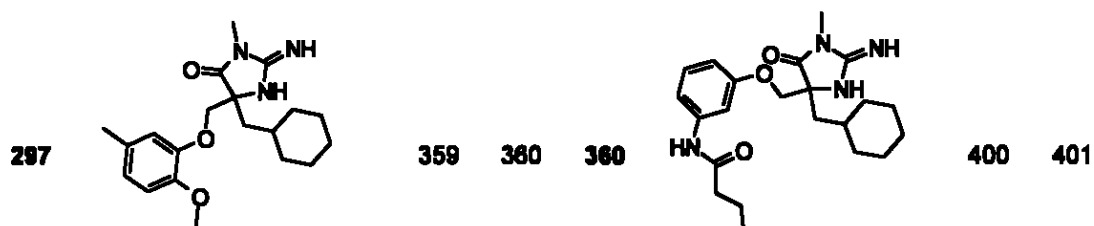
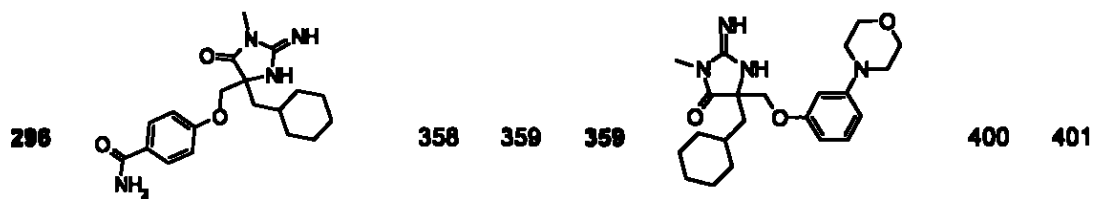
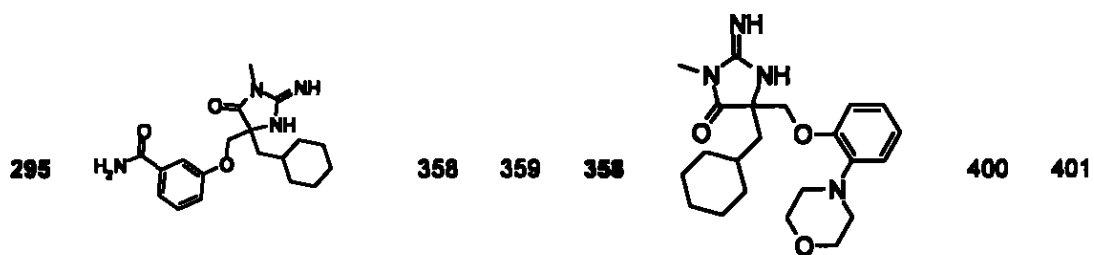


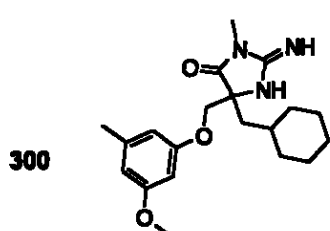
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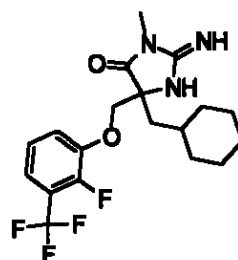
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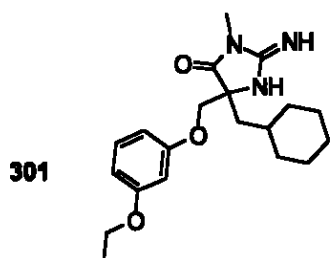




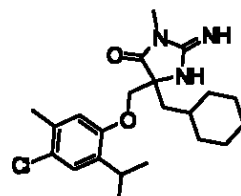
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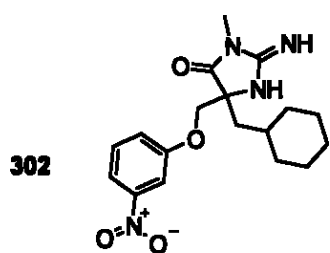
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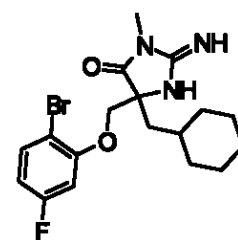
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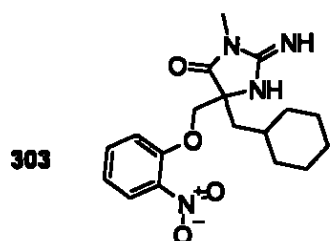
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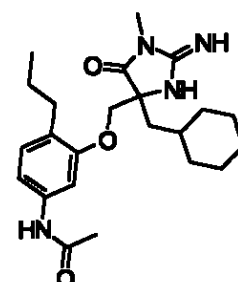
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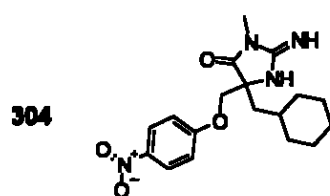
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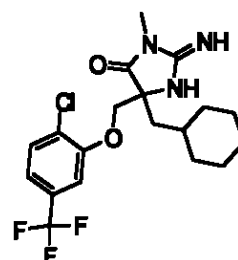
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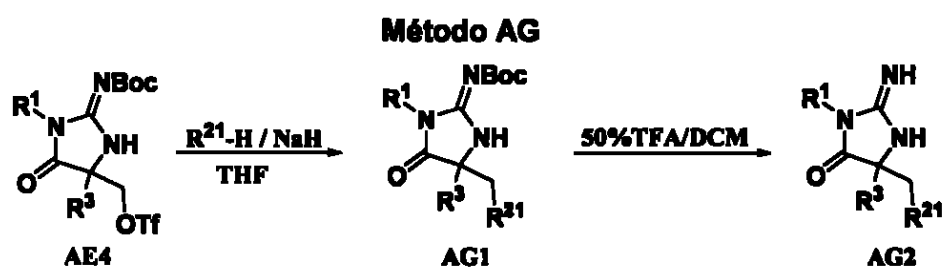
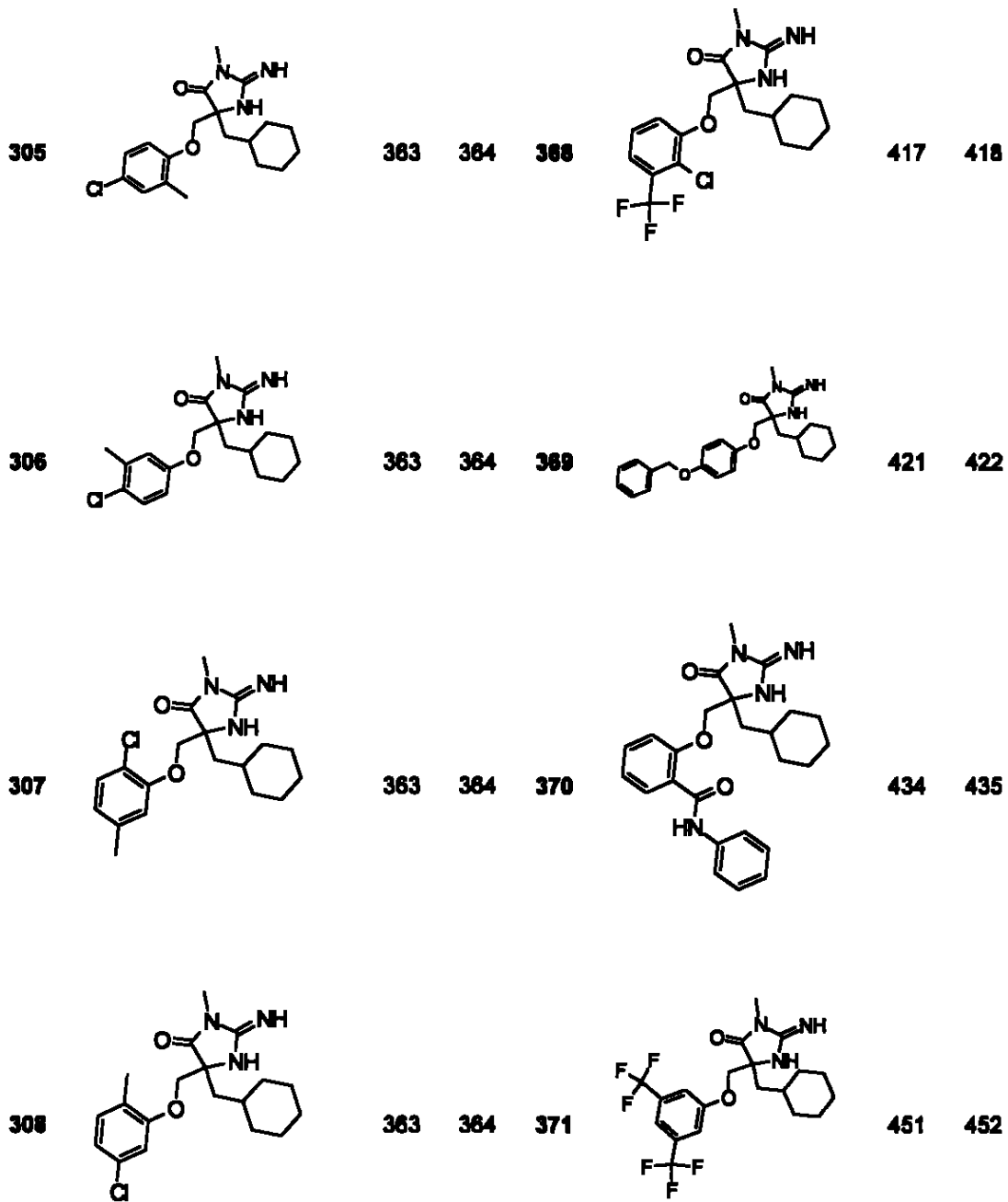


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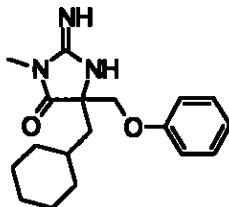
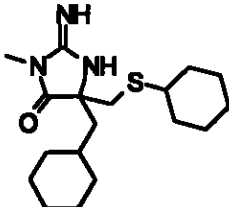
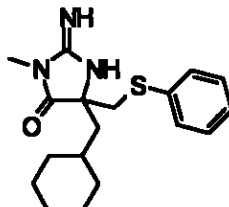
Método AG, Etapa 1:

Se trató $R^{21}\text{-H}$ ($R^{21} = \text{PhS-}$) (33 μl , 0,318 mmol) con NaH (10,2 mg, 60% en aceite mineral) en 0,5 ml de THF anhidro. Se agregó una solución de AE4 ($R^1 = \text{Me}$, $R^3 = \text{ciclohexilmetilo}$) (20 mg, 0,0424 mmol) en 0,5 ml de THF anhidro. La mezcla de reacción se agitó a temperatura ambiente durante la noche antes de dividirla entre éter y una solución acuosa saturada de NaHCO_3 . La fase acuosa se extrajo con éter dos veces. Las fases orgánicas combinadas se lavaron con salmuera dos veces y se secaron sobre NaSO_4 anhidro. El producto crudo se purificó por columna evaporativa con EtOAc/hexano para proporcionar 9 mg de AG1 ($R^{21} = \text{PhS-}$, $R^1 = \text{Me}$, $R^3 = \text{ciclohexilmetilo}$) (49,2% de rendimiento).

Método AG, Etapa 2:

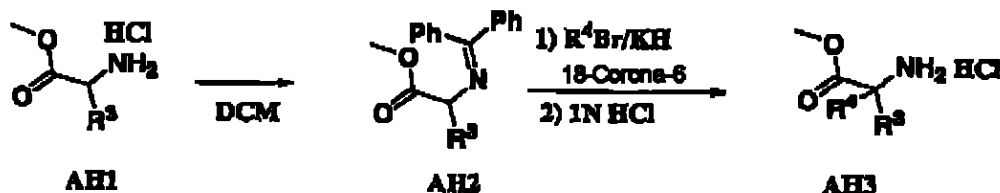
Se trató AG1 ($R^{21} = \text{PhS-}$, $R^1 = \text{Me}$, $R^3 = \text{ciclohexilmetilo}$) con 50% de TFA de acuerdo con la Etapa 6 del método H para obtener AG2 ($R^{21} = \text{PhS-}$, $R^1 = \text{Me}$, $R^3 = \text{ciclohexilmetilo}$).

Se sintetizaron los compuestos siguientes usando métodos similares.

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
372		315	316	374		337	338
373		331	332				

646
659

Método AH



Método AH, Etapa 1:

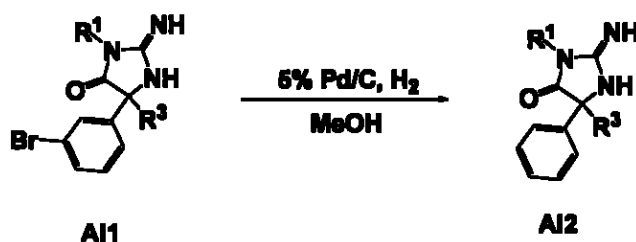
Se agregó benzofenona imina (3,27g, 18,04 mmoles) a una suspensión de AH1 (R^3 =ciclohexilmetilo) (4 g, 18,04 mmoles) en 65 ml de DCM. La mezcla de reacción se agitó a temperatura ambiente durante la noche bajo N_2 antes de filtrar el sólido, y el solvente se evaporó. El residuo se disolvió en 100 ml de éter, se lavó dos veces con agua y se secó sobre MgSO_4 anhidro. El producto crudo se purificó por columna evaporativa para proporcionar 5,08 g (80,57% de rendimiento) de AH2 (R^3 =ciclohexilmetilo).

Método AH, Etapa 2:

Una solución de AH2 (R^3 =ciclohexilmetil) (1g, 2,86mmoles) en 12 ml THF anhidro, se agregó a una suspensión de 18-corona-6 (0,76g, 2,86mmoles) y 30% de KH en aceite mineral (1,16g, 8,58mmoles) en 4ml THF anhidro bajo N_2 . La mezcla se enfrió en un baño de hielo y se agregó luego R^4Br (R^4 =3-piridilmetil, en forma de la sal de bromhidrato). La mezcla de reacción se agitó en un baño de hielo durante 30 minutos y a temperatura ambiente durante 2 horas más antes de apagar la reacción con 2ml de HOAc/THF/ H_2O (0,25:0,75:1). La mezcla se diluyó con 40ml de EtOAc/ H_2O (1:1). La fase acuosa se extrajo con EtOAc 3 veces. La fase orgánica combinada se lavó con salmuera 3 veces y se secó sobre MgSO_4 anhidro. El producto crudo se purificó por cromatografía en columna para proporcionar 0,44g (rendimiento 35,14%) del producto, el cual se trató con HCl 1N (2,2ml, 2,22mmoles) en 3ml de éter en un baño de hielo seguido de agitación a temperatura ambiente durante la noche. La fase acuosa se evaporó y purificó sobre columna de fase inversa C-18 para proporcionar 0,22g (66% de rendimiento) de AH3 (R^4 =3-piridilmetilo; R^3 =ciclohexilmetil).

647
655

Método A1

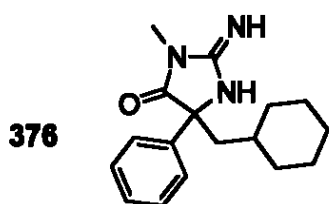


A una solución del compuesto A11 ($R^1=\text{Me}$, $R^3=\text{n-Bu}$) (34mg, 0,105mmol) en metanol (1ml) se le agregó 10% de Pd/C (5mg). La mezcla se mantuvo bajo un balón de H_2 durante 1 hora. Después de filtración del catalizador, el filtrado se concentró para obtener el producto crudo. El residuo se purificó por RP HPLC para obtener el compuesto A12 ($R^1=\text{Me}$, $R^3=\text{n-Bu}$) (25mg, 100%). PM observado ($\text{M}+\text{H}$) 246,1; Masa exacta 245,15. ^1H RMN (400 MHz, CD_3OD): δ = 7,59 (m, 2H), 7,36 (m, 3H), 3,17 (s, 3H), 2,17 (m, 2H), 1,27 (m, 4H), 0,86 (t, 3H, $J=7,2\text{Hz}$).

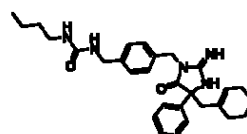
Se sintetizaron los compuestos siguientes usando un método similar:

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
375		283	284	380		463	464

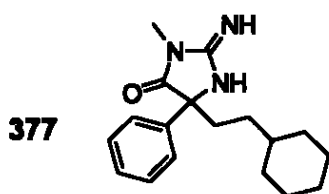
648
656



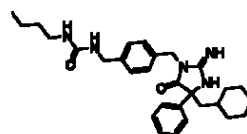
285 286 381



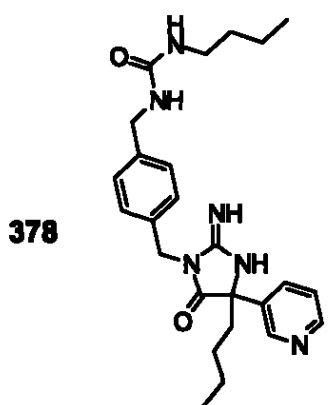
487 488



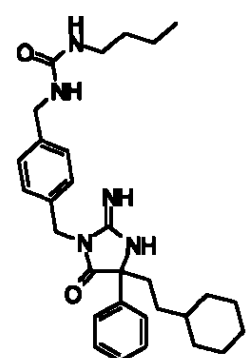
299 300 382



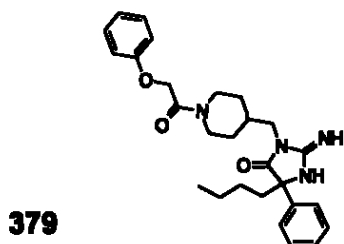
489 490



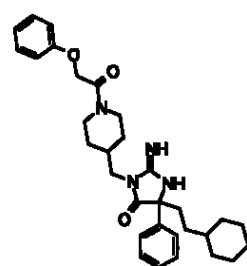
450 451 383



503 504

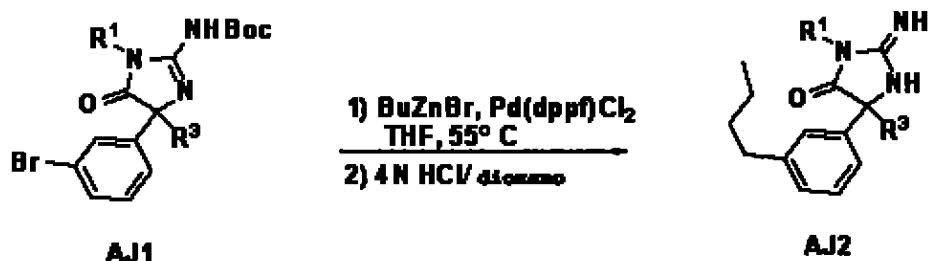


462 463 384



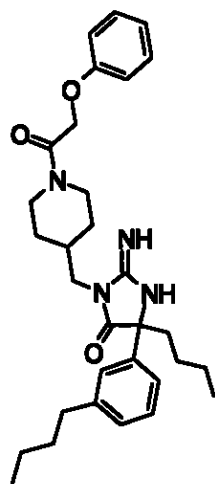
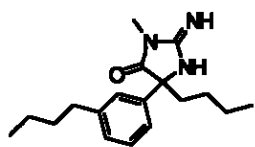
516 517

Método AJ



A una mezcla del compuesto **AJ1** (R¹=Me, R³=n-Bu) (70mg, 0,165mmol) y bromuro de butilzinc (1,32ml, 0,6mmol) se le agregó Pd(dppf)Cl₂. La mezcla se desgasificó, se selló y se calentó a 55°C durante 1 día. La mezcla se diluyó con CH₂Cl₂ y NH₃/H₂O. La capa orgánica se separó, se secó, se concentró y purificó por RP HPLC para obtener un producto que se trató luego con HCl/dioxano 4N durante 30 minutos para proporcionar el compuesto **AJ2**(R¹=Me, R³=n-Bu) (12mg, 25%). PM observado (M+H) 302,1; ¹H RMN (400 MHz, CD₃OD): δ = 7,32 (m, 3H), 7,22 (m, 1H), 3,19 (s, 3H), 2,65 (m, 2H), 2,20 (m, 2H), 1,60 (m, 2H), 1,38 (m, 4H), 1,24 (m, 2H), 0,92 (m, 6H).

Se sintetizó el compuesto siguiente de manera similar:

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
386		518	519	385		301	302

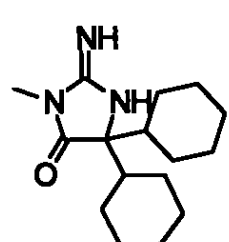
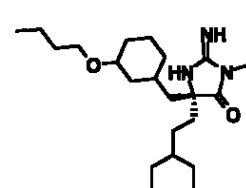
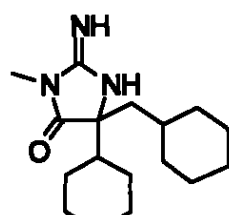
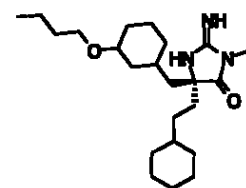
650
658

Método AK

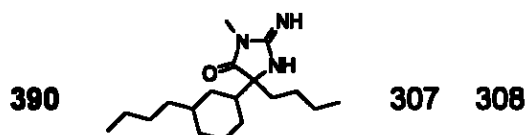
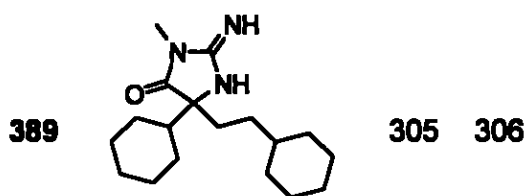


A una solución de AK1 ($R^1=\text{Me}$, $R^3=\text{n-Butilo}$, $R^{21}=\text{n-Bu}$) (9mg, 0,03mmol) en metanol (1ml) se le agregó 5% de P/C (5mg), Rh/C (5mg) y HCl concentrado (0,05ml). La mezcla se mantuvo bajo H_2 345 Kpa (50 psi) durante 2 días. Después de filtración del catalizador, el filtrado se concentró para obtener el compuesto AK2 ($R^1=\text{Me}$, $R^3=\text{n-butilo}$, $R^{21}=\text{n-Bu}$) PM observado (M+H) 308,1. ^1H RMN (CD_3OD): $\delta = 3,16$ (s, 3H), 1,80 (m, 6H), 1,26 (m, 16H), 0,88 (m, 6H).

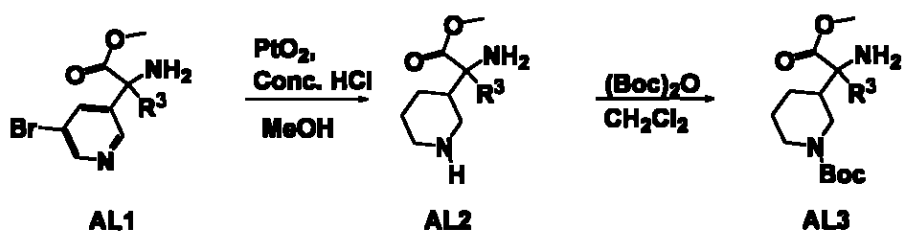
Los compuestos siguientes se sintetizaron un método similar:

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
387		277	278	391		391	392
388		291	292	392		391	392

651
659



Método AL



Método AL, Etapa 1:

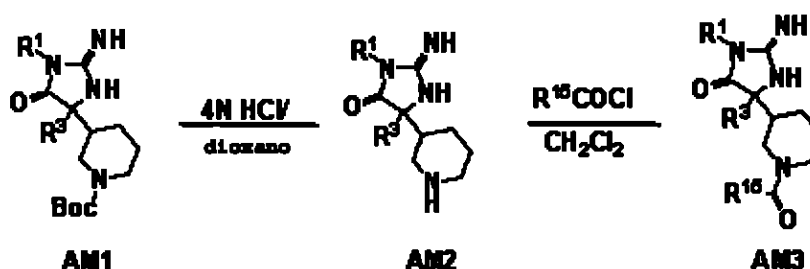
A una solución del compuesto AL1 ($R^3=n\text{-Bu}$) (418mg, 1,39mmoles) en metanol (8ml) se le agregó PtO_2 (40mg) y HCl concentrado (0,4ml). La mezcla se hidrogenó 345 kpa (50psi) durante 1 día. Después de filtración del catalizador, el filtrado se concentró. El residuo crudo se basificó a pH=11-12 con NaOH 1N. Esta mezcla se extrajo con acetato de etilo. La capa orgánica se separó, se secó y se concentró para proporcionar el compuesto AL2 ($R^3=n\text{-Bu}$) (316mg, 100%).

652
660

Método AL, Etapa 2:

A una solución del compuesto **AL2** ($R^3=n\text{-Bu}$) (300mg, 1,32mmoles) en diclorometano (6ml) se le agregó $(\text{BOC})_2\text{O}$ (316mg, 1,45mmoles). La mezcla se agitó a temperatura ambiente durante 1,5 horas. Se diluyó con agua y diclorometano. La capa orgánica se separó, se secó y se concentró para obtener el compuesto **AL3** ($R^3=n\text{-Bu}$) (464mg, 100%).

Método AM



Método AM, Etapa 1:

Se trató el compuesto **AM1** ($R^1=\text{Me}$, $R^3=n\text{-Butilo}$) con HCl 4N en dioxano durante 2 horas. La mezcla se concentró para obtener el compuesto **AM2** en forma de sal de HCl ($R^1=\text{Me}$, $R^3=n\text{-Butilo}$). PM observado ($M+H$) 470,1; ^1H RMN (CD_3OD): δ = 7,28 (m, 2H), 6,96 (m, 3H), 4,80 (m, 2H), 4,56 (m, 1H), 4,00 (m, 1H), 3,64 (m, 4H), 3,37 (m, 2H), 3,12 (m, 1H), 3,00 (m, 1H), 2,90 (m, 1H), 2,72 (m, 1H), 2,38 (m, 1H), 2,12-1,62 (m, 8H), 1,35 (m, 6H), 1,12 (m, 1H), 0,91 (m, 3H).

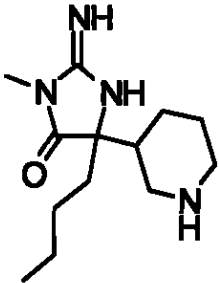
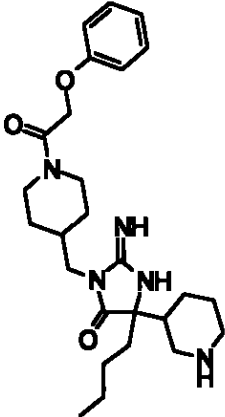
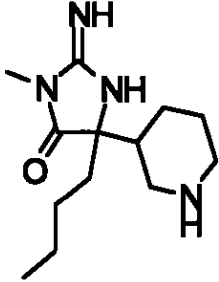
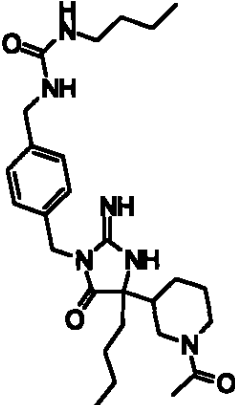
Método AM, Etapa 2:

A una solución del compuesto **AM2** ($R^1=\text{Me}$, $R^3=n\text{-Butilo}$) (32mg, 0,068mmol) en diclorometano (1ml) se le agregó cloruro de acetilo (5ul, 0,072mmol). La mezcla se agitó durante 2 horas. Luego se diluyó con CH_2Cl_2 y agua. La capa orgánica se separó, se secó, se concentró y se purificó por RP HPLC para obtener el compuesto **AM3** ($R^1=\text{Me}$, $R^3=n\text{-Butilo}$ y $R^{15}=\text{Me}$) PM observado ($M+H$) 512,3; ^1H RMN (400 MHz, CDCl_3): δ = 7,27 (m, 2H), 6,98 (m, 1H), 6,92 (m, 2H), 4,65 (s, 2H), 4,50 (m, 2H), 3,98 (m, 1H), 3,70 (m, 1H), 3,41

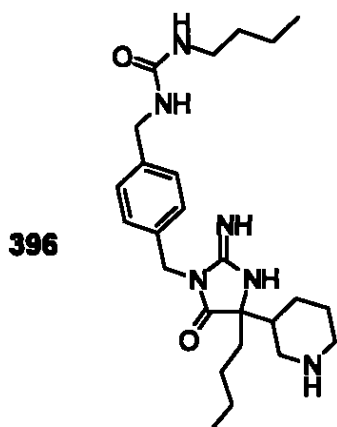
653
664

(m, 2H), 2,98 (m, 2H), 2,62 (m, 1H), 2,50 (m, 1H), 2,47 (m, 1H), 2,02 (m, 5H), 1,75 (m, 6H), 1,26 (m, 7H), 0,84 (m, 3H).

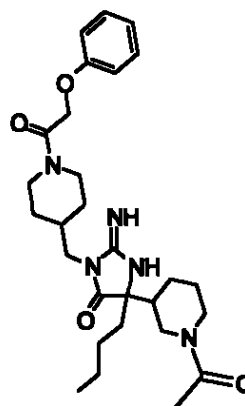
Se sintetizaron los compuestos siguientes usando un método similar:

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
394		252	253	397		469	470
395		252	253	398		498	499

654
662

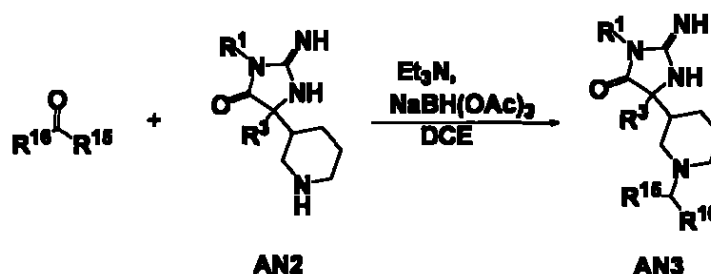


456 457 399



511 512

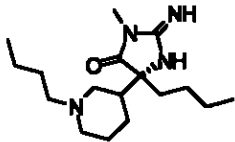
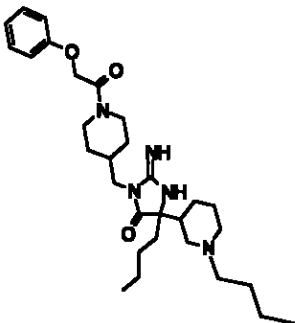
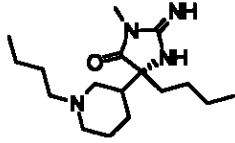
Método AN



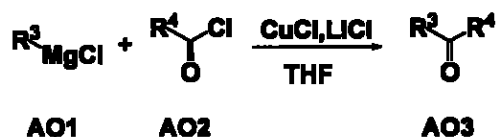
A una solución del compuesto **AN2** ($R^1=4\text{-N-(}\alpha\text{-fenoxiacetil)}$ piperidinilmetilo, $R^3=n\text{-Butilo}$) (28mg, 0,06mmol) en dicloroetano (2ml) se le agregó butiraldehído (5,3ul, 0,06mmol), trietilamina (8,4ul, 0,06mmol) y $\text{NaBH}(\text{OAc})_3$ (18mg, 0,084mmol). La mezcla se agitó durante la noche. Luego se diluyó con diclorometano y agua. La capa orgánica se separó, se secó, se concentró y se purificó por RP HPLC para obtener **AN2** ($R^1=4\text{-N-(}\alpha\text{-fenoxiacetil)}$ piperidinilmetilo, $R^3=n\text{-Butilo}$, $R^{15}=\text{propilo}$ y $R^{16}=\text{H}$) (5,4mg, 17%). PM observado ($M+H$) 526,1; masa exacta 525,37. ^1H RMN (CD_3OD): δ = 7,28 (m, 2H), 6,96 (m, 3H), 4,76 (m, 2H), 4,55 (m, 1H), 4,05 (m, 1H), 3,77 (m, 1H), 3,61 (m, 3H), 3,50 (m, 1H), 3,11 (m, 4H), 2,85 (m, 1H), 2,68 (m, 1H), 2,38 (m, 1H), 2,05 (m, 2H), 1,95 (m, 2H), 1,73 (m, 5H), 1,39 (m, 8H), 1,10 (m, 1H), 0,99 (m, 3H), 0,92 (m, 3H).

Se sintetizó el compuesto siguiente usando un método similar:

655
663

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
400		308	309	402		525	526
401		308	309				

Método AO

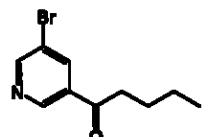


Una mezcla de cloruro de cobre (2,06g, 20,8mmoles) y cloruro de litio (1,76g, 41,6mmoles) en 100ml de THF se enfrió hasta -78°C. Esta mezcla, se le agregó gradualmente una solución 2,0M de AO1(R³=n-butilo) (10ml, 20mmoles). La reacción se calentó hasta -60°C, y se inyectó AO2 (R⁴=m-Br-Ph) (2,9ml, 22mmoles). La mezcla se agitó a -60°C durante 15 minutos y luego se calentó rápidamente a temperatura ambiente removiendo el baño de hielo seco. La reacción se apagó con agua y con NaHCO₃ saturado. Después de adición de éter dietílico, se formó un montón de precipitado y se filtró. A partir del filtrado

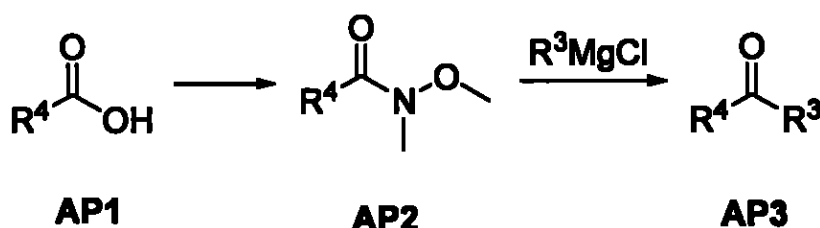
656
669

bifásico, se separó la capa orgánica, se secó, se concentró y se purificó por cromatografía de gel de sílice (10% EtOAc/hexano) para obtener la cetona AO3 ($R^4=m\text{-BrPh}$, $R^3=n\text{-Bu}$) (3,93g, 82%). PM observado ($M+H$) 241,1; masa exacta 240,01. ^1H RMN (400 MHz, CDCl_3): δ = 8,07 (m, 1H), 7,88 (m, 1H), 7,64 (m, 1H), 7,34 (m, 1H), 2,94 (t, 3H, $J=7,2\text{Hz}$), 1,71 (m, 2H), 1,40 (m, 2H), 0,95 (t, 3H, $J=7,6\text{Hz}$).

Se prepararon las cetonas siguientes de acuerdo con el Método 9:

Estructura	PM observada ($M+H$)	Masa exacta
	242,1	241,01

Método AP



Método AP, Etapa 1:

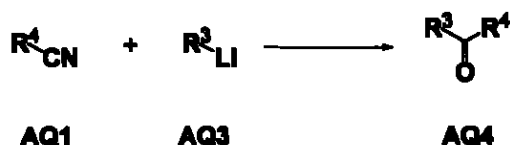
A una solución de AP1 ($R^4=3\text{-Bromofenilo}$) (5g, 25mmoles) en diclorometano (10ml) se le agregó clorhidrato de N,O-dimetilhidroxilamina (2,56g, 26,25mmoles) y luego se le agregó en porciones 4-metilmorfolina (2,95ml, 26,25mmoles). EDCI (5,04g, 26,25mmoles). La mezcla de reacción se agitó a temperatura ambiente durante la noche y luego se apagó con HCl 1N (60ml). La mezcla se extrajo con diclorometano. La capa orgánica se lavó con HCl 1N y salmuera, se secó sobre Na_2SO_4 , y se concentró para proporcionar la amida de Weinreb AP2 ($R^4=m\text{-Bromofenilol}$) (5,96g, 98%). PM observado ($M+H$) 244,1; masa exacta 243,99. ^1H RMN (CDCl_3): δ = 7,78 (m, 1H), 7,58 (m, 2H), 7,24 (m, 1H), 3,51 (s, 3H), 3,32 (s, 3H). Este material se usó en la etapa siguiente sin purificación.

657
665

Método AP, Etapa 2:

A una suspensión de doladuras de magnesio (1,19g, 48,8mmoles) en 30ml de THF se le agregó por goteo a una solución de R^3Br (R^3 =ciclohexiletilo) (5,73ml, 36,6mmoles) en 24ml de THF. Después de la a de la mitad de la solución de bromuro, se agregaron varios cristales de iodo para iniciar la reacción. La mezcla se tornó turbia y emanó calor. El resto de la solución de bromuro se agregó por goteo. La mezcla se agitó a temperatura ambiente durante 30 minutos, y luego se enfrió a 0°C, y se agregó AP2 (R^4 =m-BromoFenilo) (5,96g, 24,4mmoles). La mezcla se agitó a temperatura ambiente guante 3 horas y luego se apagó con HCl 1N hasta que no quedó Mg(0) residual. Las fases se separaron, y la capa acuosa se extrajo con éter. Las capas orgánicas combinadas se lavaron con salmuera, se secaron y concentraron. El producto crudo se purificó por cromatografía evaporativa (15% de EtOAc/hexano) para obtener la cetona AP3 (R^4 =m-BromoFenilo, R^3 =Ciclohexiletilo) (8,06g, 100%). PM observado (M+H) 295,2; masa exacta 294,06. ^1H RMN (400 MHz, $CDCl_3$): δ = 8,18 (m, 1H), 7,85 (m, 1H), 7,64 (m, 1H), 7,33 (m, 1H), 2,94 (t, 3H, J =7,2Hz), 1,70 (m, 9H), 1,63 (m, 4H).

Método AQ

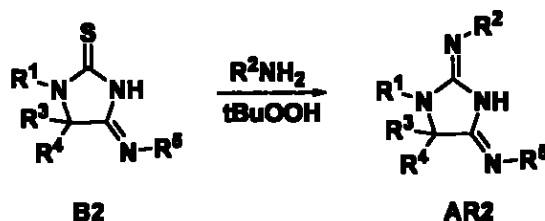


A una solución a -78°C de AQ1 (R^4 = ciclopropilo) (2,55 g, 38,0 mmoles) en éter dietílico (100 ml) se le agregó AQ3 (R^3 =n-Bu) (38 ml, 1,5 M en hexanos, 57 mmoles). Después de 45 minutos, el baño refrigerante se extrajo. Después de 3 horas a temperatura ambiente, se apagó la reacción por adición de agua por goteo y luego se diluyó adicionalmente con EtOAc y agua. Las fases se separaron y la capa acuosa se extrajo con EtOAc (2X). Las porciones orgánicas se combinaron, se lavaron con salmuera, se secaron sobre $MgSO_4$, y se concentraron. Este residuo crudo se sometió a cromatografía en columna (gel de sílice, 0%→100% CH_2Cl_2 /hexanos) para proporcionar la cetona AQ4

658
666

(R⁴=ciclopropilo, R³=n-Butilo) (2,57 g, 20,4 mmol, 54%). ¹H RMN (CDCl₃) δ 2,52 (t, J = 7,2 Hz, 2 H), 1,90 (m, 1 H), 1,57 (m, 2 H), 1,30 (m, 2 H), 0,98 (m, 2 H), 0,89 (t, J = 7,6 Hz, 3 H), 0,83 (m, 2 H).

Método AR



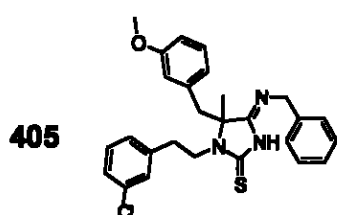
Método AR:

El compuestos B2 (R¹=m-Cl-Fenetilo, R³=Me, R⁴=i-butilo y R⁵=bencilo) se convirtió a AR2 (R¹=m-Cl-Fenetilo, R³=Me, R⁴=i-butilo y R⁵=bencilo) usando el método A etapa 3.

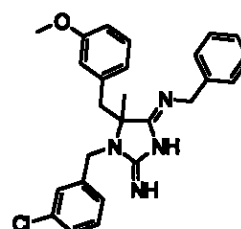
Se sintetizaron los compuestos siguientes usando métodos similares.

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
403		396	397	407		340	NA
404		354	NA	408		382	NA

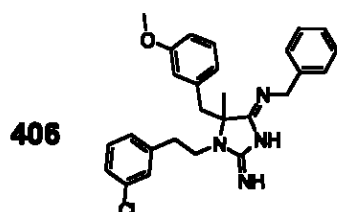
659
667



477 NA 409

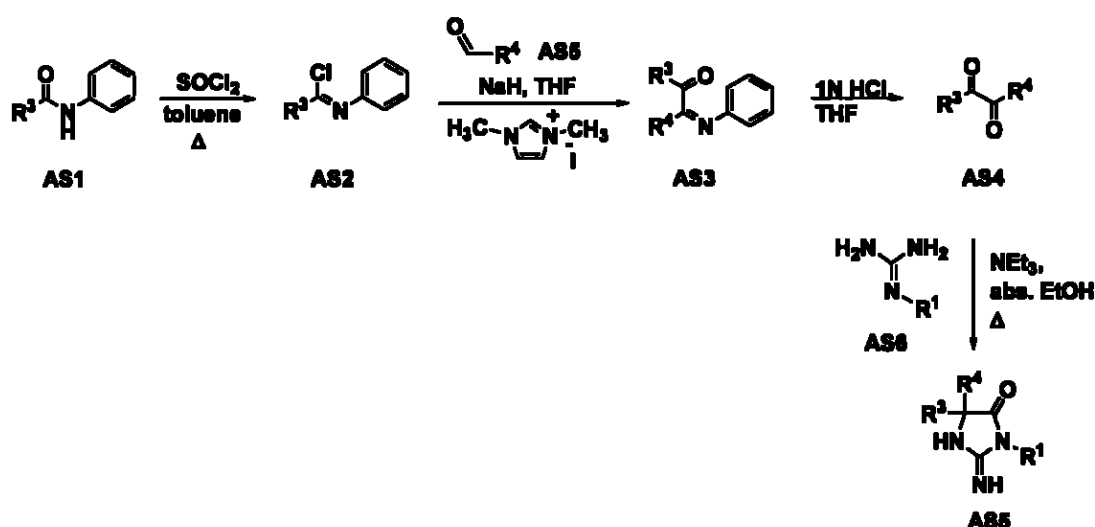


446 NA



460 NA

Método AS



Método AS, Etapa 1:

A una mezcla de AS1 ($R^3=Ph$) (3,94 g) en tolueno (10 ml) se le agregó cloruro de tionilo (1,61 ml) y la mezcla resultante se calentó bajo reflujo durante 6 horas (hasta que cesó el desprendimiento de HCl). La mezcla de reacción se mantuvo durante la noche a temperatura ambiente antes de concentrarla *al vacío*. Se agregó tolueno (10 ml) y la mezcla se concentró nuevamente *al vacío*. La mezcla de reacción se disolvió en CH_2Cl_2 , se agregó bicarbonato de sodio

660
588

sólido, se filtró y luego la solución de CH_2Cl_2 se concentró *al vacío* para proporcionar **AS2** ($\text{R}^3=\text{Ph}$).

Método AS, Etapa 2:

A **AS2** ($\text{R}^3=\text{Ph}$) (0,645 g) y **AS5** ($\text{R}^4=4\text{-clorofenilo}$) (0,464 g), y ioduro de 1,3-dimetilimidazolio (0,225 g) en THF anhidro (20 ml) se le agregó hidruro de sodio al 60% en aceite (0,132 g). La mezcla resultante se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se concentró y dividió en H_2O y Et_2O . La solución de Et_2O seca se concentró al vacío para proporcionar un residuo de color Amarillo que se colocó sobre placas de gel de sílice preparativas y se eluyó con CH_2Cl_2 para proporcionar **AS3** ($\text{R}^3=\text{Ph}$, $\text{R}^4=p\text{-ClPh}$). (Miyashita, A., Matsuda, H., Hiagaskino, T., Chem. Pharm. Bull., 1992, 40 (10), 2627-2631).

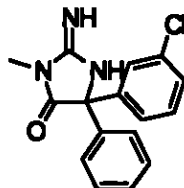
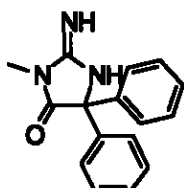
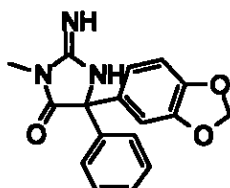
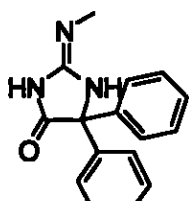
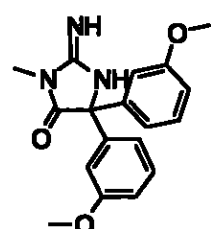
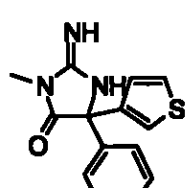
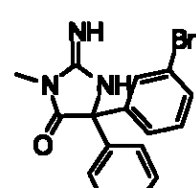
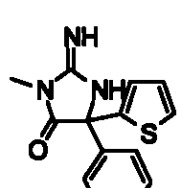
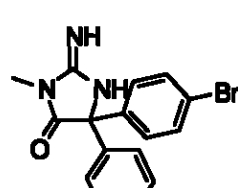
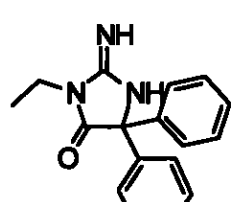
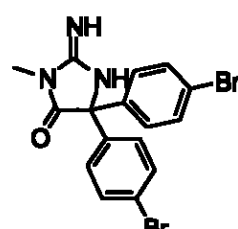
Método AS, Etapa 3:

Se agregó ácido clorhídrico (1N, 1,5 ml) a **AS3** ($\text{R}^3=\text{Ph}$, $\text{R}^4=p\text{-ClPh}$) en THF (10 ml) y la solución resultante se agitó a temperatura ambiente durante 20 horas. La mezcla de reacción se concentró al vacío y luego se dividió entre CH_2Cl_2 y H_2O . El CH_2Cl_2 seco se concentró *al vacío* para proporcionar un residuo el cual se colocó sobre placas de gel de sílice preparativas y se eluyó con CH_2Cl_2 :hexano 1:1 para proporcionar **AS4** ($\text{R}^3=\text{Ph}$, $\text{R}^4=p\text{-ClPh}$).

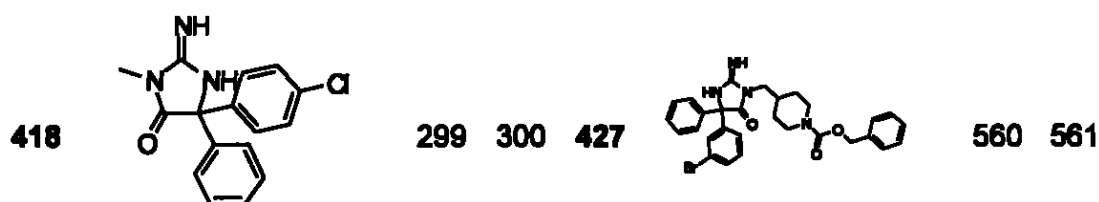
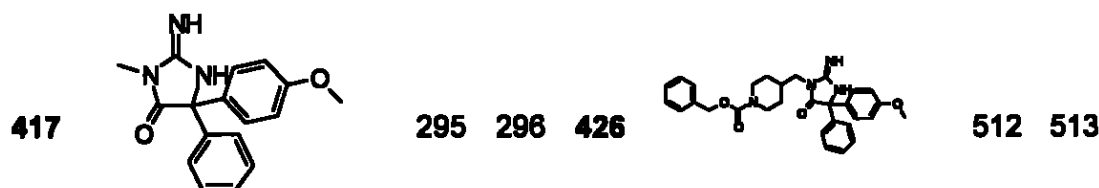
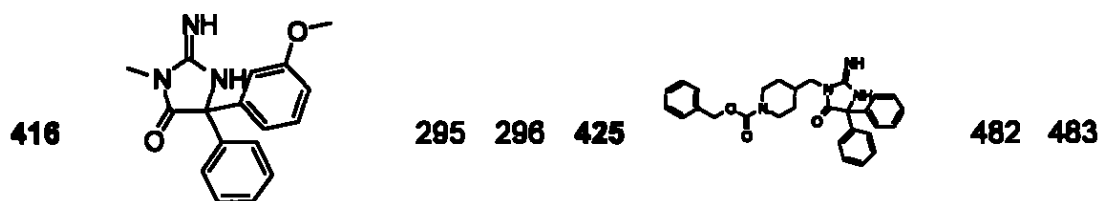
Método AS, Etapa 4:

Se mezclaron **AS4** ($\text{R}^3=\text{Ph}$, $\text{R}^4=p\text{-ClPh}$) (0,12 g) y metilguanidina, HCl (**AS6**, $\text{R}^1=\text{Me}$) (0,055 g) en EtOH absoluto (5 ml) con trietilamina (0,2 ml) y luego se calentó bajo reflujo durante 20 horas. La mezcla resultante se concentró y luego se dividió entre CH_2Cl_2 y H_2O . El CH_2Cl_2 seco se concentró *al vacío* para proporcionar un residuo el cual se colocó sobre placas de gel de sílice preparativas y se eluyó con CH_2Cl_2 :MeOH 9:1 para proporcionar **AS5** ($\text{R}^3=\text{Ph}$, $\text{R}^4=p\text{-ClPh}$ y $\text{R}^1=\text{Me}$).

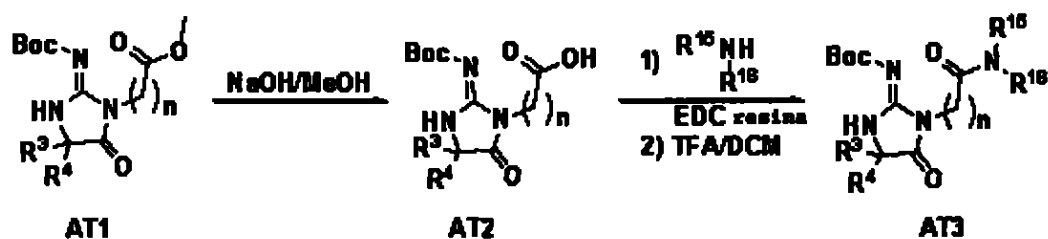
Se sintetizaron los compuestos siguientes usando métodos similares.

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
				419		299	300
411		265	266	420		309	310
412		265	266	421		325	326
413		271	272	422		343	344
414		271	272	423		343	344
415		279	280	424		421	422

662
570



Método AT



Método AT, Etapa 1:

AT1, preparado usando un método similar al Método H, Etapa 1,2 y 3, ($n=4$, $R^3=R^4=n\text{-Bu}$) (0,146 g) en MeOH (3 ml) y NaOH 1N (0,727 ml) se agitaron durante la noche a temperatura ambiente. La mezcla se concentró y luego se dividió en agua (pH ~3, se ajustó usando HCl concentrado) y EtOAc. La capa de EtOAc seca se concentró *al vacío* para proporcionar AT2 ($n=4$, $R^3=R^4=n\text{-Bu}$).

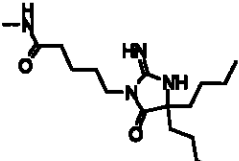
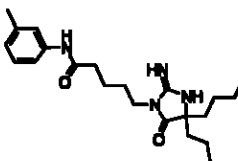
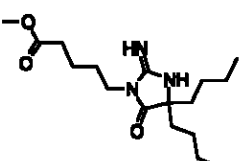
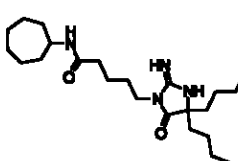
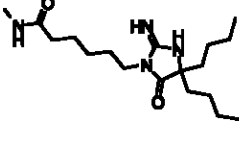
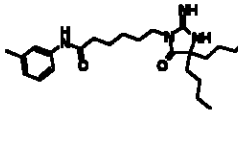
663

671

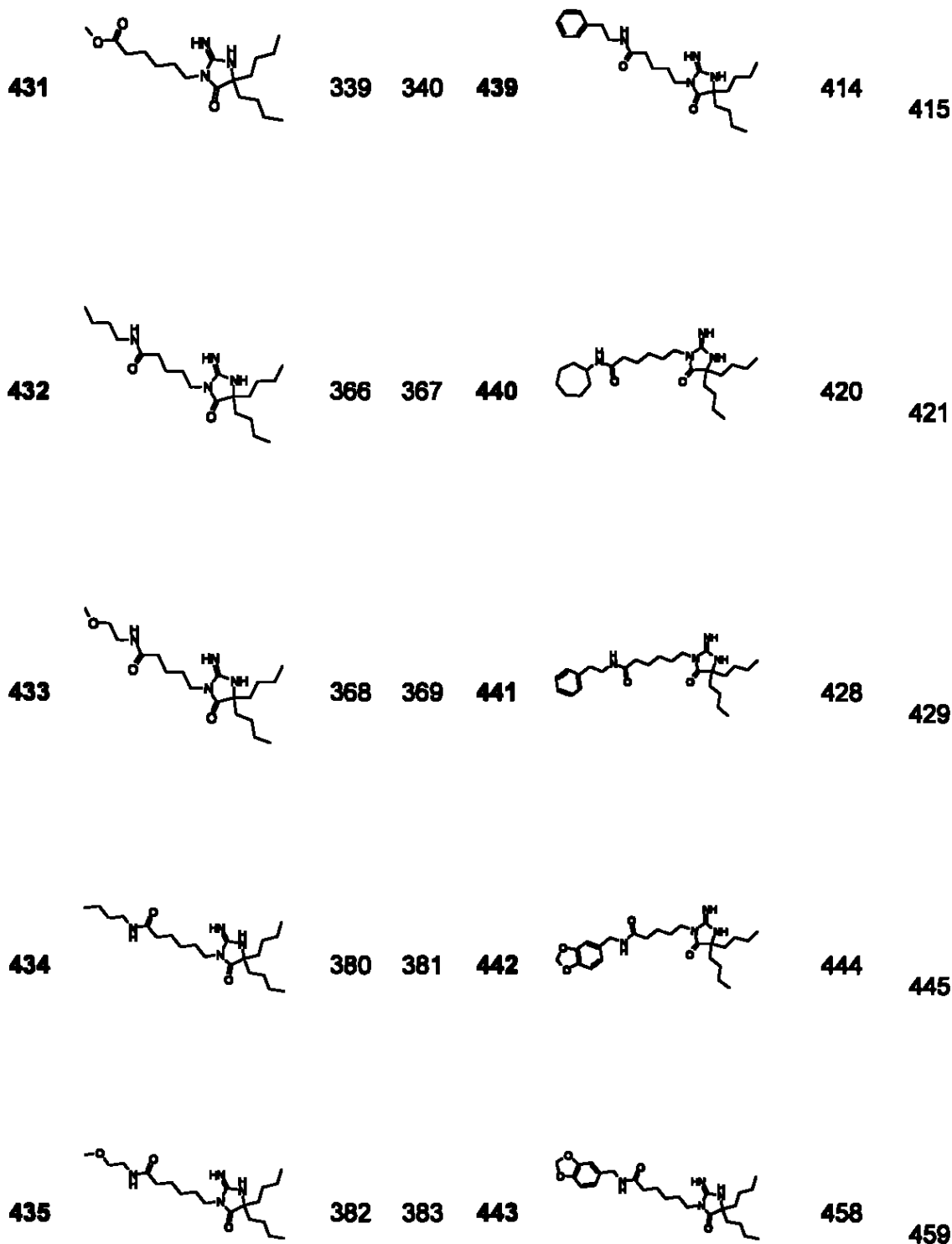
Método AT, Etapa 2:

Se trató el compuesto AT2 ($n=4$, $R^3=R^4=n\text{-Bu}$) (0,012 g) en MeCN (1 ml) se trató el compuesto con resina EDC (0,12 g, 1,44 mmoles/g), HOBT (0,004 g) en THF (1 ml), y *n*-butilamina ($R^{15}=H$, $R^{16}=n\text{-butilo}$) (0,007 ml). La reacción se llevó a cabo durante la noche a temperatura ambiente antes de agregar Argonaut PS-resina NCO (0,150 g), PS-resina de poliamina (0,120g) y THF (2 ml) y la mezcla se agitó durante 4 horas. La mezcla de reacción se filtró y la resina se lavó con THF (2 ml). La fase orgánica combinada se secó y concentró al vacío antes de tratar el residuo con HCl 1N en MeOH (1ml) durante 4 horas seguido de evaporación del solvente para proporcionar AT3 ($n=4$, $R^3=R^4=n\text{-Bu}$, $R^{15}=H$ y $R^{16}=n\text{-Butilo}$).

Se sintetizaron los compuestos siguientes usando un método similar.

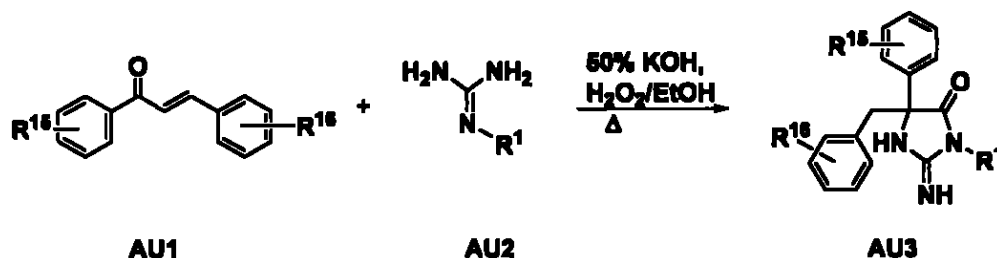
#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
428		324	325	436		400	401
429		325	326	437		406	407
430		338	339	438		414	415

664
672



665
673

Método AU



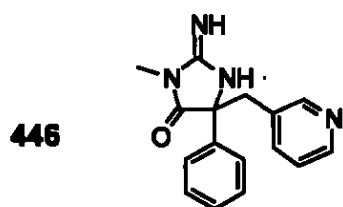
Se adaptó un procedimiento publicado (Varga, I.; Nagy, T.; Kovcsdi, I.; Benet-Buchholz, J.; Dormab, G.; Urge, L.; Darvas, F. *Tetrahedron*, 2003, (59) 655-662).

AU1 ($R^{15}=H$, $R^{16}=H$) (0,300 g), preparado de acuerdo con el procedimiento descrito por Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R., (*Vogel's Textbook of Practical Organic Chemistry*. 5th ed. Longman: new York, 1989; pp1034-1035), AU2 (sal de HCl, $R^1=Me$) (0,237 g), 50% KOH (0,305 ml), 30% H_2O_2 (0,115 ml) y EtOH (4,6 ml) se calentaron durante 2 horas. La mezcla de reacción se concentró y extrajo con CH_2Cl_2 . La solución orgánica seca se concentró al vacío para proporcionar un residuo el cual se colocó sobre placas de gel de sílice preparativas fluyendo con $CH_2Cl_2:MeOH$ 9:1 para proporcionar AU3 ($R^{15}=H$, $R^{16}=H$, $R^1=Me$).

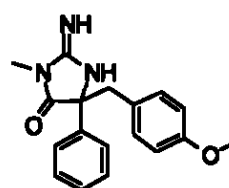
Se sintetizaron los compuestos siguientes usando un método similar:

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
444		265	266	448		285	286
				449		309	310

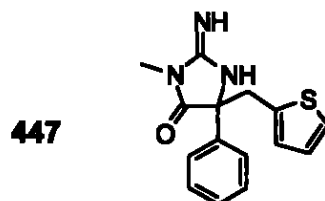
666
674



280 281 450

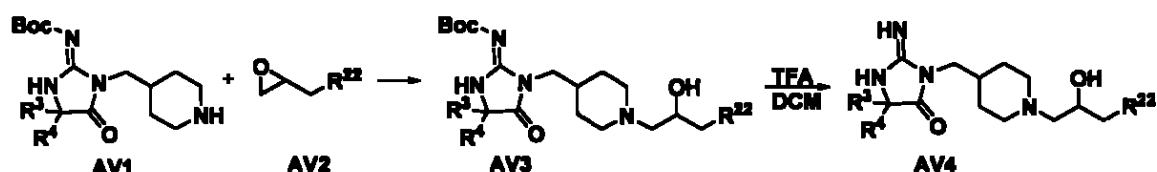


309 310



285 286

Método AV



Método AV, Etapa 1:

En un tubo de microondas, AV1 (R^3 =Me, R^4 =Bu-i) (0,0012 g) y AV2 (R^{22} =OPh) (0,0059 ml) en *decir* isopropanol (2 ml) se colocó en un microondas a 125°C durante 5 minutos. La mezcla de reacción se concentró *al vacío* para proporcionar AV3 (R^3 =Me, R^4 =i-Bu, R^{22} =OPh).

Método AV, Etapa 2:

AV3 (R^3 =Me, R^4 =i-Bu, R^{22} =OPh) en CH_2Cl_2 (1 ml) y TFA (1 ml) se agitó durante 2 horas y se concentró *al vacío* y se purificó sobre Prep LCMS para proporcionar AV4 (R^3 =Me, R^4 =i-Bu, R^{22} =OPh).

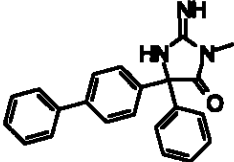
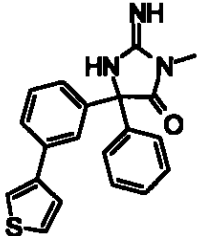
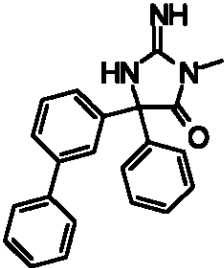
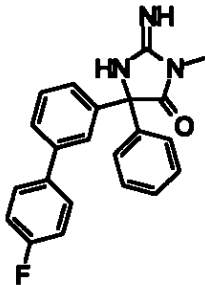
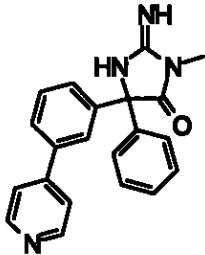
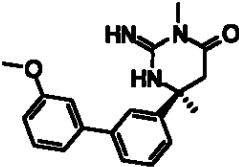
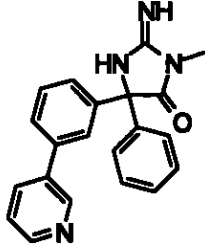
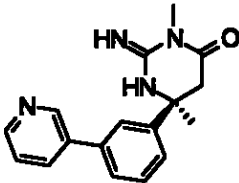
Se sintetizaron los compuestos siguientes de manera similar:

Método AW



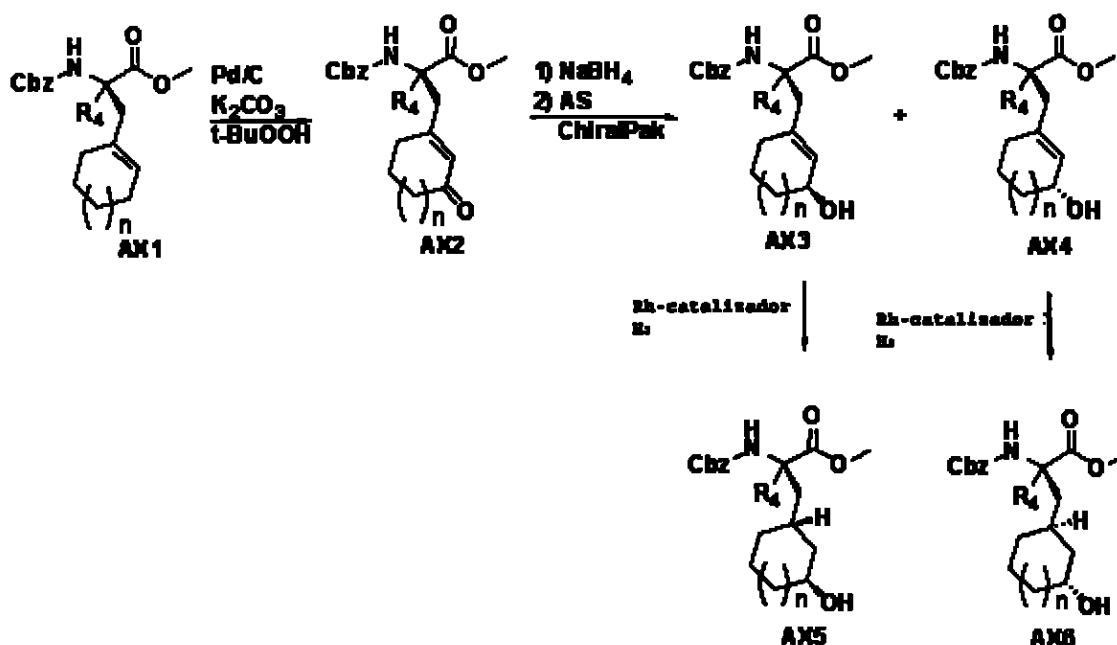
Se compuestos siguientes se sintetizaron de manera similar.

668
678

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
454		341	342	458		347	348
455		341	342	459		359	360
456		342	343	460		323	324
457		342	343	461		294	295

669
677

Método AX



Método AX, Etapa 1.

Se adaptó a un procedimiento de la literatura (J-Q Yu and E.J. Corey, *Organic Letters*, 2002, 4, 2727-2730).

A una solución de 400 ml de DCM de AX1 (n=1, R⁴=fenetilo) (52 gramos) en un baño de hielo se agregaron 5 g de Pd/C (5% w/w), 50 g de carbonato de potasio y 100 ml de t-BuOOH anhidro. La mezcla se agitó al aire durante la noche antes de diluirla con DCM y lavarla con agua. El residuo después de remoción del solvente orgánico y secado, se cromatografió usando acetato de etilo/hexanos para proporcionar 25 g de AX2 (n=1, R⁴=fenetilo).

Método AX, Etapa 2.

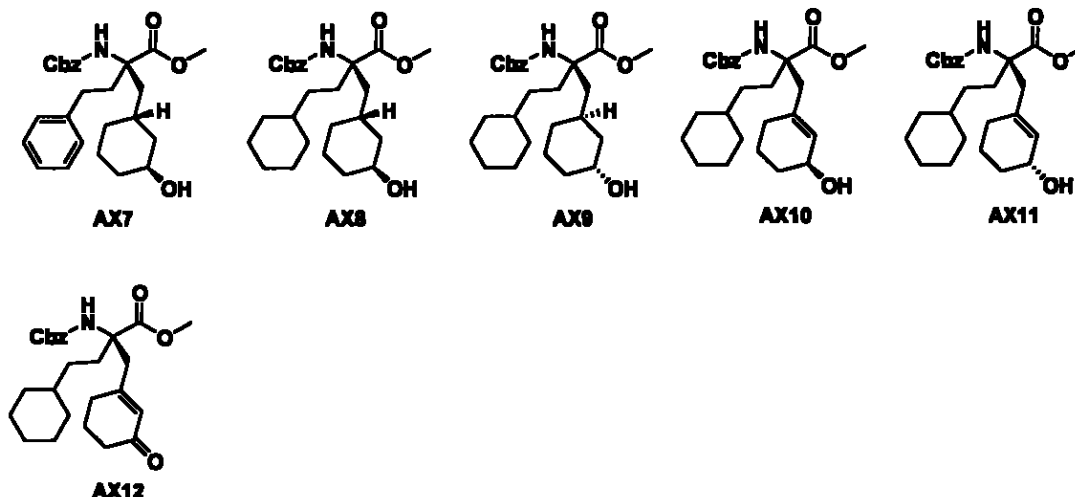
Una solución de AX2 (4,5 g, n=1, R⁴=fenetilo) en MeOH (50 ml) se trató con 0,4 g de borohidruro de sodio y la reacción se agitó durante 30 minutos antes de remover el solvente y el residuo se cromatografió para proporcionar una mezcla de AX3 (n=1, R⁴=fenetilo) y AX4 (n=1, R⁴=fenetilo) que se separó usando una columna AS chiralpak eluida con 8% IPA en Hexano (0,05% DEA) para obtener 2,1 g de AX3 (n=1, R⁴=fenetilo) como primera fracción y 2,2 g de AX4 (n=1, R⁴=fenetilo) como segunda fracción.

670
87

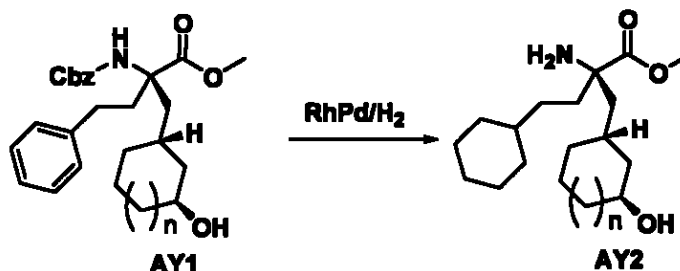
Método AX, Etapa 3.

A 100 ml de una solución metabólica de AX4 ($n=1$, R^4 =fenetilo) (2,2 g) y 1,1'-bis(di-*i*-propilfosfino)ferroceno tetrafluorborato de (1,5-ciclooctadieno)rodio (I) (0,4 g, 0,57 mmol) se hidrogenó a 379 kpa (55 psi) durante la noche. La reacción se concentró y el aceite de color castaño se purificó por cromatografía con gel de sílice para proporcionar AX6 ($n=1$, R^4 =fenetilo) (1,7g).

Se generaron los compuestos siguientes usando un método similar.



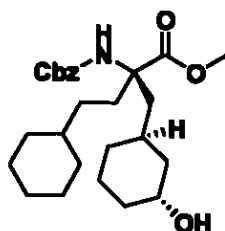
Método AY



Una solución de AY1 ($n = 1$; 1,5g, 3,4 mmoles), 5% Rh/C (1,5g), 5% Pd/C (0,5g) en AcOH (30 mL) se agitó en un aparato Parr a 379 kpa (55 psi) durante 18 horas. El recipiente se inundó con N_2 , y la reacción se filtró a través de una almohadilla de celite. Después de concentración, se obtuvo AY2 que se llevó a cabo sin purificación. EM m/e: 312,0 (M+H).

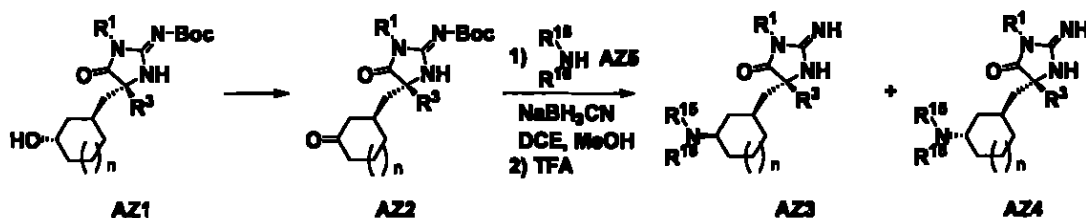
Se generó AY3 usando un método similar.

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AY3

Método AZ



Método AZ, Etapa 1

A una solución de **AZ1** ($n=1$, $R^1=Me$, $R^3=2$ -ciclohexiletilo) (0,441 g, 1,01 mmoles), generada a partir de **AY2** usando **Método C** y **Método H** Etapa 3, en DCM se le agregó Periodinano de Dess-Martin (0,880 g, 2,07 mmoles). La reacción se agitó durante 3 horas a temperatura ambiente. La reacción se apagó con H_2O y se diluyó con EtOAc. Después de remoción de la fase orgánica, la capa acuosa se extrajo con EtOAc (3x). Los orgánicos combinados se secaron (Na_2SO_4), se filtraron, y se concentraron. El residuo se purificó por cromatografía de gel de sílice (0-100% EtOAc/hexanos) para proporcionar **AZ2** ($n=1$, $R^1=Me$, $R^3=2$ -ciclohexiletilo) (0,408 g, 0,94 mmol, 93% de rendimiento). EM m/e: 434,1 (M+H).

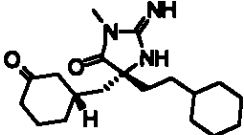
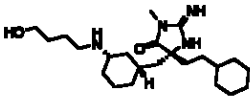
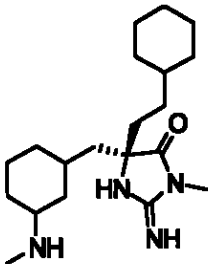
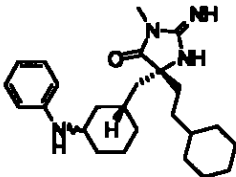
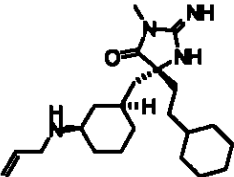
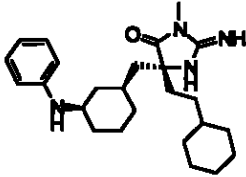
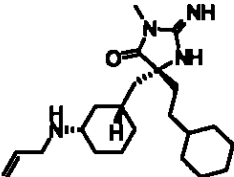
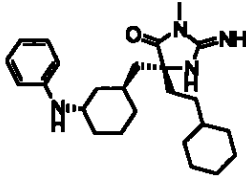
Método AZ Etapa 2:

A una solución de **AZ2** ($n=1$, $R^1=Me$, $R^3=2$ -ciclohexiletilo) (0,011 g, 0,025 mmol) y **AZ5** ($R^{15}=H$ y $R^{16}=m$ -piridilmetilo) (0,0067 mL, 0,066 mmol) en DCE (1,8 mL) y MeOH (0,2 mL) se le agregó AcOH (4 gotas) y MP-resina de cianoborohidruro (0,095 g, 2,42 mmol/g). La reacción se agitó durante 40 horas a temperatura ambiente. La reacción se trató con NH_3 7N/MeOH, y la solución se filtró. Después de concentración, el residuo se purificó por HPLC de gel de sílice (0-4% [(5% 7N NH_3 /MeOH)/MeOH]/(50%DCM/hexanos) para proporcionar

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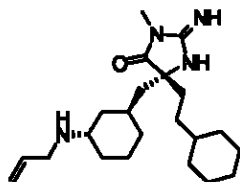
la fracción 1 y la fracción 2, en las cuales, después de remoción del solvente, se trataron con 20% de TFA en DCM durante 3 horas a temperatura ambiente para proporcionar **AZ4** (n=1, R¹=Me, R³=2-ciclohexiletilo, R¹⁵=H y R¹⁶=m-piridilmetilo) (0,005 g, 0,009 mmol) y el **AZ3** (n=1, R¹=Me, R³=2-ciclohexiletilo, R¹⁵=H y R¹⁶=m-piridilmetilo) (0,012 g, 0,022 mmol) respectivamente.

Se generaron los compuestos siguientes usando métodos similares.

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
462		333	334	504		406	407
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464		374	375	506		410	411
465		374	375	507		410	411

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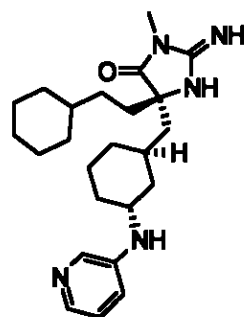
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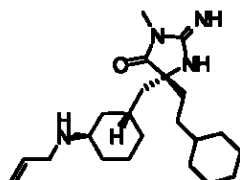
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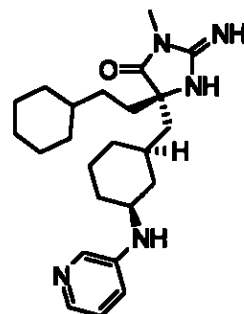
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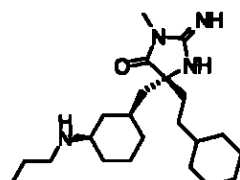
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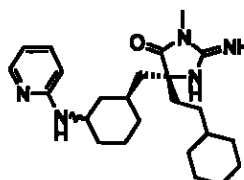
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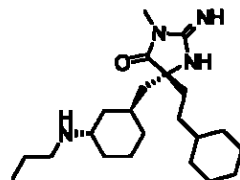
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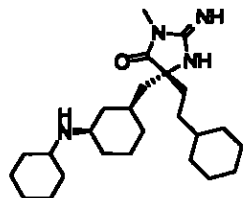
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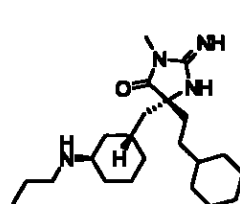
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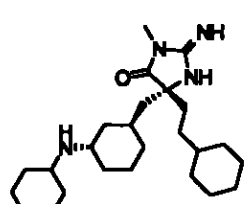
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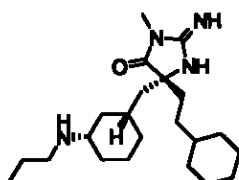


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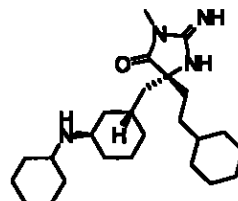
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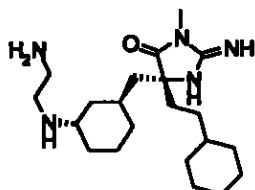
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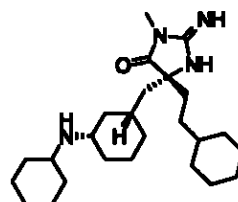
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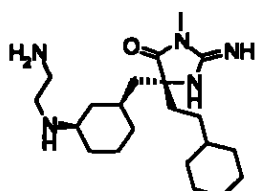
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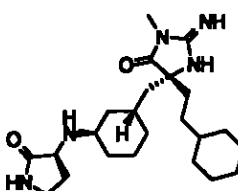
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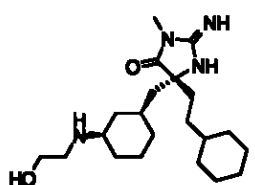
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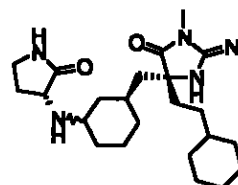
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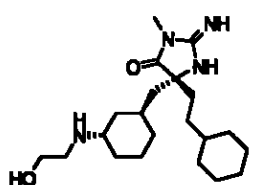
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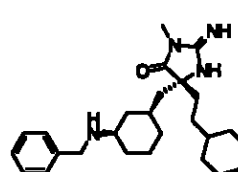
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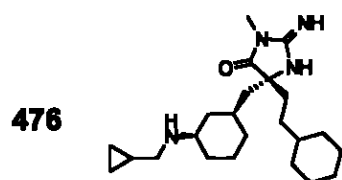
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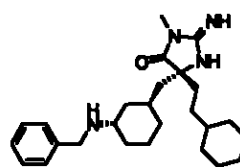
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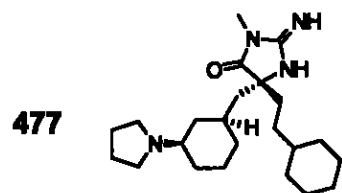
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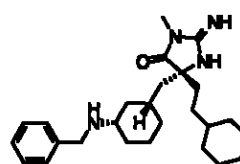
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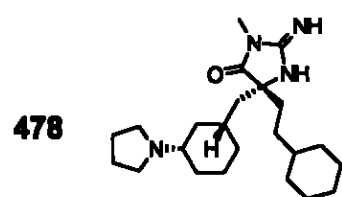
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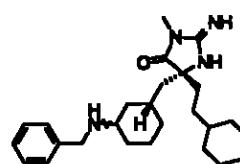
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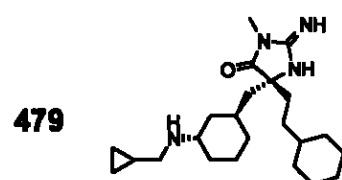
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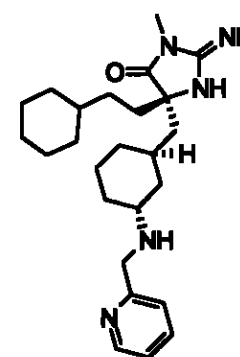
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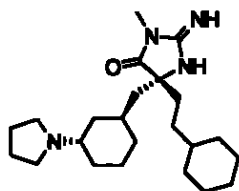


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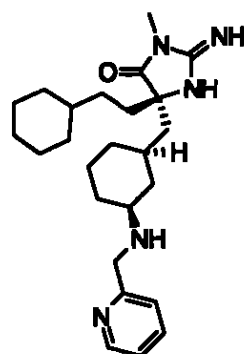
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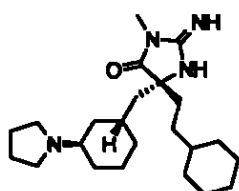
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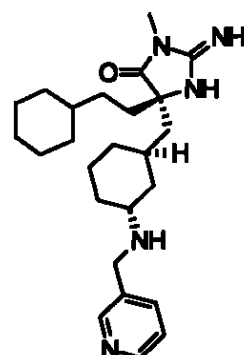
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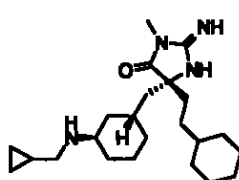
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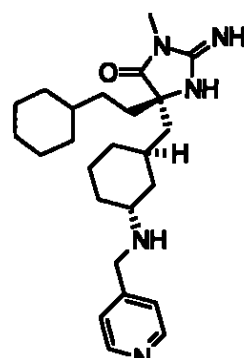
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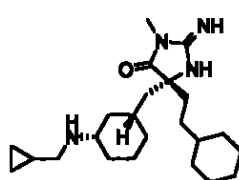
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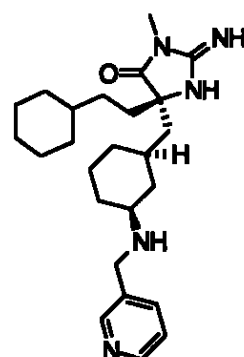
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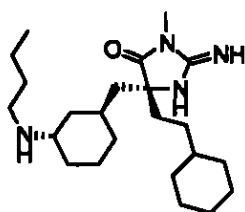


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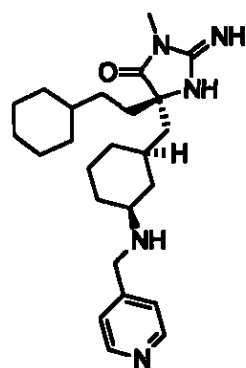
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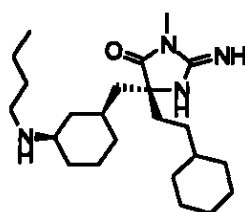
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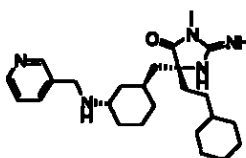
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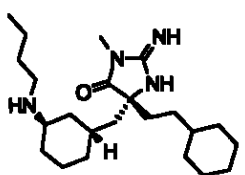
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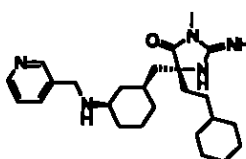
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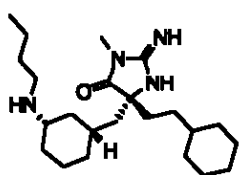
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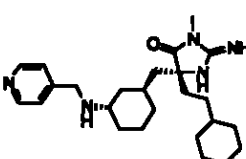
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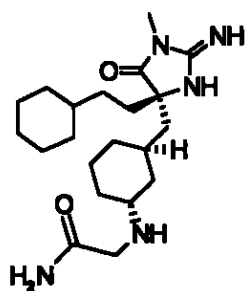
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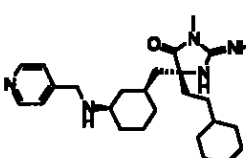
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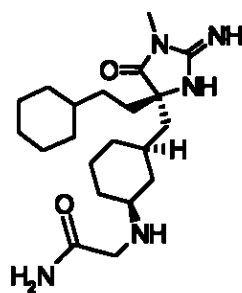


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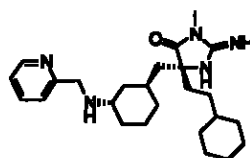
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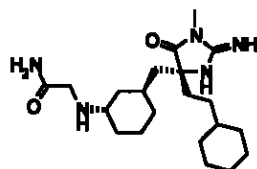
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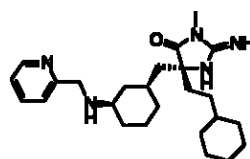
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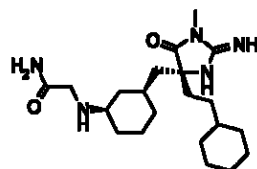
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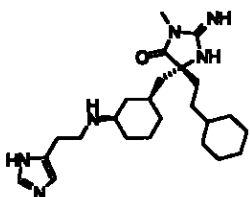
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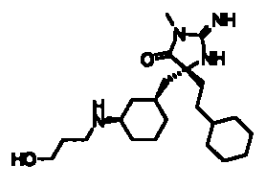
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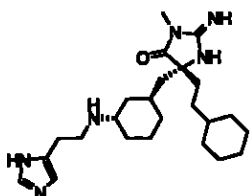
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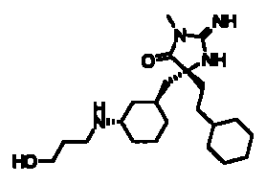
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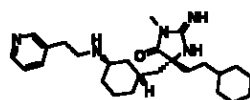
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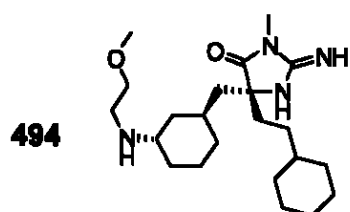
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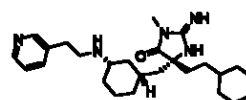
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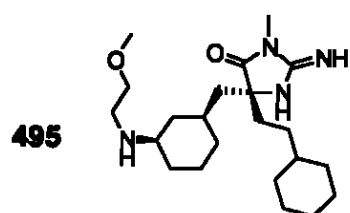
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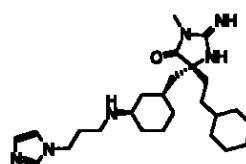
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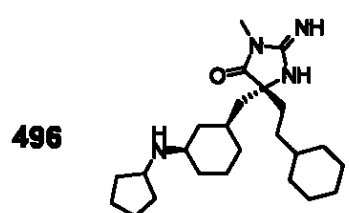
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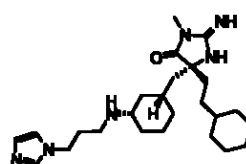
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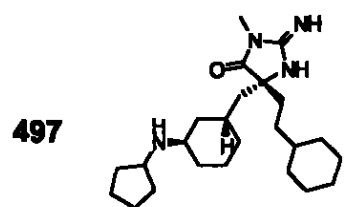
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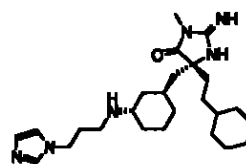
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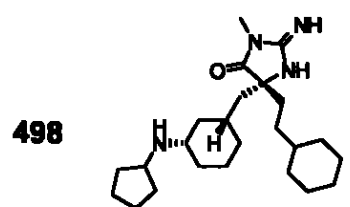
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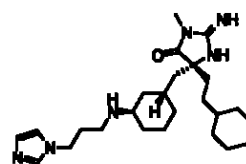
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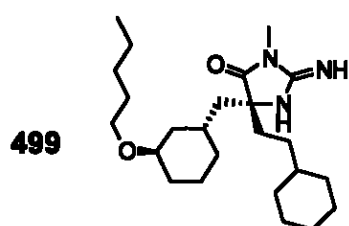
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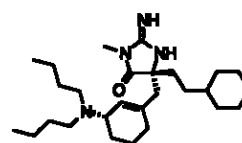
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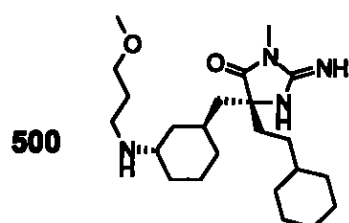
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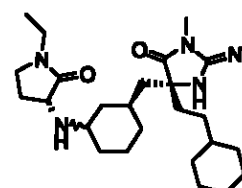
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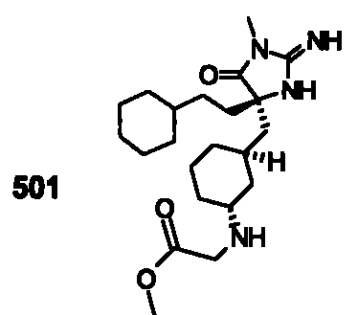
407

542



445

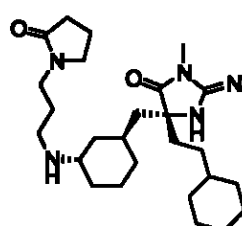
446



406

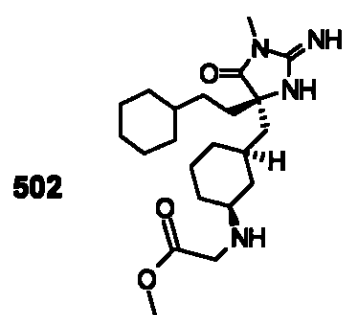
407

543



459

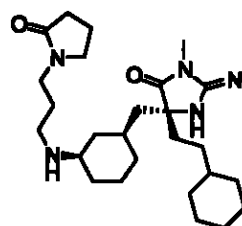
460



406

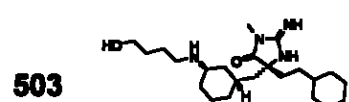
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544



459

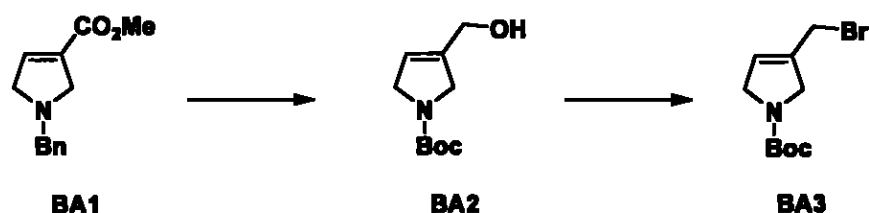
460



406

407

Método BA



Método BA, Etapa 1:

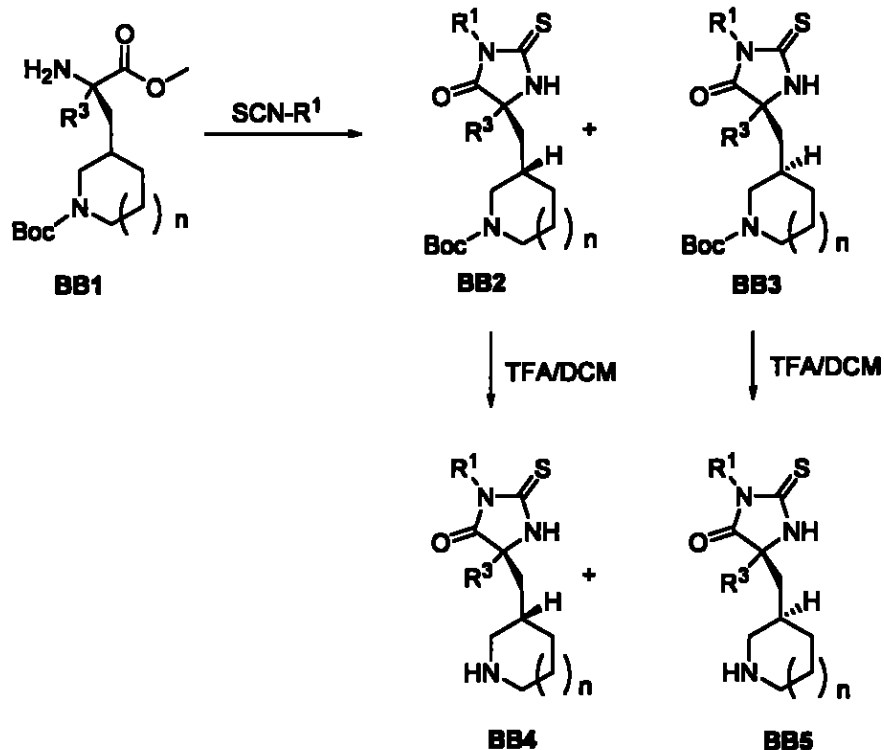
BA1, preparado de acuerdo con un procedimiento de la literatura (Terao, Y; Kotaki, H; Imai, N and Achiwa K. Chemical and Pharmaceutical Bulletin, **33** (7), 1985, 2762-2766) se convirtió a **BA2** usando un procedimiento descrito por Coldham, I; Crapnell, K.M; Fernandez, J-C; Moseley J.D. and Rabot, R. (*Journal of Organic Chemistry*, **67** (17), 2002, 6185-6187).

^1H RMN(CDCl_3) para **BA2**: 1,42 (s, 9H), 4,06 (d, 4H), 4,09 (s, 1H), 4,18 (s, 2H), 5,62 (d, 1H).

Método BA, Etapa 2:

Se generó **BA3** a partir de **BA2** usando un procedimiento de la literatura descrito por Winkler J. D.; Axten J.; Hammach A. H.; Kwak, Y-S; Lengweiler, U.; Lucero, M. J.; Houk, K. N. (*Tetrahedron*, **54** 1998, 7045-7056). Datos analíticos para el compuesto **BA3**: EM m/e: 262,1, 264,1 (M+H). ^1H RMN(CDCl_3) 1,43 (s, 9H), 3,98 (s, 2H), 4,11 (d, 4H), 5,78 (d, 1H).

Método BB



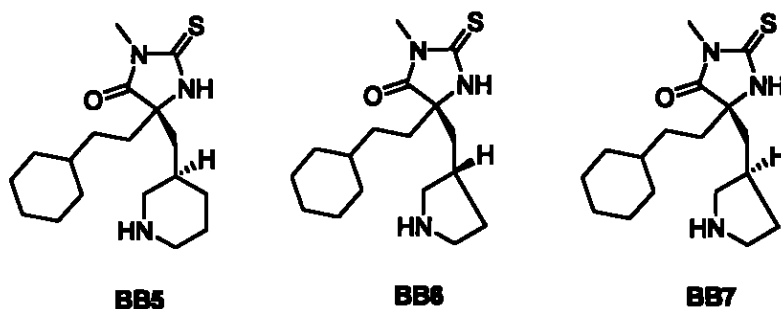
Método BB, Etapa 1;

El compuesto **BB1** ($n=1$, $\text{R}^1=\text{Me}$, $\text{R}^3=\text{ciclohexiletilo}$) se convirtió a **BB2** ($n=1$, $\text{R}^1=\text{Me}$, $\text{R}^3=\text{ciclohexiletilo}$) y **BB3** ($n=1$, $\text{R}^1=\text{Me}$, $\text{R}^3=\text{ciclohexiletilo}$) los cuales se separaron a través de una columna de gel de sílice eluida con EtOAc en Hexano (0-15%).

Método BB, Etapa 2;

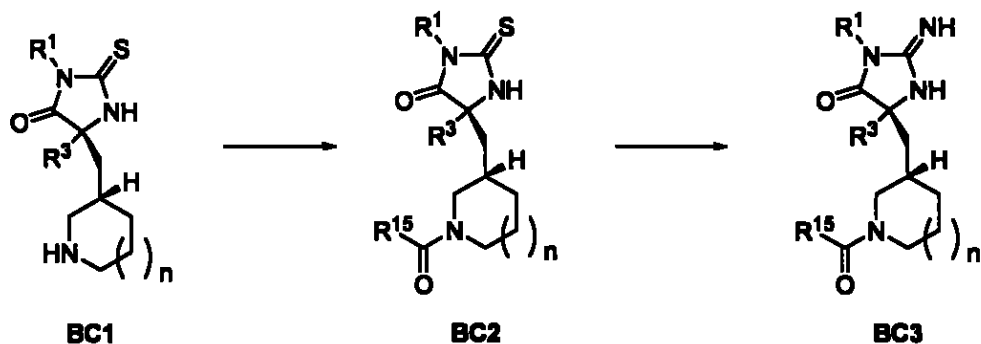
Se generó el compuesto **BB4** ($n=1$, $\text{R}^1=\text{Me}$, $\text{R}^3=\text{ciclohexiletilo}$) a partir de **BB2** ($n=1$, $\text{R}^1=\text{Me}$, $\text{R}^3=\text{ciclohexiletilo}$) usando 20% TFA en DCM.

Se generaron los compuestos siguientes usando un método similar:



683 697

Método BC



Método BC, Etapa 1;

Se obtuvo el compuesto BC2 (n=1, R¹=Me, R³=ciclohexiletilo y R¹⁵=m-Piridilo) a partir de BC1 (n=1, R²=Me, R³=ciclohexiletilo) usando el método L etapa 2.

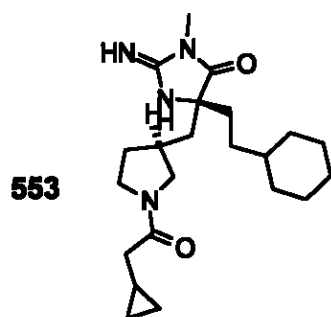
Método BC, Etapa 2;

Se obtuvo el compuesto BC3 (n=1, R¹=Me, R³=ciclohexiletilo y R¹⁵=m-Piridilo) a partir de BC2(n=1, R¹=Me, R³=ciclohexiletilo y R¹⁵=m-Piridilo) usando el método L etapa 3.

Se generaron los compuestos siguientes usando un método similar:

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
552		374	375	574		411	412

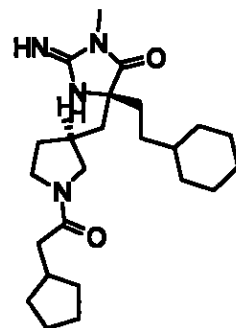
684 692



388

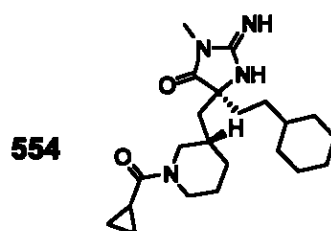
389

575



416

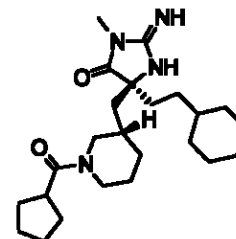
417



388

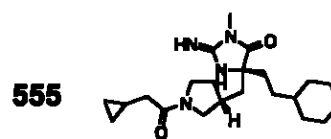
389

576



416

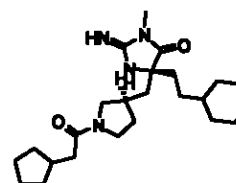
417



388

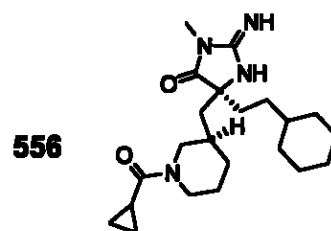
389

577



416

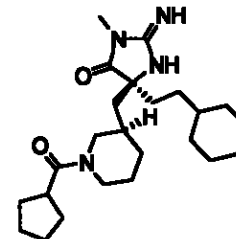
417



388

389

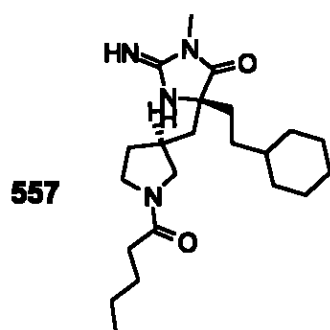
578



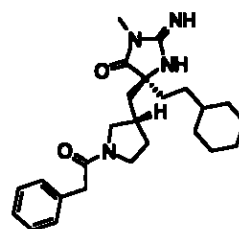
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417

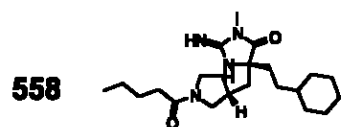
605 683



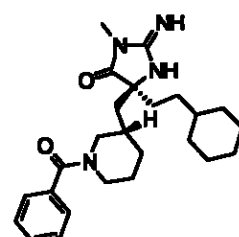
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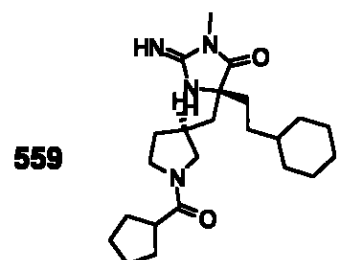
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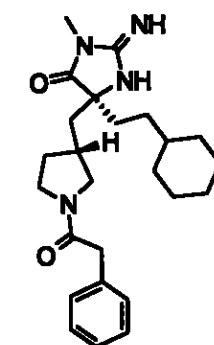
390 391 580



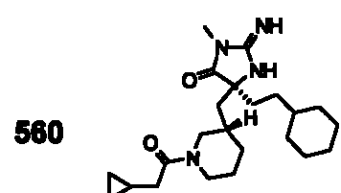
424 425



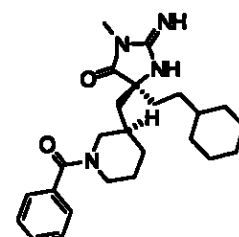
402 403 581



424 425



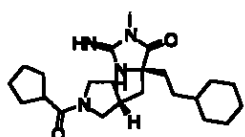
402 403 582



424 425

686
694

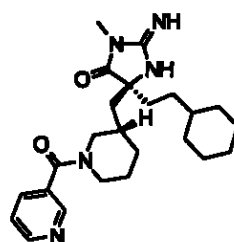
561



402

403

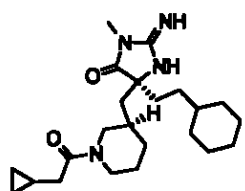
583



425

426

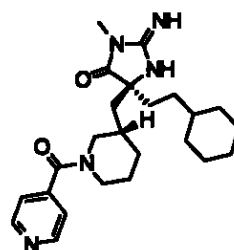
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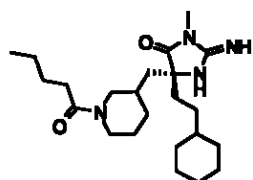
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425

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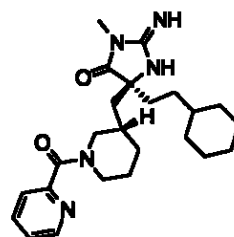
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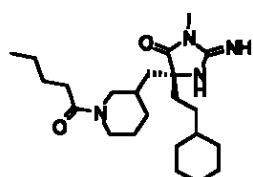
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425

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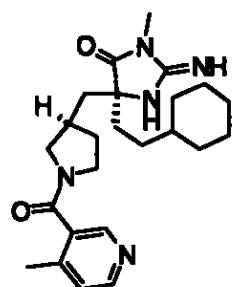
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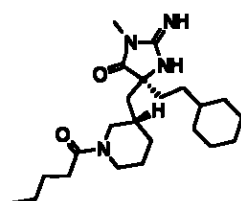


425

426

687 605

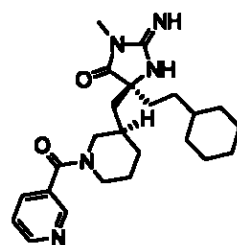
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404

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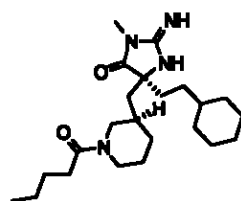
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425

426

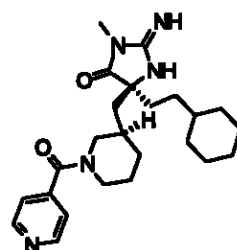
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404

405

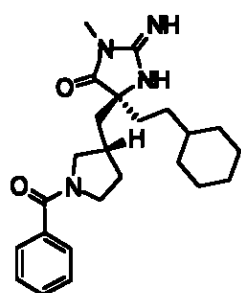
588



425

426

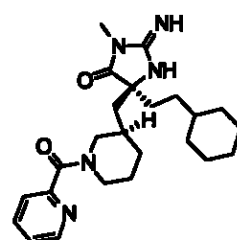
567



410

411

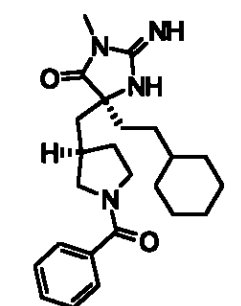
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425

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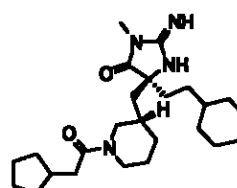
568



410

411

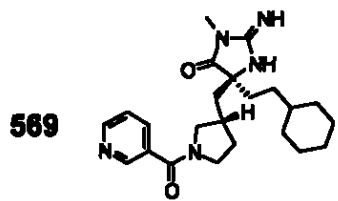
590



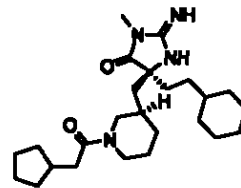
430

431

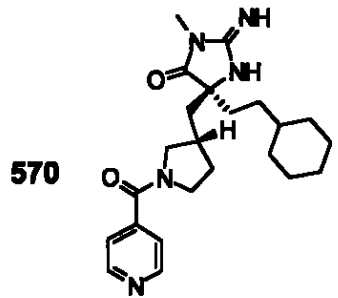
688 698



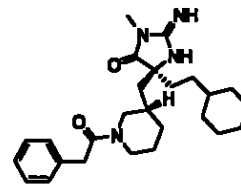
411 412 591



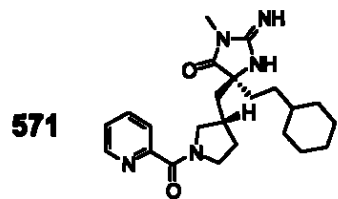
430 431



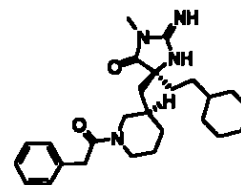
411 412 592



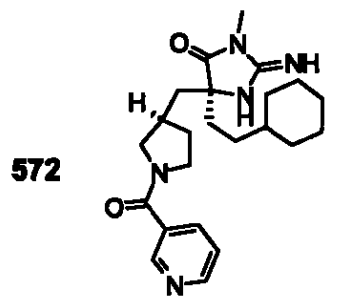
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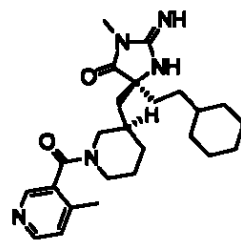
411 412 593



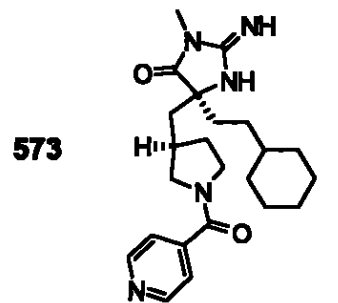
438 439



411 412 594

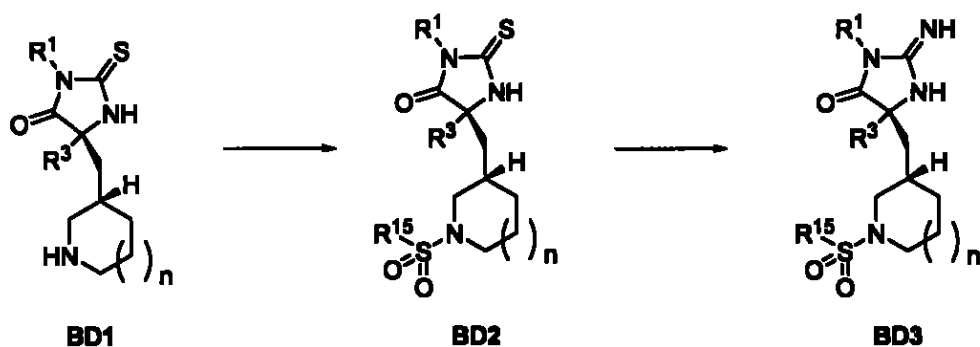


439 440



411 412

Método BD



Método BD, Etapa 1;

El compuesto BD2 ($n=1$, $R^1=Me$, $R^3=ciclohexiletilo$ y $R^{15}=Ph$) se obtuvo a partir de BD1 ($n=1$, $R^2=Me$, $R^3=ciclohexiletilo$) usando el Método N, Etapa 1.

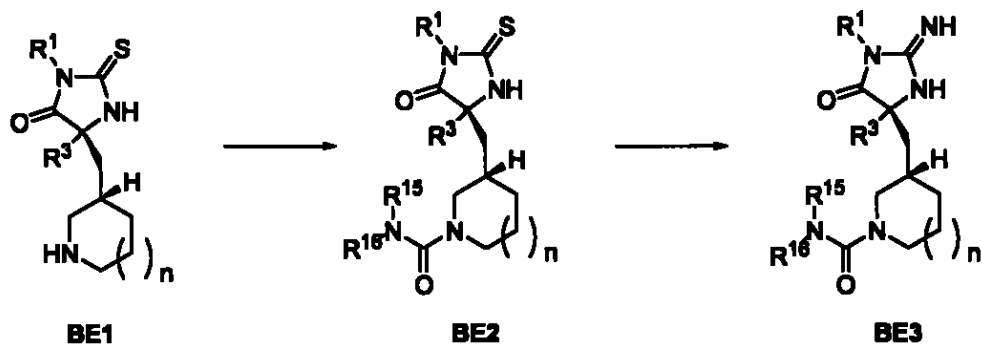
Método BD, Etapa 2;

El compuesto BD3 ($n=1$, $R^1=Me$, $R^3=ciclohexiletilo$ y $R^{15}=Ph$) se obtuvo a partir de BD2 ($n=1$, $R^1=Me$, $R^3=ciclohexiletilo$ and $R^{15}=m-Piridilo$) usando el Método N, Etapa 2.

Se generaron los compuestos siguientes usando un método similar:

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
595		440	441	596		460	461

Método BE

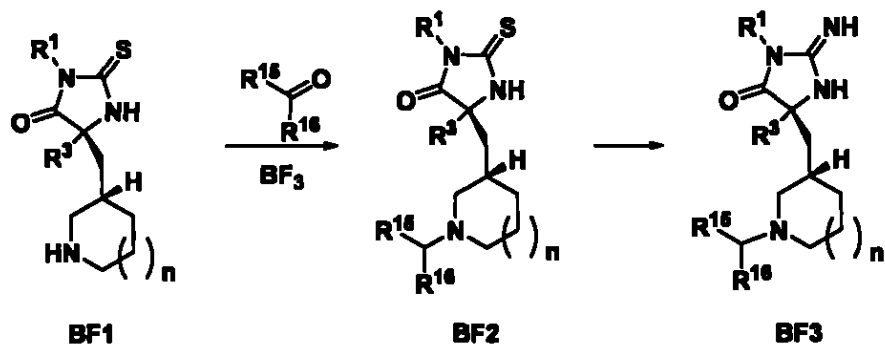


Se adaptó un método similar al Método M para estas transformaciones.

Los compuestos siguientes generaron métodos similares.

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
597		405	406	598		439	440

Método BF



Método BF, Etapa 1:

Se usó un método similar al Método T, Etapa 1 para la síntesis de BF2 (n = 1, R¹=Me y R³=fenetilo, R¹⁵=H y R¹⁶=n-propilo).

691 694

Método BF, Etapa 2:

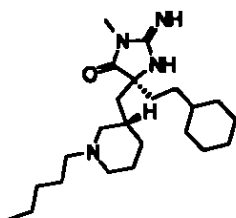
Se adaptó un método similar al método L Etapa 3 para esta transformación.

Se generaron los compuestos siguientes usando métodos similares.

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
599		376	377	604		397	398
600		390	391	605		397	398
601		390	391	606		397	398

682 260

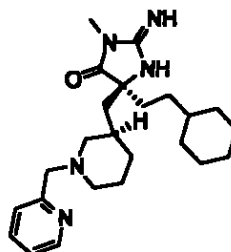
602



390

391

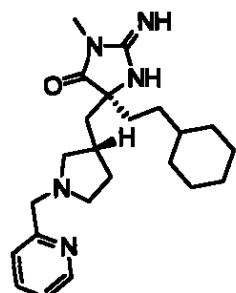
607



411

412

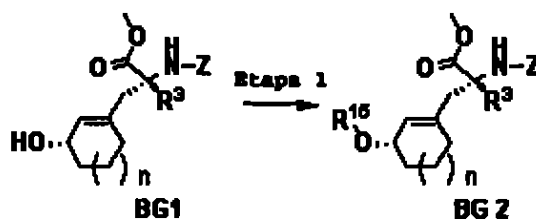
603



397

398

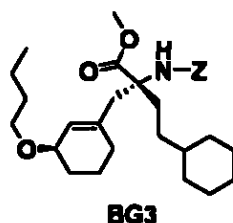
Método BG



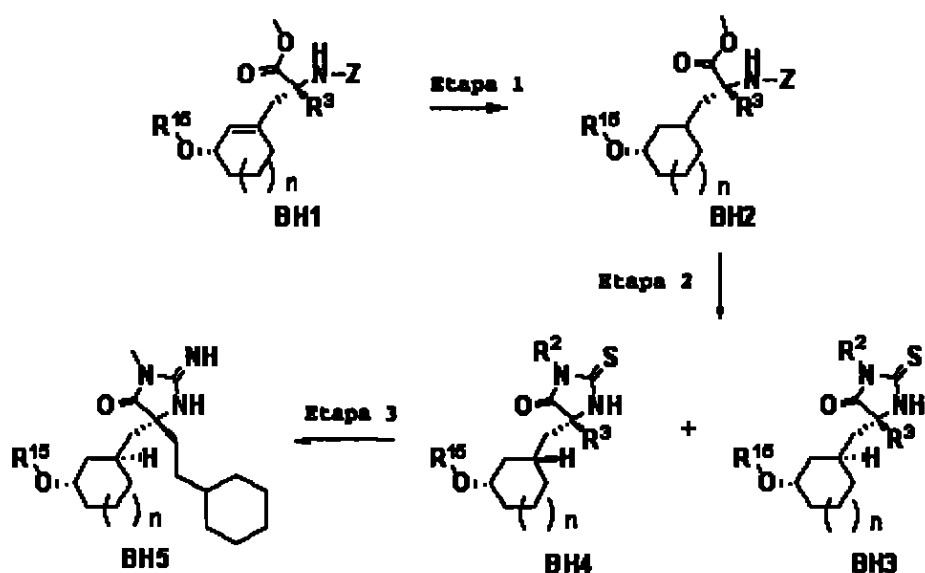
Método BG:

A una solución de **BG1** ($n=1$, R^3 =ciclohexiletilo) (0,136 g, 0,31 mmol) en CH_2Cl_2 se le agregó 2,6-lutidina, AgOTf, y yoduro de butilo. La reacción se agitó a temperatura ambiente durante 96 horas. La reacción se filtró a través de una almohadilla de Celite, y la solución se concentró. El residuo se purificó por cromatografía de sílice (0-100% EtOAc/hexanos) para proporcionar **BG2** ($n=1$, R^3 =ciclohexiletilo, R^{15} =n-butilo) (0,124 g, 0,25 mmol, 80% de rendimiento). EM m/e : 426,1 (M-OBu).

Se preparó el compuesto siguiente usando un método similar:



Método BH



Método BH, Etapa 1.

El compuesto **BH1** ($n=1$, R^3 =ciclohexiletilo y R^{15} =n-butilo) (0,060 g, 0,12 mmol) y 5% $\text{Pd}(\text{OH})_2/\text{C}$ (0,040 g) en EtOAc (1 mL)/MeOH (0,2 mL) se agitó bajo una atmósfera de H_2 durante 20 horas a temperatura ambiente. La reacción se filtró a través de una almohadilla de Celite, y la solución se concentró. La mezcla de producto crudo **BH2** ($n=1$, R^3 =ciclohexiletilo y R^{15} =n-butilo) se llevó a cabo en la etapa siguiente sin purificación.

694
702

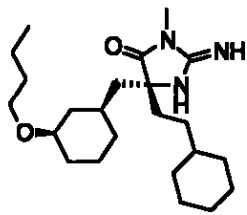
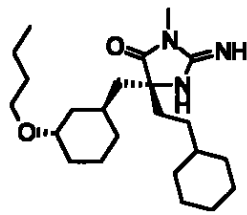
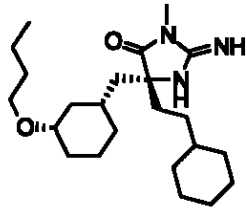
Método BH, Etapa 2.

Se convirtió una solución de BH2 ($n=1$, R^3 =ciclohexiletilo y R^{15} =n-butilo) a una mezcla del producto de BH4 y BH3 usando un método similar al Método C Etapa 1. La mezcla se purificó por cromatografía de gel de sílice usando EtOAc/hexanos para proporcionar BH4 ($n=1$, R^2 =Me, R^3 =ciclohexiletilo y R^{15} =n-butilo) (0,032 g, 0,078 mmol, 56% de rendimiento) y BH3 ($n=1$, R^2 =Me, R^3 =ciclohexiletilo y R^{15} =n-butilo) (0,008 g, 0,020 mmol, 14% de rendimiento). Para BH4 ($n=1$, R^2 =Me, R^3 =ciclohexiletilo y R^{15} =n-butilo), EM m/e: 409,1(M+H). Para BH3 ($n=1$, R^2 =Me, R^3 =ciclohexiletilo y R^{15} =n-butilo), EM m/e: 409,1 (M+H).

Método BH, Etapa 3.

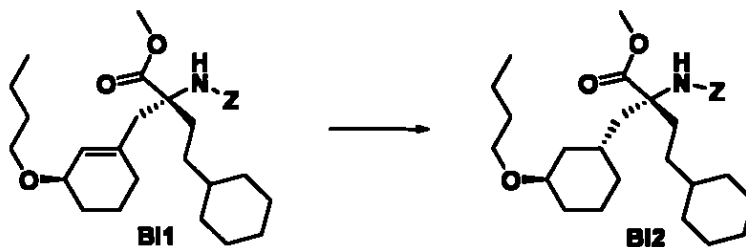
El compuesto BH4 ($n=1$, R^2 =Me, R^3 =ciclohexiletilo y R^{15} =n-butilo) (0,032 g, 0,078 mmol) se convirtió a BH5 ($n=1$, R^2 =Me, R^3 =ciclohexiletilo y R^{15} =n-butilo) (0,016 g, 0,043 mmol, 57% de rendimiento) usando un método similar al Método A, etapa 3. EM m/e: 392,1 (M+H).

Se preparó el compuesto siguiente usando un método similar:

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
608		391	392	610		391	392
609		391	392				

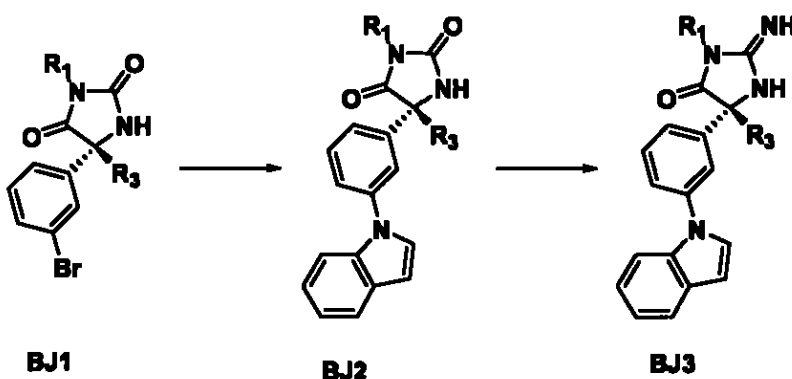
695
703

Método BI



Una solución de BI1(0,020 g, 0,040 mmol) en DCM (1 mL) se desgasificó usando un método de congelación/bombeo/descongelación (4 veces). Al finalizar el cuarto ciclo se agregó catalizador de Crabtree y el sistema se evacuó. Mientras se descongelaba, el sistema se cargó con gas hidrógeno, y la reacción se agitó a temperatura ambiente durante 16 horas bajo atmósfera de H₂. La reacción se concentró, y el aceite de color castaño se purificó por HPLC de fase inversa para proporcionar BI2(0,011 g, 0,022 mmol, 55% de rendimiento). EM m/e: 368,2 (M+H).

Método BJ



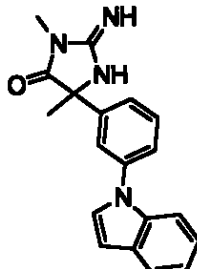
Método BJ, Etapa 1

Una mezcla de 2 ml de solución de dioxano de BJ1 (R¹=Me, R³=Me) (140 mg, 0,5 mmol) generada usando el método BK Etapas 1 & 2, indol (1,2 eq), t-Butóxido de potasio (1,4 eq), Pd₂(dba)₃ (0,02 eq) y 2-di-t-butilfosfinobifenilo (0,04 eq) se irradió en un horno de microondas a 120°C durante 10 minutos y la mezcla se separó a través de una columna de gel de sílice para proporcionar BJ2(R¹=Me, R³=Me) (0,73 mg).

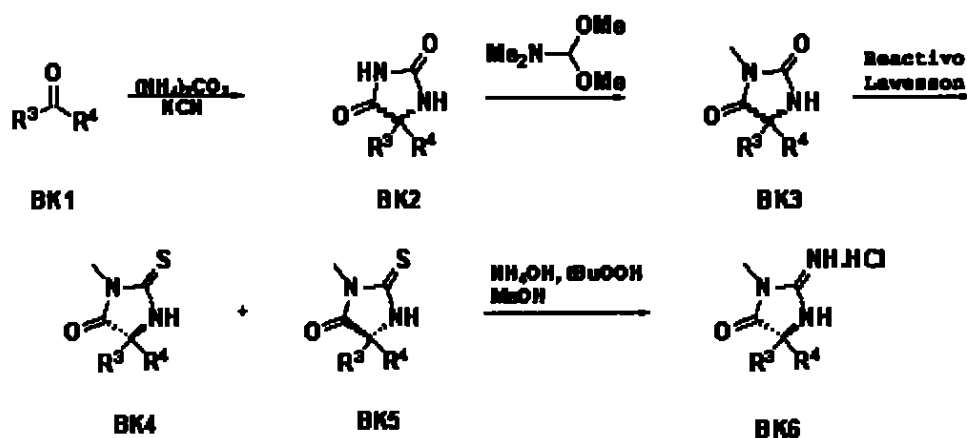
696
704

Método BJ, Etapa 2

BJ2 ($R^1=Me$, $R^3=Me$) se convirtió a BJ3 ($R^1=Me$, $R^3=Me$) usando el Método BK, Etapas 3 & 4. Obs. Masa para BJ3 ($R^1=Me$, $R^3=Me$): 319,2.

#	Estructura	PM	Obs. m/e
614		318	319

Método BK



Método BK, Etapa 1:

Se preparó hidantoina BK2 ($R^3=N$ -bencil-3-piperidilo, $R^4=n$ -Bu) de acuerdo con el Método D, Etapa 1 a partir de la correspondiente cetona BK1 ($R^3=N$ -bencil-3-piperidilo, $R^4=n$ -Bu). Datos analíticos para BK2 ($R^3=N$ -bencil-3-piperidilo, $R^4=n$ -Bu): (M+H) = 330,1.

697
205

Método BK, Etapa 2:

A una suspensión de hidantoina BK2 (R^3 =N-bencil-3-piperidilo, R^4 =n-Bu) (138 mg, 0,419 mmol) en DMF (1,5 ml) se le agregó dimetilformamida dimetilacetal (0,11 ml, 0,84 mmol). La mezcla resultante se calentó en un baño de aceite a 100°C durante 16 horas y luego se enfrió a temperatura ambiente y se concentró al vacío. Este residuo crudo se purificó por cromatografía en columna (MeOH/DCM) para proporcionar el producto BK3 (R^3 =N-bencil-3-piperidilo, R^4 =n-Bu) (140 mg, 0,408 mmol, 97%), (M+H) = 344,1.

Método BK, Etapa 3:

A una solución de una porción de BK3 (R^3 =N-bencil-3-piperidilo, R^4 =n-Bu) (70 mg, 0,20 mmol) en tolueno (1 ml) se le agregó reactivo de Lawesson's (107 mg, 0,26 mmol). La mezcla resultante se colocó en un baño de aceite a 60°C durante 16 horas. Luego a 100°C durante 24 horas. Después de enfriar a temperatura ambiente la reacción se apagó por adición de varias gotas de HCl 1N y luego se dividió con EtOAc y KOH 1N. Las fases se separaron y la capa acuosa se extrajo con EtOAc (2X). Las porciones orgánicas se combinaron, se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron, y se concentraron. El residuo crudo se purificó por TLC preparativa (1000 μm de sílice, 15% de EtOAc/DCM) para proporcionar dos diastereómeros BK4 separados (R^3 =N-bencil-3-piperidilo, R^4 =n-Bu) (24 mg, 0,067 mmol, 33%, EM: (M+H) = 360,2) y BK5 (R^3 =N-bencil-m-piperidilo, R^4 =n-Bu) (22 mg, 0,062 mmol, 31%, EM: (M+H) = 360,2).

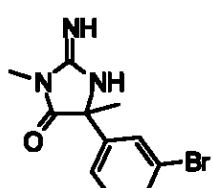
Método BK, Etapa 4:

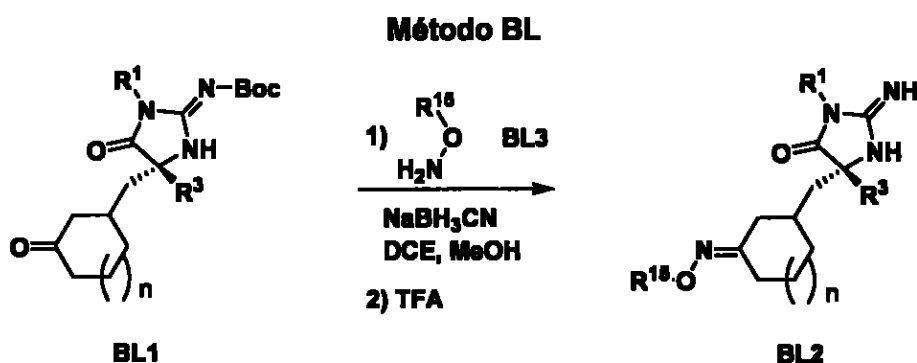
Se trató el diastereómero BK5 (R^3 =N-bencil-3-piperidilo, R^4 =n-Bu) con NH_4OH (2 ml) y peróxido de hidrógeno de *t*-butilo (70% acuoso, 2 ml) en MeOH (4 ml) durante 24 horas. Después de concentración, la muestra cruda se purificó por TLC preparativa (1000 mm de sílice, 7,5% NH_3 7N/MeOH en DCM). La muestra resultante se disolvió en DCM (1 ml), se trató con HCl 4N en dioxano durante 5 minutos, y finalmente se concentró para proporcionar los productos diastereoméricos BK7 (R^3 =N-bencil-3-piperidilo, R^4 =n-Bu) (12 mg, 0,029 mmol, 43%). ^1H RMN (CD_3OD) δ 7,60 (m, 2 H), 7,49 (m, 3 H), 4,39 (ABq, J_{AB} = 12,8 Hz, $\Delta\nu_{AB}$ = 42,1 Hz, 2 H), 3,69 (m, 1 H), 3,39 (br d, J = 13,6 Hz, 1 H), 3,20 (s, 3 H),

698
Jde

2,96 (m, 2 H), 2,45 (m, 1 H), 1,99 (m, 1 H), 1,92-1,78 (m, 3 H), 1,68 (br d, $J = 12,4$ Hz, 1 H), 1,50 (dq, $J_a = 3,6$ Hz, $J_q = 12,8$ Hz, 1 H), 1,36-1,22 (m, 4 H), 1,03 (m, 1 H), 0,90 (t, $J = 7,2$ Hz, 3 H). LCEM: t_R (doblemente protonado) = 0,52 min, (simplemente protonado) = 2,79 min; (M+H) para ambos picos = 343,2.

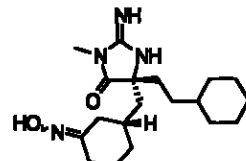
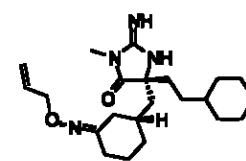
Los compuestos siguientes se sintetizaron usando métodos similares.

#	Estructura	PM	Obs. m/e
615		281	282



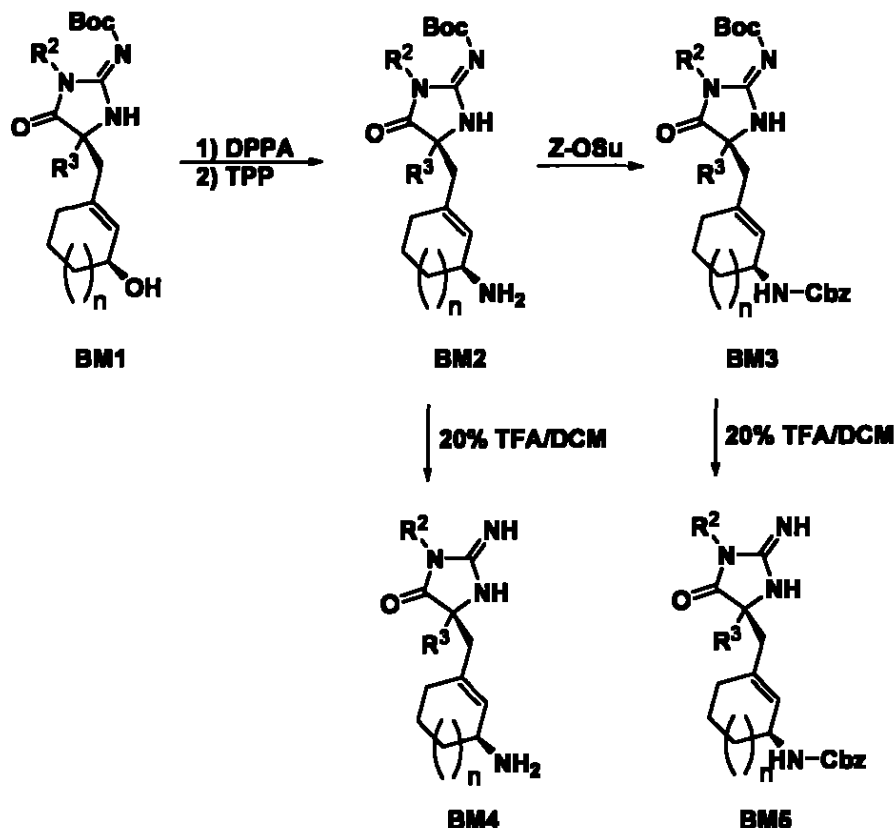
2ml de Solución metabólica de BL1 ($n=1$, R^3 =ciclohexiletilo, R^1 =Me) (10 mg) se le agregó BL3 (sal de HCl, R^{15} =H, 2 eq) y NaOAc (2 eq) y la mezcla se calentó a 60 C durante 16 horas. Después de remoción del solvente, el residuo se trató con 20% de TFA en DCM durante 30 min antes de evaporar el solvente y el residuo se purificó usando HPLC de fase inversa para proporcionar BL2 ($n=1$, R^3 =ciclohexiletilo, R^1 = Me y R^{15} = H).

Se sintetizaron los compuestos siguientes usando métodos similares.

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
616		348	349	617		388	389

699
208

Método BM



Método BM, Etapa 1:

A una solución de tolueno (3ml) de **BM1** ($n=1$, R^3 =ciclohexiletilo, R^2 =Me) (0,050 mg) se le agregó 1,5 eq de difenilfosforilazida y 1,5 eq de DBU y la solución se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con EtOAc y se lavó con 1% de HOAc acuoso antes de secar la capa orgánica y el solvente se evaporó. El residuo se cromatografió usando EtOAc/Hex para proporcionar un producto que se trató con trifenilfosfina (2 eq) en THF (1% de agua) durante la noche para proporcionar **BM2** ($n=1$, R^3 =ciclohexiletilo, R^2 =Me) después de purificación de fase inversa.

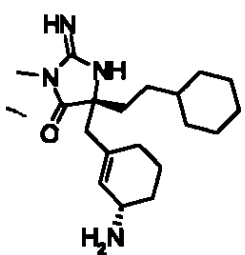
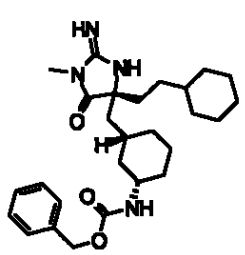
Método BM Etapa 2:

A una solución en DCM de **BM2** ($n=1$, R^3 =ciclohexiletilo, R^2 =Me) se agregó un equivalente de benciloxycarbonilo-OSu y la reacción se agitó durante la noche antes de evaporar el solvente y el residuo se cromatografió para proporcionar **BM3** ($n=1$, R^3 =ciclohexiletilo, R^2 =Me).

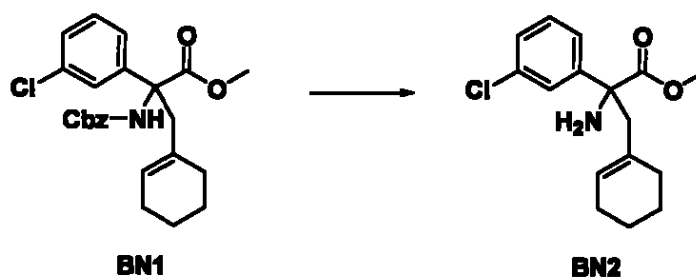
700
703

Los compuestos **BM4** ($n=1$, R^3 =ciclohexiletilo, R^2 =Me) y **BM5** ($n=1$, R^3 =ciclohexiletilo, R^2 =Me) se generaron a partir de **BM2** ($n=1$, R^3 =ciclohexiletilo, R^2 =Me) y **BM3** ($n=1$, R^3 =ciclohexiletilo, R^2 =Me) a través de desprotección Boc.

Los compuestos siguientes se sintetizaron usando un método similar:

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
618		332	333	619		468	469

Método BN



Se hidrogenó una mezcla de $\text{Pd}(\text{OAc})_2$ (9 mg), trietilamina (17 microlitro), trietilsilano (11 microlitro) y **BN1** (20 mg) en DCM a 1 atmósfera a temperatura ambiente durante 1,5 horas antes de filtrar la reacción a través de una almohadilla de Celite pad para obtener **BN2** después de remoción del solvente.

Método BO

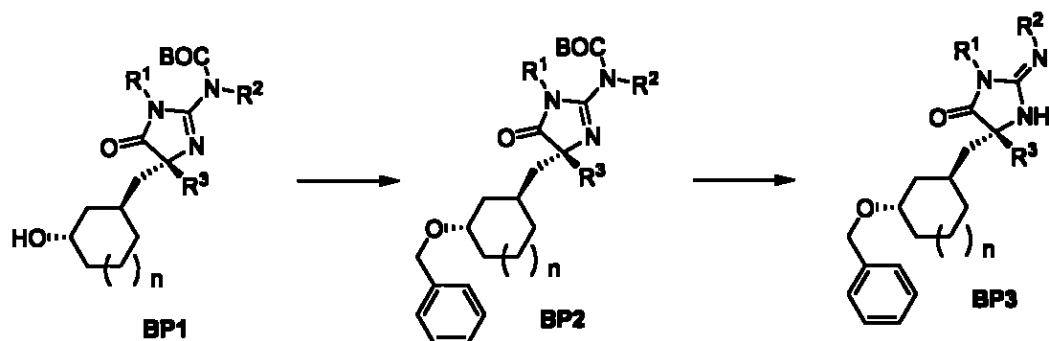
Se generaron los compuestos siguientes a través de desprotección boc del correspondiente material de partida usando 50% de TFA en DCM, a temperatura ambiente durante 30 minutos.

701
702

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
620		266	267	624		288	289
621		266	267	625		320	321
622		274	275	626		320	321
623		274	275				

702
710

Método BP



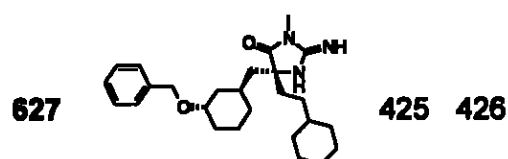
Método BP, Etapa 1

A una solución de BP1 ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3 = \text{ciclohexiletilo}$) (0,012 g, 0,028 mmol) en CH_2Cl_2 (0,5 mL) se le agregó 2,6-lutidina (0,010 mL, 0,086 mmol), AgOTf (0,024 g, 0,093 mmol), y bromuro de bencilo (0,010 mL, 0,084 mmol). La reacción se agitó a temperatura ambiente durante 16 horas. El sólido se filtró, y después de concentración el residuo se purificó por HPLC de fase inversa para proporcionar BP2 ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3 = \text{ciclohexiletilo}$) (0,010 g, 0,019 mmol). EM m/e: 526,1 (M+H).

Método BP, Etapa 2

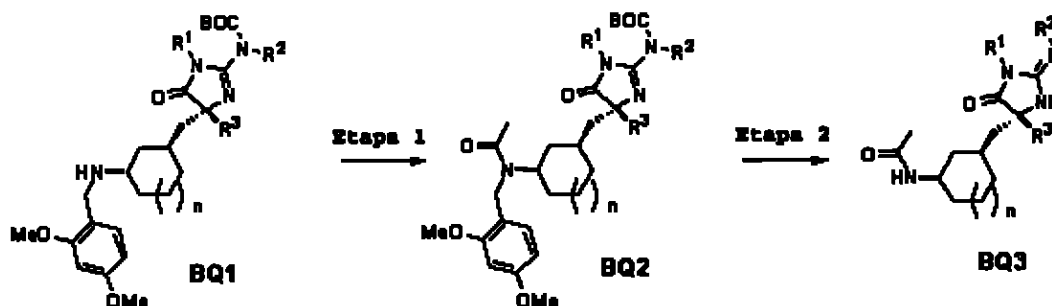
BP3 ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3 = \text{ciclohexiletilo}$) se preparó a partir de BP2 ($n=1$, $R^1=\text{Me}$, $R^2=\text{H}$, $R^3 = \text{ciclohexiletilo}$) usando 30% de TFA/DCM. EM m/e: 426,1 (M+H).

#	Estructura	PM	Obs. m/e
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7/11/14

Método BQ



Método BQ Etapa 1:

Se preparó BQ1 de acuerdo con el Método AZ.

A una solución de BQ1 ($n=1$, $R^1=Me$, $R^2=H$, $R^3 =$ ciclohexiletilo) (0,004 g, 0,007 mmol) en CH_2Cl_2 (0,3 mL) se le agregó DIEA (0,007 mL, 0,040 mmol), ácido acético (0,001 mL, 0,017 mmol), HOBt (0,003 g, 0,019 mmol), y EDCI (0,003 g, 0,016 mmol). La reacción se agitó a temperatura ambiente durante 16 horas. La reacción se concentró y purificó por HPLC de fase inversa para proporcionar BQ2 ($n=1$, $R^1=Me$, $R^2=H$, $R^3 =$ ciclohexiletilo) (0,003 g, 0,005 mmol). EM m/e: 627,1 (M+H).

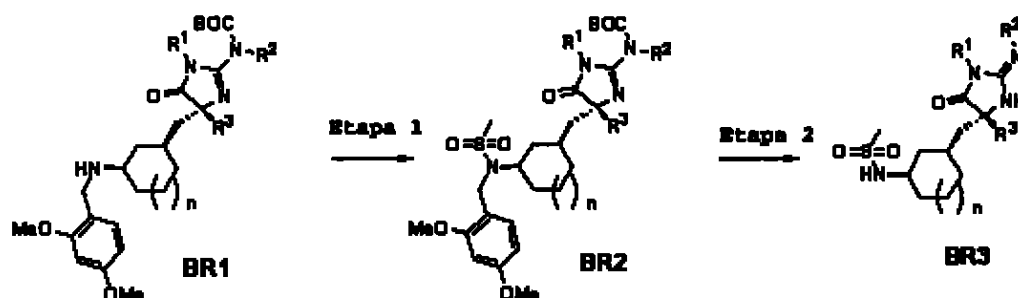
Método BQ Etapa 2:

Se trató BQ2 ($n=1$, $R^1=Me$, $R^2=H$, $R^3 =$ ciclohexiletilo) (0,003 g, 0,005 mmol) con 20% de TFA/ CH_2Cl_2 (1 mL) en presencia de PS-resina de tiofenol (0,030 g, 1,42 mmol/g) durante 3 horas. La solución se filtró y concentró para producir BQ3 ($n=1$, $R^1=Me$, $R^2=H$, $R^3 =$ ciclohexiletilo) (0,002 g, 0,005 mmol). EM m/e: 377,2 (M+H).

#	Estructura	PM	Obs. m/e
628		376	377

704
712

Método BR



Método BR, Etapa 1:

A una solución de BR1 ($n=1$, $R^1=Me$, $R^2=H$, $R^3 =$ ciclohexiletilo) (0,004 g, 0,007 mmol) en piridina (0,2 ml) se le agregó DMAP (unos pocos cristales) y cloruro de metilsulfonilo (3 gotas). La reacción se agitó a temperatura ambiente durante 6 días. La reacción se apago con agua y se diluyó con CH_2Cl_2 . La capa orgánica se extrajo en la fase acuosa con CH_2Cl_2 (3 veces). Después de concentración se purificó el residuo de color castaño mediante HPLC de fase inversa para proporcionar BR2($n=1$, $R^1=Me$, $R^2=H$, $R^3 =$ ciclohexiletilo) (0,003 g, 0,004 mmol). EM m/e: 663,2 (M+H).

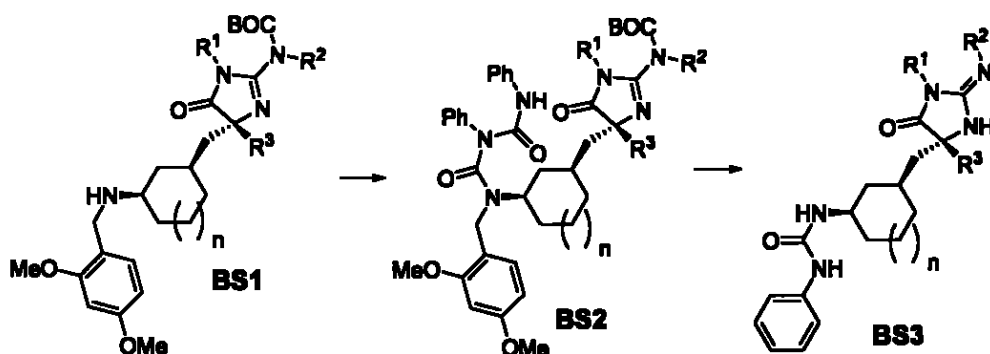
Método BR, Etapa 2:

Se preparó BR3 ($n=1$, $R^1=Me$, $R^2=H$, $R^3 =$ ciclohexiletilo) a partir de BR2($n=1$, $R^1=Me$, $R^2=H$, $R^3 =$ ciclohexiletilo) siguiendo un procedimiento similar al Método BQ Etapa 2. EM m/e: 413,1 (M+H).

#	Estructura	PM	Obs. m/e
629		412	413

705
713

Método BS



Método BS Etapa 1:

A una solución de **BS1** ($n=1$, $R^1=Me$, $R^2=H$, R^3 = ciclohexiletilo) (0,003 g, 0,006 mmol) en CH_2Cl_2 (0,3 mL) se le agregó isocianato de fenilo (2 gotas). La reacción se agitó a temperatura ambiente durante 16 horas. La reacción se concentró y purificó por HPLC de fase inversa para proporcionar **BS2** ($n=1$, $R^1=Me$, $R^2=H$, R^3 = ciclohexiletilo) (0,002 g, 0,002 mmol). EM m/e: 823,5 (M+H).

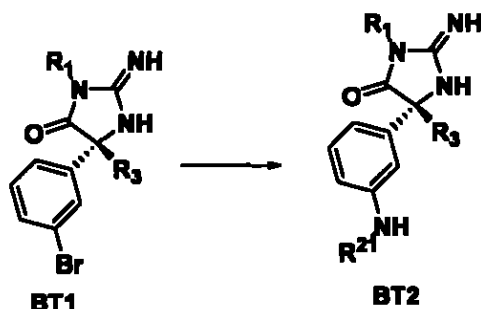
Método BS Etapa 2:

El compuesto **BS2** ($n=1$, $R^1=Me$, $R^2=H$, R^3 = ciclohexiletilo) se sometió a las mismas condiciones del Método BQ Etapa 2. La mezcla cruda preparada anteriormente se trató con LiOH (0,006 g, 0,25 mmol) en MeOH (0,3 mL) durante 2 horas. La reacción se concentró y el residuo se purificó por HPLC de fase inversa para proporcionar **BS3** ($n=1$, $R^1=Me$, $R^2=H$, R^3 = ciclohexiletilo) (0,0012 g, 0,002 mmol). EM m/e: 454,1 (M+H).

#	Estructura	PM	Obs. m/e
630		453	454

706
714

Método BT



Método BT:

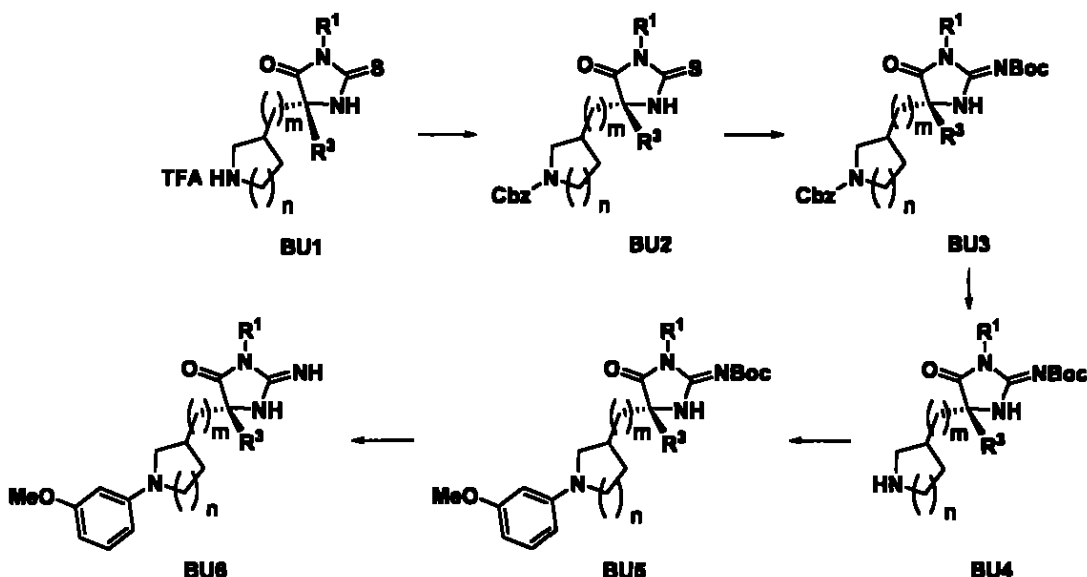
Se agregaron al frasco de fondo redondo el compuesto BT1 ($R^1=Me$, $R^3=Me$) (100 mg, 0,29 mmol), tolueno anhidro (2 ml), 3-aminopiridina (55 mg, 0,58 mmol) y 2-(di-*ter*-butil fosfino) bifenilo (17 mg, 0,058). La solución fue luego desgasificada con N_2 durante 2 minutos antes de agregar NaO-*t*-Bu (61 mg, 0,638 mmol) y $Pd_2(dba)_3$ (27 mg, 0,029 mmol). La reacción se agitó a 80°C durante 22 horas. Después de enfriar a temperatura ambiente, la reacción se vertió en agua fría y se extrajo con CH_2Cl_2 . La capa orgánica combinada se secó luego sobre Na_2SO_4 . Después de filtración, el residuo concentrado se separó por TLC ($CH_3OH:CH_2Cl_2=1:10$) y HPLC de fase inversa (10%-100% de acetonitrilo en agua, p/0,1% de ácido fórmico) para producir el compuesto deseado BT2 ($R^1=Me$, $R^3=Me$ and $R^{21}=m$ -piridilo) como la sal de formiato (23,6 mg, sólido blanco, 20%). ^1H RMN ($CDCl_3$) δ 7,50-6,90 (m, 13 H), 3,14 (s, 3H) EM m/e 358 (M+H).

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
631		347	348	632		356	357
633		357	358	635		357	358

707
715



Método BU



Método BU, Etapa 1,

A un frasco de fondo redondo que contenía BU1 ($m = 1$, $n = 1$, $R^1 = \text{Me}$, $R^3 = \text{Ciclohexiletilo}$) (99 mg, 0,307 mmol) d la sal de ácido trifluoracético del derivado pirrolidina en 5 ml de DCM se le agregaron (86 μL , 0,614 mmol) de trietilamina seguido de adición de (76 mg, 0,307 mmol) N-(bencilloxycarbonilo)succinimida. La temperatura ambiente durante 18 horas. La mezcla se diluyó con DCM y se extrajo con solución saturada de NaHCO_3 , y luego agua. La porción orgánica se recogió y se secó sobre Na_2SO_4 , se filtró y se concentró *al vacio*. Se purificó por cromatografía con gel de sílice (elusión con 0 a 60% de EtOAc/hexanos) para proporcionar BU2 ($m = 1$, $n = 1$, $R^1 = \text{Me}$, $R^3 = \text{Ciclohexiletilo}$) (130 mg, 0,284 mmol, 93% de rendimiento). EM m/e: 458,1 (M+H).

Método BU, Etapa 2,

A una solución de BU2 ($m = 1$, $n = 1$, $R^1 = \text{Me}$, $R^3 = \text{Ciclohexiletilo}$) (130 mg) en 1 ml de MeOH en un frasco de reacción se le agregó 0,5 ml de una solución de 70% de

708
7/6

tBuOOH en agua y 0,5 ml de NH_4OH . El frasco se selló y se agitó a temperatura ambiente durante 72 horas. La mezcla se concentró al vacío. La mezcla se diluyó con MeOH y se agregó una mezcla de 30 mg de NaHCO_3 y Boc_2O (87 mg, 0,398 mmol). La mezcla de la solución se agitó a temperatura ambiente durante 18 horas antes de concentrarla y el residuo se concentró por cromatografía de sílice usando EtOAc/hexanos para proporcionar BU3 ($m = 1$, $n = 1$, $\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{Ciclohexiletilo}$) (90 mg, 0,167 mmol, 58% de rendimiento). EM m/e: 541,1, 441,1 (M+H).

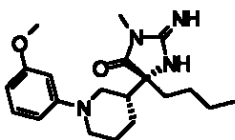
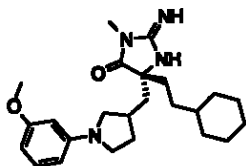
Método BU, Etapa 3,

Una solución de BU3 ($m = 1$, $n = 1$, $\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{Ciclohexiletilo}$) (90mg, 0,167 mmol) en 5 ml de MeOH se hidrogenó usando 100 mg de $\text{Pd}(\text{OH})_2\text{-C}$ (20% w/w) a 1 atmósfera durante 1 hora. La mezcla de reacción se filtró a través de una almohadilla de tierra de diatomeas y la almohadilla se lavó con MeOH. La concentración de las porciones orgánicas recogidas *al vacío* proporcionó BU4 ($m = 1$, $n = 1$, $\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{Ciclohexiletilo}$) (47 mg 0,116 mmol, 70% de rendimiento). EM m/e: 407,1 (M+H).

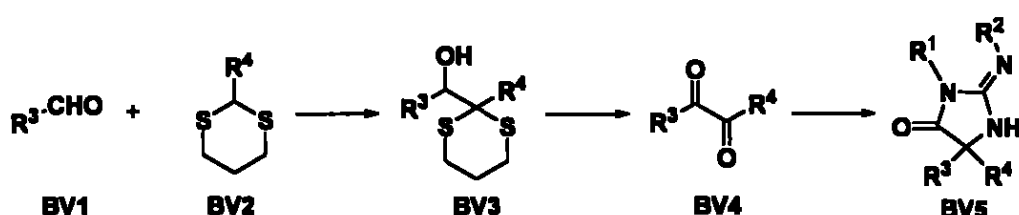
Método BU, Etapa 4,

Un frasco que contenía 10 mg de tamices moleculares 4 Å en polvo se agregaron ácido 3-metoxifenil borónico (60 mg, 0,395 mmol) y luego 3 ml de MeOH anhidro. A esta mezcla se le agregó piridina (100 ml, 0,650 mmol), $\text{Cu}(\text{OAc})_2$ (7 mg, 0,038 mmol), y BU4 ($m = 1$, $n = 1$, $\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{ciclohexiletilo}$) (7,83 mg, 0,019 mmol) y la mezcla se agitó a temperatura ambiente durante 96 horas antes de apagarla con 0,25 ml de amoníaco 7N en solución de metanol. La mezcla de reacción se extrajo con agua y DCM y las capas orgánicas se secaron y concentraron al vacío. El residuo se purificó por HPLC de fase inversa para proporcionar un producto que se trató con 5 ml de 40% de TFA en DCM durante 5 horas. Después de remoción de los volátiles, el residuo se purificó usando un sistema de HPLC de fase inversa para proporcionar BU5 ($m = 1$, $n = 1$, $\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{ciclohexiletilo}$ y $\text{R}^{21} = m\text{-MeOPh}$) como sal de ácido fórmico (0,7 mg, 0,0015 mmol, 30,1% de rendimiento). EM m/e: 413,1 (M+H).

709
272

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
637		358	359	638		412	413

Método BV



Método BV Etapa 1:

El método se adaptó de un procedimiento de la literatura (Page et al., *Tetrahedron* 1992, 35, 7265-7274)

Una solución de hexano de nBuLi (4,4 mL, 11 mmoles) se agregó a una solución a -78°C de BV2 (R⁴ = fenilo) (2,0 g, 10 mmoles) en THF (47 mL). Después de 60 minutos a -78°C, se agregó una solución de BV1 (R³ = 3-bromo-4-fluorfenilo) (2,24 g, 11 mmoles) y la reacción se calentó lentamente a temperatura ambiente durante 18 horas. La mezcla de reacción se apagó con una solución saturada de cloruro de amonio y se extrajo con CH₂Cl₂ (2 x), se secó sobre MgSO₄ y se concentró al vacío. El aceite resultante se sometió a cromatografía de gel de sílice usando 4-10% de EtOAc/Hexanos para proporcionar un sólido blanco BV3 (R³ = 3-bromo-4-

710
710

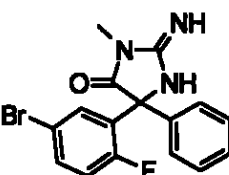
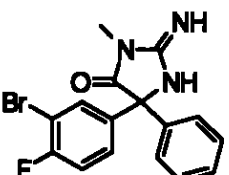
fluorfenilo y R^4 = fenilo) (1,69 g, 4,23 mmoles, 42%). ^1H NMR (CDCl_3) δ 7,61 (m, 2 H), 7,27 (m, 3 H), 6,94 (m, 1 H), 6,92 (m, 1 H), 6,68 (m, 1 H), 3,15 (bs, 1 H), 2,57-2,73 (m, 4 H), 1,89 (m, 2 H).

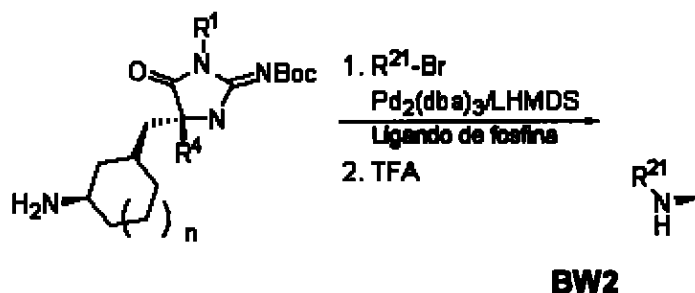
Método BV Etapa 3:

Una solución de BV3 (R^3 = 3-bromo-4-fluorfenilo y R^4 = fenilo) (1,69 g, 4,23 mmoles) en acetona (40 mL) se agregó lentamente mediante un embudo de adición a una solución a 0°C de N-bromosuccinimida (NBS, 11,3 g, 63,3 mmoles) en acetona (200 mL) y agua (7,5 mL). La mezcla se calentó lentamente a temperatura ambiente y se apagó después de 60 minutos con 10% de Na_2SO_3 acuoso. Después de diluir con CH_2Cl_2 , las capas se separaron, y la capa orgánica se lavó con agua (2x), salmuera (1x) y se secó sobre MgSO_4 . La concentración al vacío proporcionó un aceite, el cual se sometió a cromatografía de gel de sílice usando 5% de EtOAc/Hexanos para obtener un sólido BV4 (R^3 = 3-bromo-4-fluorfenilo y R^4 = fenilo) (690 mg, 2,24 mmoles, 53%). ^1H NMR (CDCl_3) δ 8,19 (m, 1 H), 7,93 (m, 3 H), 7,66 (m, 1 H), 7,50 (m, 2 H), 7,20 (m, 1 H).

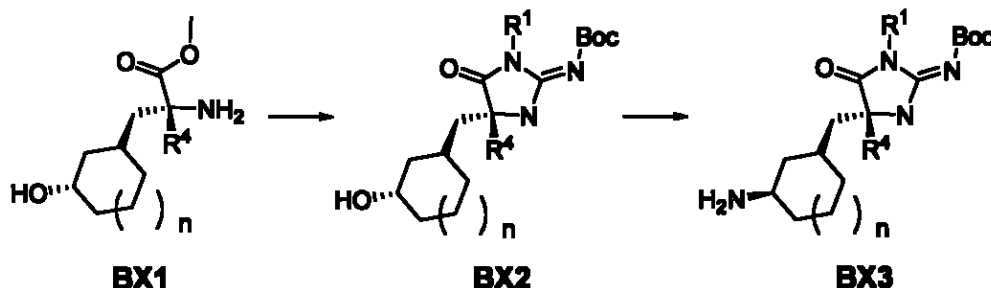
Método BV, Etapa 4:

BV5 (R^3 = 3-bromo-4-fluorfenilo y R^4 = fenilo y R^1 = Me y R^2 = H) se preparó a partir de BV4 (R^3 = 3-bromo-4-fluorfenilo y R^4 = fenilo) utilizando el Método AS, Etapa 4.

#	Estructura	PM	Obs. m/e	#	Estructura	PM	Obs. m/e
639		361	362	640		361	NA

711
719**Método BW**

A un recipiente secado en homo se agregó $\text{Pd}_2(\text{dba})_3$ (15.4 mg, 0.0168 mmol) y 2-(Di-*t*-butilfosfino)bifenilo (10.0 mg, 0.0336 mmol) seguido de la adición de una solución de **BW1** ($\text{R}^4 = \text{Me}$; $\text{R}^1 = \text{Me}$ y $n=1$) (56.8 mg, 0.168 mmol) en 2 ml de THF anhidro. Se añadió 2-bromopiridina (17.0 ml, 0.178 mmol) y luego 0.80 ml de una solución 1.0 N de LHMDS en THF. La mezclas de reacción se agitaron a 35°C durante 90 min seguido de la adición de MeOH y filtración con una almohadilla de gel de sílice. La purificación por cromatografía en gel de sílice (0 a 100% EtOAc en hexanos) dio el producto que luego se trató con 5 ml de una solución al 30% de TFA en DCM para dar **BW2** luego de concentración y purificación mediante columna de fase reversa ($\text{R}^4 = \text{Me}$; $\text{R}^1 = \text{Me}$; $\text{R}^{22} = 2\text{-piridilo}$ y $n=1$) (69.3 mg, 99%). ES_LCMS (m/e): 416.2

Método BX**Método BX, Etapa 1**

A una solución de **BX1** ($\text{R}^4 = \text{Me}$ y $n = 1$) (0.78g, 3.63 mmol) en 10 ml de DMF anhidra, se añadió N-Boc-N'-metil tiourea (0.70g, 3.70 mmol), EDCI.HCl (0.90g, 4.71 mmol), y diisopropiletilamina (2.5 ml). La mezcla se agitó a temperatura ambiente durante 16h antes de interrumpir la reacción con agua y se extrajo con EtOAc (3 x 50 ml). La solución orgánica se secó, se concentró y el residuo fue cromatografiado

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220

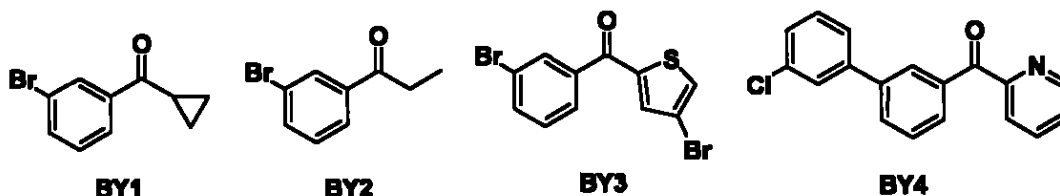
usando una columna de gel de sílice para dar **BX2** ($R^1 = R^4 = \text{Me}$ y $n = 1$) (1.23g, 100%). ES_LCMS (m/e): 340.1

Método BX, Etapa 2

A una solución de **BX2** ($R^1 = R^4 = \text{Me}$ y $n = 1$) (1.23g, 3.63 mmol) en 40 ml de THF anhidro se añadió trifenilfosfina (1.43g, 5.44 mmol) y la mezcla se enfrió hasta alcanzar 0°C seguido de la lenta adición de diisopropilcarbodiimida (1.07 ml, 5.44 mmol). Luego de que la mezcla se agitara durante 15 min a 0°C, se añadió nicotinoil azida (Synthesis, 2004 (17), 2886) (0.66g, 4.71 mmol) en una porción y se dejó que la reacción alcanzara temperatura ambiente, tras lo cual se agitó durante 3h. La reacción se diluyó con EtOAc (200 ml) y se lavó con agua (3 x 100 ml). El residuo de la capa orgánica se purificó usando una columna de gel de sílice para dar el producto azida que se hidrogenó usando 20% Pd(OH)₂ /C (0.64 mg) en MeOH para dar **BX3** ($R^1 = R^4 = \text{Me}$ y $n = 1$). ES_LCMS (m/e): 339.1.

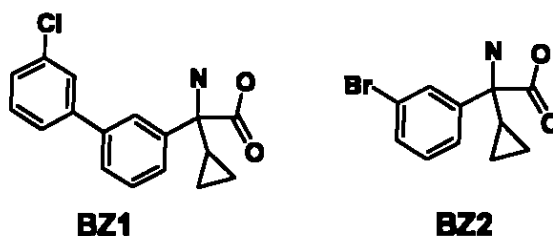
Método BY

Los siguientes compuestos se sintetizaron usando métodos similares a los Métodos AO o AP.



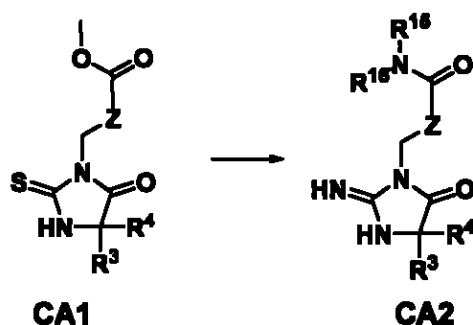
Método BZ

Se generaron los siguientes aminoácidos usando métodos similares al Método D



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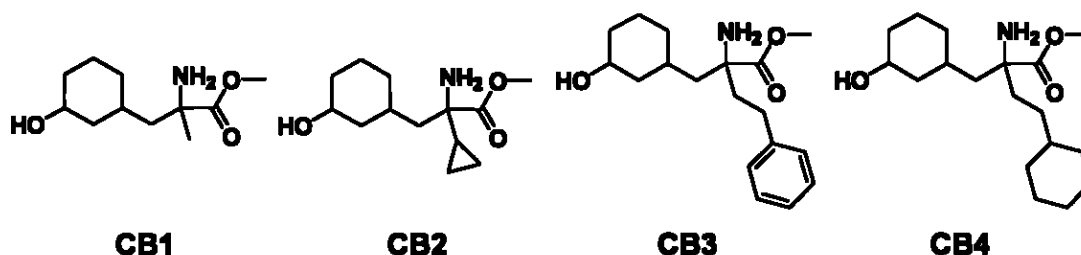
Método CA



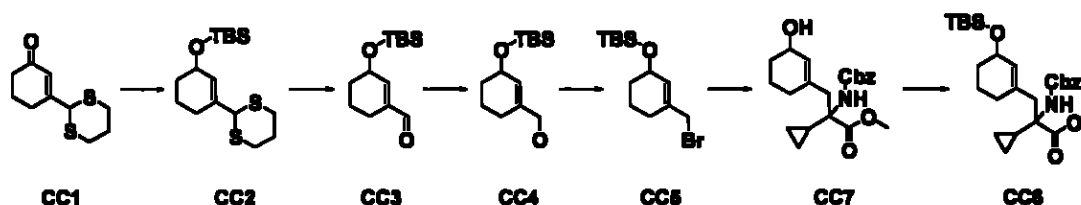
El compuesto CA2 ($R^3 = R^4 = \text{Ph}$; $Z = m\text{-fenileno}$, $R^{15} = \text{H}$ y $R^{16} = \text{ciclopentilo}$) se obtuvo a partir de CA1 ($R^3 = R^4 = \text{Ph}$; $Z = m\text{-fenileno}$, $R^{15} = \text{H}$ y $R^{16} = \text{ciclopentilo}$) usando un método similar al Método G.

Método CB

Se sintetizaron los siguientes compuestos usando métodos similares al Método E y/o AX.



Método CC



Método CC, Etapa 1.

A una solución metanólica (20 ml) de CC1 (5 g) enfriada a 0 °C se le añadió borohidruro de sodio (1 eq) y la reacción se agitó durante 30 min antes de que la mezcla de reacción se evaporara hasta sequedad, luego se extrajo con DCM/agua. Se reunieron las fracciones de DCM, se secaron (MgSO_4), se filtraron y se concentraron hasta sequedad. El producto crudo se disolvió en 20 ml. de DCM anhidro. A esta solución se le añadió t-butildimetilclorosilano (2 eq.) e imidazol (2

714
722

eq.). La reacción se agitó durante la noche a temperatura ambiente hasta interrumpirla con DCM y NaHCO_3 saturado. La fase orgánica se secó (MgSO_4), se filtró y se evaporó hasta sequedad para dar el producto crudo **CC2**.

Método CC, Etapa 2.

Se adaptó un procedimiento de la literatura (Aust. J. Chem. 1990, 43(7), 1195). Se añadió el compuesto **CC2** (50 g) en 80 ml. de THF a óxido mercurico (1.5 eq.) y borotri fluoruro eterato (1.6 eq.) en 540 ml. de THF/ H_2O (5:1) y la mezcla se agitó en nitrógeno durante 2 h hasta interrumpir la reacción con NaHCO_3 saturado (ac.) y éter. La fase de éter se secó en Na_2SO_4 anh., se filtró usando una almohadilla de sílice y se concentró para dar **CC3** crudo.

Método CC, Etapa 3.

A **CC3** (10.4 grams) en 200 ml de MeOH se le añadió 1.1 eq. de borohidruro de sodio y la mezcla se agitó durante 30 min hasta que la mezcla de reacción se concentró y el residuo se particionó en DCM/ H_2O . La fase orgánica se secó sobre Na_2SO_4 , se filtró y se concentró. El residuo se cromatografió para dar el producto **CC4**.

Método CC, Etapa 4.

Al compuesto **CC4** (2.5) en 5 ml. de DCM anhidro se le añadió Bis(1,2-difenilfosfino)etano (DPPE; 1.2 eq.) seguido de tetrabromuro de carbono (1.1eq.) a 0°C y la reacción se agitó durante 30 min. La reacción fue apagada con hexano y aplicada a una almohadilla de sílice. La solución orgánica se evaporó para dar el producto **CC5** en forma de aceite. $^1\text{H-NMR}$ (CDCl_3) δ 5.72, br s, 1H; 4.18, t, 1H; 3.83, q, 2H; 2.00-2.10, m, 2H; 1.76-1.81, m, 2H; 1.43-1.56, m, 2H; 0.84, s, 9H; 0.03, s, 6H.

Método CC, Etapa 5.

El compuesto **CC6** se generó a partir de **CC5** usando un procedimiento similar al Método E. El compuesto crudo **CC6** se purificó por cromatografía evaporativa (gradiente 0-10% EtOAc en hexano). Se aislaron dos isómeros durante la purificación, el isómero A eluyó en primer lugar seguido por el isómero B.

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223

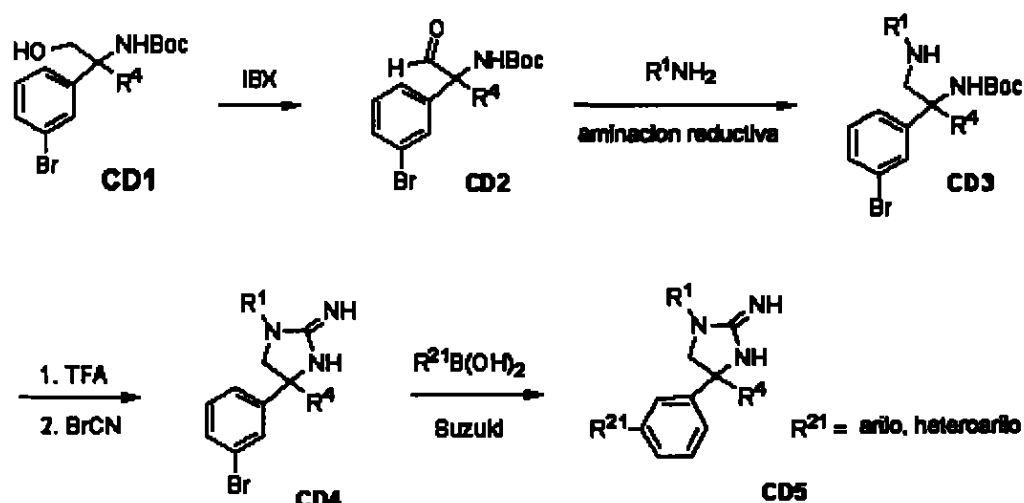
ISÓMERO A: $^1\text{H-NMR}$ (CDCl_3) δ 7.26-7.37, m, 5H; 5.57, s, 1H; 5.38, s, 1H; 5.02, q, 2H; 4.08, br s, 1H; 3.67, s, 3H; 3.08, d, 1H; 2.58, d, 1H; 1.80-1.92, m, 1H; 1.60-1.75, m, 3H; 1.32-1.44, m, 3H; 0.83, s, 9H; 0.35-0.45, m, 4H; 0.01, s, 6H.

ISÓMERO B: $^1\text{H-NMR}$ (CDCl_3) δ 7.286-7.36, m, 5H; 5.56, s, 1H; 5.39, s, 1H; 5.06, q, 2H; 4.15, br s, 1H; 3.71, s, 3H; 3.06, d, 1H; 2.70, d, 1H; 1.60-1.90, m, 4H; 1.33-1.48, m, 3H; 0.87, s, 9H; 0.37-0.51, m, 4H; 0.03, s, 6H. Rendimiento: 26% isómero A y 22% isómero B.

Método CC, Etapa 6.

El compuesto CC7 se obtuvo a partir de CC6 (isómero B) por medio de tratamiento con 1 N TBAF en THF durante 30 min seguido de extracción con éter/agua. La fase orgánica se separó y se lavó cuatro veces con agua. Se reunió la fase acuosa y se lavó una vez con Et_2O (pH ~6 to 7). La fase orgánica se secó sobre Na_2SO_4 , se filtró y se evaporó para dar el producto CC7 con un 94% de rendimiento. $^1\text{H-NMR}$ (CDCl_3) δ 7.28-7.39, m, 5H; 5.58, br s, 1H; 5.49, br s, 1H; 5.10, d, 1H; 5.02, d, 1H; 4.09, br s, 1H; 3.72, s, 3H; 3.14, d, 1H; 2.70, s, 1H; 1.79-1.87, m, 2H; 1.67-1.79, m, 1H; 1.53-1.67, m, 2H; 1.44-1.53, m, 2H; 1.31-1.39, m, 1H; 0.35-0.54, m, 4H

Método CD



Etapa 1: *ter*-butil 2-(3-bromofenil)-1-oxopropan-2-ilcarbamato

A una solución de *ter*-butil 2-(3-bromofenil)-1-hidroxipropan-2-ilcarbamato (CD1; $\text{R}^4 = \text{Me}$) (1.5 g, 4.6 mmol) en EtOAc (150 ml) a reflujo se le añadió IBX (3.82 g, 13.6 mmol, 3 eq). Se continuó el reflujo durante otras 2 h y luego la mezcla se

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enfrió hasta temperatura ambiente. El precipitado de color blanco se filtró y el filtrado se concentró. El residuo se purificó por cromatografía en gel de sílice eluyendo con EtOAc/hexanos para dar 1.0 g (66%) de *ter*-butil 2-(3-bromofenil)-1-oxopropan-2-il carbamato (CD₂; R⁴ = Me) en forma de aceite incoloro. ¹H NMR (CDCl₃) δ 9.42 (s, 1H), 7.69 (m, 1H), 7.60 (m, 1H), 7.55-7.40 (m, 2H), 5.85 (bs, 1H), 1.96 (s, 3H), 1.56 (s, 9H).

Etapas 2: *ter*-Butil 2-(3-bromofenil)-1-(metilamino)propan-2-ilcarbamato

A una solución de *ter*-butil 2-(3-bromofenil)-1-oxopropan-2-ilcarbamato (CD₂; R⁴ = Me) (1.0 g, 3 mmol) en dicloroetano (50 ml) se le añadió metilamina (0.48 g, 6.1 mmol, 2 eq) en agua (40%) y 1 ml de AcOH. Se dejó la solución en agitación a temperatura ambiente durante 1 h y se agregó triacetoxiborohidruro de sodio (1.8 g, 8.5 mmol, 2.8 eq). La mezcla resultante se agitó a temperatura ambiente durante 16 h y se apagó con MeOH. Luego de agitar durante 30 min, la mezcla se concentró al vacío. El residuo se purificó por cromatografía en gel de sílice eluyendo con EtOAc/MeOH para dar 0.62 g (60%) de *ter*-butil 2-(3-bromofenil)-1-(metilamino)propan-2-ilcarbamato (CD₃; R¹ = Me, R⁴ = Me) en forma de aceite incoloro. ¹H NMR (CDCl₃) δ 7.47 (bs, 1H), 7.37 (m, 1H), 7.27 (m, 1H), 7.23 (m, 1H), 5.97 (bs, 1H), 3.18-2.82 (m, 2H), 2.45 (s, 3H), 1.74 (s, 3H), 1.40 (s, 9H). MS (ESI) *m/e* 342.9 (M+H)⁺.

Etapas 3: 4-(3-Bromofenil)-1,4-dimetilimidazolidin-2-imina

Se disolvió *ter*-butil 2-(3-bromofenil)-1-(metilamino)propan-2-ilcarbamato (CD₃; R¹ = Me, R⁴ = Me) (0.62 g, 1.8 mmol) en TFA al 25% en DCM (25 ml) y la mezcla se dejó en agitación a temperatura ambiente durante 1 h. La mezcla se concentró al vacío y el residuo se redisolvió en CHCl₃ (20 ml). La solución se lavó con 15% NaOH (10 ml) y la capa acuosa se extrajo con CHCl₃ (3 x 10 ml). La capa orgánica combinada se secó sobre MgSO₄ y se concentró al vacío para dar 0.33 g (76%) de 2-(3-bromofenil)-N¹-metilpropan-1,2-diamina cruda en forma de aceite incoloro. ¹H NMR (CDCl₃) δ 7.65 (t, J = 1.7 Hz, 1H), 7.41-7.34 (m, 2H), 7.21 (t, J = 7.8 Hz, 1H), 2.86 (dd, J = 11.7, 0.6 Hz, 1H), 2.64 (dd, J = 11.7, 0.6 Hz, 1H), 2.38 (s, 3H), 1.54 (bs, 3H), 1.43 (s, 9H). MS (ESI) *m/e* 242.9 (M+H)⁺. El compuesto se usó en la etapa siguiente sin purificación adicional.

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25

A una solución de 2-(3-bromofenil)-N¹-metilpropan-1,2-diamina (0.12 g, 0.50 mmol) en EtOH (10 ml) se le añadió BrCN (0.073 g, 0.70 mmol, 1.4 eq). La mezcla se agitó a temperatura ambiente durante 16 h y luego se concentró al vacío. El residuo se redisolvió en CHCl₃ (20 ml) y la solución se lavó con 15% NaOH (10 ml). La capa acuosa se extrajo con CHCl₃ (3 x 10 ml) y la capa orgánica combinada se secó (MgSO₄), y se concentró para dar 0.14 g (100%) de 4-(3-bromofenil)-1,4-dimetilimidazolidin-2-imina (CD4; R¹ = Me, R⁴ = Me) en forma de aceite incoloro. ¹H NMR (CDCl₃) δ 7.42 (t, J = 1.7 Hz, 1H), 7.35 (dd, J = 8.1, 1.7 Hz, 2H), 7.15 (t, J = 8.1 Hz, 1H), 3.62 (d, J = 9.3 Hz, 1H), 3.53 (d, J = 9.0 Hz, 1H), 3.08 (s, 3H), 1.56 (bs, 3H). MS (ESI) *m/e* 268.1, 270.1 (M+H)⁺.

Etapas 4: 4-(3-(3,4-Difluorofenil)fenil)-1,4-dimetilimidazolidin-2-imina

Una mezcla de 4-(3-bromofenil)-4-metiloxazolidin-2-imina (0.027 g, 0.1 mmol, 1 eq), ácido 3,4-difluorofenil bórico (0.020 g, 0.13 mmol, 1.3 eq), FibreCa (20 mg), etanol anhidro (2 ml), y una solución acuosa 1N de K₂CO₃ (0.12 ml, 0.12 mmol, 1.2 eq) se calentó en un reactor de microondas (Emrys Optimizer) a 110°C durante 15 min. La mezcla se transfirió a una columna pre-rellena de Si-carbonato (2 g, 0.79 mmol/g), la cual había sido acondicionada con MeOH/DCM (1:1). La columna se eluyó con 1:1 MeOH/DCM (3 x 3 ml) y los eluyentes se recogieron y concentraron para dar 0.019 g (63%) de 4-(3-(3,4-difluorofenil)fenil)-1,4-dimetilimidazolidin-2-imina (CD5; R¹ = Me, R⁴ = Me, R²¹ = 3,4-difluorofenil) en forma de sólido de color blanco. ¹H NMR (CDCl₃) δ 7.60 (s, 1H), 7.50-7.20 (m, 6H), 3.48 (m, 2H), 2.79 (s, 3H), 1.66 (s, 3H). MS(ESI) *m/e* 302.2 (M+H)⁺, HPLC (A) R_t = 5.48 min.

Alternativa al Método CD para el compuesto : R¹ = OR¹⁶

Método CD Alternativo, Etapa 2: *ter*-Butil 2-(3-bromofenil)-1-(metoxilamino)propan-2-ilcarbamato

A una solución de *ter*-butil 2-(3-bromofenil)-1-oxopropan-2-ilcarbamato (CD2; R⁴ = Me) (2.7 g, 8.2 mmol) en dicloroetano (40 ml) se le añadió clorhidrato de metoxilamina (0.89 g, 10.7 mmol, 1.3 eq) y 1 ml de AcOH. La solución se dejó agitando a temperatura ambiente durante 16 h. La mezcla de reacción se concentró para dar el intermediario oxima. La oxima se disolvió en EtOH (20 ml) y se añadió por goteo complejo de borano-piridina (0.74 g, 7.9 mmol). Luego de agitar a temperatura ambiente durante 20 min, la mezcla de reacción se concentró al vacío. El residuo se redisolvió en DCM (50 ml) y se lavó con agua (3x20 ml). La capa

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orgánica se secó (Na_2SO_4) y se concentró para dar 1.6 g (54%) de *ter*-butil 2-(3-bromofenil)-1-(metoxiamino)propan-2-ilcarbamato (CD3; $\text{R}^1 = \text{OMe}$, $\text{R}^4 = \text{Me}$). ^1H NMR (CDCl_3) δ 7.60-7.10 (m, 4H), 5.82 (s, 1H), 3.90 (s, 3H), 3.70 (m, 2H), 1.80 (s, 3H), 1.40 (s, 9H). El compuesto crudo se usó en la etapa posterior sin purificación adicional.

Método CD Alternativo, Etapa 3: 4-(3-Bromofenil)-1-metoxi-4-metilimidazolidin-2-imina

Se disolvió *ter*-Butil 2-(3-bromofenil)-1-(metoxiamino)propan-2-il carbamato (CD3; $\text{R}^1 = \text{OMe}$, $\text{R}^4 = \text{Me}$) (1.6 g, 4.4 mmol) en TFA al 25% en DCM (25 ml) y la mezcla se dejó en agitación a temperatura ambiente durante 1 h. La mezcla se concentró al vacío. El residuo se redisolvió en CHCl_3 (20 ml) y se lavó con 15% NaOH (10 ml). La capa acuosa se extrajo con CHCl_3 (3 x 10 ml). La capa orgánica combinada se secó sobre MgSO_4 y se concentró al vacío. El residuo se disolvió en EtOH (10 ml) y se añadió BrCN (0.096 g, 0.91 mmol). Luego de agitación a temperatura ambiente durante 16 h, la mezcla se concentró al vacío. El residuo se redisolvió en CHCl_3 (20 ml) y se lavó con 15% NaOH (10 ml). La capa acuosa se extrajo con CHCl_3 (3 x 10 ml). La capa orgánica combinada se secó sobre MgSO_4 y se concentró para dar 0.2 g (16%) de 4-(3-bromofenil)-1-metoxi-4-metilimidazolidin-2-imina (CD4; $\text{R}^1 = \text{OMe}$, $\text{R}^4 = \text{Me}$) en forma de aceite incoloro. ^1H NMR (CDCl_3) δ 7.65-7.35 (m, 4H), 4.02 (s, 3H), 3.98 (d, 1H), 3.91 (d, 1H), 1.94 (s, 3H).

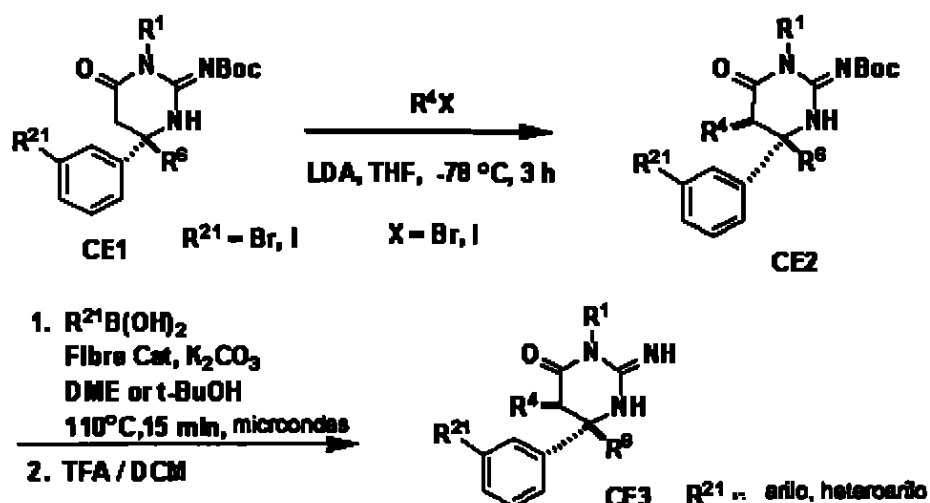
Método CD Alternativo, Etapa 4: 4-(3-(3-Clorofenil)fenil)-1-metoxi-4-metilimidazolidin-2-imina

Una mezcla de 4-(3-bromofenil)-4-metiloxazolidin-2-imina (CD4; $\text{R}^1 = \text{OMe}$, $\text{R}^4 = \text{Me}$) (0.027 g, 0.1 mmol, 1 eq), ácido 3-cloro fenilbórico (0.023 g, 0.13 mmol, 1.3 eq), FibreCat (0.020 g), etanol anhidro (2 ml), y solución acuosa 1N de K_2CO_3 (0.12 ml, 0.12 mmol, 1.2 eq) se calentó en un reactor de microondas (Emrys Optimizer) a 110°C durante 15 min. La mezcla se transfirió a una columna pre-rellena de Si-carbonato (2 g, 0.79 mmol/g), que había sido acondicionada con MeOH/DCM (1:1). La columna se eluyó con 1:1 MeOH/DCM (3x3 ml), se recolectaron los eluyentes y se concentraron para dar 0.008 g (25%) de 4-(3-(3-clorofenil)fenil)-1-metoxi-4-metilimidazolidin-2-imina (CD5; $\text{R}^1 = \text{OMe}$, $\text{R}^4 = \text{Me}$, $\text{R}^{21} = 3\text{-ClC}_6\text{H}_4$) en forma de sólido de color blanco. ^1H NMR (CDCl_3) δ 7.75-7.60 (m, 5H), 7.58-7.42 (m, 3H), 4.00

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(m, 2H), 3.97 (s, 3H), 1.97 (s, 3H). MS(ESI) m/z 316.0, 318.0 (M+H)⁺, HPLC (A) Rt = 5.64 min.

Método CE



Método CE, Etapa 1

La síntesis de CE2 ($R^1 = R^4 = \text{Me}$, $R^{21} = \text{Br}$ y $R^6 = \text{Me}$) fue adaptada a partir del procedimiento de Spanu, P. *et. al.*, Tet. Lett., 2003, 44, 671-675. Por lo tanto, a una solución de (S)-ter-butil 4-(3-bromofenil)-1,4-dimetil-6-oxo-tetrahidropirimidin-2(1H)-ilidenocarbamato (CE1; $R^1 = R^6 = \text{Me}$, $R^{21} = \text{Br}$) (0.24 g, 0.6 mmol, 1 eq) en THF (4 ml), se le añadió por goteo LDA (2M en heptano/THF, 0.6 ml, 0.12 mmol, 2 eq) con una jeringa a -78°C . Luego de agitación a -78°C durante 30 min, una solución de yodometano (0.080 ml, 0.12 mmol, 2 eq) en THF (4 ml) se añadió por goteo hasta obtener una solución de enolato de color naranja. La mezcla se agitó a -78°C durante 3 h. Se añadió agua para interrumpir la reacción y la suspensión se llevó a temperatura ambiente. La mezcla luego se particionó entre H_2O y Et_2O . La capa orgánica se separó y la capa acuosa se extrajo con Et_2O (3 x 25 ml).

Las capas orgánicas combinadas se lavaron con salmuera, se secaron (MgSO_4) y se concentraron para dar 0.38 g de un aceite de color marrón. La cromatografía en gel de sílice usando 50% EtOAc/hexanos como eluyente proporcionó 0.14 g (54%) de ter-butil (4S,5R)-4-(3-bromofenil)-1,4,5-trimetil-6-oxo-tetrahidropirimidin-2(1H)-ilidenocarbamato (CE2; $R^1 = R^4 = \text{Me}$, $R^{21} = \text{Br}$ y $R^6 = \text{Me}$) en forma de sólido de color blanco. $^1\text{HNMR}$ (CDCl_3 , 300 MHz): δ 10.16 (s, 1H), 7.46 (m,

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2H), 7.26 (m, 2H), 3.21 (s, 1H), 3.01 (m, 3H), 3.02 (m, 1H), 1.51 (s, 12H), 1.17 (d, J = 7.1 Hz, 3H). MS(ESI): MH^+ = 441.7 HPLC (A) R_t = 7.20 min.

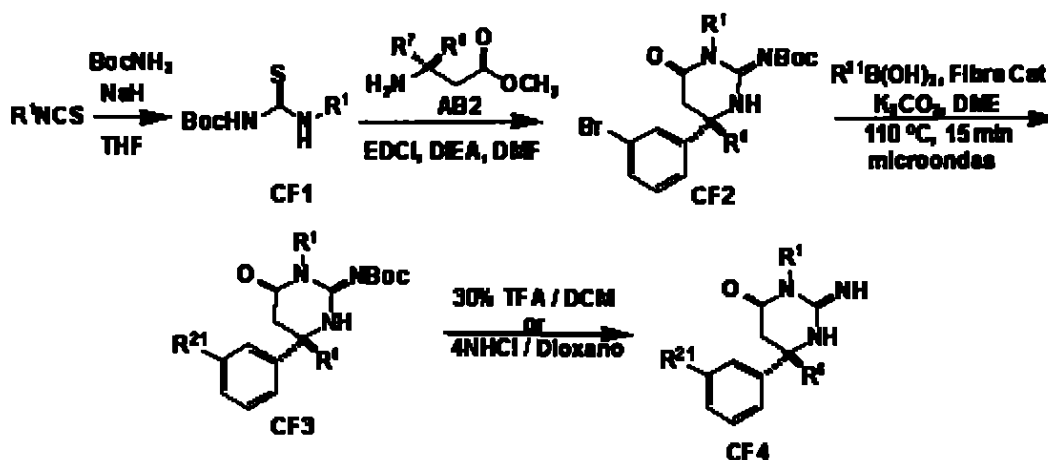
Método CE, Etapa 2

Una mezcla de (S)-ter-butil 4-(3-bromofenil)-1,4-dimetil-6-oxotetrahidropirimidin-2(1H)-ilideno carbamato (CE2; $R^1 = R^4 = Me$, $R^6 = Me$, $R^{21} = Br$) (0.25 g, 0.6 mmol), ácido 5-cianotien-1-ilbórico (0.2 g, 1.3 mmol, 2 eq), Fibreca (4.26% Pd, 0.7g), y 1N K_2CO_3 ac. (0.5 ml) se calentó a 110 °C en un recipiente para procesos Smith de 20 ml usando el sintetizador de microondas Emrys. Luego de enfriar, la mezcla de reacción fue transferida a una columna pre-rellena de Si-Carbonato columna y se leuyó con MeOH/ CH_2Cl_2 (1:1). Se concentró el eluyente para dar 0.32 g de un aceite amarillo que se purificó por cromatografía en gel de sílice (20-50% EtOAc/hexanos para dar 0.13 g (0.3 mmol, 48% de rendimiento, sin:anti ratio: 5:1) de (S)-ter-butil 4-(3-(5-cianotien-1-il)fenil)-1,4-dimetil-6-oxotetrahidro-pirimidin-2(1H)-ilidencarbamato en forma de sólido de color blanco. ^1H NMR ($CDCl_3$, 300 MHz): δ 10.15 (s, 1H), 7.58-7.53 (m, 3H), 7.53-7.38 (m, 2H), 7.23 (m, 1H), 3.32 (s, 3H), 3.16 (m, 1H), 1.57 (s, 9H), 1.23 (d, J = 6.9 Hz, 3H). MS (ESI): MH^+ = 438.7; $M+56$ = 383.1. HPLC R_t = 7.28 min (isómero sin).

Se trató (S)-ter-Butil 4-(3-(5-cianotien-1-il)fenil)-1,4-dimetil-6-oxotetrahidropirimidin-2(1H)-ilidencarbamato (23 mg, 0.05 mmol) con 1 ml de 30% TFA/ CH_2Cl_2 a temperatura ambiente durante 30 min. Se eliminaron los volátiles al vacío y el residuo se redisolvió en acetonitrilo (5 ml) y se evaporó nuevamente para dar 17 mg de iminopirimidinona cruda en forma de sólido de color amarillo. El producto crudo se purificó por HPLC (B) de fase reversa para proporcionar 10 mg (60%) de (S)-6-(3-(5-cianotien-1-il)fenil)-6-etil-2-imino-3-metil-tetrahidropirimidin-4(1H)-ona (CE3; $R^1 = R^4 = Me$, $R^6 = Me$, $R^{21} = 5$ -cianotien-1-il) en forma de sólido de color blanco. ^1H NMR ($CDCl_3$, 300 MHz): δ 11.1 (br s, 1H), 10.0 (s, 1H), 7.58-7.53 (m, 3H), 7.44 (m, 1H), 7.40-7.26 (m, 2H), 3.30 (m, 1H), 3.16 (s, 3H), 1.60 (s, 3H), 1.27 (d, J = 7.2 Hz, 3H). MS (ESI): MH^+ = 438.7; $M+56$ = 339.1. HPLC R_t = 7.24 min (isómero sin).

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Método CF



Método CF, Etapa 1.

A una solución de t-butilcarbamato (0.5 g, 4.3 mmol, 1 eq) en THF anhidro (5.0 ml) a temperatura ambiente se le añadió NaH (0.17 g, 4.3 mmol, 1 eq). La mezcla se agitó a temperatura ambiente durante 15 min. Luego una solución de metil isocianato (0.3 g, 4.2 mmol, 1 eq.) en THF anhidro (5.0 ml) se añadió por goteo. La mezcla de reacción se dejó en agitación a 25 °C durante 15 min. La mezcla luego se vertió en 30 ml de hielo-agua con agitación vigorosa. La solución de reacción se extrajo con Et₂O (2 x 25 ml). Las capas orgánicas fueron combinadas y se lavaron con salmuera (30 ml), se secaron (Na₂SO₄), y se concentraron al vacío para dar 0.42 g (50% rendimiento) de ter-butil metilcarbamatoilcarbamato CF1 (R¹ = Me) en forma de sólido de color blanco. ¹HNMR (CDCl₃, 300 MHz): δ 8.3 (br s, 1H), 3.19 (d, 3H, J = 4.8 Hz), 1.8 (br s, 1H), 1.5 (s, 9H).

Método CF, Etapa 2.

A una solución de una sal HCl de AB2 (R⁶ = 3-bromofenilo y R⁷ = Me) (0.2 g, 0.7 mmol) y CF1 (R¹ = Me) en DMF (2 ml) a temperatura ambiente se le añadió DIEA (0.5 ml, 2.8 mmol, 4 eq) y 1-[3-(dimetilamino)propil]-3-etilcarbodiimida HCl (EDCI, 0.2g, 1.0 mmol, 1.4 eq). Luego de agitación a temperatura ambiente durante 16 horas, la mezcla se diluyó con EtOAc (10 ml), se lavó con salmuera, se secó (MgSO₄), y se filtró. El filtrado se evaporó bajo presión reducida para proporcionar 0.34 g de producto crudo en forma de aceite amarillo que se purificó usando cromatografía en gel de sílice eluyendo con 20% EtOAc/hexanos para dar 0.17 g (0.4 mmol, 60%) de (S)-ter-butil 4-(3-bromofenil)-1,4-dimetil-6-oxo-tetrahidropirimidin-

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2(1H)-ilidenocarbamato (CF2; $R^1=R^6=Me$) en forma de sólido de color blanco. ^1H NMR ($CDCl_3$, 300 MHz): δ 10.63 (s, 1H), 7.42 (m, 2H), 7.24 (m, 2H), 3.21 (s, 3H), 3.2 (d, 1H, $J = 16.3$ Hz), 2.87 (d, 1H, $J = 16.1$ Hz), 1.65 (s, 3H), 1.55 (s, 9H). MS(ESI): $MH^+ = 395.7, 398.7$. HPLC $R_t = 7.11$ min.

Método CF, Etapa 3.

Una mezcla de (S)-ter-butil 4-(3-bromofenil)-1,4-dimetil-6-oxo-tetrahidropirimidin-2(1H)-ilidenocarbamato (CF2; $R^1=R^6=Me$) (0.25 g, 0.6 mmol), ácido 5-cloro-2-hidroxifenilbórico ($R^{21} = 5\text{-cloro-2-hidroxifenilo}$; 0.2 g, 1.2 mmol, 2 eq), Fibreca (4.26% de Pd, 0.7 g) y K_2CO_3 1N ac. (0.5 ml) en dimetoxietano (DME, 10 ml) o ter-butanol (10 ml) en un recipiente para procesos Smith de 20 ml equipado con barra agitadora se selló y calentó en un optimizador Emrys a 110 °C durante 15 min. Luego de enfriar, la mezcla de reacción se transfirió a una columna pre-rellena de Si-carbonato y se eluyó con $MeOH/CH_2Cl_2$ (1:1). El eluyente se recolectó y se concentró a presión reducida para dar 0.32g del producto crudo en forma de aceite. El producto crudo se purificó por cromatografía en gel de sílice (gradiente 20-50% EtOAc/hexanos) para dar 0.13 g (0.3 mmol, 48%) de (S)-ter-butil 4-(3-(3-cloro-6-hidroxifenil)-fenil)-1,4-dimetil-6-oxo-tetrahidropirimidin-2(1H)-ilidenocarbamato (CF3; $R^1 = R^6 = Me$, $R^{21} = 3\text{-cloro-6-hidroxifenilo}$) en forma de sólido de color blanco. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.48-4.32 (m, 2H), 7.20 (m, 3H), 6.84 (m, 2H), 5.68 (br s, 1H), 3.28 (d, $J = 15.7$ Hz, 1H), 3.21 (s, 3H), 2.96(d, $J = 15.3$ Hz, 1H), 1.68 (s, 3H), 1.53 (s, 9H). MS (ESI): $MH^+ = 443.7, 445.7$; $M^+-56 = 388.0$. HPLC R_t (A) = 6.99 min.

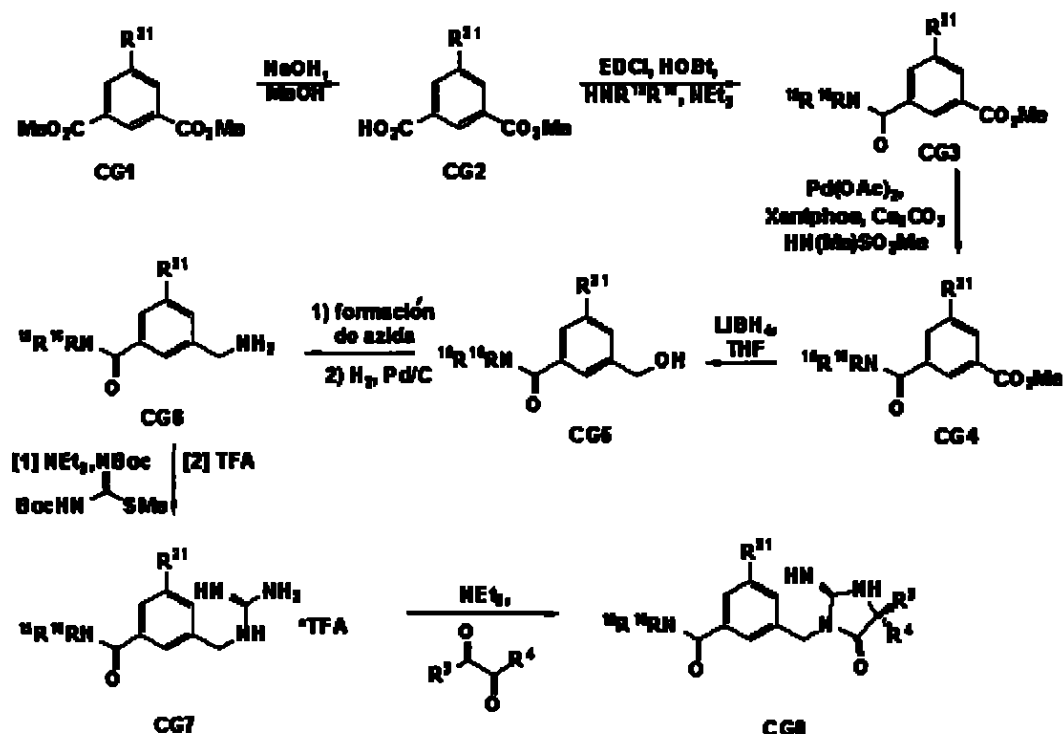
Método CF, Etapa 4.

Se trató (S)-ter-butil 4-(3-(3-cloro-6-hidroxifenil)fenil)-1,4-dimetil-6-oxo-tetrahidropirimidin-2(1H)-ilidenocarbamato (CF3; $R^1 = R^6 = Me$, $R^{21} = 3\text{-cloro-6-hidroxifenilo}$) (23 mg, 0.05 mmol) con 1 ml de 30%TFA/ CH_2Cl_2 a temperatura ambiente durante 30 min. Se eliminaron los volátiles al vacío. El residuo se redisolvió en acetonitrilo (5 ml) y se evaporó nuevamente hasta proporcionar 17 mg del producto crudo en forma de sólido de color amarillo. El producto crudo se purificó usando HPLC de fase reversa para proporcionar 10 mg (60%) de (S)-6-(3-(3-cloro-6-hidroxi-fenil)fenil)-6-etil-2-imino-3-metil-tetrahidropirimidin-4(1H)-ona (CF4; $R^1 = R^6 = Me$, $R^{21} = 3\text{-cloro-6-hidroxifenil}$) en forma de sólido de color blanco. ^1H NMR ($CDCl_3$, 300 MHz): δ 11.4 (br s, 1H), 7.6-4.25 (m, 3H), 7.24-6.84 (m, 3H), 3.68 (br s, 1H), 5.18

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(br s, 1H), 3.39 (d, $J = 16.1$ Hz, 1H), 3.20 (s, 3H), 2.95 (d, $J = 15.8$ Hz, 1H), 1.74 (s, 3H).
MS(ESI): $MH^+ = 344.1$. HPLC (A) $R_t = 5.07$ min.

Método CG



Método CG, Etapa 1;

Una solución de **CG1** ($R^{21} = Br$, 12.29 g, 45 mmol) y $NaOH$ (1.93 g, 49 mmol) en $MeOH$ (70 ml) y agua (10 ml) se sometió a reflujo durante 3 h. Luego de la eliminación de $MeOH$ al vacío, el residuo acuoso se ajustó a pH 3 y el sólido resultante se filtró, se secó al vacío para dar **CG2** ($R^{21} = Br$, 11.41 g, 98%). ^1H NMR (400 MHz, CD_3OD) δ 8.49 (m, 1 H), 8.27 (m, 1 H), 3.90 (s, 3 H).

Método CG, Etapa 2;

Una mezcla de **CG2** ($R^{21} = Br$, 11.41 g, 44 mmol), $EDCl$ (8.6 g, 45 mmol), dipropilamina (6.2 ml, 44.8 mmol), $HOBt$ (6.0 g, 44.4 mmol) y NEt_3 (10 ml, 72 mmol) en CH_2Cl_2 (100 ml) se agitó a temperatura ambiente durante 48 h. La reacción se lavó con $NaHCO_3$ sat., agua (1x), NH_4Cl (1x), agua (1x), salmuera (1x), se secó sobre $MgSO_4$, se filtró y se concentró con vacío. El material resultante fue sometido a cromatografía en gel de sílice (0% $\rightarrow$ 40% $EtOAc$ /hexanos) para dar **CG3** ($R^{21} = Br$, $R^{15} = R^{16} = Pr$, 3.62 g, 24%).

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722**Método CG, Etapa 3;**

Una mezcla de **CG3** ($R^{21} = \text{Br}$, $R^{15} = R^{16} = \text{Pr}$, 3.6 g, 10.5 mmol), $\text{HN}(\text{Me})\text{SO}_2\text{Me}$ (1.4 ml, 16.3 mmol), $\text{Pd}(\text{OAc})_2$ (355 mg, 1.58 mmol), Xantphos (1.41 g, 2.44 mmol), Cs_2CO_3 (5.17 g, 15.8 mmol) en tolueno (40 ml) se desgasificó con una corriente de N_2 durante 10 min, luego se calentó a 95°C durante 18 h. La reacción se enfrió hasta temperatura ambiente, se filtró con celite, y el filtrado se particionó entre EtOAc y agua. La capa orgánica se lavó con agua (1x), salmuera (1x), se secó sobre MgSO_4 , se filtró, y se evaporó con vacío. El residuo resultante fue sometido a cromatografía en gel de sílice en dos oportunidades (0% $\rightarrow$ 3% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) para dar **CG4** ($R^{21} = \text{N}(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 2.65 g, 68%).

Método CG, Etapa 4;

Se añadió LiBH_4 (THF 2 M, 8 ml, 16 mmol) a una solución de **CG4** ($R^{21} = \text{N}(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 2.65 g, 7.15 mmol) en THF (40 ml) a 0°C . Luego de 18 h a temperatura ambiente, la reacción fue interrumpida con HCl 1 M y se extrajo con EtOAc. La capa orgánica se lavó con salmuera (1x), se secó sobre MgSO_4 , se filtró, y se evaporó al vacío. El residuo resultante fue sometido a cromatografía en gel de sílice (0% $\rightarrow$ 5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) para dar **CG5** ($R^{21} = \text{N}(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 1.77 g, 72%).

Método CG, Etapa 5;

Una mezcla de **CG5** ($R^{21} = \text{N}(\text{Me})\text{SO}_2\text{Me}$, $R^{15} = R^{16} = \text{Pr}$, 1.77 g, 5.17 mmol), azida de sodio (404 mg, 6.21 mmol), y PPh_3 (2.85 g, 10.87 mmol) en CCl_4 (5 ml) y DMF (20 ml) se agitó a 90°C durante 5 h, luego a temperatura ambiente durante 18 h. La reacción se agitó con agua (10 ml) durante 10 min, luego se diluyó con Et_2O . La capa orgánica se trituroó con agua, se filtró, se secó sobre MgSO_4 , y se evaporó al vacío. El material resultante se usó directamente en la siguiente etapa (reducción de azida).

Método CG, Etapa 6;

El producto del método CG, etapa 5 se disolvió en EtOH (5 ml) y se agitó en presencia de 10% Pd/carbono bajo atmósfera de hidrógeno (50 psi) durante 18 h a temperatura ambiente. Se hizo pasar la mezcla de reacción por un filtro-PTFE, y el filtrado se evaporó bajo presión reducida. El material resultante fue sometido a

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cromatografía preparativa de capa delgada (5% MeOH/CH₂Cl₂) para dar CG6 (R²¹ = N(Me)SO₂Me, R¹⁵ = R¹⁶ = Pr, 130 mg, 7.5% a partir de CG5).

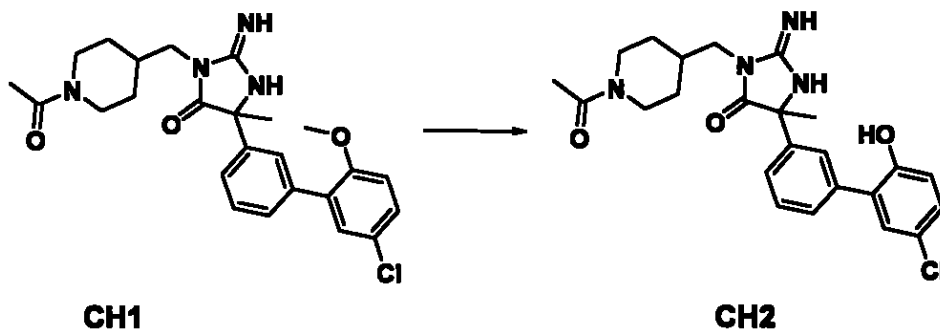
Método CG, Etapa 7;

Una mezcla de CG6 (R²¹ = N(Me)SO₂Me, R¹⁵ = R¹⁶ = Pr, 130 mg, 0.38 mmol), 1,3-di(ter-butoxicarbonil)-2-metilisotiurea (110 mg, 0.38 mmol), NEt₃ (55 µL, 0.38 mmol) en DMF (1.5 ml) se agitó a temperatura ambiente durante 48 h. Luego de eliminar los volátiles al vacío, el material resultante fue sometido a cromatografía preparativa de capa delgada (5% MeOH/CH₂Cl₂ como eluyente). El intermediario resultante (140 mg, 0.24 mmol) se trató con 50% TFA/ CH₂Cl₂ a temperatura ambiente durante 3 h, seguido de la eliminación de todos los volátiles al vacío para dar CG7 (R²¹ = N(Me)SO₂Me, R¹⁵ = R¹⁶ = Pr, 140 mg, 74% a partir CG6).

Método CG, Etapa 8;

Una mezcla de CG7 (R²¹ = N(Me)SO₂Me, R¹⁵ = R¹⁶ = Pr, 120 mg, 0.24 mmol), bencilo (50 mg, 0.24 mmol) y NEt₃ (134 µL, 0.96 mmol) en EtOH (5 ml) se calentó a 100°C durante 18 h. Luego de la evaporación de todos los volátiles, el residuo se particionó entre agua y CH₂Cl₂. La capa orgánica se lavó con salmuera (1x), se secó sobre MgSO₄, se filtró y se evaporó. El material resultante fue sometido a cromatografía preparativa de capa delgada (10% MeOH/CH₂Cl₂ como eluyente) para dar CG8 (R²¹ = N(Me)SO₂Me, R¹⁵ = R¹⁶ = Pr, R³ = R⁴ = Ph, 69 mg, 50%) como la sal formiato. ¹H NMR (400 MHz, CDCl₃) δ 7.10-7.40 (m, 13 H), 4.72 (m, 2 H), 3.34 (m, 2 H), 3.08 (s, 3 H), 3.00 (m, 2H), 2.60 (s, 3 H), 1.59 (m, 2H), 1.39 (m, 2 H), 0.92 (m, 3 H), 0.64 (m, 3 H); LCMS: 576.3 (M+H).

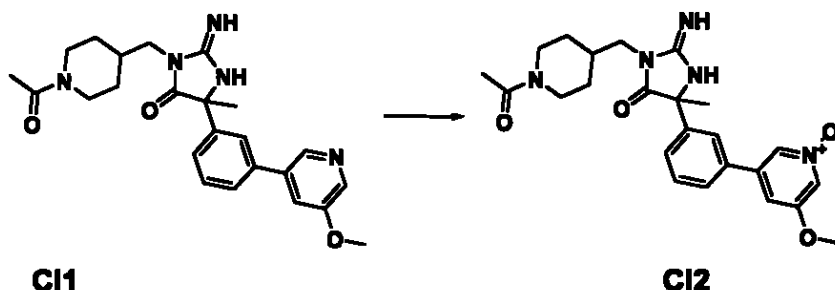
Método CH



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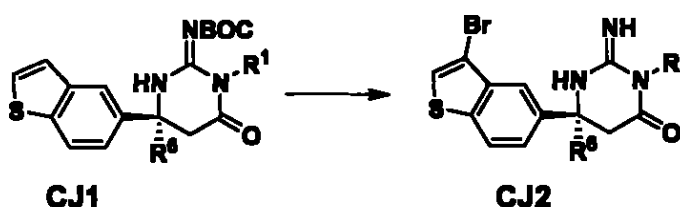
Se añadió por goteo una solución de 0.35 ml de 1 M BBr_3 en DCM (0.35 mmol) a una solución de CH1 (52 mg, 0.11 mole) en 1.5 ml DCM anhidro en una baño de hielo. La solución de reacción se agitó en baño de hielo durante 10 min. y 2 horas a temperatura ambiente. La reacción se interrumpió con 5 ml de MeOH en baño de hielo. Luego de la concentración, el producto crudo se purificó en columna fase reversa C18 para dar CH2 (37.3 mg, 67% de rendimiento) como formiato.

Método CI



Se trató una solución de CI1 (20 mg como formiato; 0.042 mmol) en 4ml de DCM con mCPBA (0.42 mmol) a temperatura ambiente durante 2 horas. La mezcla cruda se purificó en columna fase reversa C18 para dar el compuesto CI2.

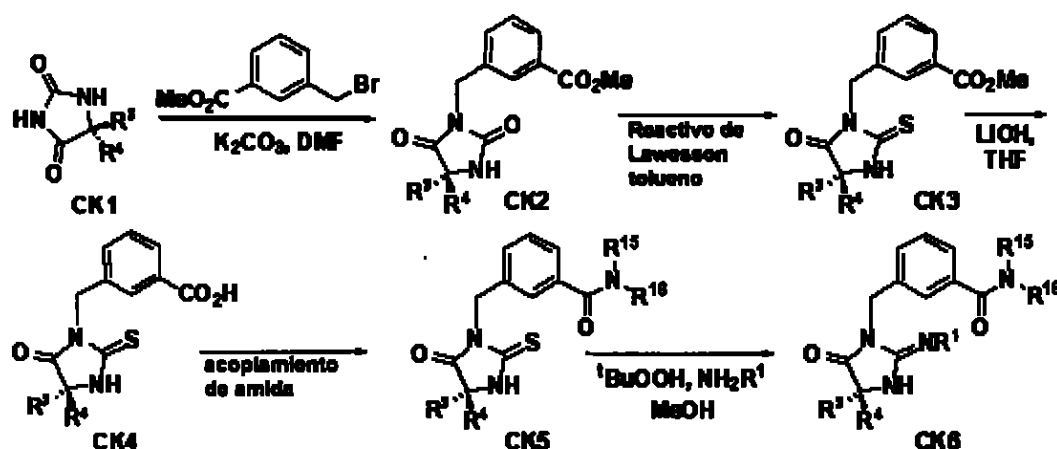
Método CJ



A una solución de CJ1 ($\text{R}^1 = \text{R}^6 = \text{Me}$; 324 mg, 0.87 mmol) en 2.5 ml CHCl_3 y 2.5 ml HOAc en baño de hielo se añadió NBS (312mg, 1.75 mmol) y la mezcla de reacción se agitó a temperatura ambiente. Una vez finalizada la reacción, la mezcla cruda se diluyó con DCM, y se lavó con $\text{Na}_2\text{S}_2\text{O}_3$ acuoso saturado, NaHCO_3 acuoso y salmuera. El producto crudo se purificó en columna instantánea para dar un producto que se trató con 50% TFA en DCM hasta obtener CJ2 ($\text{R}^1 = \text{R}^6 = \text{Me}$ 220mg, 56% rendimiento) luego de la evaporación.

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Método CK



Método CK, Etapa 1;

De manera similar a un proceso de la literatura (Molonay et al., *J. Med. Chem.* 1997, 2347-2362), se añadió metil bromometilbenzoato (7.00 g, 30.5 mmol) a una suspensión de CK1 ($R^3 = R^4 = \text{Ph}$, 7.00 g, 27.8 mmol) y K_2CO_3 (3.85 g, 27.8 mmol) en DMF (50 ml) a temperatura ambiente. Luego de 18 h, la mezcla de reacción se diluyó con agua y se extrajo con CH_2Cl_2 (3x). Las capas combinadas orgánicas se lavaron con NaHCO_3 (1x), agua (3x), se secaron sobre MgSO_4 , se filtraron y se concentraron al vacío para dar el compuesto CK2 (12.7 g, 100%)

Método CK, Etapa 2;

El compuesto CK3 se obtuvo a partir de CK2 usando el método BK, etapa 3.

Método CK, Etapa 3;

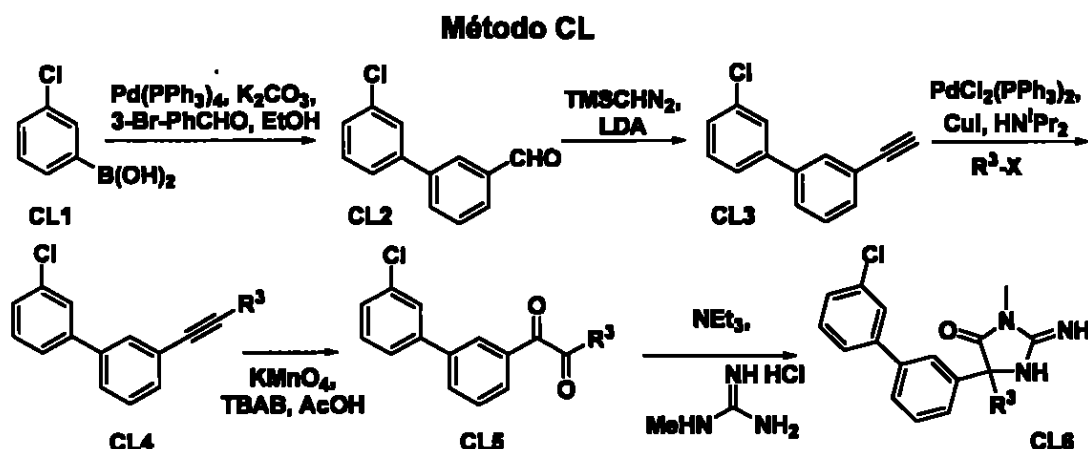
Se agitó CK3 (1.18 g, 2.83 mmol) en THF (15 ml) y LiOH 2 N (4 ml, 8 mmol) durante la noche a temperatura ambiente. La mezcla se apagó con HCl 6 N (2 ml, 12 mmol) y luego se particionó entre agua y EtOAc. La capa seca de EtOAc se concentró al vacío y el residuo se sometió a HPLC de fase reversa (gradiente de 10%→95% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ con 0.1 % HCO_2H , 30 ml/min de caudal en una columna preparativa C18 de fase reversa) hasta obtener CK4.

720
736**Método CK, Etapa 4;**

Los compuestos CK5 se obtuvieron a partir de CK4 usando el método G, etapa 2.

Método CK, Etapa 5;

Los compuestos CK6 se obtuvieron a partir de CK5 usando el método A, etapa 3.

**Método CL, Etapa 1;**

Se obtuvo CL2 a partir de CL1 (ácido 3-clorofenil bórico) siguiendo el método AW.

Método CL, Etapa 2;

Se añadió trimetilsilildiazometano (hexanos 2 M, 2.5 ml, 5.0 mmol) a una solución de LDA (recién preparada a partir de DIPA y nBuLi) en THF a -78°C . Luego de 30 min a -78°C , se añadió una solución de aldehído CL2 (900 mg, 4.13 mmol) en THF (5 ml) y la reacción lentamente fue llevada a temperatura ambiente en el curso de 3 h. La reacción fue interrumpida con agua, luego se extrajo con Et_2O (2x 100 ml). Las capas orgánicas combinadas se lavaron con salmuera (1x), se secaron sobre MgSO_4 , se filtraron, y se evaporaron al vacío. El material resultante fue sometido a cromatografía en gel de sílice (100% hexanos) para dar CL3 (752 mg, 86%). ^1H NMR (400 MHz, CDCl_3) δ 7.21-7.65 (m, 8 H), 3.08 (s, 1 H).

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737**Método CL, Etapa 3;**

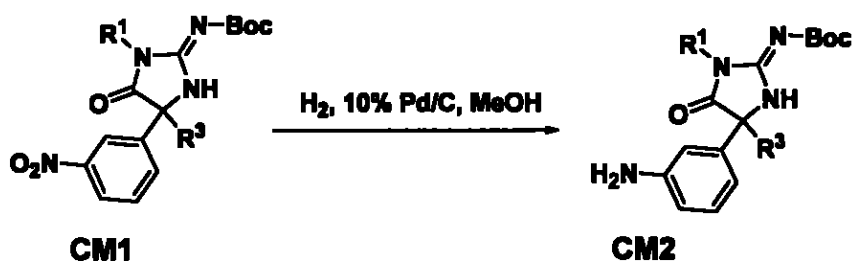
Una mezcla de CL3 (202 mg, 0.95 mmol), bromuro de arilo (Ar = 3,5-pirimidinilo, 181 mg, 1.14 mmol), Pd(dba)₂ (27 mg, 47.5 μmol), PPh₃ (25 mg, 95 μmol), CuI (18 mg, 95 μmol) y DIPA (400 μL, 285 μmol) en DMF (2 ml) se desgasificó durante 10 min en corriente de N₂, luego se calentó a 100°C durante 30 min en un Sintetizador Smith de microondas. La reacción se enfrió hasta alcanzar temperatura ambiente, se filtró y se diluyó con EtOAc. La capa orgánica se lavó con agua (1x), salmuera (1x), se secó sobre MgSO₄, se filtró, y se evaporó al vacío. El material resultante fue sometido to cromatografía en gel de sílice (0 → 20% EtOAc/hexanos) para dar CL4 (R³ = 3,5-pirimidinilo, 220 mg, 80%).

Método CL, Etapa 4;

Una mezcla de CL4 (R³ = 3,5-pirimidinilo, 210 mg, 0.72 mmol), KMnO₄ (297 mg, 1.88 mmol), bromuro de tetrabutilamonio (TBAB, 55 mg, 0.17 mmol) en AcOH (263 μL) y CH₂Cl₂ (5 ml) se agitó durante 3 h a temperatura ambiente. La mezcla de reacción se filtró con un taco de gel de sílice, eluyendo con MeOH, y el filtrado se concentró al vacío. El residuo se sometió a cromatografía preparativa de capa delgada (5% MeOH/DCM) para dar CL5 (R³ = 3,5-pirimidinilo, 154 mg, 66%).

Método CL, Etapa 5;

Se convirtió dicetona CL5 a CL6 tal como se describe en el Método CG, etapa 8. LCMS (CL6, R³ = 3,5-pirimidinilo): 378.2 (M+H).

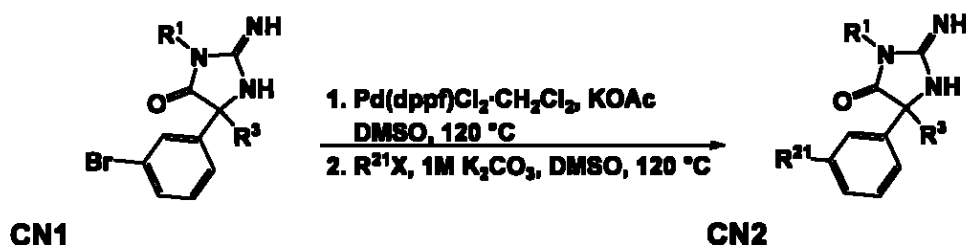
Método CM**Método CM, Etapa 1**

A un recipiente de fondo redondo se añadió CM1 (R¹ = Me, R³ = Ph; 500 mg, 1.22 mmol), metanol (20 ml) y 10% Pd/C (200 mg). La mezcla se hidrogenó

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usando un balón de hidrógeno durante 3 horas 40 min con agitación. Luego de la filtración, el residuo concentrado se purificó usando cromatografía de columna instantánea Analogix (EtOAc/Hexano=0%-50%) para producir CM2 ($R^1 = \text{Me}$, $R^3 = \text{Ph}$; 443 mg, 92%) como sólido de color blanco. MW observado ($M+H$) 381.2. (400 MHz, CD_3OD): $\delta = 9.13$ (s, br, 1H), 7.36-7.26 (m, 5H), 7.09 (m, 1H), 6.68-6.57 (m, 3H), 3.13 (s, 3H), 1.49 (s, 9H).

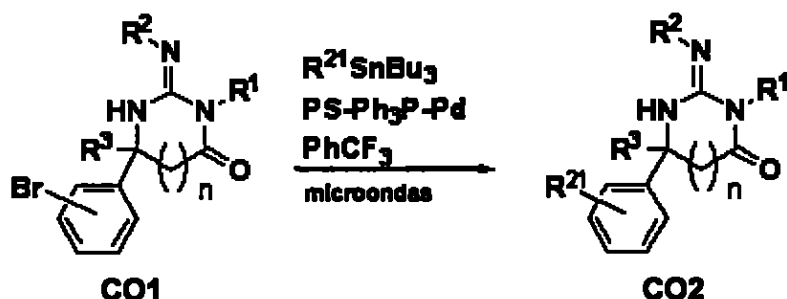
Método CN



A un tubo de presión Ace se añadió CN1 ($R^3 = \text{fenilo}$; $R^1 = \text{Me}$; 100 mg, 0.290 mmol), bis(pinacolato)diboro (81.0 mg, 0.319 mmol), KOAc (85.0 mg, 0.87 mmol), $\text{PdCl}_2(\text{dppf})_2\cdot\text{CH}_2\text{Cl}_2$ (24 mg, 0.029 mmol) y DMSO anhidro (1.0 ml). La reacción luego se calentó a 120°C (temperatura del baño de aceite) con agitación durante 2 horas 15 min. Luego de enfriar hasta alcanzar temperatura ambiente, se agregó a la reacción 3,5-dibromo piridina (206 mg, 0.87 mmol), DMSO anhidro (1.0 ml) y K_2CO_3 1M ac. (1.45 ml, 1.45 mmol). La reacción se calentó luego a 120°C con agitación durante 45 min. Luego de enfriar hasta alcanzar temperatura ambiente, la reacción fue vertida en agua fría. La capa acuosa se extrajo por DCM (3x50 ml) y la capa orgánica combinada se secó sobre Na_2SO_4 . El residuo concentrado se purificó en primer lugar por TLC preparativa (7M $\text{NH}_3/\text{MeOH}:\text{DCM}=1:10$) y luego HPLC preparativa (fase reversa, columna C-18, 0.1% $\text{HCOOH}/\text{CH}_3\text{CN}$: 0.1% $\text{HCOOH}/\text{H}_2\text{O}=10\%-100\%$) para dar el producto deseado CN2 (sal de ácido fórmico; $R^3 = \text{fenilo}$; $R^1 = \text{Me}$; $R^{21} = 3'-(5\text{-bromopiridilo})$; 53.5 mg, 40%) en forma de sólido de color blanco. MW observado ($M+H$) 421.1. (400 MHz, CD_3OD): $\delta = 8.83\text{-}8.50$ (m, br, 2H), 8.21 (s, 1H), 7.65 (m, 2H), 7.50 (m, 2H), 7.37 (m, 5H), 3.22 (s, 3H).

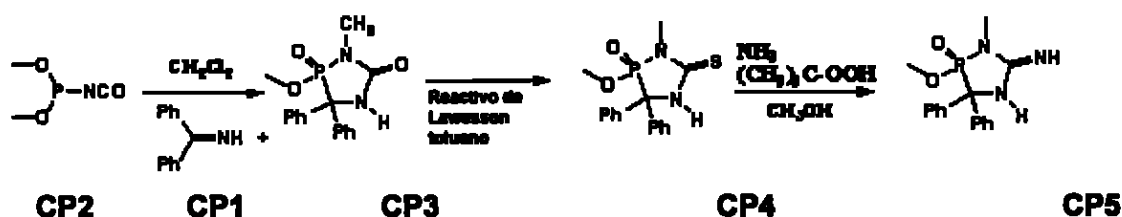
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Método CO



Se cargó un tubo de microondas con CO1 ($R^1 = \text{Me}$, $R^2 = \text{H}$; $R^3 = \text{ciclopropilo}$, $n = 0$) (30 mg, 0.097 mmol), PS- $\text{Ph}_3\text{P-Pd}$ (49 mg, 0.12 mmol), y $\text{R}^{21}\text{SnBu}_3$ ($\text{R}^{21} = 2\text{-pirazinilo}$) (43 mg, 0.12 mmol) como una solución en 1 ml de PhCF_3 . Se selló el tubo, se evacuó y se volvió a llenar con N_2 (5X). La mezcla se expuso luego a irradiación de microondas (110°C , 30 min). La mezcla resultante se filtró con copiosos lavados de MeOH. La concentración del filtrado proporcionó un producto crudo que se sometió a RP-HPLC para dar CO2 ($R^1 = \text{Me}$, $R^2 = \text{H}$; $R^3 = \text{c-Pr}$, $n = 0$, $\text{R}^{21} = 2\text{-pirazinilo}$) en forma de sal formiato (12 mg, 0.063 mmol, 35%). LCMS $\text{Rt} = 3.58 \text{ min}$, $m/e = 308.2 \text{ (M+H)}$.

Método CP



Método CP; Etapa 1: 1,4,2-Diazafosfolidin-5-ona, 2-metoxi-1-metil-3,3-difenil-2-óxido (CP3)

Usando métodos similares a los descritos por I. V. Konovalova et al. (Zhurnal Obshchei Khimii, 50(7), 1653-1654), se añade 1.0 equivalente de dimetil éster del ácido fosforisocianatidoso (CP2), a una solución de benzofenona imina (CP1) en tolueno y la mezcla se calienta a reflujo durante 4 h. La eliminación del solvente y la purificación por cromatografía evaporativa proporciona el compuesto del título (CP3).

Método CP, Etapa 2: 1,4,2-Diazafosfolidin-5-ona, 2-metoxi-1-metil-3,3-difenil-2-óxido (CP4)

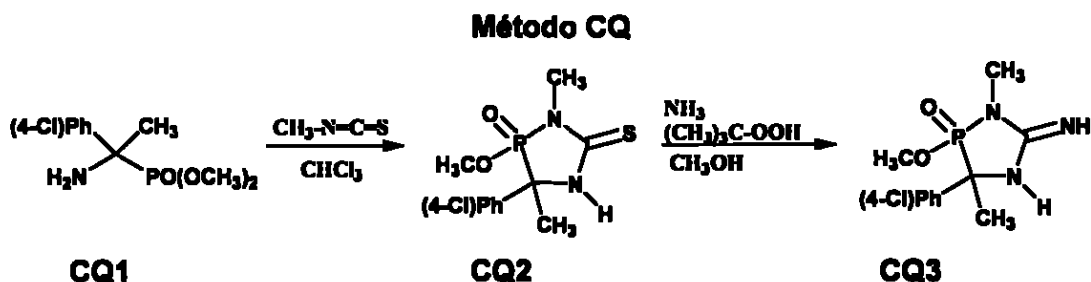
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A una solución de CP3 en tolueno (o xileno) se añade reactivo de Lawesson (1.2 equivalentes), y la mezcla se agita a reflujo durante 2 h. La mezcla se enfría y se vierte sobre agua fría. La fase orgánica se secó (MgSO_4) y se filtró, y se eliminó el solvente. El producto crudo se purificó por cromatografía evaporativa para proporcionar el compuesto del título (CP4).

Método P1, Etapa 3: 1,4,2-Diazafosfolidin-5-imina, 2-metoxi-1-metil-3,3-difenil-2-óxido (CP5)

Usando una vía similar a la descrita en el Método A, etapa 3, se usa CP4 para preparar el compuesto del título (CP5).

Como variante del Método CP, se trata benzofenona imina (CP1) con 1.0 equivalente de dimetil éster de ácido fosforisocianatidoso $[(\text{CH}_3\text{O})_2\text{P}-\text{N}=\text{C}=\text{S}]$, lo cual proporciona directamente CP4, que se convierte a CP5 tal como se describe en el Método CP, Etapa 3.

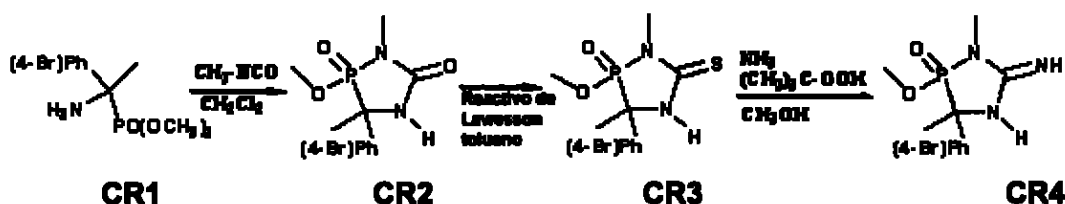


Método CQ, Etapa 1: 1,4,2-Diazafosfolidin-5-tiona, 2-metoxi-1-metil-3-metil-3-(4-cloro)fenil-2-óxido (CQ2)

Usando un método similar al descrito por R. Merten et al. [(Chem. Ber., 102, 2143 (1969))], se añade metilisotiocianato (1.2 equivalentes) a una solución de dimetil [1-amino-1-(4-cloro)fenil]etilfosfonato (CQ1) en cloroformo y la mezcla se calienta gradualmente a reflujo. Luego de 2 h a reflujo, la mezcla se enfría y el solvente se elimina por evaporación. La purificación del producto crudo por cromatografía evaporativa proporciona el compuesto del título.

Método CQ, Etapa 2: 1,4,2-Diazafosfolidin-5-imina, 2-metoxi-1-metil-3-metil-3-(4-cloro)fenil-2-óxido (CQ3)

Usando una vía similar a la descrita en el Método A, etapa 3, se usa CQ2 para preparar el compuesto del título.

733
9/11**Método CR**

Método CR, Etapa 1: 1,4,2-Diazafosfolidin-5-ona, 2-metoxi-1-metil-3-metil-3-(4-bromo)fenil-2-óxido (CR2)

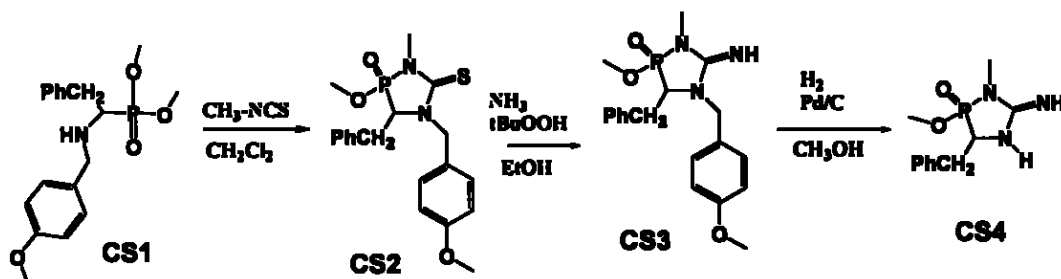
Usando una forma similar a la descrita por R. Merten et al. [(Chem. Ber., 102, 2143 (1969)), se añade metilisocianato (1.2 equivalentes) a una solución de dimetil [1-amino-1-(4-bromo)fenil]etilfosfonato (CR1) en cloroformo y la mezcla se calienta gradualmente a reflujo. Luego de 2 h a reflujo, la mezcla se enfría y el solvente se elimina por evaporación. La purificación del producto crudo por cromatografía evaporativa proporciona el compuesto del título (CR2).

Método CR, Etapa 2: 1,4,2-Diazafosfolidin-5-ona, 2-metoxi-1-metil-3-metil-3-(4-bromo)fenil-2-óxido (CR3)

A una solución de CR2 en tolueno o xileno se añade reactivo de Lawesson (1.2 equivalentes), y la mezcla se agita a reflujo durante 2 h. La mezcla se enfría y se vierte en agua fría. La fase orgánica se secó (MgSO_4) y se filtró, y se eliminó el solvente. El producto crudo se purifica por cromatografía evaporativa para proporcionar el compuesto del título.

Método CR, Etapa 3: 1,4,2-Diazafosfolidin-5-imina, 2-metoxi-1-metil-3-metil-3-(4-bromo)fenil-2-óxido (CR4)

Usando una vía similar a la descrita en el Método A, etapa 3, se usa CR3 para preparar el compuesto del título.

Método CS

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742**Método CS, Etapa 1: 1,4,2-Diazafosfolidin-5-ona, 2-metoxi-4-(4-metoxi)fenilmetil)-1-metil-3-fenilmetil-2-óxido (CS2)**

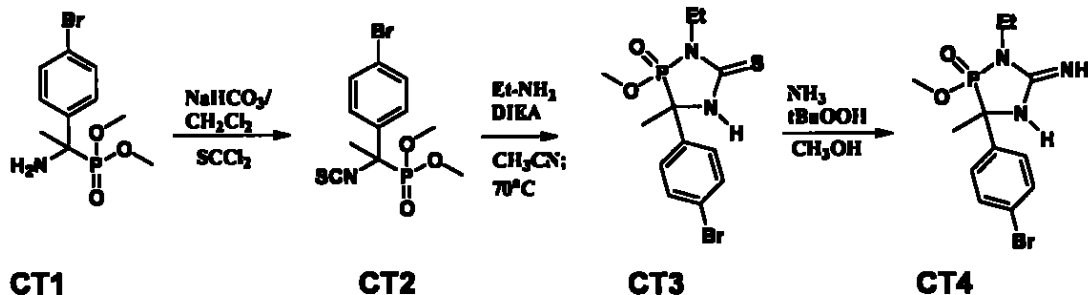
Usando una forma similar a la descrita por R. Merten et al. [(Chem. Ber., 102, 2143 (1969)), metilisotiocianato (1.2 equivalentes) se añade a una solución de dimetil [1-(4-metoxi)fenilmetilamino-2-(4-bromo)fenil]etilfosfonato (CS1) en cloroformo y la mezcla se calienta gradualmente a reflujo. Luego de 2 h a reflujo, la mezcla se enfría y el solvente se elimina por evaporación. La purificación del producto crudo por cromatografía evaporativa proporciona el compuesto del título.

Método CS, Etapa 2: 1,4,2-Diazafosfolidin-5-imina, 2-metoxi-4-(4-metoxi)fenilmetil)-1-metil-3-fenilmetil-2-óxido (CS3)

Usando una vía similar a la descrita en Método A, etapa 3, se usa CS2 para preparar el compuesto del título.

Método CS, Etapa 3: 1,4,2-Diazafosfolidin-5-imina, 2-metoxi-1-metil-3-fenilmetil-2-óxido (CS4).

Una solución de CS3 en metanol se hidrogenó a 1 atm en presencia de 5 mol% Pd/C, tras lo cual se obtuvo el compuesto del título luego de filtración y purificación por cromatografía evaporativa.

Método CT**Método CT, Etapa 1: Dimetil-[(4-bromofenil)-1-isotiocianato]etilfosfonato**

A una mezcla de CT1 en DCM y bicarbonato de sodio acuoso 0.1 N (1.0 equivalente) se añade tiofosgeno (1.5 equivalentes), y la mezcla se agita durante 4 h

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a temperatura ambiente. Se añadió agua, y se secó la fase orgánica (MgSO_4), se filtró y se concentró para dar el producto CT2 que se usó sin purificación.

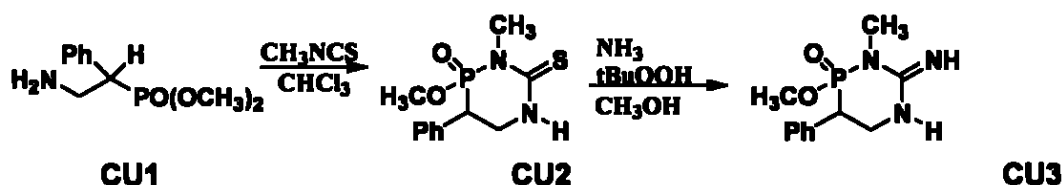
Método CT, Etapa 2: 1,4,2-Diazafosfolidin-5-ona, 2-metoxi-1-etil-3-(4-bromo)fenil-2-óxido (CT3)

A una solución de CT2 en acetonitrilo se añade etilamina (2 equivalentes) y diisopropiletilamina (2 equivalentes) y la solución se lleva lentamente a reflujo durante 2 h. Luego de eliminar el solvente, el producto se purifica por cromatografía evaporativa para dar el producto del título.

Método CT Etapa 3: 1,4,2-Diazafosfolidin-5-imina, 2-metoxi-1-etil-3-(4-bromo)fenil-2-óxido (CT4)

Usando una vía similar a la descrita en Método A, etapa 3, se usa CT3 para preparar el compuesto del título.

Método CU

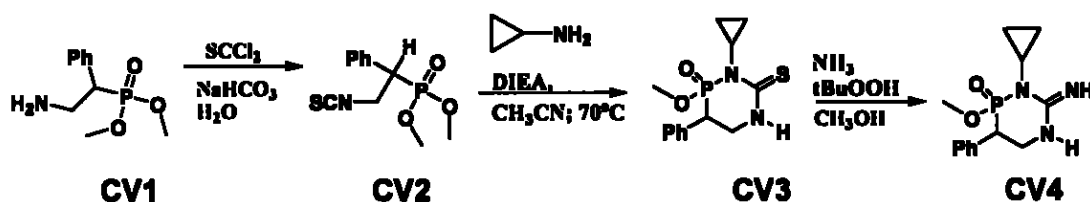


Método CU, Etapa 1: 1,5,2-Diazafosforin-6(1H)-ona, 1-metil-2-metoxi-3-fenil-2-óxido (CU2)

Usando una forma similar a la descrita por R. Merten et al. [(Chem. Ber., 102, 2143 (1969)), metilisotiocianato (1.2 equivalentes) se añade a una solución de dimetil (2-amino-1-fenil)etilfosfonato (CU1) en cloroformo y la mezcla se calienta gradualmente a reflujo. Luego de 2 h a reflujo, la mezcla se enfría y se elimina el solvente por evaporación. La purificación del producto crudo por cromatografía evaporativa proporciona el compuesto del título.

Método CU, Etapa 2: 1,5,2-Diazafosforin-6(1H)-imina, 1-metil-2-metoxi-3-fenil-2-óxido (CU3)

Usando una vía similar a la descrita en Método A, etapa 3, CU2 se usa para preparar el compuesto del título.

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744**Método CV****Método CV, Etapa 1: Dimetil (2-isotiocianato-1-fenil)etilfosfonato (CV2)**

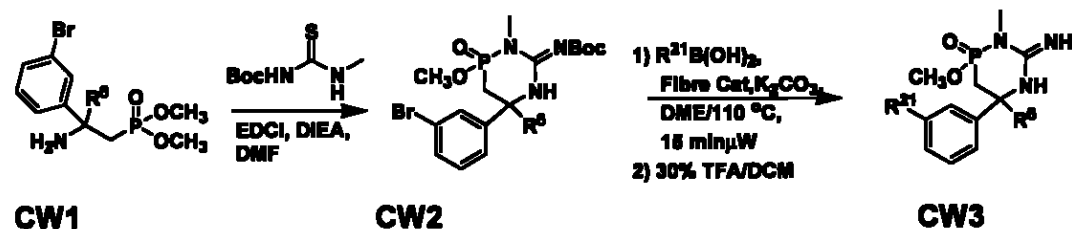
A una mezcla de CV1 en cloruro de metileno y bicarbonato de sodio acuoso 0.1 N (1.0 equivalente) se añade tiofosgeno (1.5 equivalentes), y la mezcla se agita durante 4 h a temperatura ambiente. Se añadió agua, y la fase orgánica se secó (MgSO₄), se filtró y se concentró para dar el producto que se usó sin purificación.

Método CV, Etapa 2: 1,5,2-Diazafosforin-6(1H)-tione, 1-ciclopropil-2-metoxi-3-fenil-2-óxido (CV3)

A una solución de CV2 en acetonitrilo se añade ciclopropilamina (2 equivalentes) y diisopropiletilamina (2 equivalentes) y la solución se calienta a reflujo durante 2 h. Luego de eliminar el solvente, el producto se purifica por cromatografía evaporativa para dar el producto del título.

Método CV Etapa 3: 1,4,2-Diazafosfolidin-5-imina, 2-metoxi-1-ciclopropil-3-(4-bromo)fenil-2-óxido (CV4)

Usando una vía similar a la descrita en Método A, etapa 3, se usa CV3 para preparar el compuesto del título.

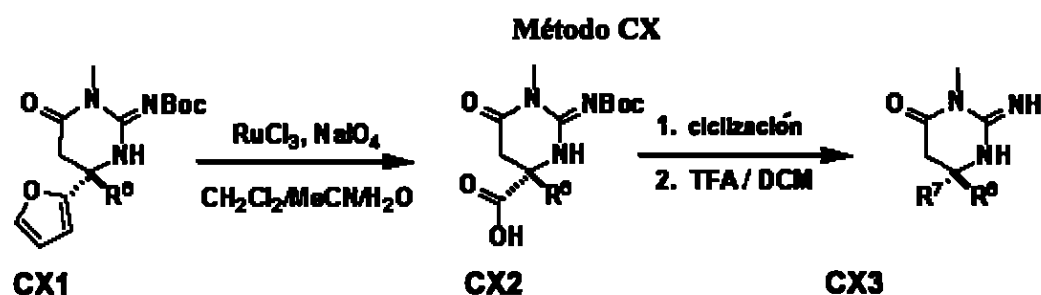
Método CW

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245**Método CW; Etapa 1: Boc-1,5,2-diazafosforin-5-imina, 2-metoxi-1-metil-4-(3-*arilfenil*)-2-óxidos (CW2)**

La reacción de *ter*-butil metilcarbamotioilcarbamato con CW1 ($R^6 = \text{Me}$) usando EDCI y DIEA en DMF proporciona CW2 ($R^6 = \text{Me}$) luego de la purificación.

Método CW; Etapa 2: 1,5,2-Diazafosforin-5-imina, 2-metoxi-1-metil-4-(3-(*m*-cianofenilfenil)-2-óxidos (CW3)

Siguiendo el procedimiento de Sauer, D. R. *et al*, *Org. Lett.*, 2004, 6, 2793-2796, la reacción de Suzuki de CW2 ($R^6 = \text{Me}$) con ácidos aril bóricos usando catalizadores Pd soportados en polímero tales como Fibre Ca o PS-PPh₃-Pd bajo condiciones de calentamiento por microondas proporciona CW3 ($R^6 = \text{Me}$ y $R^{21} = m\text{-CN-Ph}$) de la invención luego de la posterior desprotección de Boc.

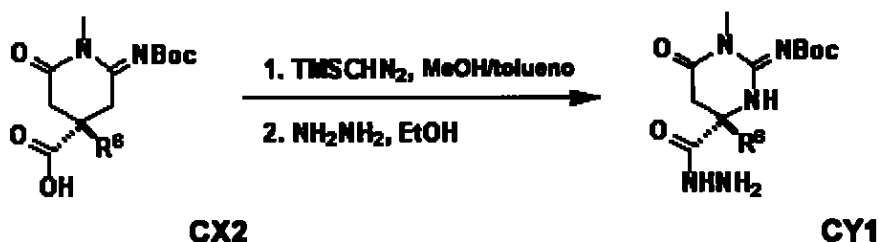
**Método CX, Etapa 1, ácido (S)-2-(*ter*-Butoxicarbonil)-1,4-dimetil-6-oxo-hexahidropirimidina-4-carboxílico**

A una solución de (S)-*ter*-butil 4-(furan-2-il)-1,4-dimetil-6-oxo-tetrahidropirimidin-2(1H)-ilidenocarbamato CX1 ($R^6 = \text{Me}$) (1.12 g, 3.64 mmol, preparada usando el Método CF) en DCM (7 ml) se añadió MeCN (7 ml) y H₂O (10.5 ml), seguido de RuCl₃·H₂O (7.6 mg, 0.036 mmol, 1 mol%), y NaIO₄ (11.6 g, 54.2 mmol, 15 eq). La mezcla se agitó a temperatura ambiente durante 2 h. La mezcla se diluyó con DCM (100 ml) y la capa orgánica se separó, se secó (Na₂SO₄), y se concentró para dar 0.90 g (86%) de ácido (S)-2-(*ter*-butoxicarbonil)-1,4-dimetil-6-oxo-hexahidropirimidina-4-carboxílico CX2 ($R^6 = \text{Me}$) en forma de sólido de color marrón. ¹H NMR (CD₃OD): δ 3.17 (s, 3H), 3.02 (m, 2H), 1.63 (s, 9H), 1.57 (s, 3H).

Método CX, Etapa 2, (6S)-2-imino-3,6-dimetil-6-(3-(3-(trifluorometil)fenil)-1,2,4-oxadiazol-5-il)-tetrahidropirrimidin-4(1H)-ona (CX3)

A una solución de ácido (S)-2-(ter-butoxicarbonil)-1,4-dimetil-6-oxo-hexahidropirimidina-4-carboxílico (CX2, $R^6 = \text{Me}$, 0.035 g, 0.12 mmol) en DMF (0.24 ml) se añadió TBTU (0.040 mg, 0.12 mmol, 1 eq), HOBT (0.0035 mg, 0.024 mmol, 0.2 eq), y DIEA (0.107 ml, 0.60 mmol, 5 eq). La mezcla se agitó a temperatura ambiente durante 10 min y luego se añadió N'-hidroxi-3-(trifluorometil)benzamidina (0.028 mg, 0.13 mmol, 1.1 eq). Luego de agitación durante otras 2 h, la mezcla de reacción se diluyó con EtOAc (20 ml), se lavó con H_2O (10 ml) y salmuera saturada (10 ml), y se concentró al vacío. El residuo crudo se disolvió en THF (0.4 ml) y luego se añadió TBAF (1M en THF, 0.099 ml, 0.9 eq). La mezcla se agitó a temperatura ambiente durante 2 h. Se añadió EtOAc (20 ml) to la mezcla de reacción, que se lavó con H_2O (10 ml) y salmuera saturada (10 ml), y se concentró al vacío. El residuo se trató con 30% TFA/DCM (1 ml) a temperatura ambiente durante 1. La mezcla de reacción se concentró al vacío y el producto crudo se purificó en HPLC (B) de fase reversa para dar 0.015 g (26%) de (6S)-2-imino-3,6-dimetil-6-(3-(3-(trifluorometil)fenil)-1,2,4-oxadiazol-5-il)-tetrahidropirrimidin-4(1H)-ona (CX3; $R^6 = \text{Me}$, $R^7 = 3-(3-(\text{trifluorometil})\text{fenil})-1,2,4\text{-oxadiazol-5-il})$) en forma de sólido de color blanco. ^1H NMR (CD_3OD): δ 8.40 (m, 2H), 8.04 (d, 1H, $J = 6.9$ Hz), 7.90 (t, 1H, $J = 8.1$ Hz), 3.81 (m, 2H), 3.39 (s, 3H), 1.82 (s, 3H). MS (ESI): $\text{MH}^+ = 354.2$, HPLC (A) $R_t = 6.234$ min.

Método CY



(S)-2-(ter-Butoxicarbonil)-1,4-dimetil-6-oxo-hexahidropirrimidina-4-carbohidrazida

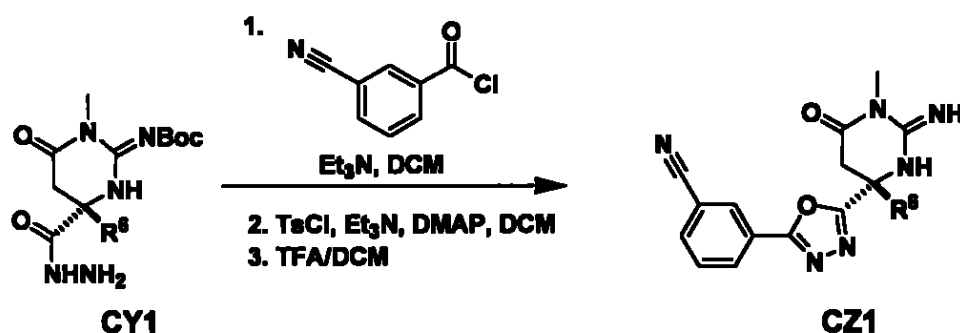
A una solución de ácido (S)-2-(ter-butoxicarbonil)-1,4-dimetil-6-oxo-hexahidropirimidina-4-carboxílico CX2 ($R^6 = \text{Me}$) (0.357 g, 1.25 mmol) en 1:5 MeOH/tolueno (3 ml) se añadió TMSCHN₂ (2M en hexano, 1.9 ml, 3.8 mmol, 3 eq). La mezcla se agitó a temperatura ambiente durante 2 h. La mezcla se concentró al

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vacío para dar 0.37 g (100%) de (S)-metil 2-(ter-butoxicarbonil)-1,4-dimetil-6-oxo-hexahidropirimidina-4-carboxilato en forma de sólido de color marrón. ^1H NMR (CDCl_3): δ 8.80 (s, 1H), 3.70 (s, 3H), 3.14 (s, 1H), 2.79 (s, 2H), 1.53 (s, 9H), 1.50 (s, 3H).

A una solución de (S)-metil 2-(ter-butoxicarbonil)-1,4-dimetil-6-oxo-hexahidropirimidina-4-carboxilato (0.074 g, 0.25 mmol) en EtOH (0.5 ml) se añadió NH_2NH_2 (0.023 ml, 0.75 mmol, 3 eq) y la mezcla se agitó a temperatura ambiente durante 4 h. La mezcla se concentró al vacío para dar 0.074 g (100%) de (S)-2-(ter-butoxicarbonil)-1,4-dimetil-6-oxo-hexahidropirimidina-4-carbohidrazida (CY1, $\text{R}^6=\text{Me}$) en forma de sólido de color amarillo. ^1H NMR (CDCl_3) δ 8.95 (s, 1H), 3.11 (s, 3H), 2.28 (m, 2H), 1.50 (s, 9H), 1.47 (s, 3H).

Método CZ



3-(5-((S)-2-imino-1,4-dimetil-6-oxo-hexahidropirimidin-4-il)-1,3,4-oxadiazol-2-il)benzonitrilo

A una solución de (S)-2-(ter-butoxicarbonil)-1,4-dimetil-6-oxo-hexahidropirimidina-4-carbohidrazida (CY1; $\text{R}^6 = \text{Me}$, 0.037 g, 0.12 mmol) en DCM (0.3 ml) a 0 °C se añadió Et_3N (0.035 ml, 0.24 mmol, 2 eq) seguido de cloruro de 3-cianobenzoylo (0.027 g, 0.16 mmol, 1.3 eq). La mezcla se agitó a temperatura ambiente durante 6 h. La mezcla se diluyó con DCM (20 ml), se lavó con H_2O (10 ml) y salmuera saturada (10 ml), y se concentró al vacío. El residuo se trató luego con TsCl (0.035 g, 0.18 mmol, 1.5 eq), Et_3N (0.046 ml, 0.31 mmol, 2.6 eq), y DMAP (0.002 g, 0.016 mmol, 0.13 eq) en DCM (0.25 ml) a temperatura ambiente durante 16 h. La mezcla se diluyó con DCM (20 ml), se lavó con H_2O (10 ml) y salmuera saturada (10 ml), y se concentró al vacío. El residuo se trató con 30% TFA/DCM (1 ml) a temperatura ambiente durante 1 h. La mezcla se concentró al vacío y el residuo se purificó en HPLC de fase reversa (B) para dar 0.006 g (12%) de 3-(5-((S)-2-imino-

ma de

CY1

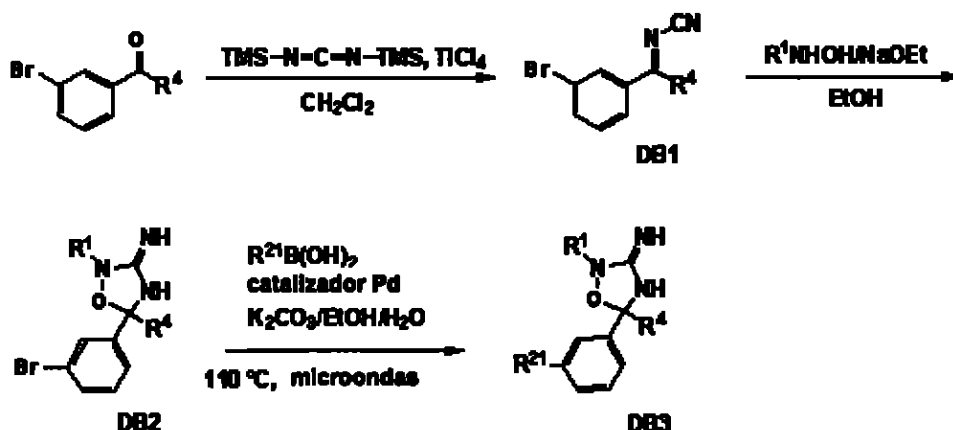
DA1

(S)-6-(5-(3-Clorofenilamino)-1,3,4-oxadiazol-2-il)-2-imino-3,6-dimetil-tetrahidropirimidin-4(1H)-ona

A una solución de (S)-2-(ter-butoxicarbonil)-1,4-dimetil-6-oxo-hexahidropirimidina-4-carbohidrazida (CY1, R^6 = Me, 0.030 g, 0.10 mmol) en DCM (0.25 ml) se añadió 3-clorofenilisocianato (0.015 ml, 0.20 mmol, 2 eq). La mezcla se agitó a temperatura ambiente durante 3 h y los volátiles se eliminaron al vacío. El residuo se trató con TsCl (0.020 g, 0.10 mmol, 1 eq), Et_3N (0.083 ml, 0.60 mmol, 6 eq), y DMAP (0.002 g, 0.016 mmol, 0.16 eq) en DCM (0.25 ml) a temperatura ambiente durante 16 h. La mezcla se diluyó con DCM (20 ml), se lavó con H_2O (10 ml) y salmuera saturada (10 ml), y se concentró al vacío. El residuo se trató con 30% TFA/DCM (1 ml) a temperatura ambiente durante 1 h. La mezcla se concentró al vacío y el residuo se purificó en HPLC de fase reversa (B) para dar 0.006 g (10%) de (S)-6-(5-(3-clorofenilamino)-1,3,4-oxadiazol-2-il)-2-imino-3,6-dimetil-tetrahidropirimidin-4(1H)-ona (DA1; R^6 = Me). ^1H NMR (CD_3OD , 300 MHz): δ 7.78 (t, 1H), 7.47 (m, 2H), 7.17 (dt, 1H), 3.53 (m, 2H), 3.36 (s, 3H), 1.78 (s, 3H). MS (ESI): MH^+ = 335.3. HPLC (A) R_t = 5.710 min.

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Método DB

Método DB, Etapa 1; (1-(3-Bromofenil)etilideno)cianamida (DB1, R⁴ = Me)

Seguendo el procedimiento de Cuccia, S.J.; Fleming, L.B.; France, D.J. *Synth. Comm.* 2002, 32 (19), 3011-3018: 3-Bromoacetofenona (2.0 g, 10 mmol, 1 eq), se disolvió en 20 ml DCM. Una solución 1.0 N de tetracloruro de titanio en DCM (20 ml, 20 mmol, 2 eq) se añadió por goteo durante 15 min y la mezcla resultante se agitó a 25 °C durante 1 h. Se añadió bis-trimetilsilicarbodiimida (5.0 ml, 22 mmol, 2.2 eq) en 5 ml de DCM durante 15 min y la reacción se agitó durante 16 h bajo argón. La reacción se vertió sobre 200 ml de una mezcla de agua/hielo y se extrajo con 3 x 200 ml de DCM. La fase orgánica combinada se secó sobre MgSO₄, se filtró, y se concentró para dar 2.3 g (100%) de (1-(3-bromofenil)etilideno)cianamida (DB1, R⁴ = Me) en forma de sólido de color blanco: ¹H NMR (CDCl₃) δ 8.16 (t, J = 1.8 Hz, 1H), 7.94 (dd, J = 1.7, 1.1 Hz, 1H), 7.76 (dd, J = 1.7, 1.1 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 2.82 (s, 3H).

Método DB, Etapa 2; 5-(3-Bromofenil)-2,5-dimetil-1,2,4-oxadiazolidin-3-imina (DB2, R⁴ = Me)

A una solución de sal HCl metilhidroxilamina (0.19 g, 2.2 mmol, 1 eq) en etanol (25 ml) a 25 °C se añadió una solución al 21% de NaOEt en etanol (0.75 ml, 2.0 mmol, 0.9 eq) seguido de (1-(3-bromofenil) etilideno) cianamida (0.50 g, 2.2 mmol, 1 eq). Luego de agitación a 25 °C durante 10 min, el solvente se eliminó al vacío. El residuo se redisolvió en CH₂Cl₂ (25 ml), la mezcla se filtró, y el solvente se eliminó al vacío para dar 0.5 g (83%) de 5-(3-bromofenil)-2,5-dimetil-1,2,4-oxadiazolidin-3-imina (DB2, R¹ = Me, R⁴ = Me) en forma de aceite incoloro: ¹H NMR (CDCl₃) δ 7.63 (t, J =

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750

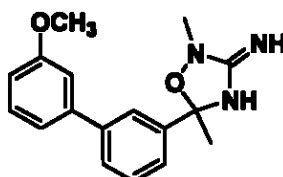
1.8 Hz, 1H), 7.52 (dd, $J = 2.0, 1.1$ Hz, 1H), 7.38 (dd, $J = 2.0, 1.1$ Hz, 1H), 7.29 (t, $J = 7.9$ Hz, 1H), 3.28 (s, 3H), 1.88 (s, 3H). MS (ESI) m/e 270.0, 272.0 ($M+H$)⁺.

Método DB, Etapa 3; 5-(3-(3-Clorofenil)fenil)-2,5-dimetil-1,2,4-oxadiazolidin-3-imina

A una solución de 5-(3-bromofenil)-2,5-dimetil-1,2,4-oxadiazolidin-3-imina (25 mg, 0.093 mmol) y ácido 3-clorofenil bórico (17 mg, 0.11 mmol) en etanol (1 ml) se añadió una solución acuosa 1 M de K_2CO_3 (0.22 ml, 0.22 mmol) y PS- PPh_3 -Pd (46 mg, 0.0046 mmol). La muestra se calentó en un optimizador a microondas Emrys a 110°C durante 10 min. La resina se filtró y se enjuagó alternativamente tres veces con CH_2Cl_2 (5 ml) y CH_3OH (5 ml). Los filtrados combinados fueron concentrados y el residuo se purificó por HPLC prep de fase reversa para dar 12.3 mg (44%) de 5-(3-(3'-clorofenil)-fenil)-2,5-dimetil-1,2,4-oxadiazolidin-3-imina (DB3; $R^1 = Me$, $R^4 = Me$, $R^{21} = 3$ -clorofenilo) en forma de aceite incoloro: ^1H NMR ($CDCl_3$) δ 7.69 (s, 1H), 7.58 (m, 2H), 7.49 (m, 3H), 7.37 (m, 2H), 3.29 (s, 3H), 1.94 (s, 3H). MS (ESI) m/e 302.0, 304.0 (M^+H)⁺.

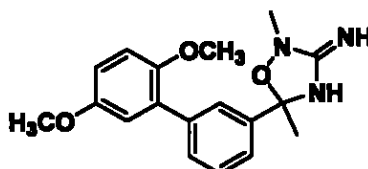
Usando un procedimiento similar, también fueron preparados los siguientes compuestos.

5-(3-(3-Metoxifenil)fenil)-2,5-dimetil-1,2,4-oxadiazolidin-3-imina



^1H NMR ($CDCl_3$) δ 7.72 (s, 1H), 7.62 (dt, 1H), 7.49 (m, 2H), 7.38 (t, $J = 8.2$ Hz, 1H), 7.20 (m, 1H), 7.14 (t, 1H), 6.93 (m, 1H), 3.88 (s, 3H), 3.27 (s, 3H), 1.95 (s, 3H). MS m/e 298.1 (M^+H)

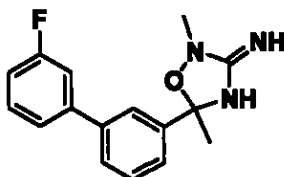
5-(3-(2,5-Dimetoxifenil)fenil)-2,5-dimetil-1,2,4-oxadiazolidin-3-imina



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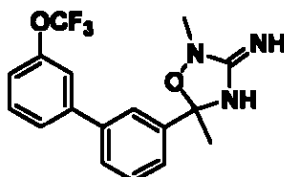
^1H NMR (CDCl_3) δ 7.67 (s, 1H), 7.57 (m, 1H), 7.45 (m, 2H), 6.92 (m, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 3.27 (s, 3H), 1.95 (s, 3H). MS m/e 328.1 (M^+H)

5-(3-(3-Fluorofenil)fenil)-2,5-dimetil-1,2,4-oxadiazolidin-3-imina



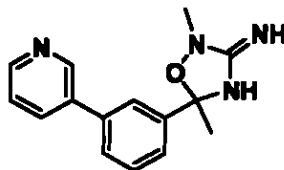
^1H NMR (CDCl_3) δ 7.71 (s, 1H), 7.60 (m, 1H), 7.50 (m, 2H), 7.41 (m, 2H), 7.31 (m, 1H), 7.08 (m, 1H), 3.29 (s, 3H), 1.94 (s, 3H). MS m/e 286.0 (M^+H)

5-(3-(3-Trifluorometoxifenil)fenil)-2,5-dimetil-1,2,4-oxadiazolidin-3-imina



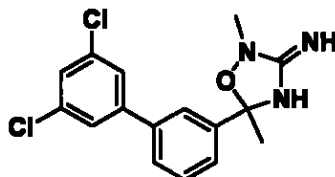
^1H NMR (CDCl_3) δ 7.70 (s, 1H), 7.59 (m, 1H), 7.55 (m, 1H), 7.50 (m, 2H), 7.46-7.48 (m, 2H), 7.26 (m, 1H), 3.29 (s, 3H), 1.95 (s, 3H). MS m/e 352.1 (M^+H)

5-(3-(3-Piridil)fenil)-2,5-dimetil-1,2,4-oxadiazolidin-3-imina



^1H NMR (CD_3OD) δ 9.17 (s, 1H), 8.84 (m, 2H), 8.08 (m, 1H), 7.99 (s, 1H), 7.88 (m, 1H), 7.72 (m, 2H), 3.37 (s, 3H), 2.00 (s, 3H). MS m/e 269.1 (M^+H)

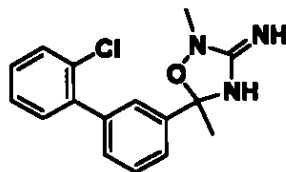
5-(3-(3,5-Diclorofenil)fenil)-2,5-dimetil-1,2,4-oxadiazolidin-3-imina



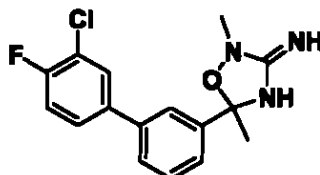
^1H NMR (CDCl_3) δ 7.66 (s, 1H), 7.54 (m, 1H), 7.52 (m, 2H), 7.47 (m, 2H), 7.38 (m, 1H), 3.30 (s, 3H), 1.94 (s, 3H). MS m/e 336.1 (M^+H)

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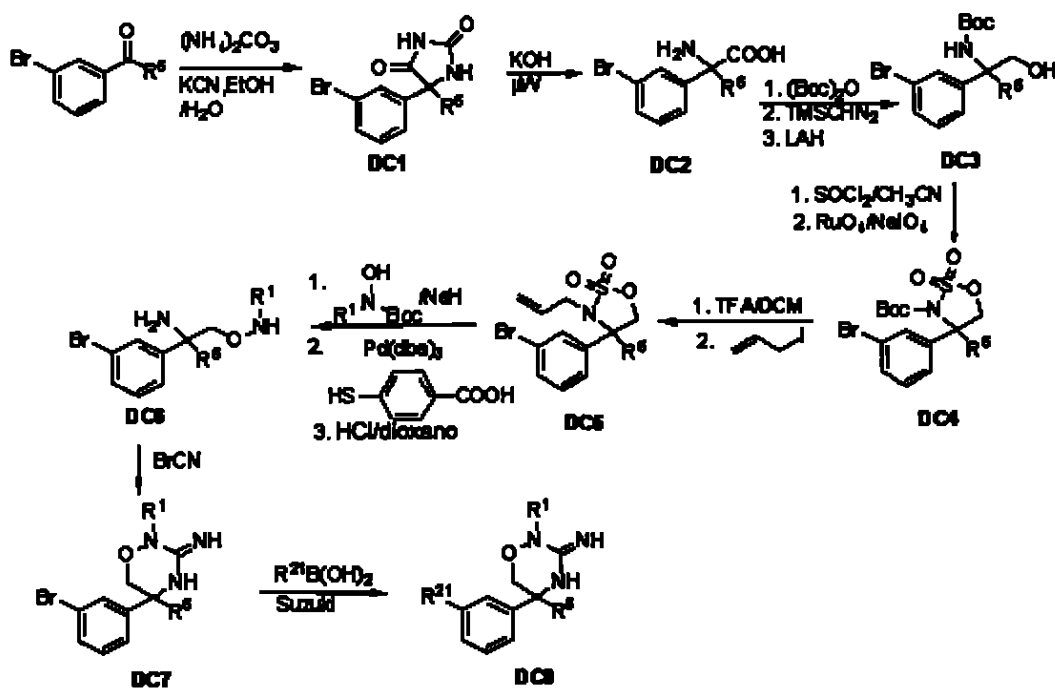
5-(3-(2-Clorofenil)fenil)-2,5-dimetil-1,2,4-oxadiazolidin-3-imina

 $^1\text{H NMR}$ (CDCl_3) δ 7.59 (m, 1H), 7.50 (m, 4H), 7.34 (m, 3H), 3.28 (s, 3H), 1.95 (s, 3H).MS m/e 302.1 (M^+H)

5-(3-(3-Cloro-4-fluorofenil)fenil)-2,5-dimetil-1,2,4-oxadiazolidin-3-imina

 $^1\text{H NMR}$ (CDCl_3) δ 7.65 (m, 2H), 7.48-7.54 (m, 4H), 7.22 (m, 1H), 3.30 (s, 3H), 1.94 (s, 3H). MS m/e 320.1 (M^+H)

Método DC



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753**Método DC, Etapa 1, 5-(3-Bromofenil)-5-metilimidazolidina-2,4-diona**

Una mezcla de 3-bromoacetofenona (10 g, 50 mmol), KCN (8.16 g, 130 mmol, 2.5 eq) y $(\text{NH}_4)_2\text{CO}_3$ (21.7 g, 225 mmol, 4.5 eq) en EtOH/ H_2O (1:1, 110 ml) se calentó a 60°C durante 16 h. La mezcla de reacción se enfrió hasta alcanzar 0 °C. El precipitado resultante se filtró, se lavó con agua, hexano, y luego se secó para dar 12.6 g (93%) de 5-(3-bromofenil)-5-metilimidazolidina-2,4-diona en forma de sólido blancuzco (DC1; $\text{R}^6 = \text{Me}$). ^1H NMR (CD_3OD) δ 7.64 (s, 1H), 7.45 (t, $J = 9.7$ Hz, 2H), 7.26 (t, $J = 7.6$ Hz, 1H), 1.68 (s, 3H).

Método DC, Paso 2, Ácido 2-amino-2-(3-bromofenil)propanoico

Se disolvió 5-(3-bromofenil)-5-metilimidazolidin-2,4-diona (DC1; $\text{R}^6 = \text{Me}$) (1.5 g, 5.6 mmol) en 15 mL de 1N KOH, se calentó a 185 °C en un reactor de microonda (Emrys Optimizer) durante 2 h. A continuación, la mezcla se acidificó cuidadosamente usando HCl concentrado hasta pH ~2. La mezcla se extrajo una vez con Et₂O (20 mL). La capa acuosa se concentró in vacuo para dar 1.6 g (100%) de ácido 2-amino-2-(3-bromofenil)-2-propanoico (DC2; $\text{R}^6 = \text{Me}$) como un sólido blancuzco. ^1H RMN (CD_3OD) δ 7.75 (t, $J = 2.0$, 1H), 7.66 (m, 1H), 7.56 (m, 1H), 7.45 (t, $J = 8.1$ Hz, 1H), 1.99 (s, 3H).

Método DC, Paso 3, ácido 2-(3-bromofenil)-2-(ter-butoxicarbonil)propanoico

A una solución del ácido 2-amino-2-(3-bromofenil)-propanoico (DC2; $\text{R}^6 = \text{Me}$) (10.5 g, 43 mmol) en 1N KOH (105 mL) y dioxano (70 mL) a 0°C se agregó $(\text{Boc})_2\text{O}$ (20.6 g, 95 mmol, 2.2 eq). La mezcla se agitó a TA durante 16 h. La mezcla de reacción se concentró a 100 mL. Se agregó EtOAc (100 mL) y la mezcla se enfrió a 0 °C. Luego de acidificar con 2N KHSO_4 a pH 2 – 3, la capa acuosa se extrajo con EtOAc (3 x 50 mL). La capa de EtOAc combinada se lavó con H_2O (2 x 50 mL), se secó (Na_2SO_4), y concentró para dar 11.7 g (79%) de ácido 2-(3-bromofenil)-2-(ter-butoxicarbonil) propanoico como un sólido blanco. ^1H RMN (CDCl_3) δ 7.61 (s, 1H), 7.41 (m, 2H), 7.24 (m, 1H), 1.98 (s, 3H), 1.44 (s, 9H).

A una solución del ácido 2-(3-bromofenil)-2-(ter-butoxicarbonil) propanoico (11.3 g, 32.8 mmol) en MeOH (35 mL) se agregó tolueno (175 mL) seguido de TMSCHN_2 (2M en hexano, 44 mL, 98 mmol, 3 eq). La mezcla se agitó a TA durante 16 h. Los solventes se evaporaron y el residuo se cromatografió sobre sílice mediante elución con EtOAc/hexanos para dar 11.8 g (100%) de metil 2-(3-

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bromofenil)-2-(*ter*-butoxicarbonil)propanoato como un aceite amarillo. ^1H RMN (CDCl_3) δ 7.59 (t, $J = 1.8$ Hz, 1H), 7.36-7.44 (m, 2H), 7.21 (t, $J = 8.0$ Hz, 1H), 5.92 (s, 1H), 3.70 (s, 3H), 1.97 (s, 3H), 1.36 (br s, 9H).

A una solución de metil 2-(3-bromofenil)-2-(*ter*-butoxicarbonil) propanoato (11.8 g, 33 mmol) en THF (150 mL) a -78°C se agregó polvo de LAH (3.1 g, 82.0 mmol, 2.5 eq). La mezcla se agitó a -78°C y se dejó calentar a TA durante 16 h. La mezcla se enfrió a 0°C y la reacción se templó mediante la adición lenta de 3 mL de H_2O . La mezcla se diluyó con DCM (500 mL) seguido de la adición de 1N NaOH (6 mL) y H_2O (9 mL). Luego de agitar a 0°C durante 30 min, la mezcla se filtró y el filtrado se concentró para dar 10 g (95%) de *ter*-butil 2-(3-bromofenil)-1-hidroxiopropan-2-ilcarbamato (DC3; $\text{R}^b = \text{Me}$) como un aceite incoloro. ^1H RMN (CDCl_3) δ 7.49 (t, $J = 1.8$ Hz, 1H), 7.35-7.39 (m, 1H), 7.27-7.30 (m, 1H), 7.21 (t, $J = 7.8$ Hz, 1H), 3.72 (m, 2H), 1.57 (s, 3H), 1.41 (br s, 9H).

Método DC, Paso 4; 3-(*ter*-Butoxicarbonil)-4-(3-bromofenil)-4-metil-[1,2,3]-oxatiazolidin-2,2-dióxido

A una solución de SOCl_2 (5.7 mL, 2.5 eq) en CH_3CN seco (37 mL) bajo argón enfriada a -40°C se agregó *ter*-butil 2-(3-bromofenil)-1-hidroxiopropan-2-ilcarbamato (DC3; $\text{R}^4 = \text{Me}$) (10.3 g, 31 mmol) en CH_3CN seco (27 mL) se agregó gota a gota, seguido de la adición de piridina seca (12.4 mL, 160 mmol, 5 eq). La mezcla se dejó entonces calentar a TA durante una hora. La mezcla se concentró hasta aproximadamente 30 mL. Se agregó EtOAc (30 mL) y el precipitado se filtró. El filtrado se concentró in vacuo para dar 10.4 g (89%) de 3-(*ter*-butoxicarbonil)-4-(3-bromofenil)-4-metil-[1,2,3]-oxatiazolidin-2-óxido como un aceite incoloro. ^1H RMN (CDCl_3) δ 7.64 (t, $J = 2.0$ Hz, 1H), 7.36-7.53 (m, 2H), 7.24 (m, 1H), 4.52 (q, $J = 9.5$ Hz, 2H), 1.86 (s, 3H), 1.42 (br s, 9H).

A una solución de 3-(*ter*-butoxicarbonil)-4-(3-bromofenil)-4-metil-[1,2,3]-oxatiazolidin-2-óxido (10.4 g, 28 mmol) en CH_3CN (50 mL) a 0°C se agregó RuO_4 (0.5% en .ac. estabilizado, 50 mg, 0.1% por peso) en H_2O (10 mL) y NaIO_4 (8.9 g, 41.5 mmol, 1.5 eq) en H_2O (35 mL). La mezcla se agitó a TA durante 2 horas. La mezcla se dividió entre Et_2O (200 mL) y H_2O (50 mL). La capa orgánica se separó y la capa acuosa se extrajo con Et_2O (3 x 50 mL). La capa orgánica combinada se secó (Na_2SO_4), y se concentró para dar 10.8 g (100%) de 3-(*ter*-butoxicarbonil)-4-(3-bromofenil)-4-metil-[1,2,3]-oxatiazolidin-2,2-dióxido (DC4; $\text{R}^b = \text{Me}$) como un sólido

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blanco (~ 10.8 g, rendimiento: 100%). ^1H RMN (CDCl_3) δ 7.56 (t, $J = 1.8$ Hz, 1H), 7.48-7.52 (m, 1H), 7.38-7.44 (m, 1H), 7.30 (t, $J = 8.0$ Hz, 1H), 4.41 (dd, $J_1 = 9.3$ Hz, $J_2 = 20.4$ Hz, 2H), 2.01 (s, 3H), 1.39 (s, 9H).

Método DC, Paso 5; 3-Alil-4-(3-bromofenil)-4-metil-[1,2,3]-oxatiazolidin-2,2-dióxido

3-(*ter*-Butoxicarbonil)-4-(3-bromofenil)-4-metil-[1,2,3]-oxatiazolidin-2,2-dióxido (DC4; $\text{R}^6 = \text{Me}$) (10.8 g, 28 mmol) se disolvió en 25% TFA en DCM (40 mL, 5 eq) y la mezcla se dejó reposar a TA durante 3 h. La mezcla se concentró in vacuo para dar 7.3 g (91%) de 4-(3-bromofenil)-4-metil-[1,2,3]-oxatiazolidin-2,2-dióxido como un sólido amarillo. ^1H RMN (CDCl_3) δ 7.59 (t, $J = 1.8$ Hz, 1H), 7.48-7.52 (m, 1H), 7.39-7.42 (m, 1H), 7.30 (t, $J = 8.1$ Hz, 1H), 4.59 (m, 2H), 1.82 (s, 3H).

A una solución de 4-(3-bromofenil)-4-metil-[1,2,3]-oxatiazolidin-2,2-dióxido (7.3 g, 25 mmol) en DCM (77 mL) se agregó yoduro de alilo (9.1 mL, 100 mmol, 4 eq), seguido de BnBu_3NCl (0.39 g, 1.3 mmol) y 40% NaOH (28 mL). La mezcla se agitó a TA durante 16 h. La capa orgánica se separó y el solvente se evaporó. La cromatografía de gel de sílice empleando 5-20% EtOAc/hexanos dio 8.3 g (100%) de 3-alil-4-(3-bromofenil)-4-metil-[1,2,3]-oxatiazolidin-2,2-dióxido (DC5; $\text{R}^6 = \text{Me}$) como un aceite incoloro. ^1H RMN (CDCl_3) δ 7.64 (t, $J = 1.8$ Hz, 1H), 7.46-7.54 (m, 2H), 7.31 (t, $J = 8.0$ Hz, 1H), 5.77-5.89 (m, 1H), 5.19-5.33 (m, 2H), 4.38 (dd, $J_1 = 8.7$ Hz, $J_2 = 23.7$ Hz, 2H), 3.46-3.68 (m, 2H), 1.83 (s, 3H).

Método DC, Paso 6; N-(2-(3-bromofenil)-2-amino)prop-1-oxil)-metilamina

A una suspensión de NaH (60%, 0.14 g, 1.5 eq) en 0.5 mL de DMF anhidro se agregó *ter*-butil hidroximetilcarbamato (0.52 g, 1.5 eq) en 1.5 mL de DMF. Luego de agitar a TA durante 15 min, se agregó gota a gota una solución de 3-alil-4-(3-bromofenil)-4-metil-[1,2,3]-oxatiazolidin-2,2-dióxido (DC5; $\text{R}^6 = \text{Me}$) (0.78 g, 2.3 mmol) en 6 mL de DMF anhidro. La mezcla se agitó a TA durante 16 h. La mezcla se dividió entre EtOAc (10 mL) y 1N HCl (3 mL). La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (3 x 5 mL). La capa orgánica combinada se secó sobre Na_2SO_4 y se concentró para dar 0.45 g (41%) de un producto que se utilizó sin purificación.

A una solución del producto anterior (3.86 g, 8.1 mmol) en THF (30 mL) se agregó una mezcla pre-agitada (15 min) de $\text{Pd}_2(\text{dba})_3$ (0.51 g, 0.41 mmol) y 1,4-bis(difenilfosfo)butano (0.25 g, 0.41 mmol) en THF (5 mL), seguida de tiosalicílico (2.2 g, 1.2 eq). La mezcla se agitó a TA durante 16 h. El solvente se evaporó y el

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residuo se cromatografió sobre sílice mediante elución con 50% EtOAc/hexanos para dar 1.3 g (37%) del producto como un aceite que se disolvió en 4M HCl/dioxano (11 mL) y la mezcla se agitó a TA durante 2 h. El solvente se evaporó in vacuo y el residuo se diluyó con CHCl_3 (10 mL) seguido del tratamiento con 1N NaOH a pH ~ 12. La capa orgánica se separó y la capa acuosa se extrajo con CHCl_3 (3 x 10 mL). La capa orgánica combinada se secó (Na_2SO_4) y se concentró para dar 0.56 g (76%) de N-(2-(3-bromofenil)-2-amino)prop-1-oxi)-metilamina (DC6; $\text{R}^0 = \text{Me}$, $\text{R}^1 = \text{Me}$) como un aceite incoloro. ^1H RMN (CDCl_3) δ 7.74 (t, $J = 1.8$ Hz, 1H), 7.41-7.50 (m, 2H), 7.26 (t, $J = 8.0$ Hz, 1H), 3.85 (dd, $J_1 = 9.6$ Hz, $J_2 = 28.8$ Hz, 2H), 2.72 (s, 3H), 1.48 (s, 3H).

Método DC, Paso 7; 5-(3-Bromofenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina

A una solución de N-(2-(3-bromofenil)-2-amino)prop-1-oxi)-metilamina (DC6; $\text{R}^0 = \text{Me}$, $\text{R}^1 = \text{Me}$) (0.76 g, 2.9 mmol) en EtOH (10 mL) se agregó BrCN (0.46 g, 4.4 mmol, 1.5 eq). Luego de agitar a TA durante 16 h, la mezcla se concentró. El residuo se redisolvió en CHCl_3 (20 mL) y se lavó con 2N NaOH (10 mL). La capa acuosa se extrajo con CHCl_3 (3 x 10 mL). La capa orgánica combinada se secó sobre Na_2SO_4 y se concentró para dar 0.82 g (100%) de 5-(3-bromofenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina (DC7; $\text{R}^0 = \text{Me}$, $\text{R}^1 = \text{Me}$) como un aceite amarillo pálido. ^1H RMN (CDCl_3) δ 10.59 (s, 1H), 8.12 (br s, 1H), 7.46 (m, 2H), 7.29 (m, 2H), 4.14 (dd, $J_1 = 11.5$ Hz, $J_2 = 57.7$ Hz, 2H), 3.39 (s, 3H), 1.69 (s, 3H).

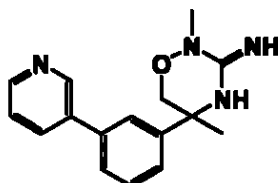
Método DC, Paso 8; 5-(3-(3-Cianofenil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina

Una mezcla de 5-(3-bromofenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina (DC7; $\text{R}^0 = \text{Me}$, $\text{R}^1 = \text{Me}$) (0.025 g, 0.088 mmol, 1 eq), ácido 3-cianofenilborónico (0.019 g, 0.13 mmol, 1.5 eq), FibreCat (40 mg), etanol anhidro (1.5 mL), y una solución acuosa 1N K_2CO_3 (0.12 mL, 0.12 mmol, 1.4 eq) en un frasco para microondas se calentó en un reactor de microonda (Emrys Optimizer) a 110°C durante 15 min. La mezcla se filtró, se concentró y se purificó mediante HPLC prep (B) para dar 0.012 g (44%) de 5-(3-(3-cianofenil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina (DC8; $\text{R}^0 = \text{Me}$, $\text{R}^1 = \text{Me}$, $\text{R}^{21} = 3\text{-cianofenil}$) como un sólido blanco. ^1H RMN (CDCl_3) δ 10.67 (s, 1H), 8.05 (br s, 1H), 7.85 (m, 2H), 7.50-7.66 (m, 5H), 7.35 (m, 1H), 4.22 (dd, $J_1 = 11.8$ Hz, $J_2 = 48.6$ Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). EM m/z 307.3 (M^+H)

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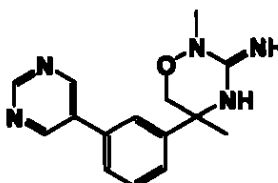
Usando un procedimiento similar, también se prepararon los siguientes compuestos:

5-(3-(3-Piridil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina



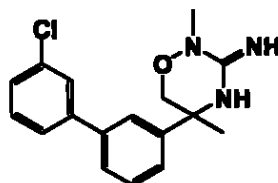
^1H RMN (CDCl_3) δ 10.85 (s, 1H), 9.13 (s, 1H), 8.76 (m, 1H), 8.65 (m, 1H), 7.92 (m, 2H), 7.81 (s, 1H), 7.60 (m, 2H), 7.44 (m, 1H), 4.26 (dd, $J_1 = 11.8$ Hz, $J_2 = 37.4$ Hz, 2H), 3.41 (s, 3H), 1.77 (s, 3H). EM m/e 283.2 (M^+H)

5-(3-(5-Pirimidil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina



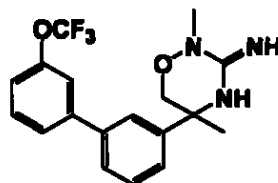
^1H RMN (CDCl_3) δ 10.77 (br s, 1H), 10.42 (s, 1H), 9.26 (s, 1H), 9.07 (s, 1H), 7.84 (br s, 1H), 7.57-7.63 (m, 3H), 7.46 (m, 1H), 4.23 (dd, $J_1 = 11.5$ Hz, $J_2 = 45.9$ Hz, 2H), 3.41 (s, 3H), 1.77 (s, 3H). EM m/e 284.2 (M^+H)

5-(3-(3-Clorofenil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina



^1H RMN (CDCl_3) δ 10.63 (s, 1H), 8.00 (br s, 1H), 7.48-7.55 (m, 5H), 7.31-7.740 (m, 3H), 4.20 (dd, $J_1 = 11.5$ Hz, $J_2 = 54.4$ Hz, 2H), 3.39 (s, 3H), 1.76 (s, 3H). EM m/e 316.2 (M^+H)

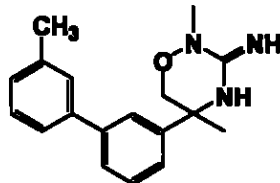
5-(3-(3-Trifluorometoxifenil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina



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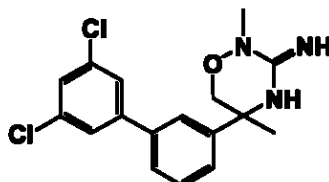
^1H RMN (CDCl_3) δ 10.72 (s, 1H), 8.03 (br s, 1H), 7.55 (m, 1H), 7.51 (m, 2H), 7.46 (m, 2H), 7.41 (m, 1H), 7.32-7.34 (dt, $J_1 = 1.6$ Hz, $J_2 = 7.2$ Hz, 1H), 7.21-7.23 (m, 1H), 4.21 (dd, $J_1 = 11.8$ Hz, $J_2 = 53.0$ Hz, 2H), 3.39 (s, 3H), 1.76 (s, 3H). EM m/e 366.2 (M^+H)

5-(3-(3-Toluil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina



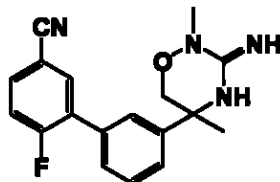
^1H RMN (CDCl_3) δ 10.61 (s, 1H), 8.07 (br s, 1H), 7.53 (m, 2H), 7.45 (m, 1H), 7.33-7.37 (m, 3H), 7.28-7.32 (m, 1H), 7.17-7.19 (m, 1H), 4.20 (dd, $J_1 = 11.8$ Hz, $J_2 = 58.2$ Hz, 2H), 3.38 (s, 3H), 2.42 (s, 3H), 1.76 (s, 3H). EM m/e 296.4 (M^+H)

5-(3-(3,5-Diclorofenil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina



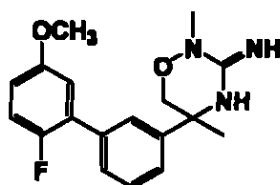
^1H RMN (CDCl_3) δ 10.71 (s, 1H), 8.06 (br s, 1H), 7.47 (m, 3H), 7.43 (m, 2H), 7.35 (m, 2H), 4.20 (dd, $J_1 = 11.7$ Hz, $J_2 = 54.9$ Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). EM m/e 350.2 (M^+H)

5-(3-(2-Fluor-5-cianofenil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina



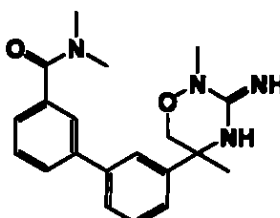
^1H RMN (CDCl_3) δ 10.50 (s, 1H), 7.86 (br s, 1H), 7.77 (dd, $J_1 = 2.1$ Hz, $J_2 = 6.9$ Hz, 1H), 7.65 (m, 1H), 7.50 (m, 2H), 7.42 (m, 1H), 7.27 (t, $J = 5.0$ Hz, 2H), 4.20 (dd, $J_1 = 12.0$ Hz, $J_2 = 50.4$ Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). EM m/e 325.1 (M^+H)

5-(3-(2-Fluor-5-metoxifenil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina



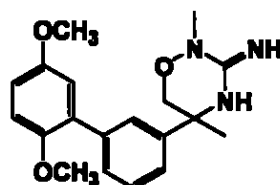
^1H RMN (CDCl_3) δ 10.53 (s, 1H), 7.94 (br s, 1H), 7.47 (m, 3H), 7.37 (m, 1H), 7.07 (t, $J = 9.5$ Hz, 1H), 6.93 (m, 1H), 6.86 (m, 1H), 4.19 (dd, $J_1 = 11.7$ Hz, $J_2 = 58.5$ Hz, 2H), 3.82 (s, 3H), 3.38 (s, 3H), 1.75 (s, 3H). EM m/e 330.1 (M^+H)

5-(3-(3-Dimetilaminocarbonilfenil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina



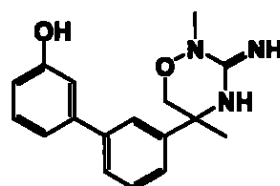
^1H RMN (CDCl_3) δ 10.58 (s, 1H), 7.95 (br s, 1H), 7.26-7.65 (m, 8H), 4.20 (dd, $J_1 = 11.5$ Hz, $J_2 = 54.7$ Hz, 2H), 3.38 (s, 3H), 3.14 (s, 3H), 3.02 (s, 3H), 1.75 (s, 3H). EM m/e 353.2 (M^+H)

5-(3-(2,5-Dimetoxifenil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina

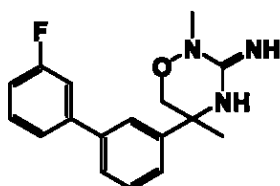


^1H RMN (CDCl_3) δ 10.50 (s, 1H), 7.99 (br s, 1H), 7.40-7.50 (m, 3H), 7.29-7.33 (m, 1H), 6.84-6.94 (m, 3H), 4.18 (dd, $J_1 = 11.5$ Hz, $J_2 = 65.4$ Hz, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.37 (s, 3H), 1.74 (s, 3H). EM m/e 342.2 (M^+H)

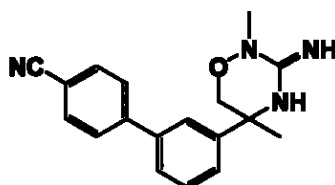
5-(3-(3-Hidroksifenil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina



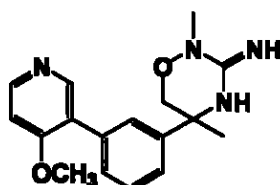
^1H RMN (CDCl_3) δ 9.75 (s, 1H), 7.39-7.54 (m, 3H), 7.21-7.30 (m, 2H), 7.10-7.12 (m, 2H), 6.82-6.84 (m, 1H), 5.83 (br s, 2H), 4.15 (dd, $J_1 = 11.5$ Hz, $J_2 = 35.7$ Hz, 2H), 3.36 (s, 3H), 1.74 (s, 3H). EM m/e 298.3 (M^+H)

5-(3-(3-Fluorofenil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina

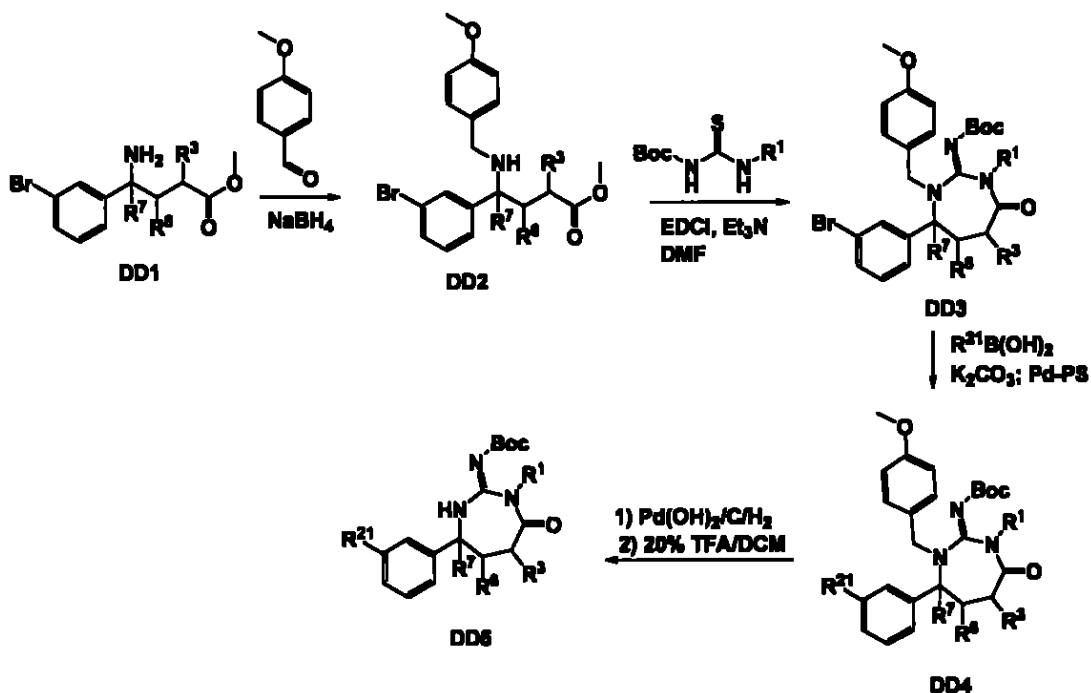
^1H RMN (CDCl_3) δ 10.77 (s, 1H), 8.15 (s, 1H), 7.25-7.56 (m, 7H), 7.01-7.08 (m, 1H), 4.20 (dd, $J_1 = 11.5$ Hz, $J_2 = 53.0$ Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). EM m/e 300.2 (M^+H)

5-(3-(4-Cianofenil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina

^1H RMN (CDCl_3) δ 10.67 (s, 1H), 8.01 (br s, 1H), 7.74 (s, 4H), 7.63 (s, 1H), 7.48-7.56 (m, 2H), 7.33-7.35 (m, 1H), 4.23 (dd, $J_1 = 11.5$ Hz, $J_2 = 47.2$ Hz, 2H), 3.40 (s, 3H), 1.76 (s, 3H). EM m/e 307.2 (M^+H)

5-(3-(4-Metoxi-3-piridil)fenil)-2,5-dimetil-1,2,4-oxadiazinan-3-imina

^1H RMN (CDCl_3) δ 10.55 (s, 1H), 8.74 (d, $J = 6.0$ Hz, 1H), 8.64 (s, 1H), 7.83 (br s, 1H), 7.49-7.53 (m, 3H), 7.37-7.42 (m, 2H), 4.20 (dd, $J_1 = 11.5$ Hz, $J_2 = 49.4$ Hz, 2H), 4.11 (s, 3H), 3.39 (s, 3H), 1.76 (s, 3H). EM m/e 313.2 (M^+H)

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761**Método DD****Método DD, Paso 1;**

A una solución de 10 mL de MeOH de DD1 ($\text{R}^3 = \text{R}^6 = \text{H}$, $\text{R}^7 = \text{Me}$, 1 g) se agregó p-metoxibenzaldehído (1 eq) y un tamiz molecular 4A (4 g). La solución se agitó durante la noche antes de la adición de borohidruro de sodio (1 eq) y la reacción se agitó durante 1 h. La mezcla de reacción se filtró y el solvente se evaporó. El residuo se cromatografió usando MeOH/DCM para dar el compuesto DD2 ($\text{R}^3 = \text{R}^6 = \text{H}$, $\text{R}^7 = \text{Me}$).

Método DD, Paso 2;

Se usó un procedimiento similar al Método CF, paso 2 para la generación de DD3 ($\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{R}^6 = \text{H}$, $\text{R}^7 = \text{Me}$).

Método DD, Paso 3;

Se usó un procedimiento similar al Método CF, paso 3 para la generación de DD4 ($\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{R}^6 = \text{H}$, $\text{R}^7 = \text{Me}$) a partir de DD3

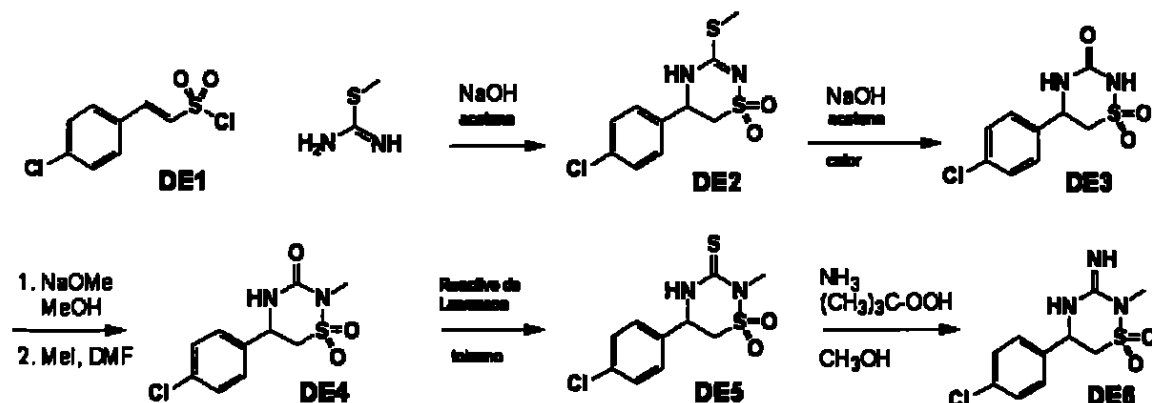
Método DD, Paso 4;

El compuesto DD4 se hidrogenó usando $\text{Pd}(\text{OH})_2/\text{C}$ en Metanol. Luego de la remoción del catalizador y el solvente, el producto crudo se trató con 20% TFA en

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DCM para dar el producto DD5 ($R^1 = \text{Me}$, $R^3 = R^6 = \text{H}$, $R^7 = \text{Me}$) luego de la purificación.

Método DE



Método DE, Paso 1: 5-(4-Clorofenil)-3-metilsulfanil-5,6-dihidro-4H-[1,2,4]tiadiazin 1,1-dióxido

El cloruro de 2-(4-Clorofenil)etenosulfonilo DE1 se trató con 1.2 equivalentes de S-metil isotiourea hemisulfato y un exceso leve de 1N NaOH en acetona. Luego de 12 h a TA la mezcla se concentró in vacuo y el precipitado se recogió para dar el compuesto del título.

Método DE, Paso 2: N-(2-(4-Clorofenil)etano-1-sulfonil)-S-metilisotiourea

Usando un método similar al descrito por K. Hasegawa y S. Hirooka (Bull. Chem. Soc. Jap., 1972, 45, 1893), N-(2-(4-clorofenil)etilen-1-sulfonil)tiourea DE2 en DMF se trató con 1N NaOH (2.4 equivalentes) y dimetilsulfato (1.2 equivalentes) a 0-10 °C. Luego de 3 h a TA, la mezcla de reacción se vertió en agua hielo. El precipitado se recogió, se lavó con agua y se secó para dar el compuesto del título DE3.

Método DE, Paso 2: 5-(4-Clorofenil)-1,1-dioxo-[1,2,4]tiadiazinan-3-ona

Usando un método similar al descrito por K. Hasegawa y S. Hirooka (Bull. Chem. Soc. Jap., 1972, 45, 1893), 5-(4-clorofenil)-3-metilsulfanil-5,6-dihidro-4H-[1,2,4]tiadiazina 1,1-dióxido DE2 en acetona se trató con 1N NaOH y la mezcla se sometió a reflujo durante 2 h. La acetona se evaporó y la mezcla se acidificó con HCl conc. para dar el compuesto del título DE3.

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763**Método DE, Paso 3: 5-(4-Clorofenil)-2-metil-1,1-dioxo-[1,2,4]tiadiazinan-3-ona**

Usando un método similar al descrito por A. Etienne et al. (Bull. Soc. Chim. Fr., 1974, 1395) 5-(4-clorofenil)-1,1-dioxo-[1,2,4]tiadiazinan-3-ona DE3 se trató con metóxido de sodio (1 equivalente) en metanol. Se agregó yoduro de metilo (1.2 equivalente) en DMF y se dejó agitar durante 12 h. Verter la mezcla en agua hielo y recoger el precipitado del compuesto del título DE4.

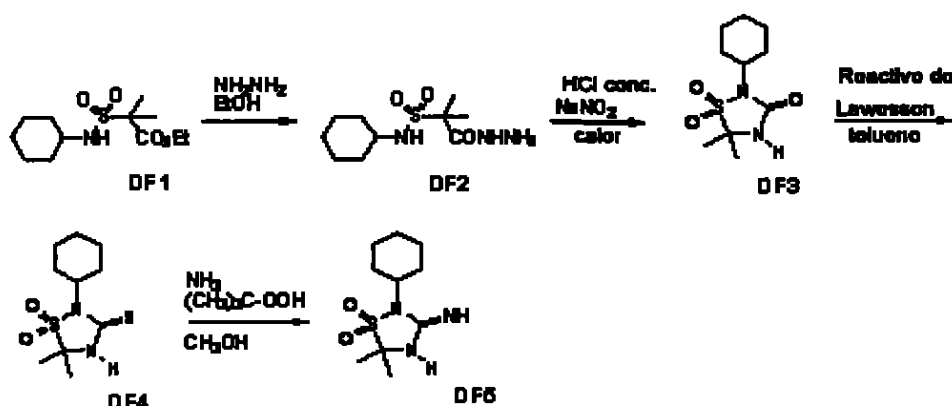
Método DE, Paso 4: 5-(4-Clorofenil)-2-metil-1,1-dioxo-[1,2,4]tiadiazinan-3-ona

A una solución de DE4 en tolueno (o xileno) se agregó reactivo de Lawesson (1.2 equivalentes), y la mezcla se agitó a reflujo durante 2 h. La mezcla se enfrió y se vertió en agua fría. La fase orgánica se secó (MgSO_4) y se filtró, y el solvente se removió. El producto crudo se purificó por cromatografía flash para dar el compuesto del título (DE5).

Método DE, Paso 5: 5-(4-Clorofenil)-2-metil-1,1-dioxo-[1,2,4]tiadiazinan-3-ilidenamina

Usando una vía similar a la descrita en el Método A, paso 3, se usó DE5 para preparar el compuesto del título (DE6).

Como una variante de este método, DE2 se trató con amoníaco y el producto resultante se trató con hidruro de sodio y yoduro de metilo en DMF para dar el producto DE6

Método DF

Método DF, Paso 1: Ciclohexilamida del ácido 2-hidrazinocarbonilpropano-2-sulfónico

Usando un método similar al descrito por S. Paik y E.H. White (Tetrahedron, 1996, 52, 5303), etil éster del ácido 2-ciclohexilsulfamoil-2-metilpropiónico DF1 (preparado mediante el método de A. De Blic et al. (Synthesis, 1982, 281)) en etanol se trató con 1.2 equivalente de 95% hidracina bajo N₂ y la mezcla se dejó reposar a TA durante 12 h. La mezcla de reacción se concentró para dar el compuesto del título DF2 que se usó directamente en el Paso 2.

Método DF, Paso 2: 2-Ciclohexil-5,5-dimetil-1,2,4-tiadiazolidin-3-ona-1,1-dióxido

Una solución de DF2 en CH₂Cl₂ se sometió a reflujo bajo N₂ durante 10 h. El solvente se removió in vacuo y el producto crudo se purificó mediante cromatografía flash para dar el compuesto del título DF3.

Método DF, Paso 3: 2-Ciclohexil-5,5-dimetil-1,2,4-tiadiazolidin-3-ona-1,1-dióxido

A una solución de DF3 en tolueno (o xileno) se agregó reactivo de Lawesson (1.2 equivalentes), y la mezcla se agitó a reflujo durante 2 h. La mezcla se enfrió y se vertió en agua fría. La fase orgánica se secó (MgSO₄) y se filtró, y el solvente se eliminó. El producto crudo se purificó por cromatografía flash para dar el compuesto del título (DF4).

Método DF, Paso 4: 2-Ciclohexil-5,5-dimetil-1,2,4-tiadiazolidin-3-imina-1,1-dióxido

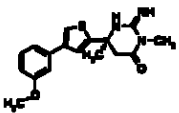
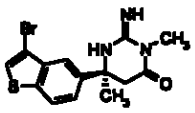
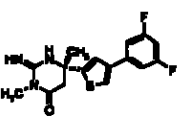
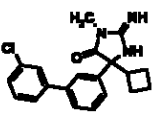
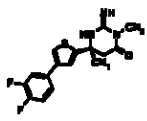
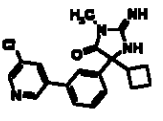
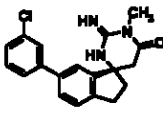
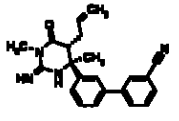
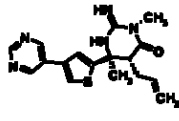
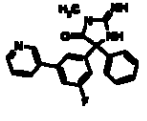
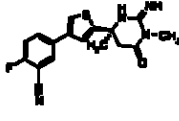
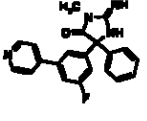
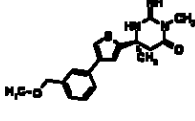
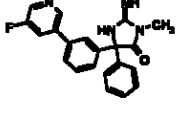
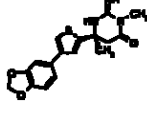
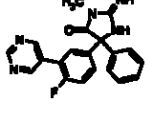
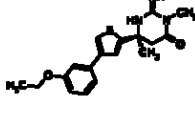
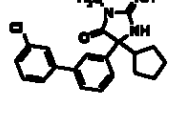
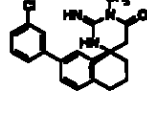
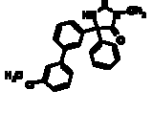
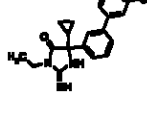
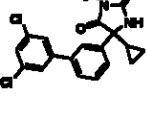
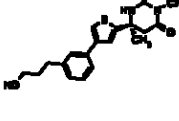
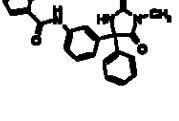
Usando una vía similar a la descrita en el Método A, Paso 3, se usó DF4 para preparar el compuesto del título (DF5).

La siguiente tabla contiene compuestos ejemplificativos que se sintetizaron con procedimiento(s) similar(es) a los métodos consignados en la columna correspondiente y cuyos datos de LCMS (obs. masa) también se enumeran.

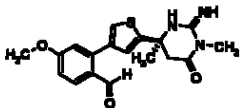
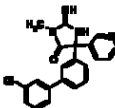
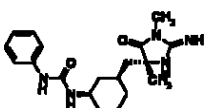
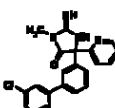
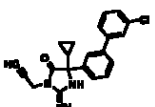
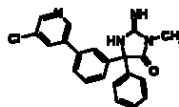
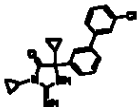
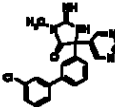
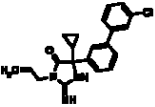
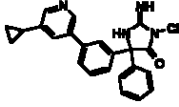
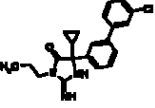
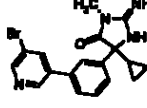
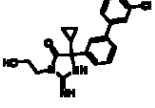
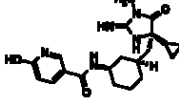
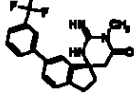
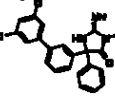
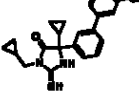
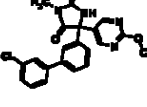
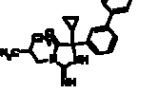
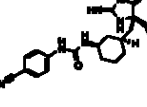
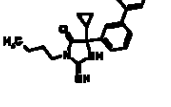
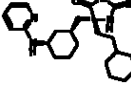
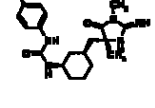
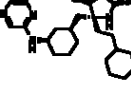
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No.	Compuestos	Método	Obs. Masa	No.	Compuestos	Método	Obs. Masa
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1492		CF	333.9	1663		AW	331.2
1493		CF	329.9	1664		CE	335.2
1494		CF	367.9	1665		AW	336.2
1495		AW	281	1666		AW	337.2
1496		CF	306	1667		CF	338.2
1497		AB	307	1668		AW	340.2
1498		CF	314	1669		CO	341.2
1499		CF	318	1670		AW	342.2
1500		CF	325	1671		AW	348.2
1501		CF	325	1672		AW	350.2

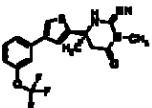
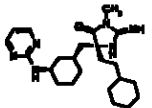
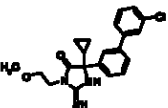
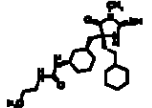
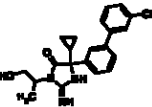
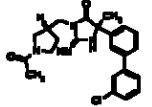
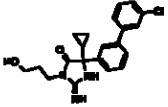
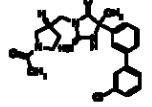
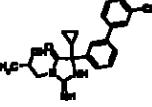
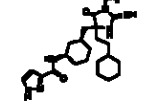
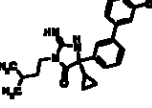
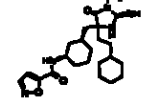
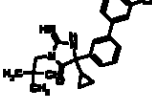
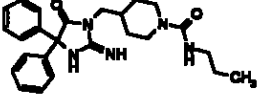
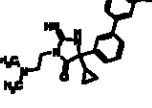
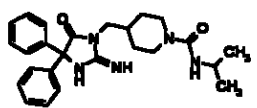
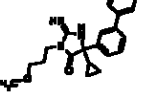
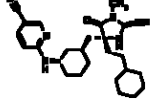
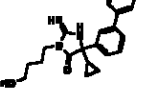
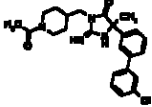
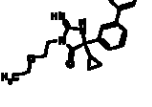
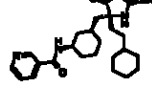
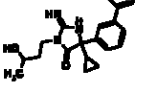
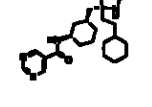
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1602		CF	330	1673		CJ	352.2
1603		CF	336	1674		AW	354.2
1604		CF	336	1675		AW	355.2
1605		AB	340	1676		CE	359.2
1606		CE	342	1677		AW	361.2
1607		CF	343	1678		AW	361.2
1608		CF	344	1679		AW	361.2
1609		CF	344	1680		AW	362.2
1610		CF	344	1681		AW	366.2
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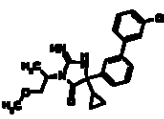
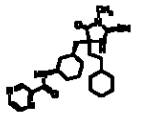
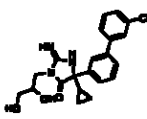
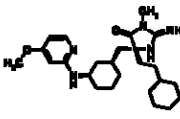
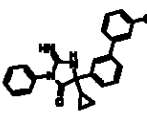
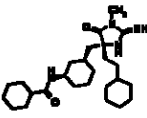
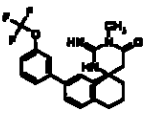
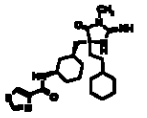
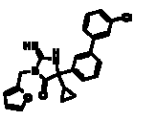
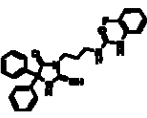
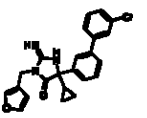
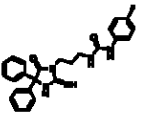
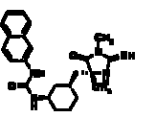
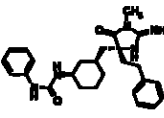
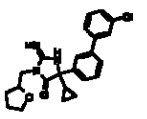
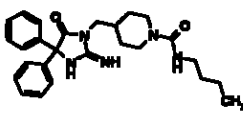
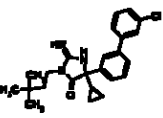
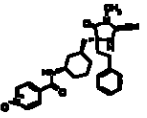
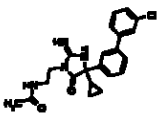
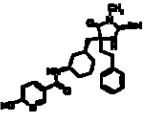
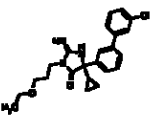
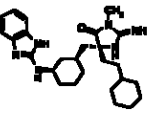
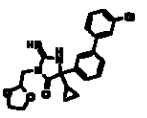
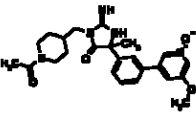
759
767

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1517		A	366	1888		CG	378.2
1518		A	366	1889		AW	383.2
1519		A	368	1890		CO	385.2
1520		A	370	1891		BQ	388.2
1521		AB	374	1892		AW	408.2
1522		A	380	1893		CL	408.2
1523		A	382	1894		BS	409.2
1524		A	382	1895		BW	412.2
1525		BS	383	1896		BW	413.2

760
~~760~~

1526		CF	384	1697		BW	413.2
1527		A	384	1698		BS	420.2
1528		A	384	1699		R	425.2
1529		A	384	1700		R	425.2
1530		A	384	1701		BQ	429.2
1531		A	386	1702		BQ	430.2
1532		A	388	1703		R	434.2
1533		A	397	1704		R	434.2
1534		A	398	1705		BW	437.2
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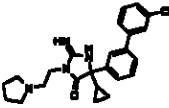
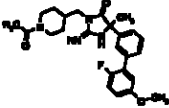
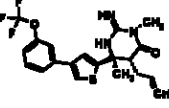
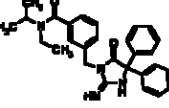
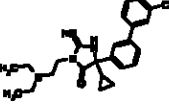
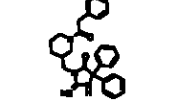
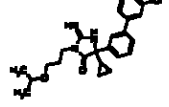
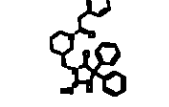
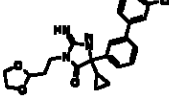
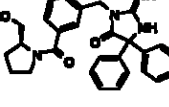
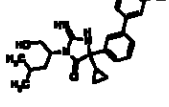
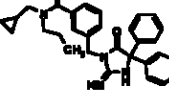
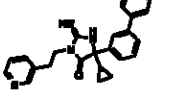
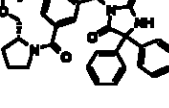
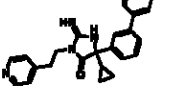
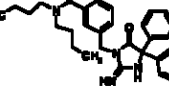
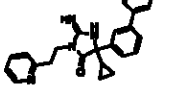
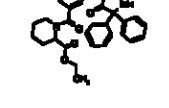
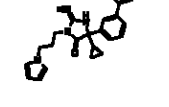
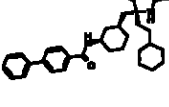
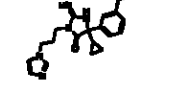
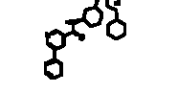
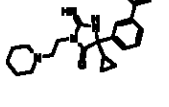
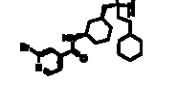
761
769

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1540		A	402	1711		BQ	445.2
1541		AB	404	1712		BQ	446.2
1542		A	406	1713		R	446.2
1543		A	406	1714		R	446.2
1544		BS	408	1715		BS	448.2
1545		A	410	1716		R	448.2
1546		A	410	1717		BQ	450.2
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1548		A	412	1719		BW	451.2
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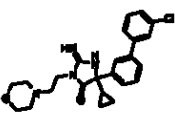
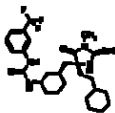
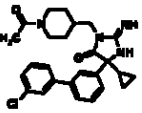
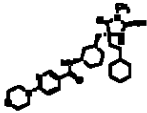
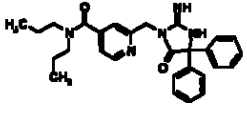
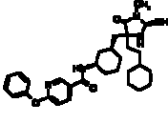
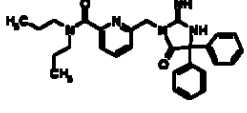
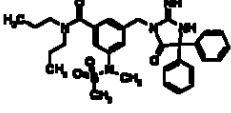
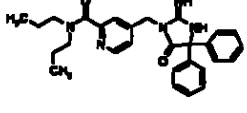
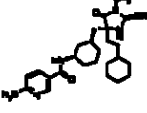
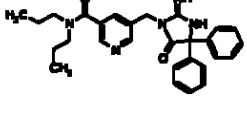
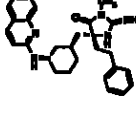
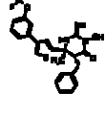
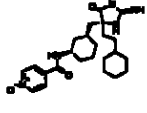
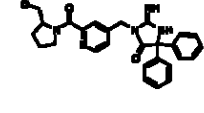
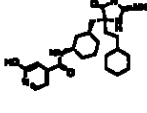
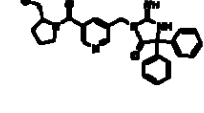
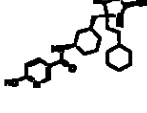
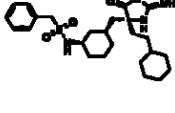
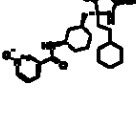
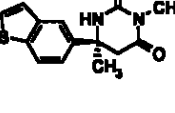
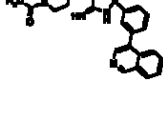
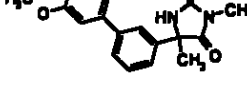
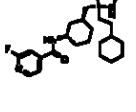
762
770

1550		A	414	1721		BQ	454.2
1551		CE	415	1722		BQ	454.2
1552		A	416	1723		AW	419.2
1553		A	417	1724		AW	423.2
1554		A	417	1725		AW	430.2
1555		A	419	1726		AW	431.2
1556		A	420	1727		AW	435.2
1557		A	421	1728		CK	439.2
1558		A	422	1729		AW	441.2
1559		A	422	1730		AW	450.3
1560		A	422	1731		CK	453.3
1561		A	423	1732		CK	453.3

763 771

1562		A	423	1733		AW	453.3
1563		CE	424	1734		CK	455.3
1564		A	425	1735		L	467.3
1565		A	426	1736		L	467.3
1566		A	426	1737		CK	469.3
1567		A	426	1738		CK	481.3
1568		A	431	1739		CK	483.3
1569		A	431	1740		CK	497.3
1570		A	431	1741		CK	525.3
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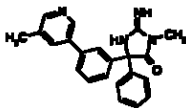
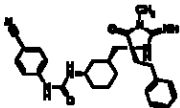
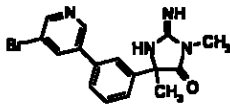
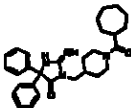
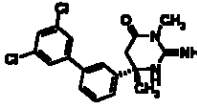
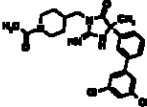
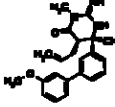
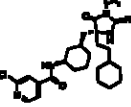
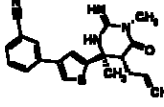
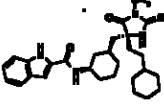
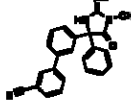
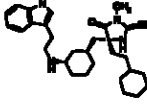
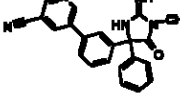
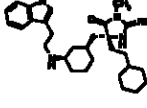
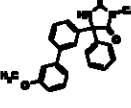
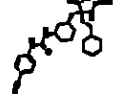
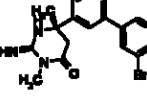
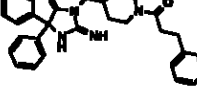
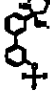
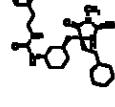
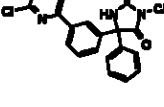
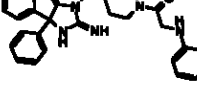
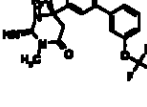
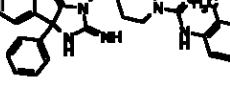
761
972

1674		A	439	1746		BS	522.3
1675		A	465	1748		BQ	525.3
1676		CG	470	1747		BQ	532.3
1677		CG	470	1749		CG	576.3
1678		CG	470	1748		BQ	455.3
1679		CG	470	1750		BW	456.3
1680		CE	474	1751		BQ	456.3
1681		CG	484	1752		BQ	456.3
1682		CG	484	1753		BS	456.3
1683		BR	489	1754		BQ	456.3
1684		CF	274.1	1755		AW	456.3
1685		AW	311.1	1756		BQ	456.3

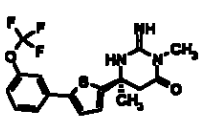
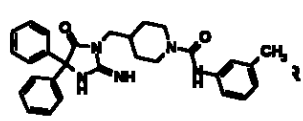
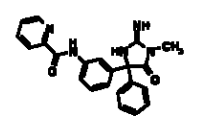
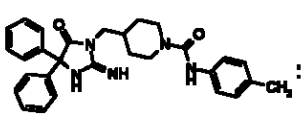
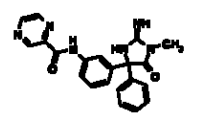
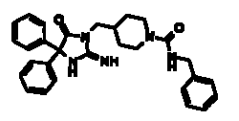
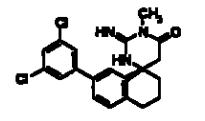
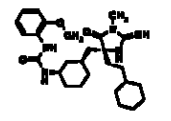
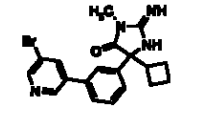
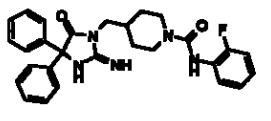
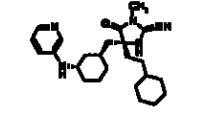
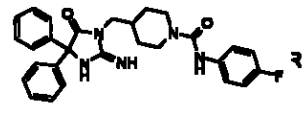
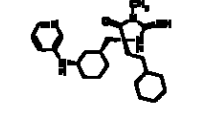
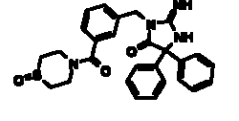
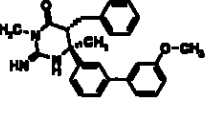
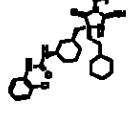
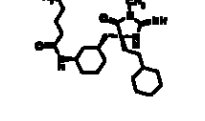
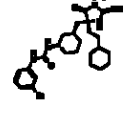
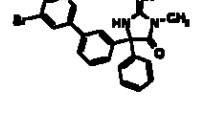
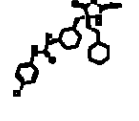
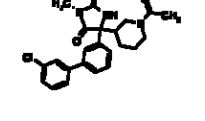
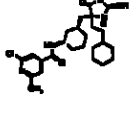
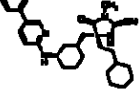
265
273

1686		AB	312.1	1767		BQ	458.3
1687		AB	318.1	1768		BQ	458.3
1688		CF	320.1	1769		BQ	458.3
1689		CF	325.1	1780		BS	460.3
1690		AB	328.1	1781		R	460.3
1691		AW	332.1	1782		BW	462.3
1692		CE	333.1	1783		BW	462.3
1693		CF	336.1	1784		BW	463.3
1694		AW	337.1	1785		BQ	464.3
1695		CF	337.1	1786		BQ	464.3
1696		CF	337.1	1787		BW	465.3
1697		CF	337.1	1788		BQ	467.3

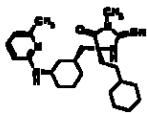
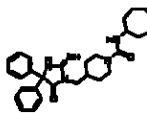
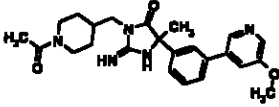
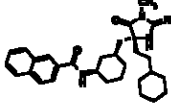
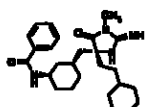
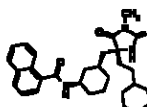
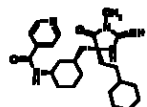
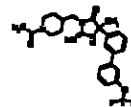
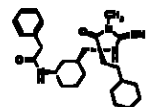
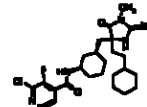
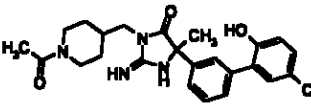
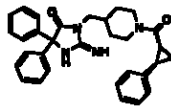
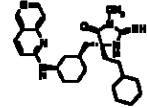
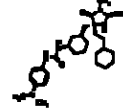
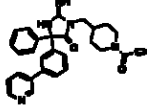
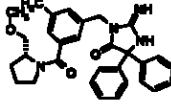
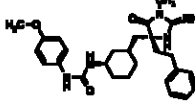
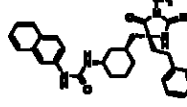
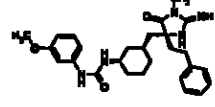
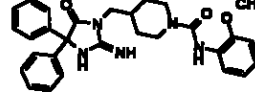
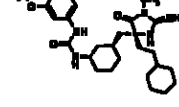
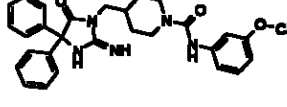
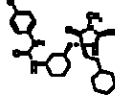
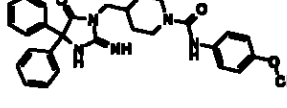
767
775

1610		AW	357.1	1781		BS	473.3
1611		AW	359.1	1782		Q	473.3
1612		AB	362.1	1783		AW	473.3
1613		CE	364.1	1784		BQ	474.3
1614		CE	365.1	1785		BQ	478.3
1615		AW	367.1	1786		AZ	478.3
1616		AW	368.1	1787		AZ	478.3
1617		AW	372.1	1788		BS	479.3
1618		CF	373.1	1789		Q	481.3
1619		AB	378.1	1790		BS	482.3
1620		AW	378.1	1791		Q	482.3
1621		CF	379.1	1792		R	482.3

768
776

1822		CF	384.1	1783		482.3
1823		BQ	386.1	1784		482.3
1824		BQ	387.1	1785		R 482.3
1825		AB	388.1	1786		BS 484.3
1826		CO	398.1	1787		R 488.3
1827		BW	412.1	1788		488.3
1828		BW	412.1	1789		CK 487.3
1829		CE	414.1	1800		BS 488.3
1830		BQ	419.1	1801		BS 488.3
1831		AW	421.1	1802		BS 488.3
1832		AM	425.1	1803		BQ 488.3
1833		AW	425.1	1804		BW 488.3

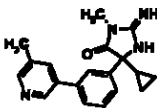
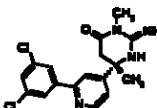
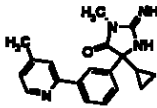
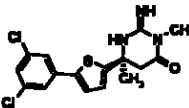
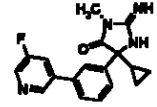
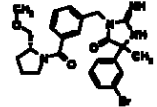
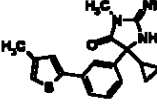
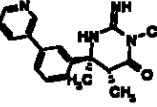
269
277

1834		BW	428.1	1808		R	488.3
1835		AW	438.1	1809		BQ	489.3
1836		BQ	438.1	1807		BQ	489.3
1837		BQ	440.1	1808		AW	489.3
1838		BQ	453.1	1809		BQ	482.3
1839			455.1	1810		Q	483.3
1840		BW	483.1	1811		BS	487.3
1841		Q	488.1	1812		CG	487.3
1842		BS	478.1	1813		BS	488.3
1843		BS	478.1	1814		R	488.3
1844		BS	484.1	1815			488.3
1845		BS	484.1	1816			488.3

770
270

1846		BQ	482.1	1817		R	500.3
1847		BW	482.1	1818		R	502.3
1848		BW	485.1	1819			502.3
1849		BW	486.1	1820		BS	504.3
1850		Q	580.1	1821		BS	504.3
1851		AW	589.1	1822		BQ	504.3
1852		BW	573.1	1823		BQ	508.3
1853		W	470.1	1824		CF	329.1, 331.1
1854		AW	307.2	1825		CF	334.0, 336.0
1855		AW	308.2	1826		CF	342.1, 344.1
1856		CP	308.2	1827		CF	352.0, 353.9
1857		AW	315.2	1828		CF	358.1, 360.1

771
774

1658		AW	321.2	1629		CF	383.1, 385.1
1659		CO	321.2	1630		CF	387.8, 389.8
1660		AW	325.2	1631		A	501.1 499
1661		AW	328.2	1632		CE	309

Ensayo D FRET de catepsina humana

Este ensayo se puede correr en formato continuo o de punto final. Se ha descrito el sustrato utilizado debajo (Y.Yasuda et al., J. Biochem. , 125, 1137 (1999)). El sustrato y la enzima están disponibles en el comercio.

El ensayo se corre en un volumen final de 30 ul utilizando una placa negra Nunc de 384 pocillos. Se pre-incubaron 8 concentraciones del compuesto con la enzima durante 30 minutos a 37°C seguido de la adición del sustrato con incubación continuada a 37°C durante 45 minutos. La proporción de incremento en la fluorescencia es lineal durante más de 1 hora y se mide al final del periodo de incubación utilizando una estación lectora de placas Molecular Devices FLEX. Se interpolaron Kis de los IC50s utilizando un valor de Km de 4 uM y la concentración de sustrato de 2,5 uM.

772
700**Reactivos**

Na-Acetato pH 5

1% de Brij-35 de reserva de 10% (Calbiochem)

DMSO

Catepsina D de hígado humano purificado (>95%) (Athens Research & Technology Cat# 16-12-030104)

Sustrato de péptido ($K_m=4\mu M$) Mca-Gly-Lys-Pro-Ile-Leu-Phe-Phe-Arg-Leu-Lys(Dnp)-D-Arg-NH₂ Bachem Cat # M-2455

Se utiliza Pepstatina como inhibidor de control ($K_i\sim 0,5nM$) y está disponible de Sigma.

Placas negras Nunc de 384 pocillos.

Condiciones de buffer de ensayo final

Acetato Na 100mM pH 5.0

0,02% de Brij-35

1% de DMSO

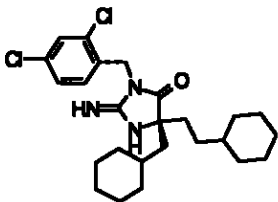
El compuesto se diluyó hasta la concentración final 3x en buffer de ensayo conteniendo 3% de DMSO. Se agregó 10 μl del compuesto a 10 μl de 2,25 nM de enzima (3x) diluida en buffer de ensayo sin DMSO, se mezcló brevemente, se rotó, y se incubó a 37°C durante 30 minutos. Se preparó 3x sustrato (7,5 μM) en 1x buffer de ensayo sin DMSO. Se agregó 10 μl de sustrato a cada pocillo, se mezcló y se rotó brevemente para iniciar la reacción. Las placas de ensayo se incubaron a 37°C durante 45 minutos y se leyeron sobre lector de placa de fluorescencia compatible 384 utilizando un 328nm Ex y 393nm Em.

Los compuestos de la presente invención muestran rangos de datos de CathDh K_i de aproximadamente 0,1 a aproximadamente 500 nM, preferentemente aproximadamente 0,1 a aproximadamente 100 nM con mayor preferencia aproximadamente 0,1 a aproximadamente 75 nM.

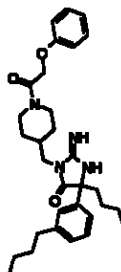
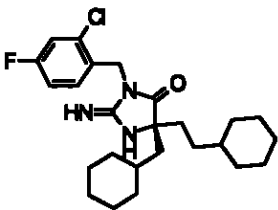
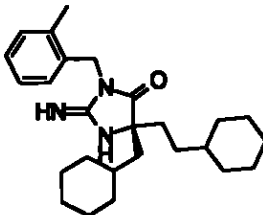
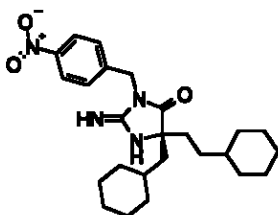
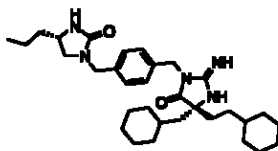
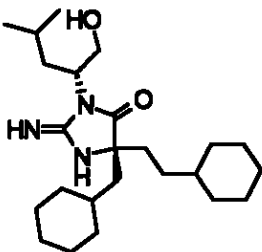
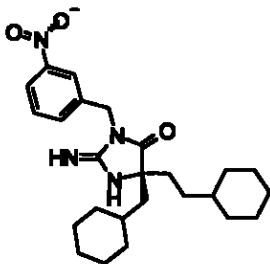
Los siguientes son ejemplos de compuestos que muestran datos de CathDh K_i bajo 75 nM.

73 701

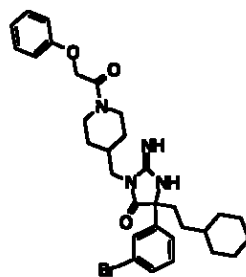
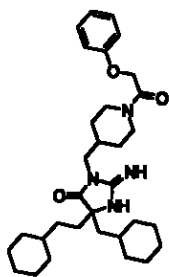
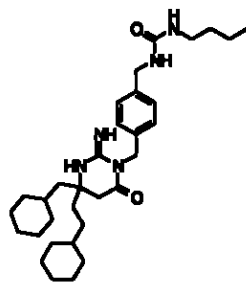
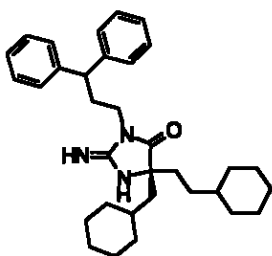
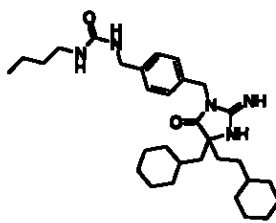
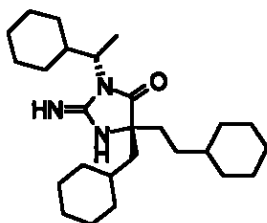
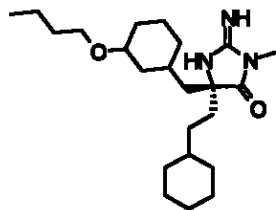
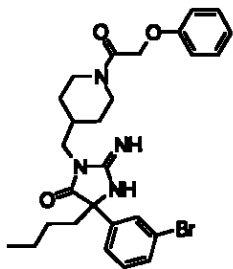
Estructura

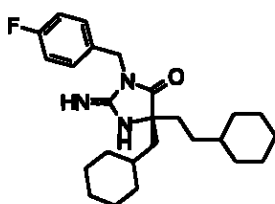


estructura

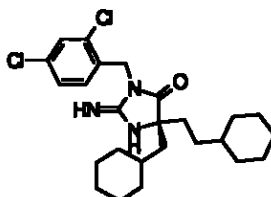


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782



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782

El siguiente compuesto



tiene un valor hCath D Ki de 0,45 nM.

Clonación de BACE-1, Expresión de Proteína y Purificación.

Una forma soluble predicha de BACE1 humano (sBACE1, correspondiente a los aminoácidos 1-454) se generó a partir del ADNc de BACE1 de longitud completa (ADNc de BACE1 humano de longitud completa en construcción de pCDNA4/mycHisA; Universidad de Toronto) mediante PCR utilizando el kit de PCR de advantage-GC ADNc (Clontech, Palo Alto, CA). Un fragmento HindIII/PmeI de pCDNA4-sBACE1myc/His fue terminado in situ utilizando Klenow y se subclonó en el sitio Stu I de pFASTBAC1(A) (Invitrogen). Un báculo de sBACE1mycHis recombinante se generó por transposición de células DH10Bac (GIBCO/BRL). Subsecuentemente, la construcción de báculo sBACE1mycHis se transfectó en células sf9 utilizando CellFectin (Invitrogen, San Diego, CA) para generar el baculovirus recombinante. Células Sf9 se desarrollaron en medio SF 900-II (Invitrogen) suplementado con 3% de FBS inactivado caliente y 0,5X solución de penicilina/estreptomicina (Invitrogen). Cinco mililitros de virus sBACEmyc/His purificado de placas de alto título se utilizó para infectar 1 litro de células sf9 en desarrollo logarítmico durante 72 horas. Las

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células intactas se convirtieron en pellets por centrifugación a 3000xg durante 15 minutos. El sobrenadante, conteniendo sBACE1 secretado, se recolectó y se diluyó 50% v/v con HEPES 100 mM, pH 8,0. El medio diluido se cargó sobre una columna de Q-sefarosa. La columna de Q-sefarosa se lavó con Buffer A (HEPES 20 mM, pH 8,0, NaCl 50 mM).

Las proteínas se eluyeron a partir de la columna Q-sefarosa con Buffer B (HEPES 20 mM, pH 8,0, NaCl 500 mM). Los picos de proteína de la columna Q-sefarosa se reunieron y se cargaron sobre una columna de Ni-NTA agarosa. La columna de Ni-NTA luego se lavó con Buffer C (HEPES 20 mM, pH 8,0, NaCl 500 mM). Las proteínas unidas luego se eluyeron con Buffer D (Buffer C+ imidazol 250 mM). Las fracciones con picos proteicos según se determinó por el Ensayo de Bradford (Biorad, CA) se concentraron utilizando un concentrador Centricon 30 (Millipore). La pureza de sBACE1 se estimó en ~90% según se evaluó mediante SDS-PAGE y tinción de Azul Commassie. El secuenciamiento de N-terminal indicó más del 90% del sBACE1 purificado contenía el prodominio; de este modo esta proteína se denomina sproBACE1.

Ensayo de Hidrólisis del Péptido

El inhibidor, sustrato de APPsw marcado EuK-biotin 25 nM (EuK-KTEEISEVNLDAEFRHDKC-biotin; CIS-Bio International, Francia), péptido APPsw no marcado de 5 μ M (KTEEISEVNLDAEFRHDK; American Peptide Company, Sunnyvale, CA), sproBACE1 7 nM, PIPES 20 mM, pH 5,0, 0.1% de Brij-35 (grado proteico, Calbiochem, San Diego, CA), y 10% de glicerol se preincubaron durante 30 min a 30°C. Las reacciones se iniciaron por la adición del sustrato en una alícuota de 5 μ l dando por resultado un volumen total de 25 μ l. Después de 3 horas a 30°C, las reacciones se terminaron por la adición de un volumen igual de buffer de detención 2x conteniendo Tris-HCl 50 mM pH 8,0, KF 0,5 M, 0,001% de Brij-35, 20 μ g/ml de SA-XL665 (proteína de aloficocianina entrecruzada acoplada a la estreptavidina; CIS-Bio International, Francia) (0,5 μ g/pocillo). Las placas se agitaron brevemente y se centrifugaron a 1200xg durante 10 segundos para convertir en pellet todo el líquido en el fondo de la placa antes de la incubación. Se realizaron mediciones de HTRF sobre un lector de placa Packard Discovery®

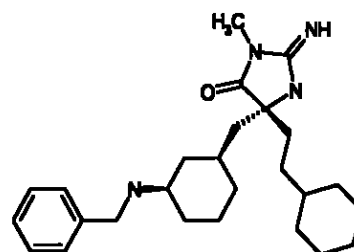
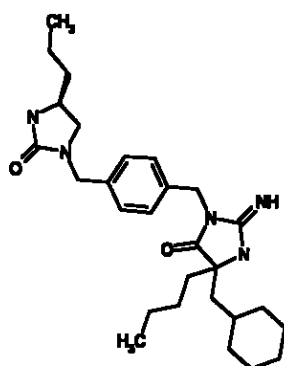
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705

HTRF utilizando luz láser de 337 nm para excitar la muestra seguida de una demora de 50 μ s y mediciones simultáneas de ambas emisiones de 620 nm y 665 nm durante 400 μ s.

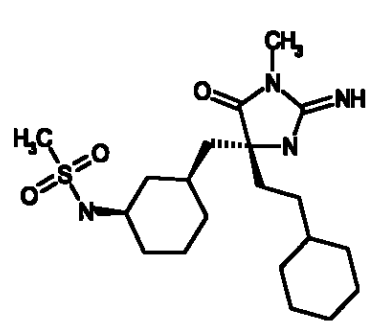
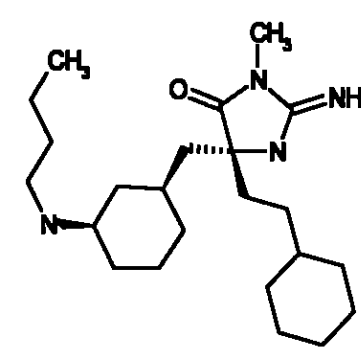
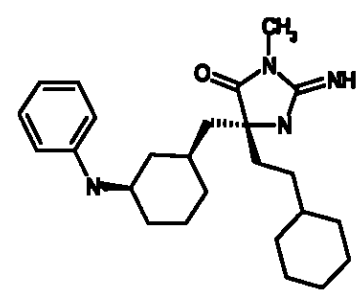
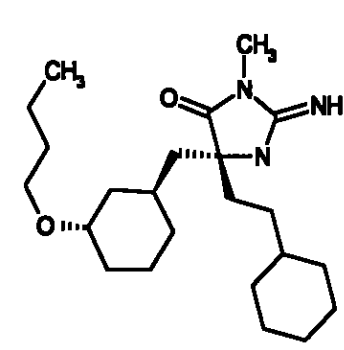
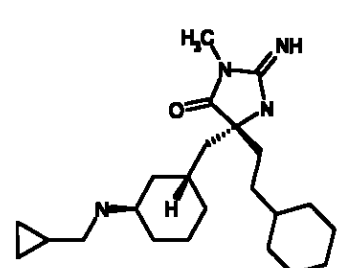
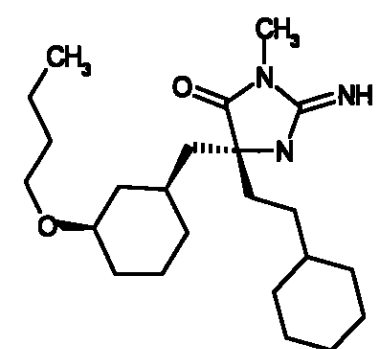
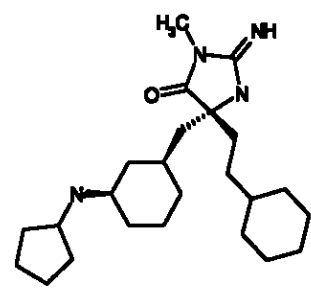
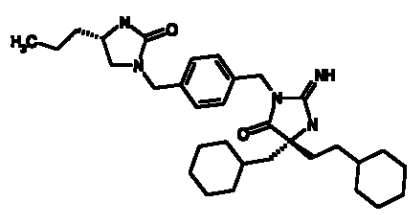
Las determinaciones IC_{50} para inhibidores, (I), se determinó mediante la medición del cambio porcentual de la fluorescencia relativa a 665 nm dividido por la fluorescencia relativa a 620 nm, (relación 665/620), en presencia de concentraciones variadas de (I) y una concentración fija de la enzima y el sustrato. El análisis de regresión no lineal de estos datos se llevó a cabo utilizando el software GraphPad Prism 3.0 seleccionando la ecuación logística de cuatro parámetros, que da lugar a una declinación variable. $Y = Fondo + (Parte\ superior - Fondo) / (1 + 10^{((LogEC50 - X) * pendiente\ de\ Hill)})$; X es el logaritmo de concentración de I, Y es el cambio en porcentaje en la relación e Y se inicia en el fondo y va hacia la parte superior con una forma sigmoidal.

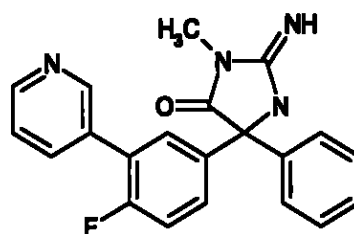
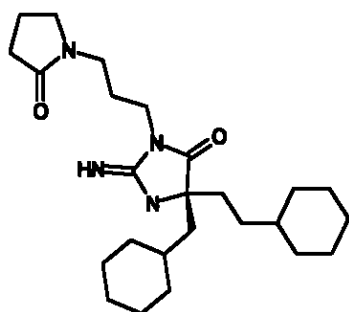
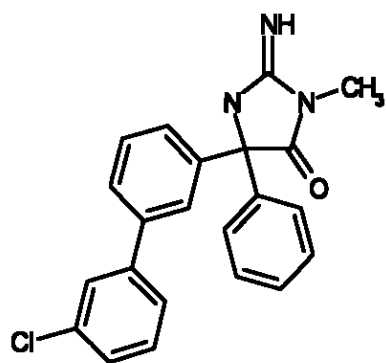
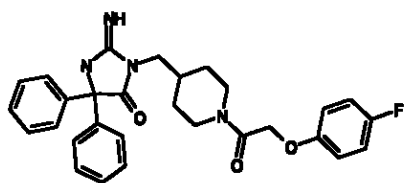
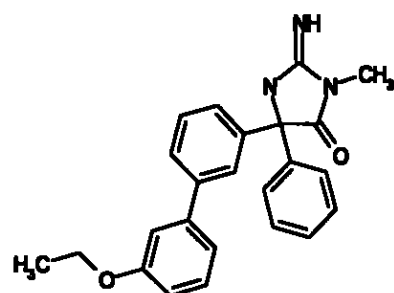
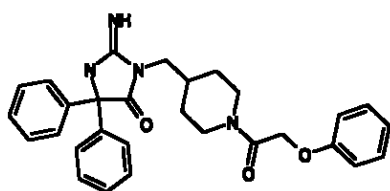
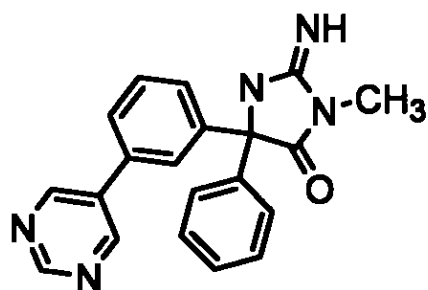
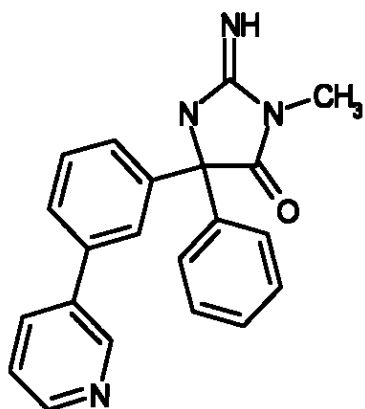
Los compuestos de la presente invención tienen un rango de IC_{50} de aproximadamente 0,001 a aproximadamente 500 μ M, preferentemente aproximadamente 0,001 a aproximadamente 100 μ M, con mayor preferencia aproximadamente 0,001 a aproximadamente 20 μ M.

Ejemplos de compuestos con BACE 1 humano con $IC_{50} < 1 \mu$ M se mencionan a continuación:

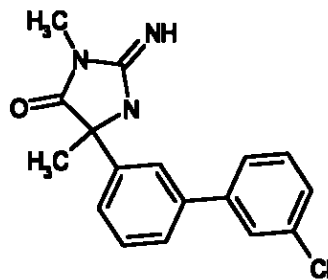
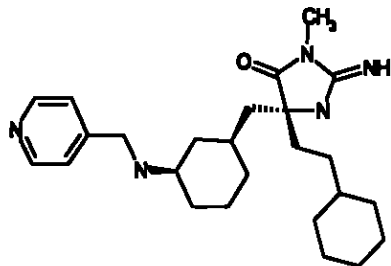
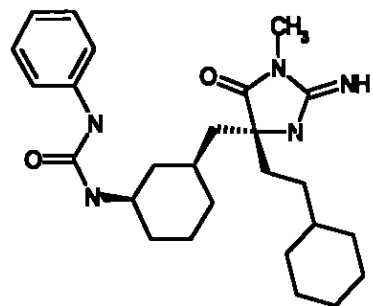
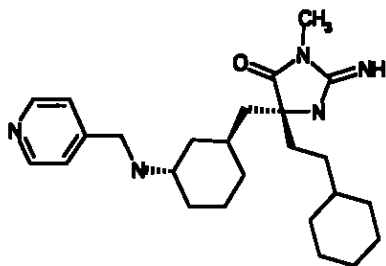
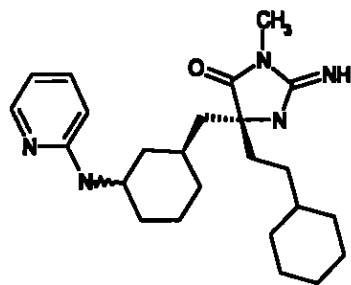
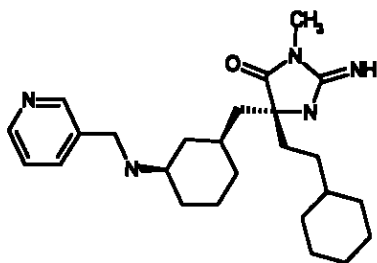
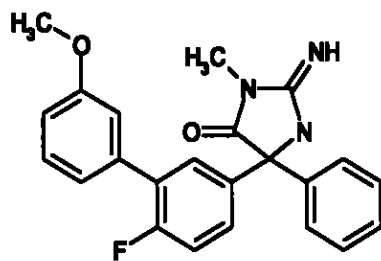
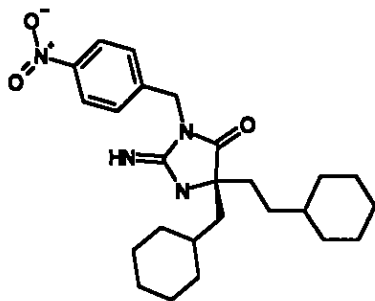


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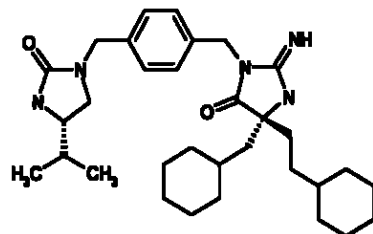
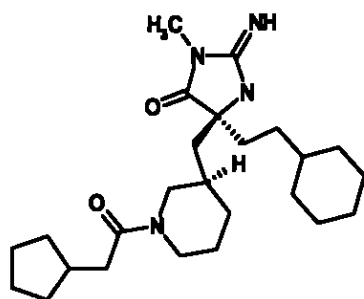
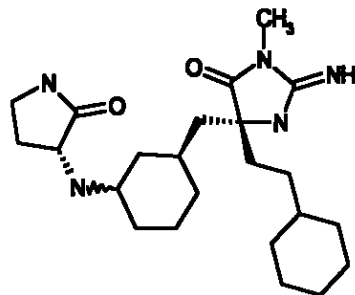
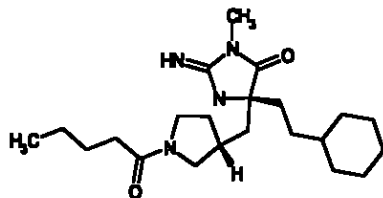
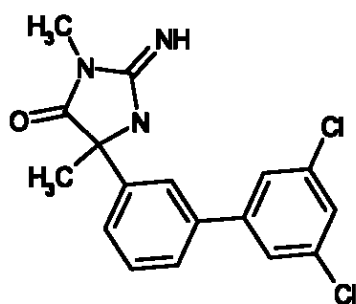
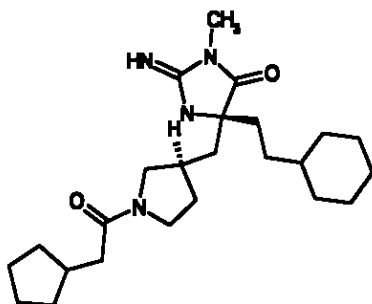
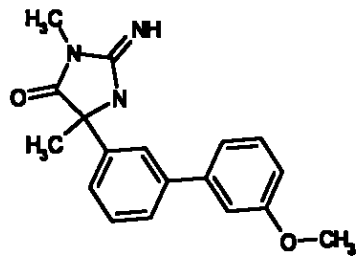
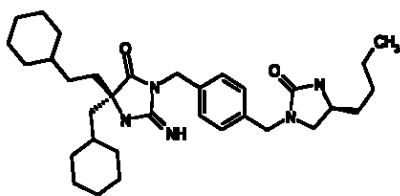


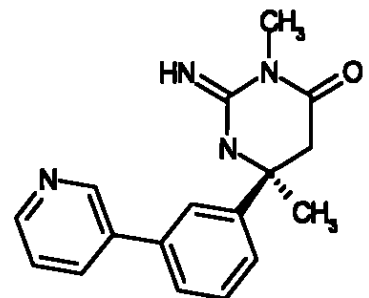
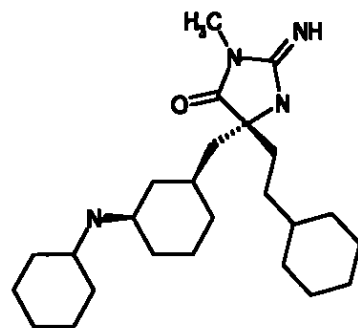
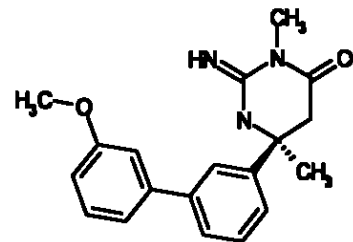
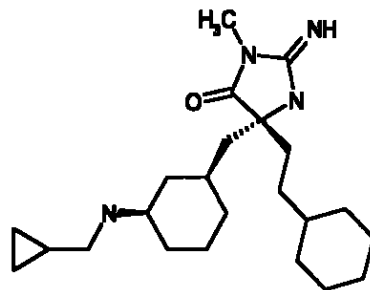
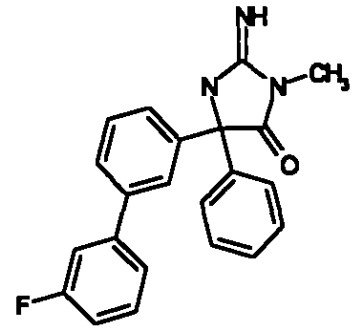
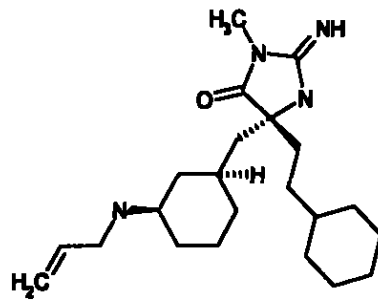
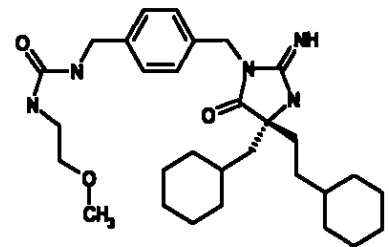
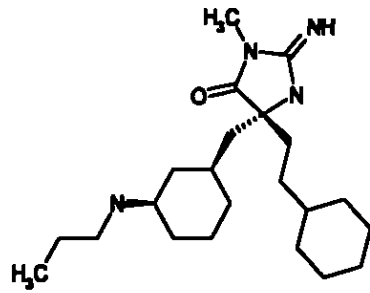
~~200~~
~~200~~

701
~~709~~



732
740



703
741

Ensayo enzimático de renina humana madura:

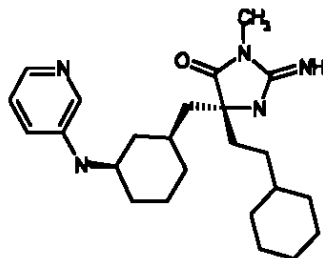
7134
702

La renina humana se clonó a partir de una genoteca de ADNc de riñón humano y se marcó mediante epítipo en el C-terminal con la secuencia V5-6His en pCDNA3.1. La pCND3.1-Renin-V5-6His se expresó de manera estable en células HEK293 y se purificó hasta >80% utilizando cromatografía de Afinidad a Ni estándar. El prodominio de la renina-V5-6His humana recombinante se eliminó por proteólisis limitada utilizando TPCK-tripsina inmovilizada para dar la renina humana madura. La actividad enzimática de la renina se monitoreó utilizando sustrato peptídico de Fluorescencia por transferencia de energía resonante (FRET), RS-1(Molecular Probes, Eugene, OR) en Tris-HCl 50mM pH 8.0, NaCl 100mM, 0.1% de Brij-35 y 5% de buffer de DMSO durante 40 mins a 30 grados Celsius en presencia o ausencia de diferentes concentraciones de compuestos de ensayo. La renina humana madura estuvo presente a 200nM. La actividad de inhibición se definió como la disminución porcentual en la fluorescencia inducida por renina al final de la incubación de 40 min en comparación con los controles con vehículo y muestras que carecen de enzimas.

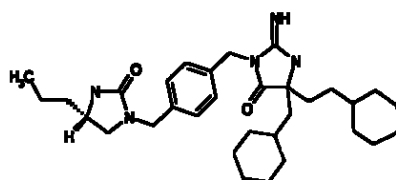
I% de Reninah a 100 μ M

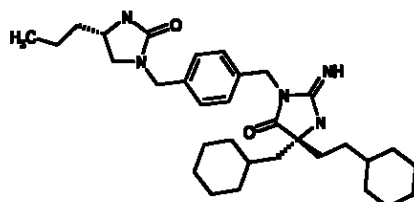
Compuesto

68.8



75.3



785
743

76.9

En el aspecto de la invención que se refiere a una combinación de al menos un compuesto de fórmula I con al menos un inhibidor de colinesterasa, se pueden utilizar inhibidores de acetil- y/o butirilcolinesterasa. Ejemplos de inhibidores de colinesterasa son tacrina, donepezil, rivastigmina, galantamina, piridostigmina y neostigmina, prefiriéndose tacrina, donepezil, rivastigmina y galantamina. Preferentemente, estas combinaciones están dirigidas al tratamiento de la enfermedad de Alzheimer.

En el aspecto de la invención que se refiere a una combinación se puede utilizar al menos un compuesto de fórmula I con al menos un agonista muscarínico m_1 o un antagonista m_2 . Ejemplos de agonistas m_1 son conocidos en la técnica. Ejemplos de antagonistas m_2 también son conocidos en la técnica; en particular antagonistas m_2 se revelan en las Patentes Estadounidenses 5.883.096; 6.037.352; 5.889.006; 6.043.255; 5.952.349; 5.935.958; 6.066.636; 5.977.138; 6.294.554; 6.043.255; y 6.458.812; y en WO 03/031412, las cuales se incorporan todas como referencia en su totalidad.

En el aspecto de la invención que se refiere a una combinación de al menos un compuesto de fórmula I y al menos otro agente, por ejemplo, un inhibidor de beta secretasa; un inhibidor de gamma secretasa; un inhibidor de HMG-CoA reductasa tal como atorvastatina, lovastatina simvastatina, pravastatina, fluvastatina y rosuvastatina; agentes no-inflamatorios no esteroideos tales como, pero no necesariamente limitados a ibuprofeno, relafeno o naproxeno; antagonistas del receptor de N-metil-D-aspartato tales como memantina; anticuerpos anti-amiloide que incluyen anticuerpos monoclonales humanizados;

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vitamina E; agonistas del receptor de acetilcolina nicotínica; agonistas inversos del receptor CB1 o antagonistas del receptor CB1; antibióticos tales como doxiciclina; secretagogos de la hormona del crecimiento; antagonistas de histamina H3; agonistas AMPA; inhibidores de PDE4; agonistas inversos de GABA_A; inhibidores de agregación amiloide; inhibidores de glicógeno sintasa beta quinasa; promotores de la actividad de alfa secretasa. Preferentemente, estas combinaciones están dirigidas al tratamiento de la enfermedad de Alzheimer.

Para preparar composiciones farmacéuticas a partir de los compuestos descritos por esta invención, los vehículos inertes, aceptables para uso farmacéutico pueden sólidos o líquidos. Las preparaciones de forma sólida incluyen polvo, comprimidos, gránulos dispersables, cápsulas, sellos y supositorios. Los polvos y comprimidos pueden contener de aproximadamente 5 a aproximadamente 95 por ciento de ingrediente activo. Los vehículos sólidos adecuados son conocidos en la técnica, por ejemplo, carbonato de magnesio, estearato de magnesio, talco, azúcar o lactosa. Los comprimidos, polvos, sellos y cápsulas se pueden utilizar como formas de dosificación sólidas adecuadas para administración oral. Ejemplos de vehículos aceptables para uso farmacéutico y métodos de obtención de varias composiciones se pueden hallar en A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Las preparaciones de forma líquida incluyen soluciones, suspensiones y emulsiones. Como ejemplo se pueden mencionar soluciones acuosas o agua-propilenglicol para inyección parenteral o el agregado de endulzantes y opacantes para soluciones orales, suspensiones y emulsiones. Las preparaciones de forma líquida además pueden incluir soluciones para administración intranasal.

Las preparaciones en aerosol adecuadas para inhalación pueden incluir soluciones y sólidos en forma de polvo, el cual puede estar en combinación con un vehículo aceptable para uso farmacéutico, tal como un gas comprimido inerte, por ejemplo, nitrógeno.

Además se incluyen preparaciones de forma sólida las cuales están destinadas a ser convertidas, brevemente antes de su uso, en preparaciones de

forma líquida para administración oral o parenteral. Tales formas líquidas incluyen soluciones, suspensiones y emulsiones.

Los compuestos de la invención además pueden administrarse por vía transdérmica. Las composiciones transdérmicas pueden tomar la forma de cremas, lociones, aerosoles y/o emulsiones y se pueden incluir en un parche transdérmico de la matriz o tipo reservorio ya que son convencionales en la técnica a este fin.

Preferentemente, el compuesto se administra por vía oral.

Preferentemente, la preparación farmacéutica está en una forma de dosificación unitaria. En tal forma, la preparación se subdivide en dosis unitarias de tamaño adecuado conteniendo cantidades apropiadas del componente activo, por ejemplo, una cantidad eficaz para lograr el fin deseado.

La cantidad de compuesto activo en una dosis unitaria de preparación puede variar o ajustarse de aproximadamente 1 mg a aproximadamente 100 mg, preferentemente de aproximadamente 1 mg a aproximadamente 50 mg, con mayor preferencia de aproximadamente 1 mg a aproximadamente 25 mg, de acuerdo con la aplicación en particular.

La dosificación real empleada puede variar dependiendo de los requerimientos del paciente y la severidad de la afección a ser tratada. La determinación del régimen de dosificación adecuado para una situación particular está dentro de la capacidad de la técnica. Por conveniencia, la dosificación diaria total puede dividirse y administrarse en porciones durante el día según sea necesario.

La cantidad y frecuencia de la administración de los compuestos de la invención y/o sus sales aceptables para uso farmacéutico estará regulada de acuerdo con el criterio del profesional actuante tomando en consideración factores tales como la edad, el estado y la contextura del paciente como así también la severidad de los síntomas a ser tratados. Un régimen de dosificación diario recomendado típico para administración oral puede variar de aproximadamente 1 mg/día a aproximadamente 300 mg/día, preferentemente 1 mg/día a 50 mg/día, en dos a cuatro dosis divididas.

Cuando un compuesto de fórmula I se utiliza en combinación con un inhibidor de colinesterasa para tratar trastornos cognitivos, estos dos componentes activos pueden co-administrarse en forma simultánea o secuencial, o una única composición farmacéutica que comprende un compuesto de fórmula I y se puede administrar un inhibidor de colinesterasa en un vehículo aceptable para uso farmacéutico. Los componentes de la combinación se pueden administrar en forma individual o conjunta en cualquier forma de dosificación parenteral u oral convencional tal como cápsula, comprimido, polvo, sello, suspensión, solución, supositorio, nasal, aspersión, etc. La dosificación del inhibidor de colinesterasa puede determinarse a partir de material publicado, y puede variar de 0,001 a 100 mg/kg de peso corporal.

Cuando deben administrarse composiciones farmacéuticas de un compuesto de fórmula I y un inhibidor de colinesterasa, se pueden administrar en un kit que comprende un único envase, un envase que comprende un compuesto de fórmula I en un vehículo aceptable para uso farmacéutico, y un envase separado que comprende un inhibidor de colinesterasa en un vehículo aceptable para uso farmacéutico, estando presentes el compuesto de fórmula I y el inhibidor de colinesterasa en cantidades de modo que la combinación sea terapéuticamente eficaz. Un kit es ventajoso para administrar una combinación cuando, por ejemplo, los compuestos deben administrarse a diferentes intervalos de tiempo o cuando están en diferentes formas de dosificación.

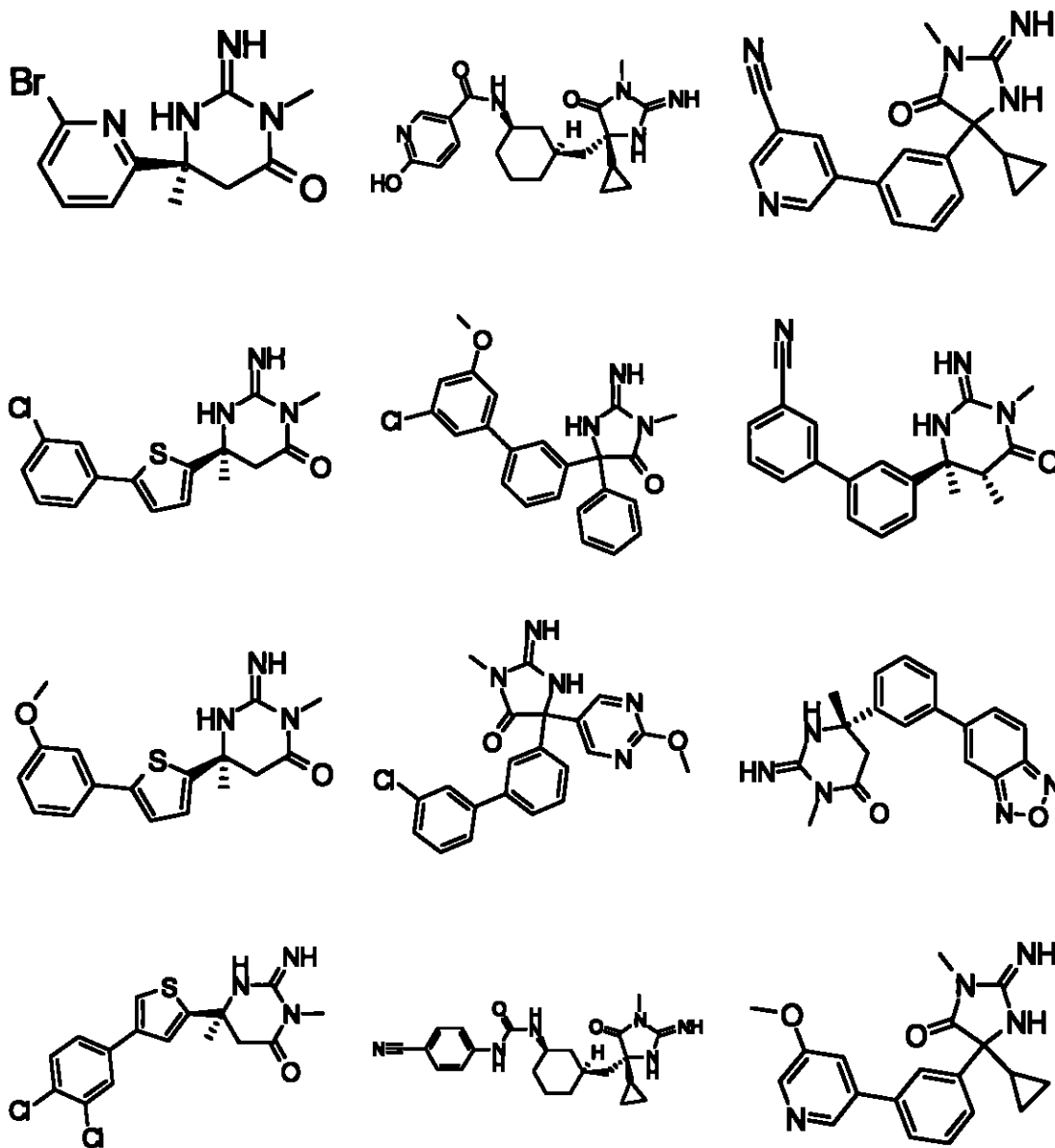
Si bien la presente invención ha sido descrita en conjunto con las realizaciones específicas establecidas anteriormente, muchas alternativas, modificaciones y variantes de las mismas serán evidentes para los expertos en la técnica. Dichas alternativas, modificaciones y variantes están dentro del espíritu y alcance de la presente invención.

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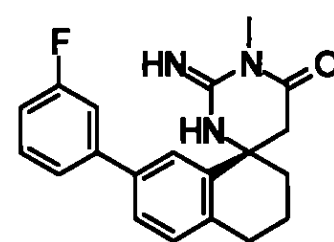
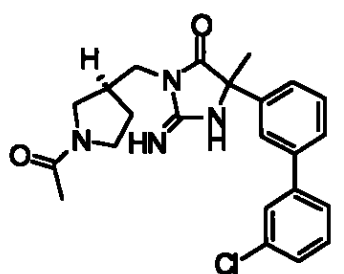
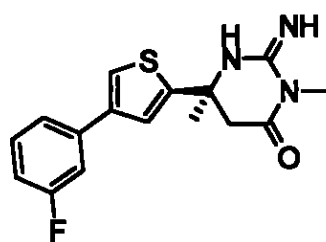
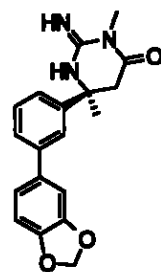
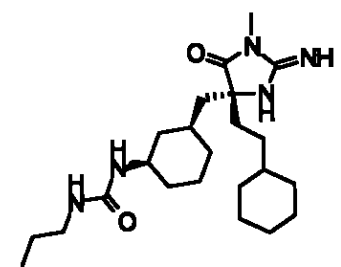
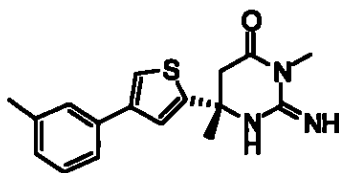
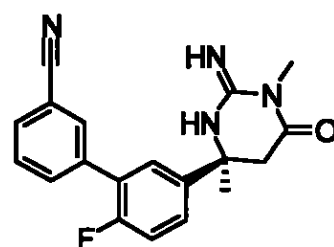
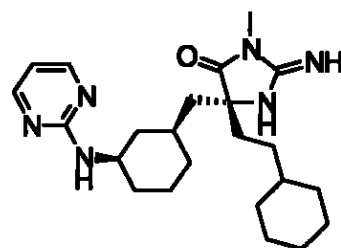
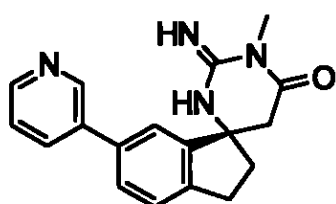
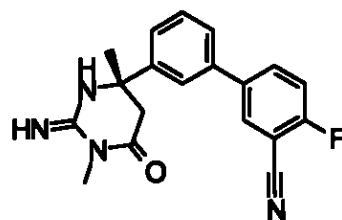
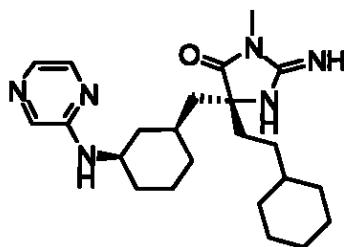
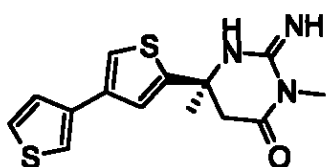
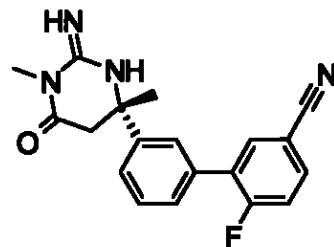
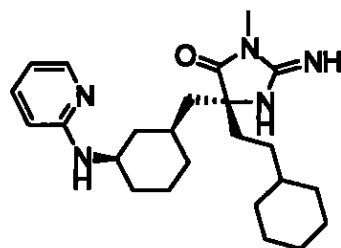
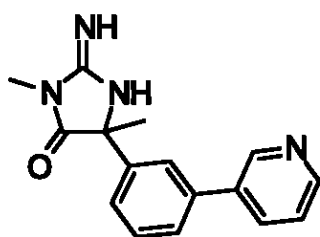
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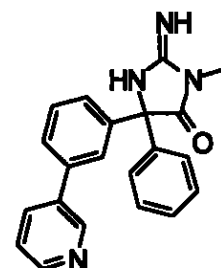
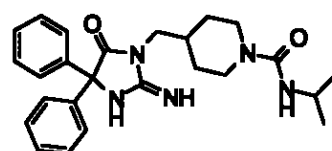
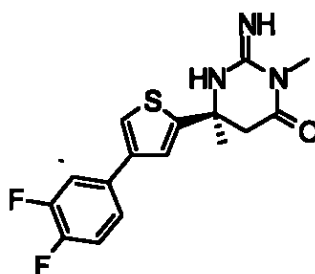
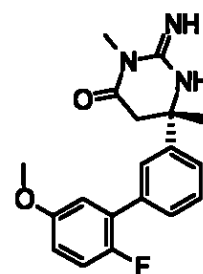
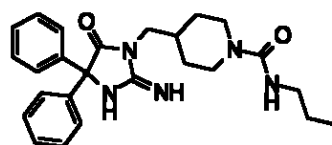
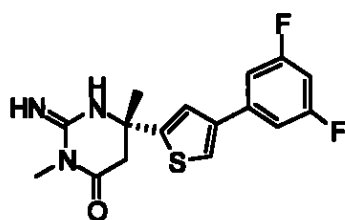
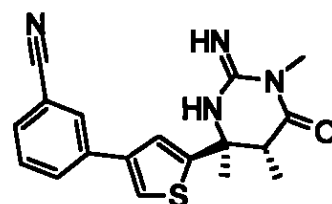
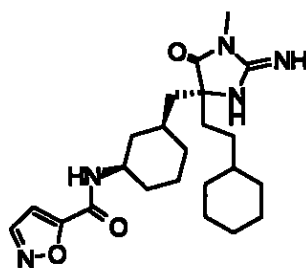
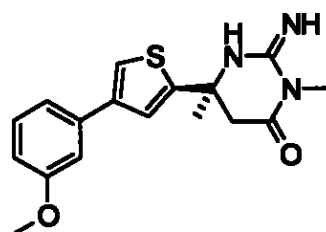
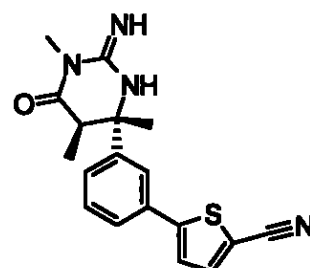
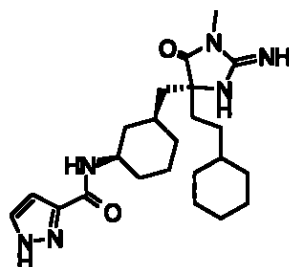
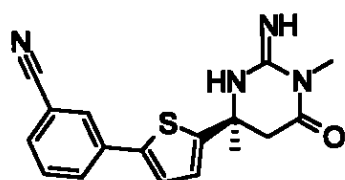
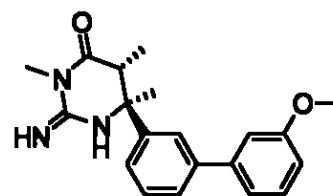
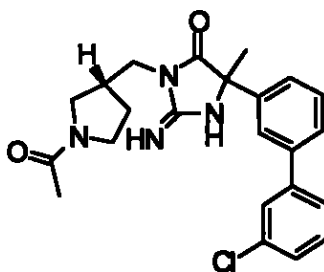
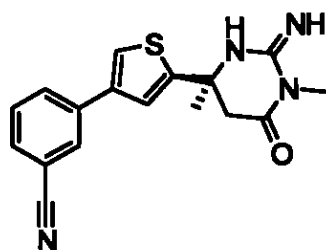
Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y de derecho exclusivo:

1. Un compuesto seleccionado del grupo integrado por

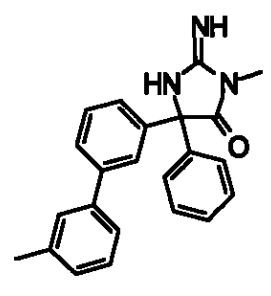
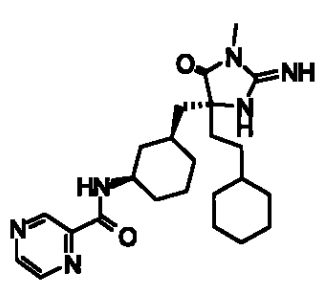
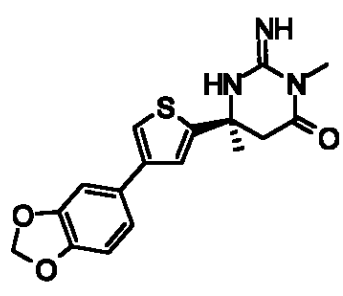
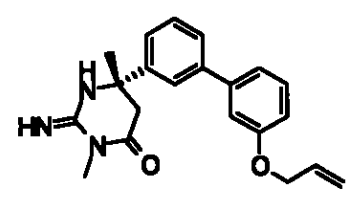
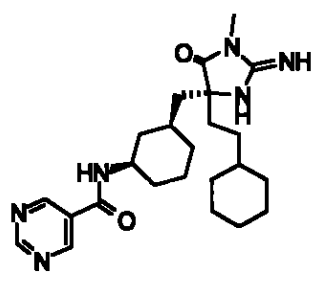
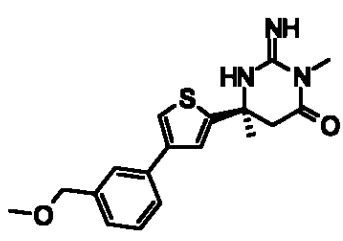
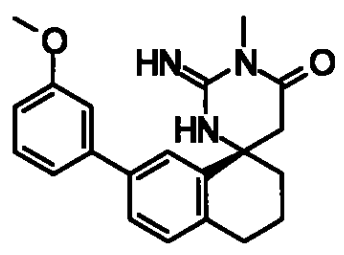
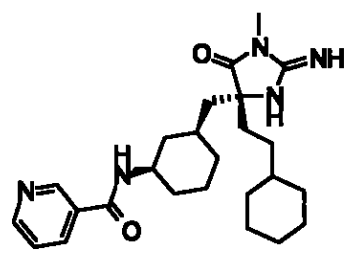
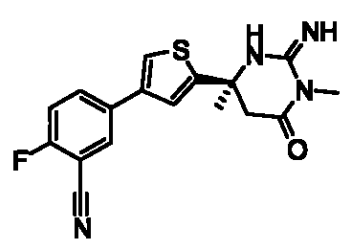
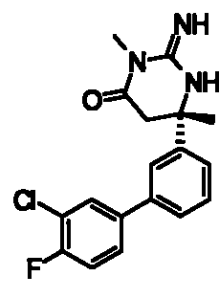
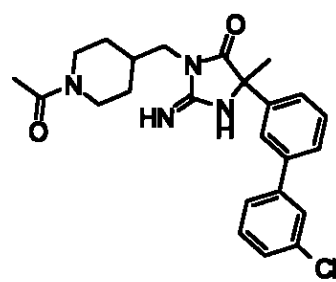
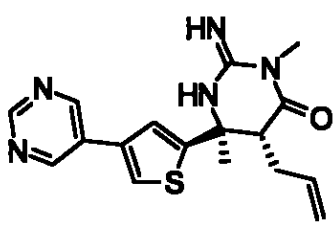
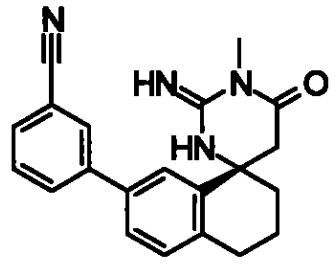
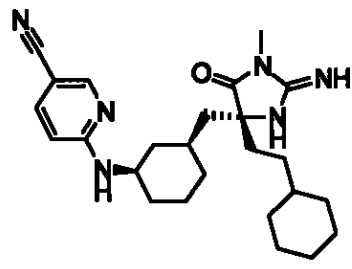
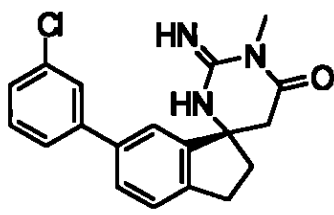


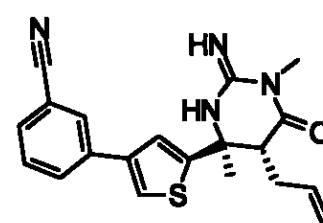
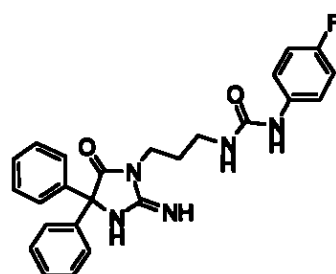
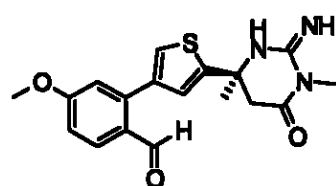
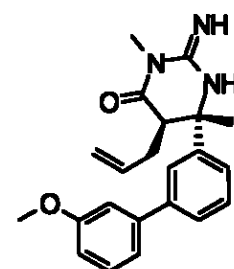
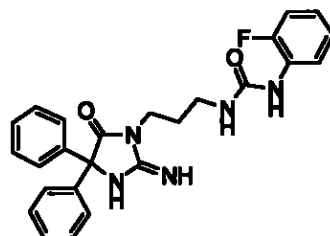
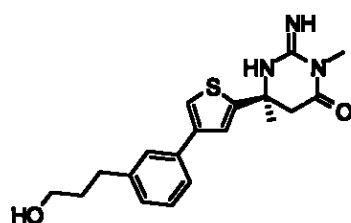
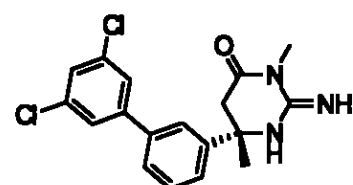
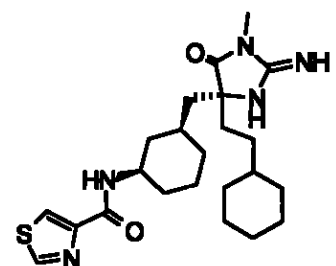
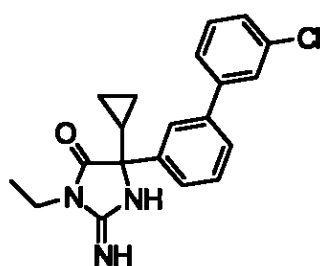
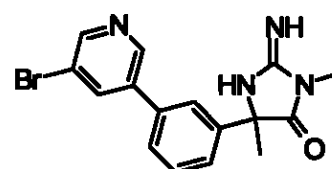
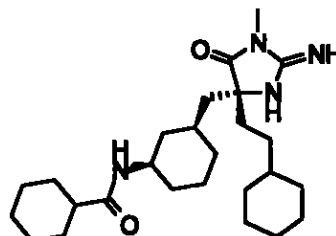
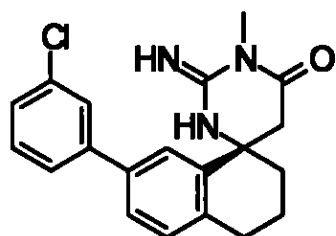
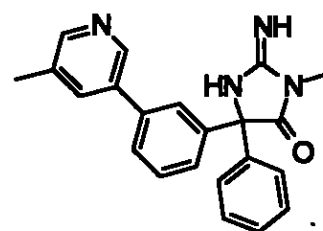
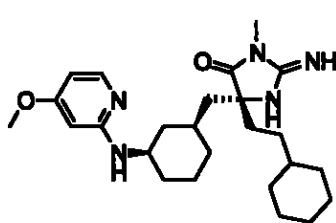
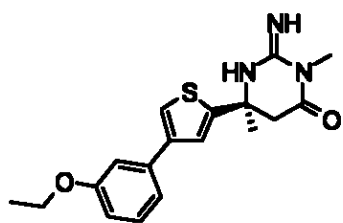
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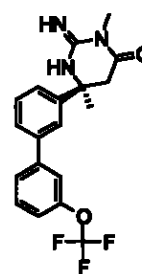
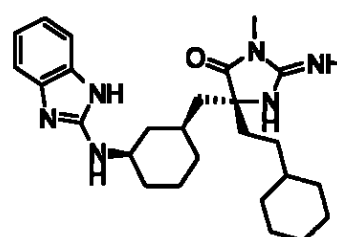
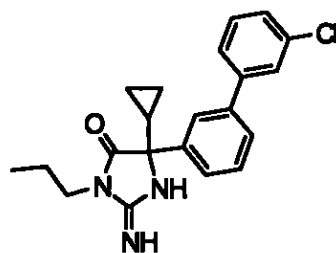
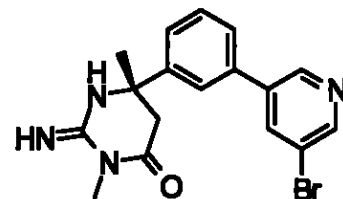
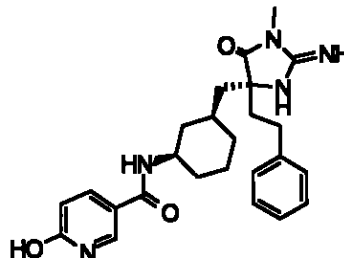
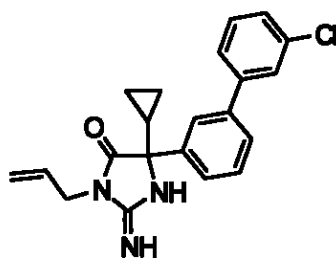
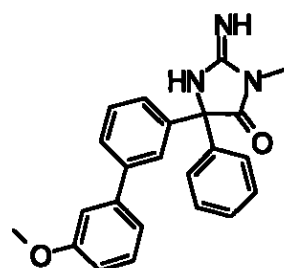
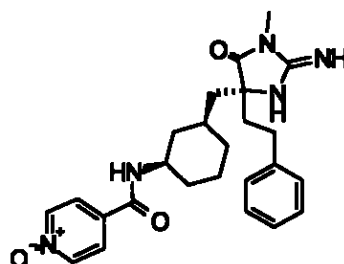
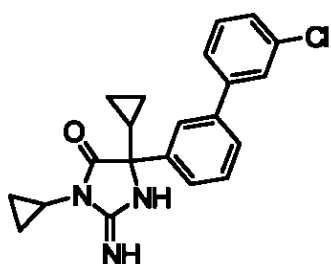
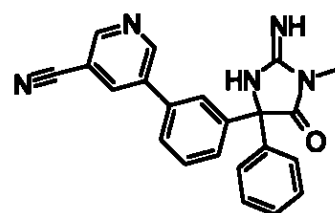
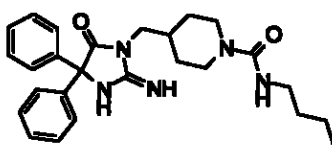
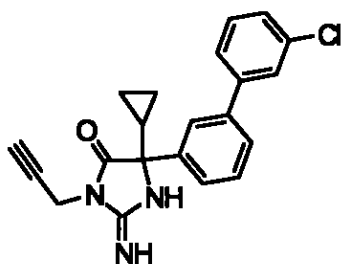
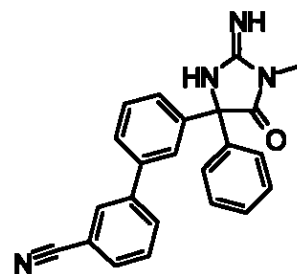
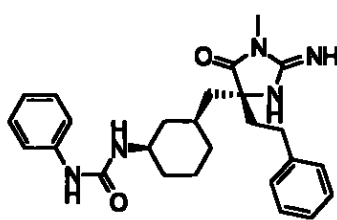
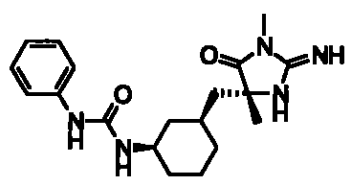
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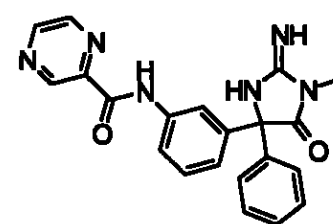
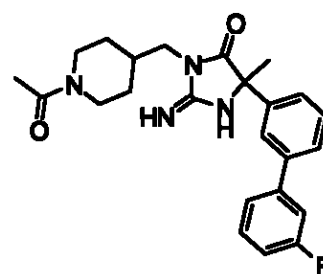
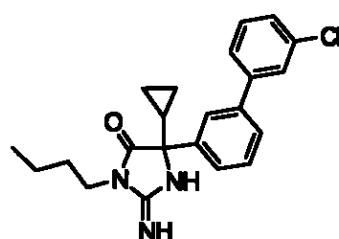
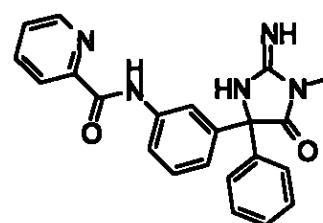
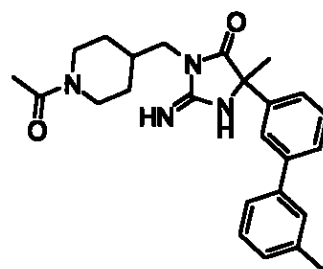
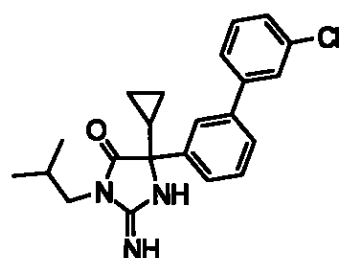
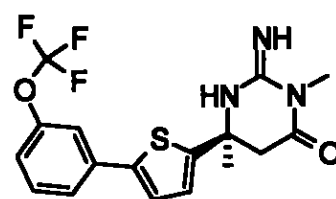
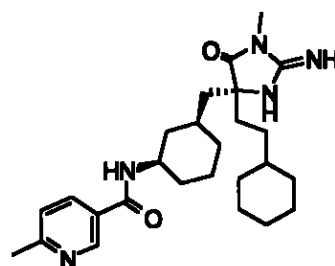
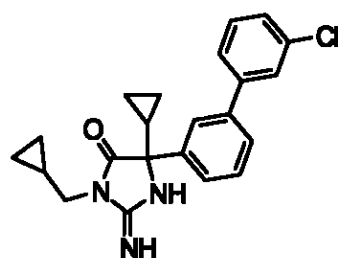
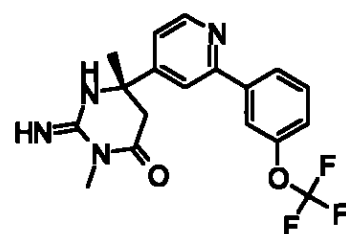
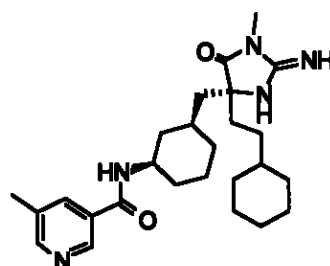
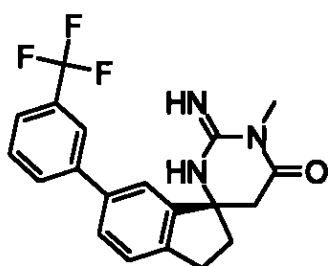
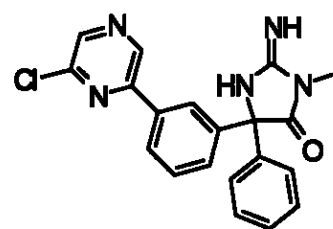
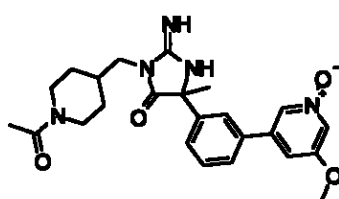
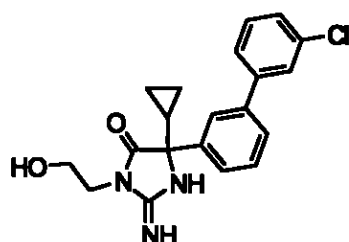
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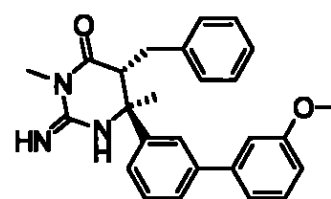
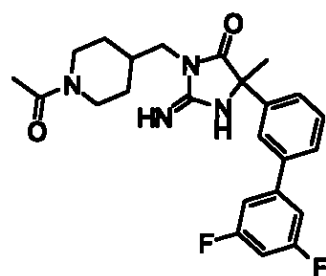
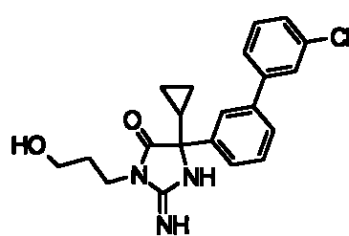
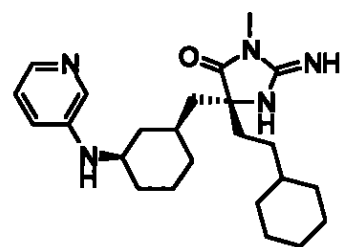
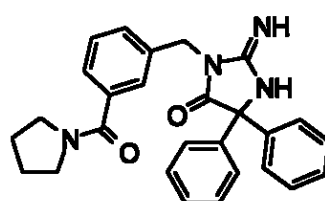
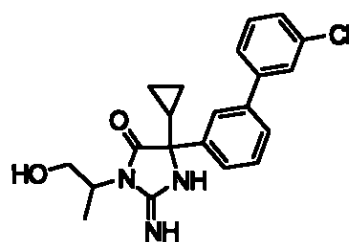
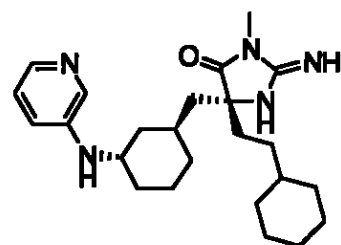
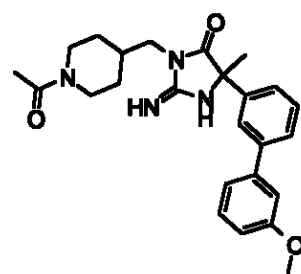
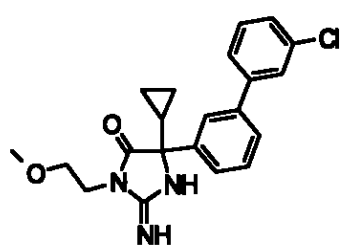
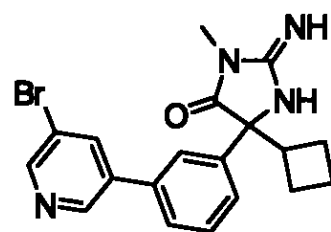
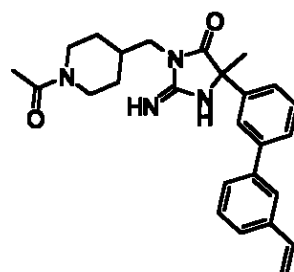
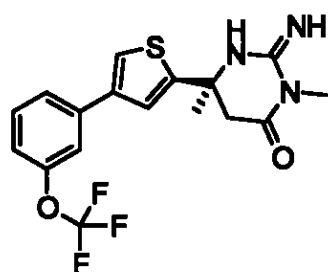
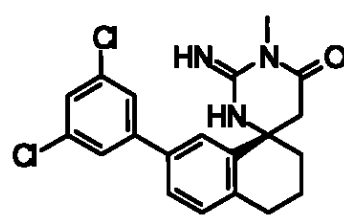
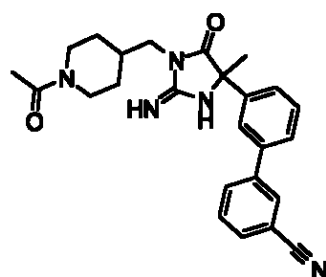
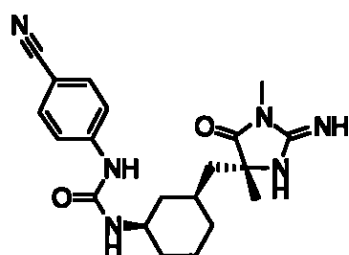


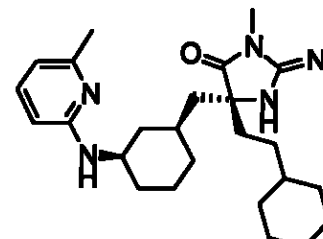
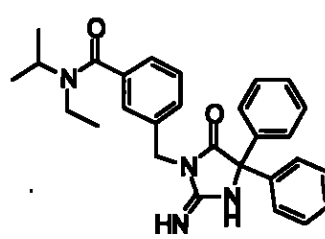
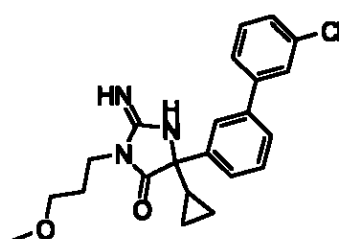
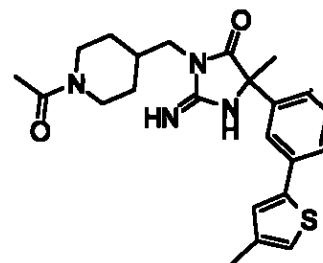
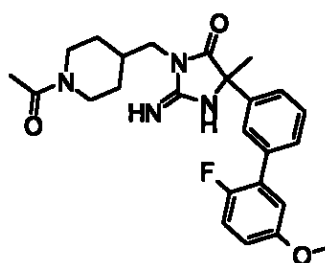
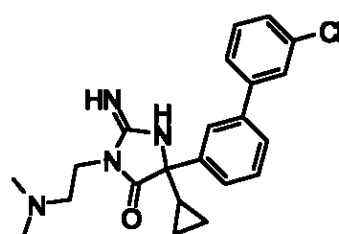
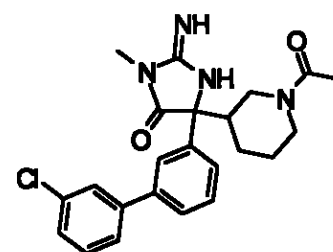
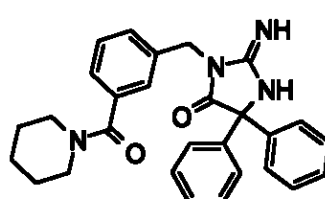
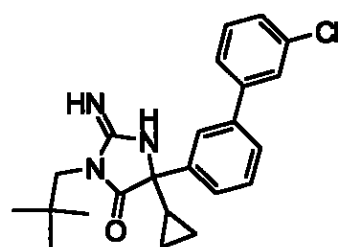
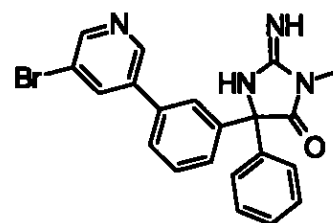
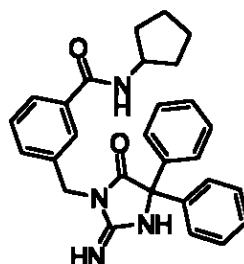
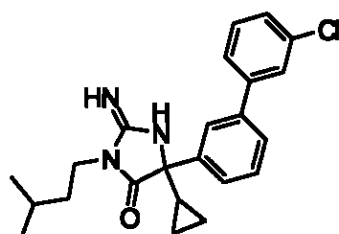
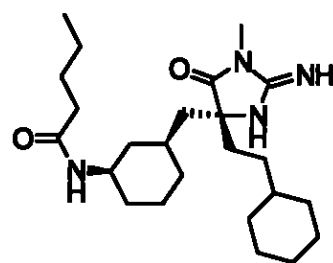
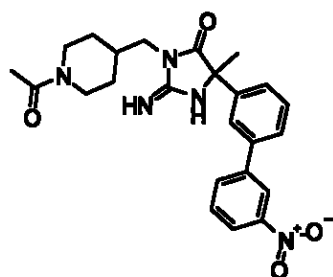
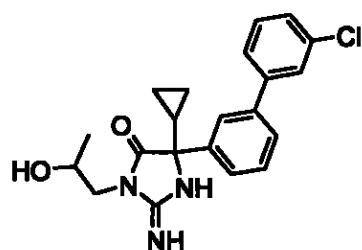


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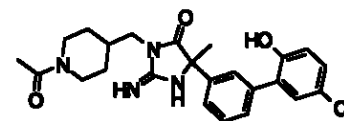
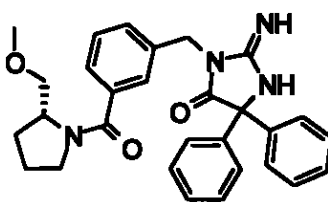
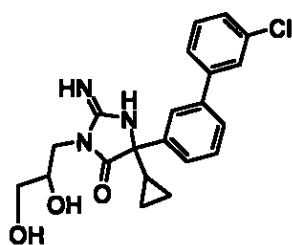
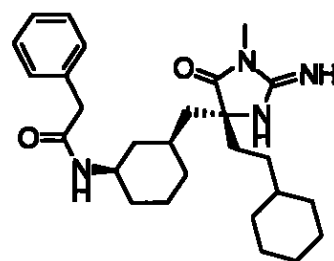
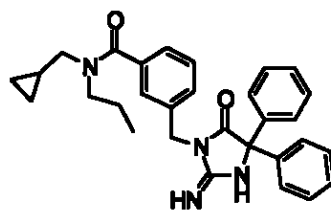
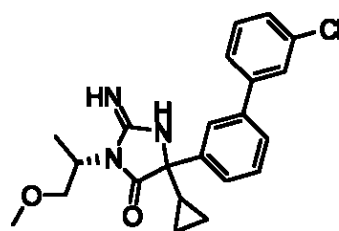
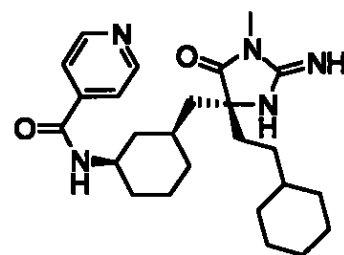
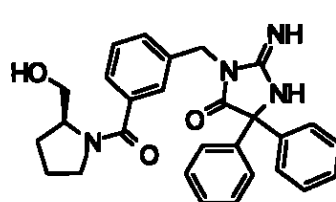
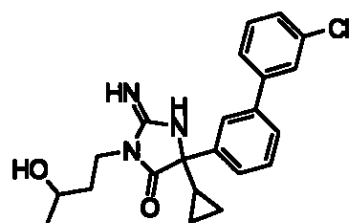
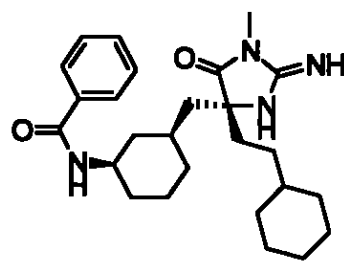
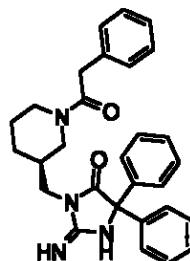
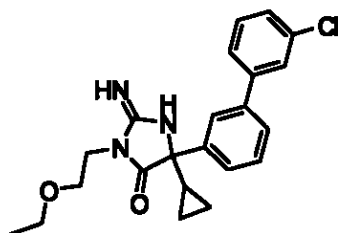
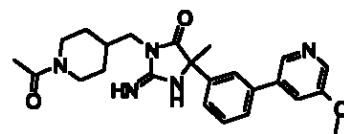
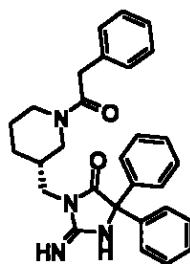
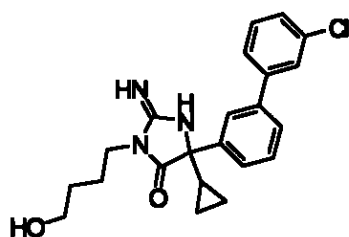




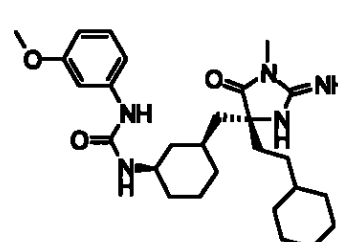
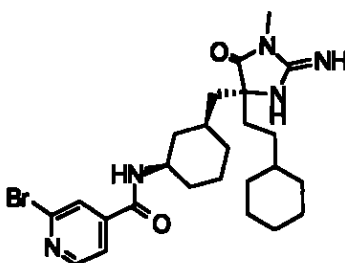
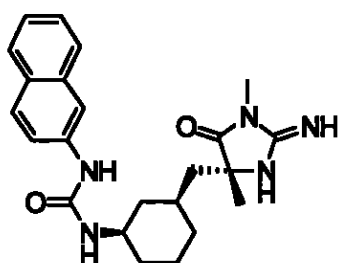
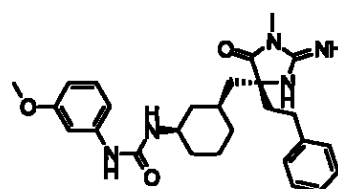
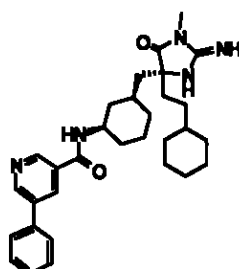
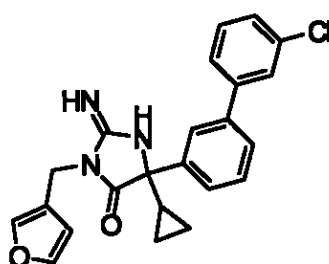
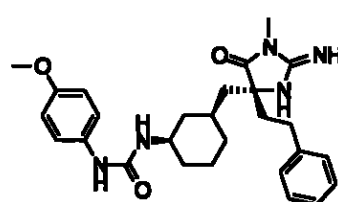
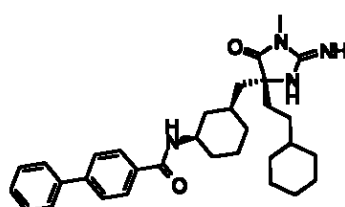
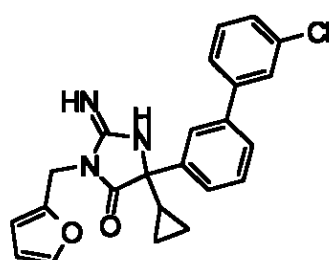
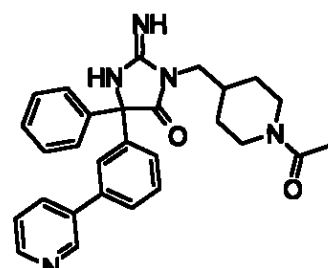
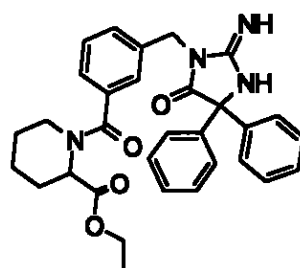
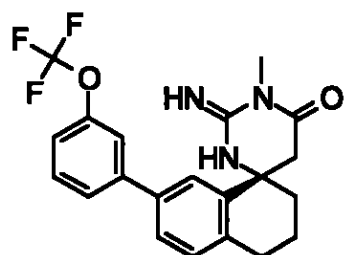
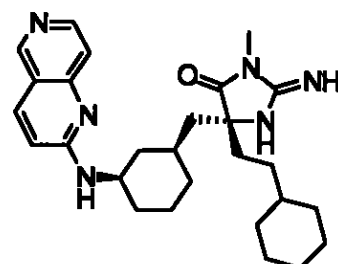
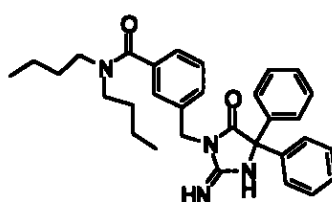
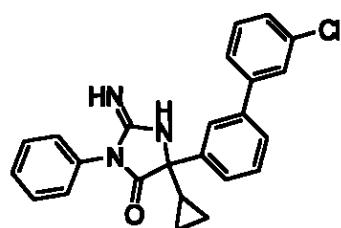


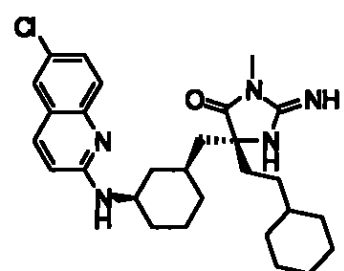
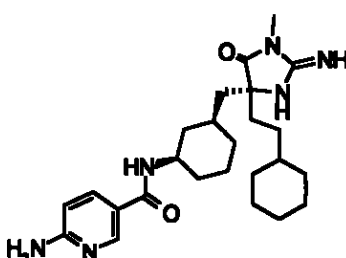
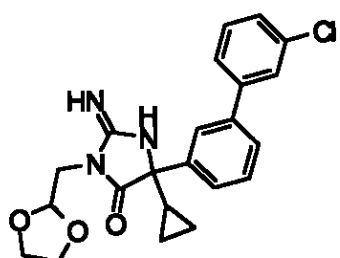
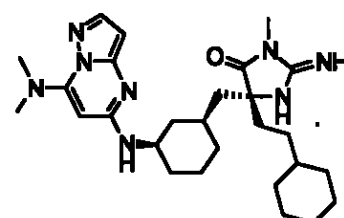
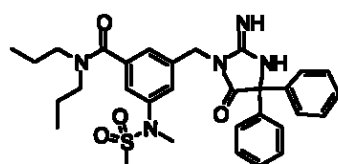
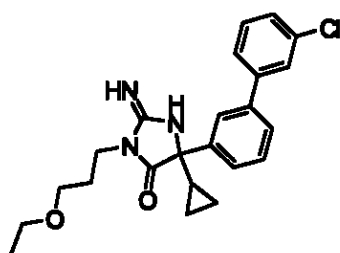
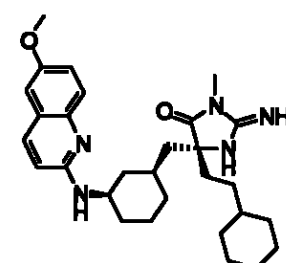
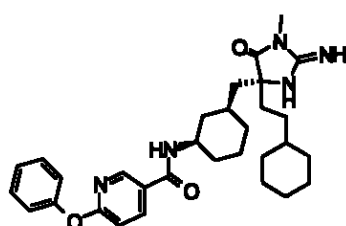
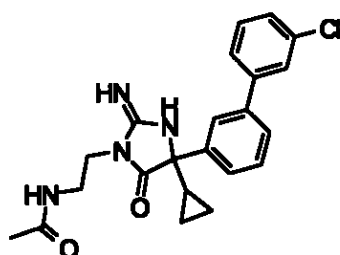
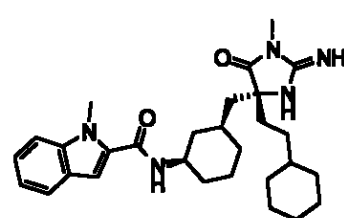
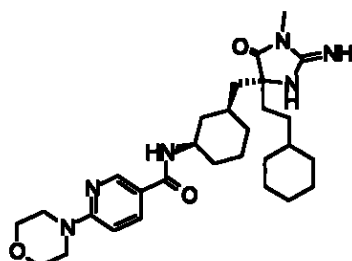
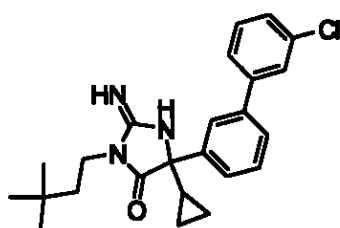
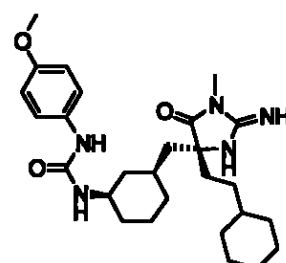
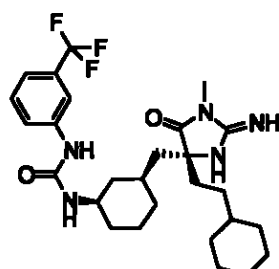
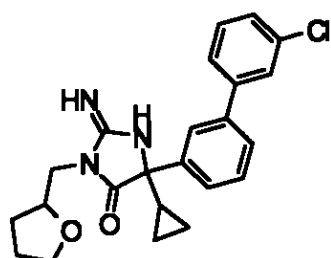


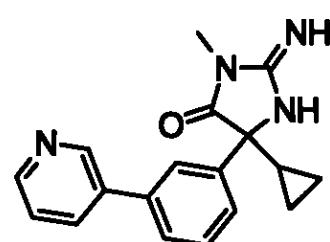
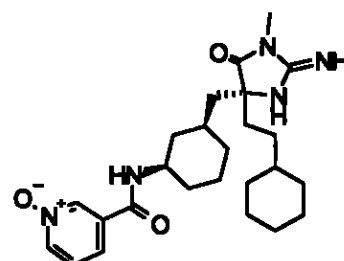
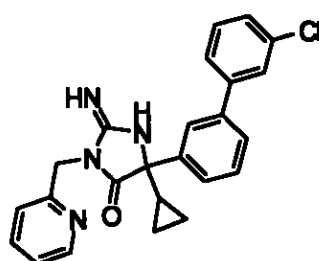
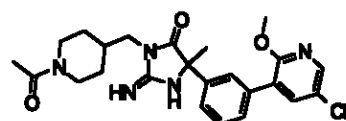
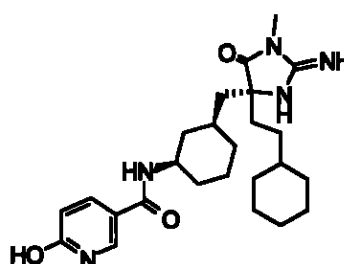
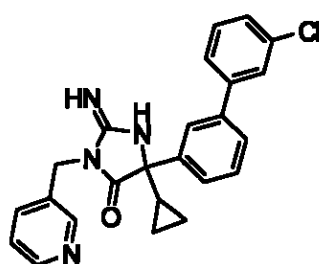
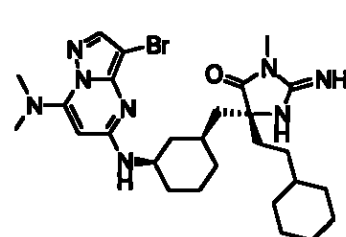
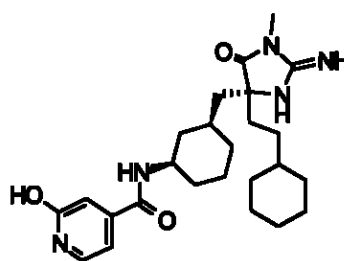
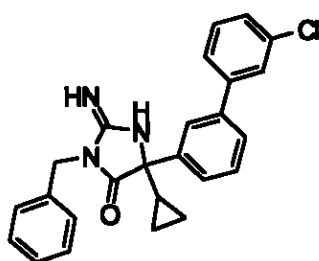
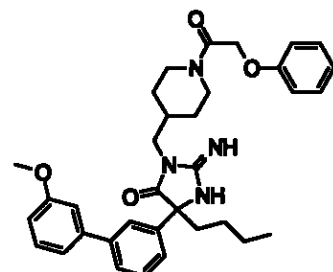
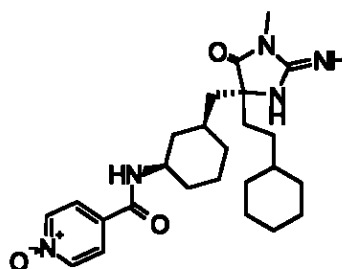
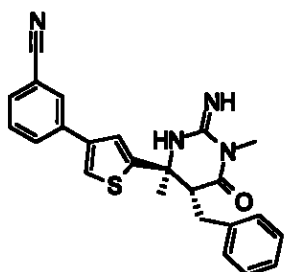
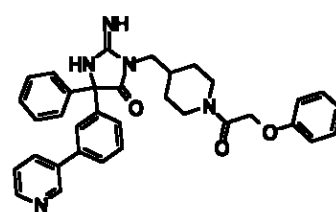
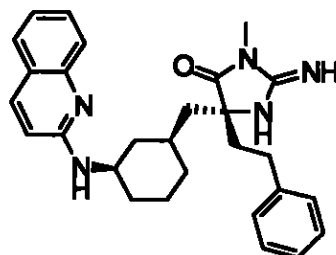
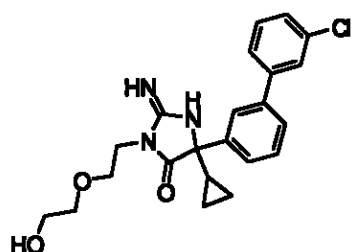
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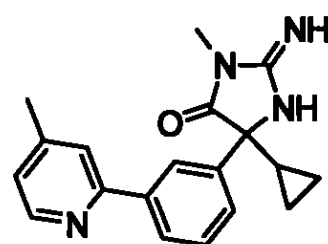
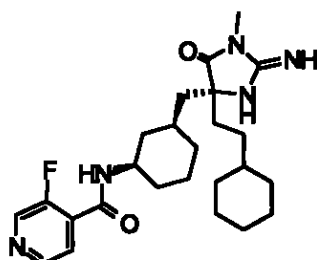
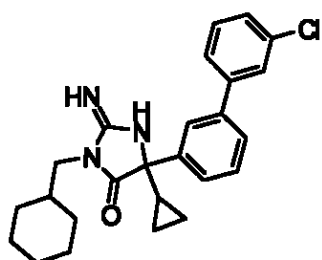
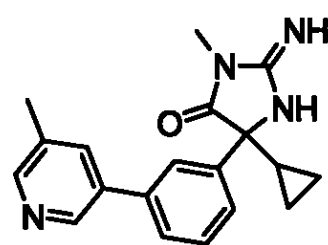
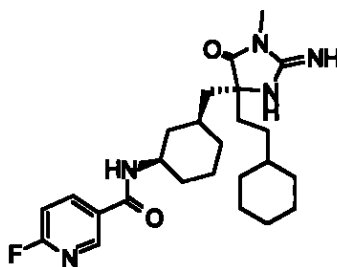
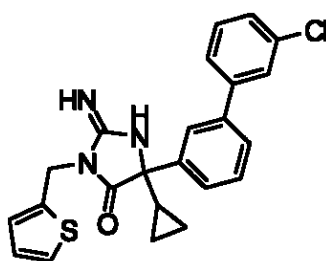
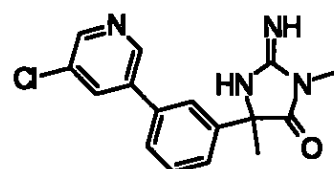
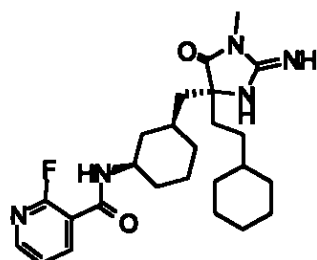
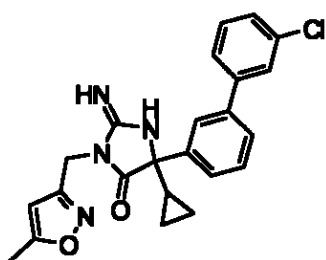
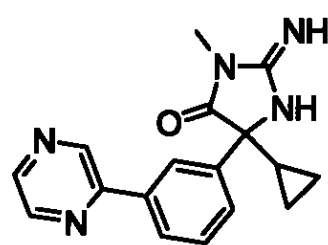
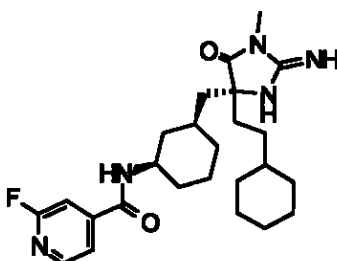
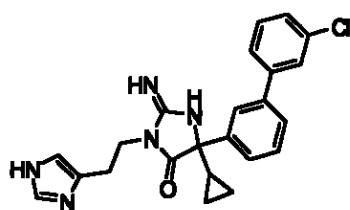
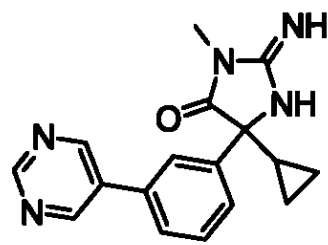
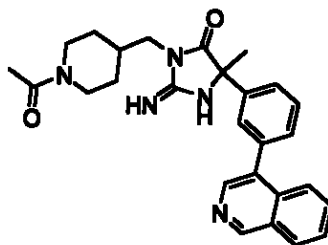
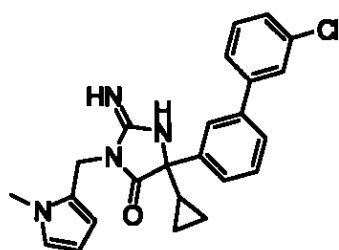


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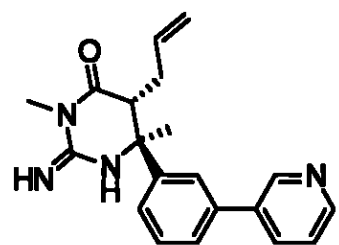
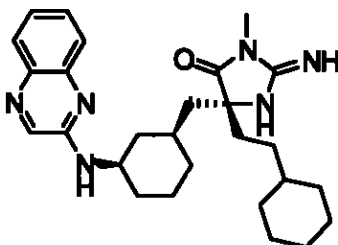
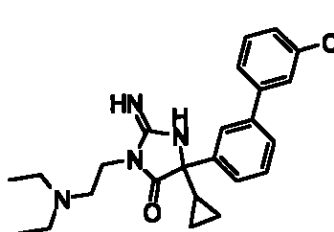
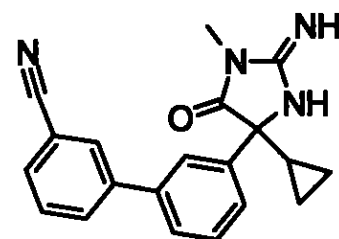
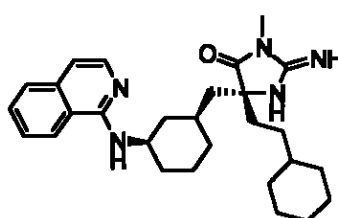
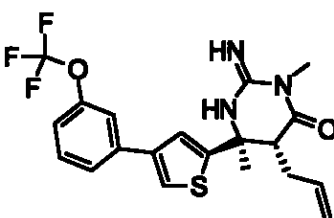
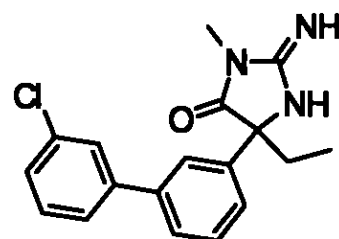
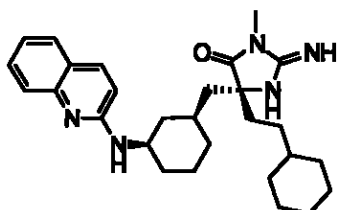
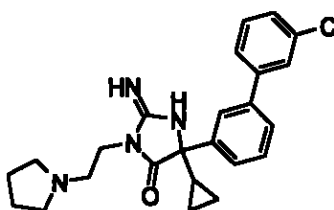
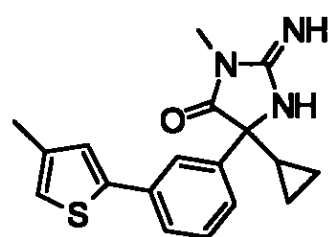
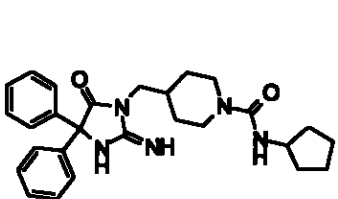
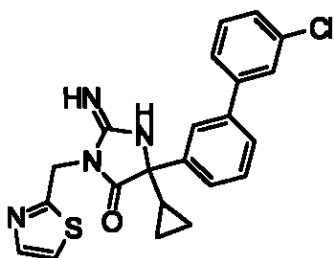
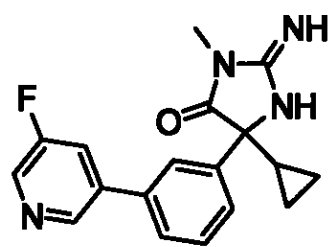
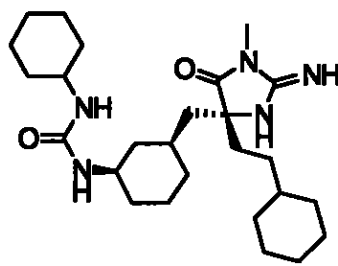
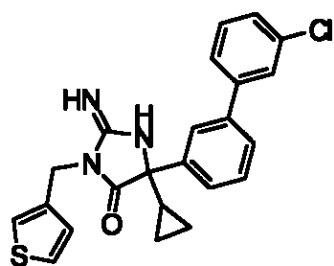




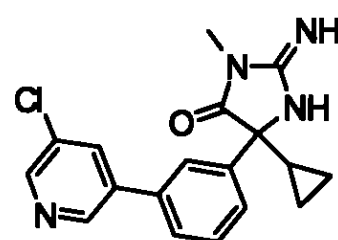
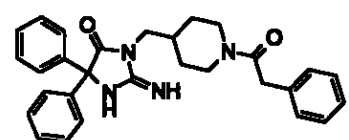
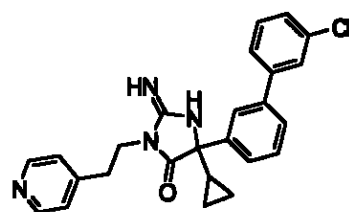
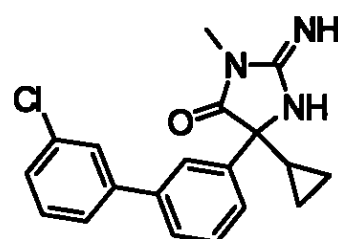
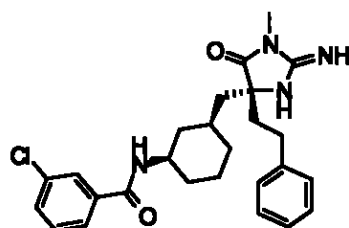
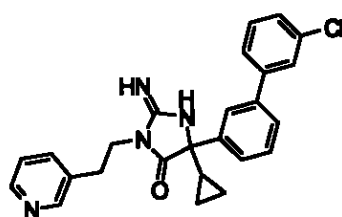
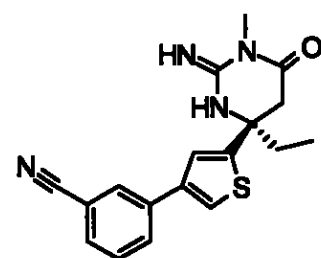
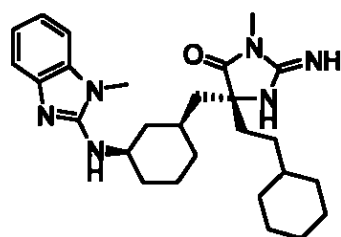
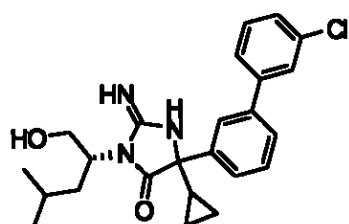
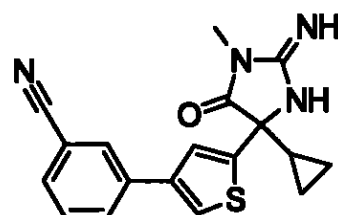
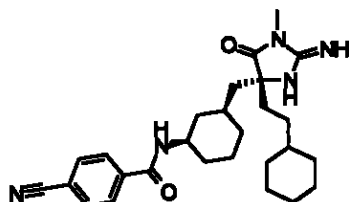
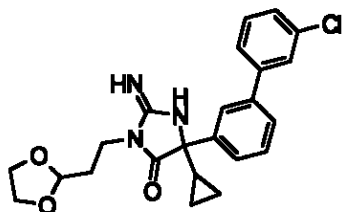
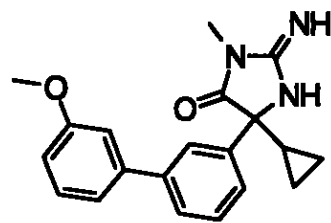
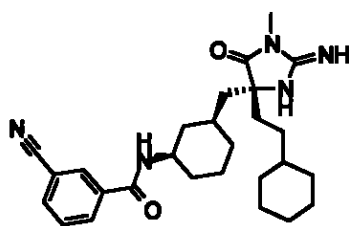
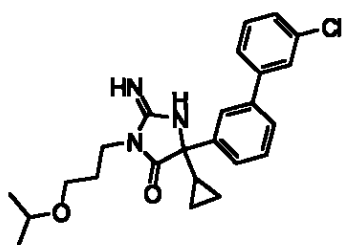


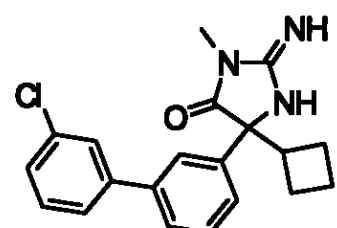
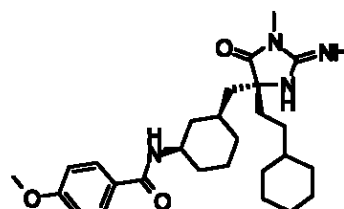
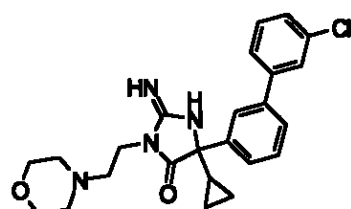
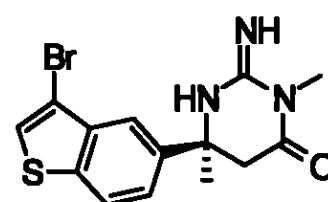
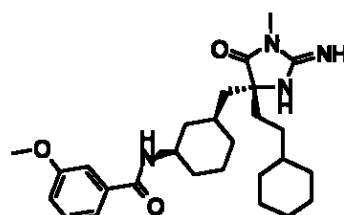
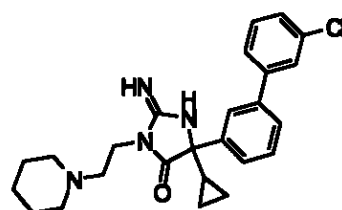
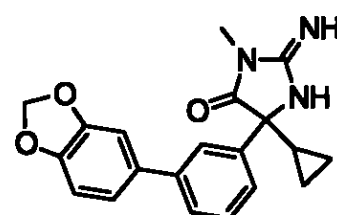
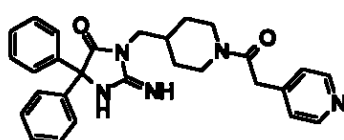
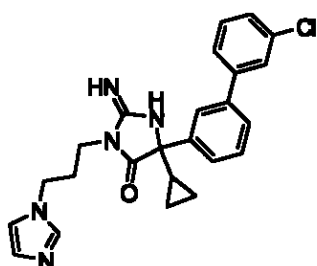
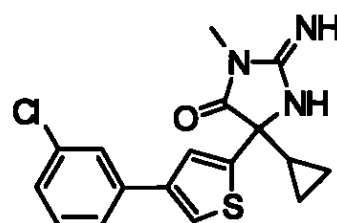
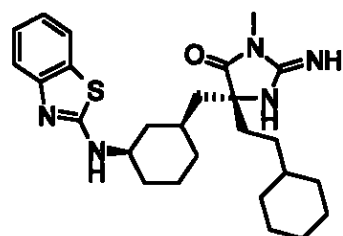
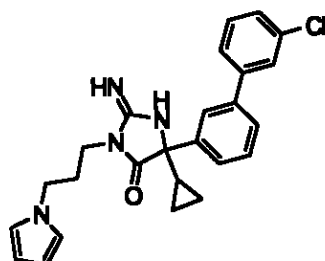
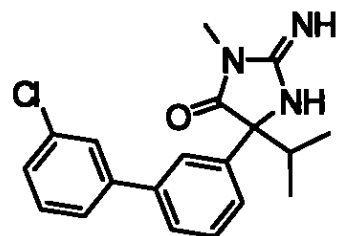
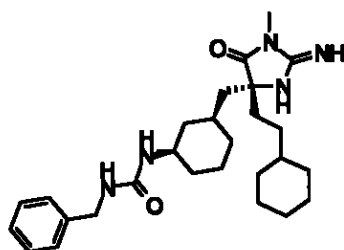
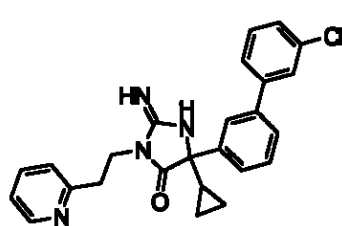


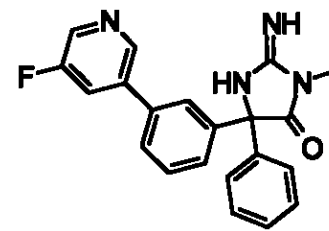
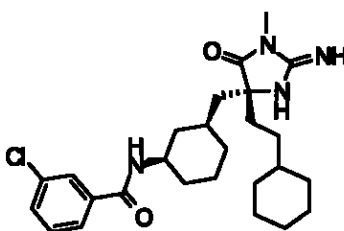
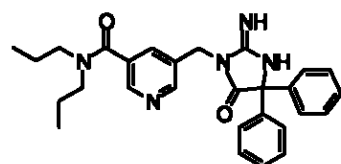
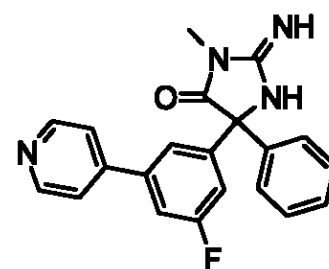
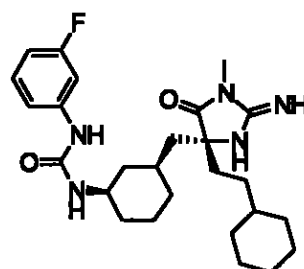
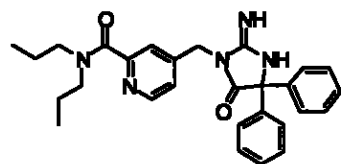
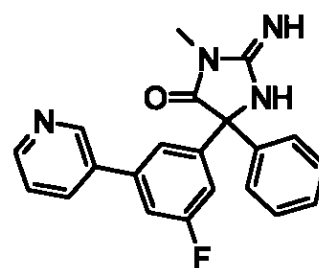
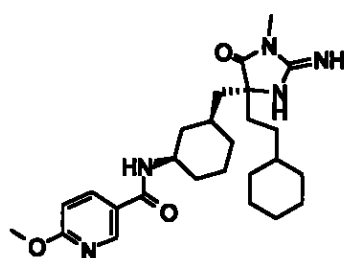
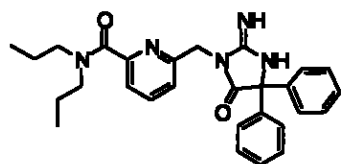
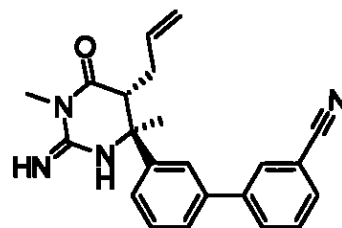
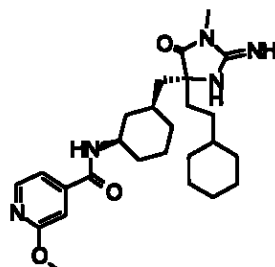
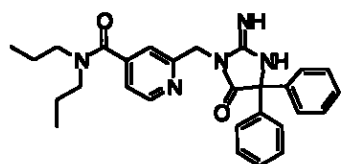
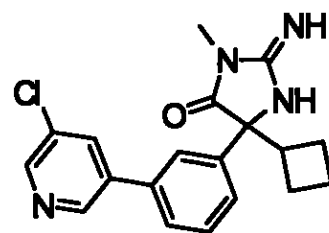
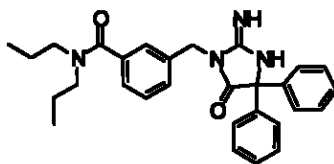
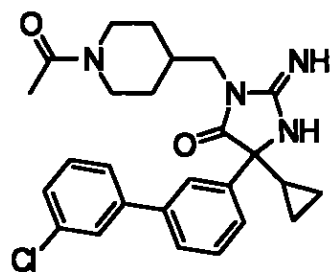
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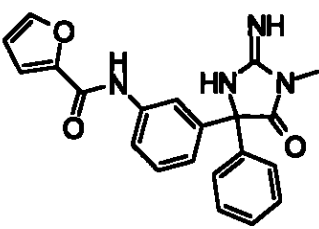
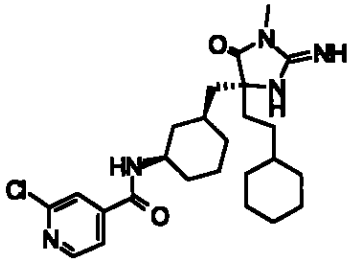
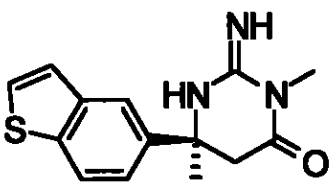
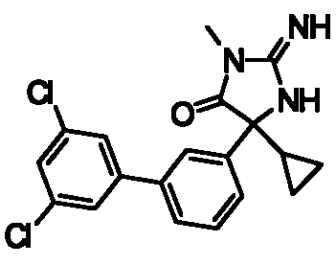
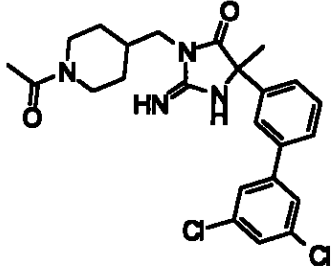
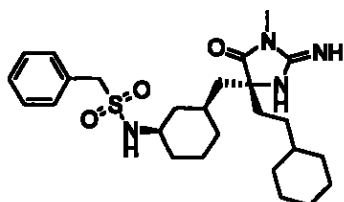
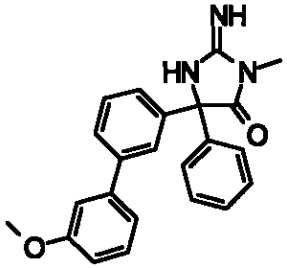
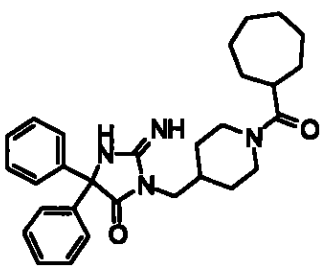
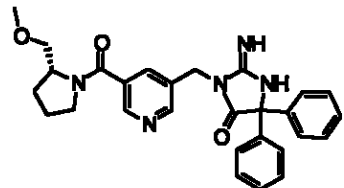
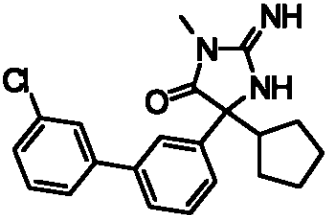
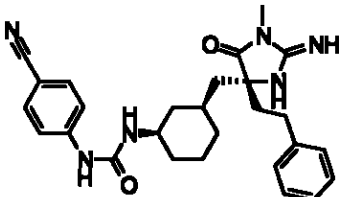
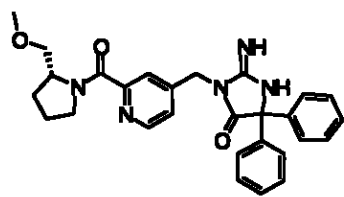
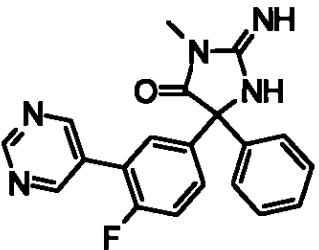
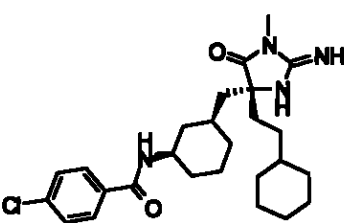
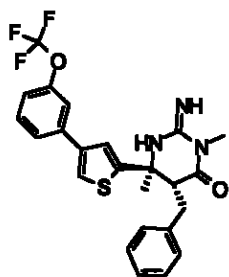
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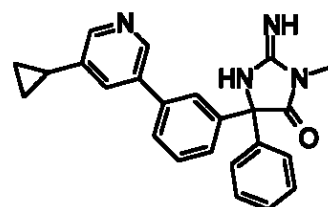
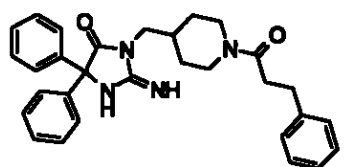
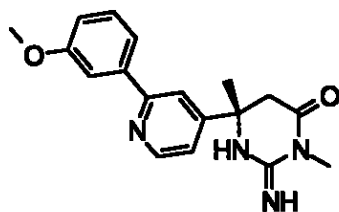
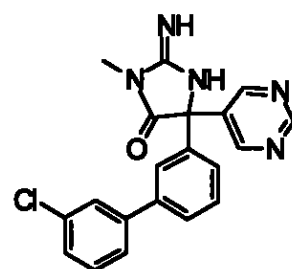
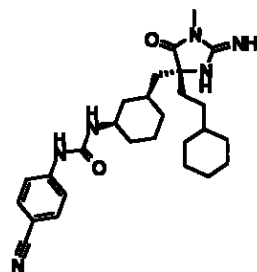
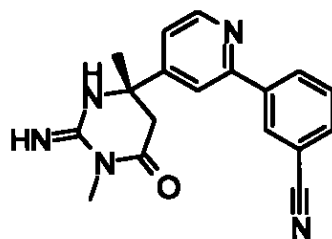
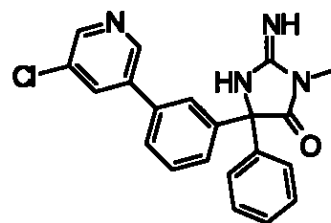
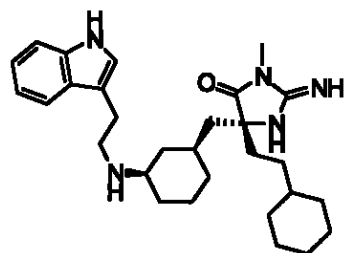
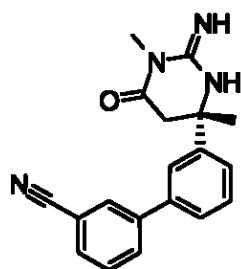
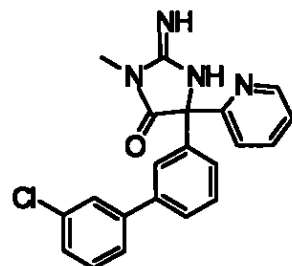
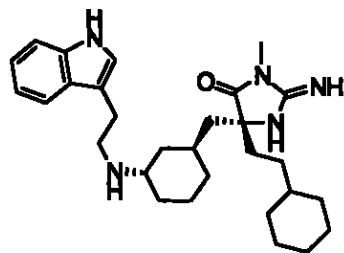
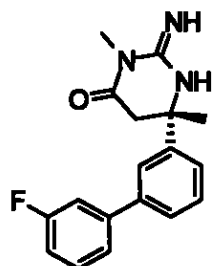
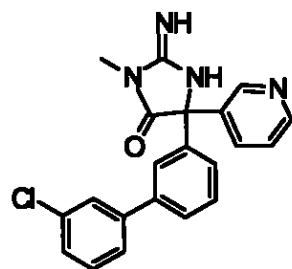
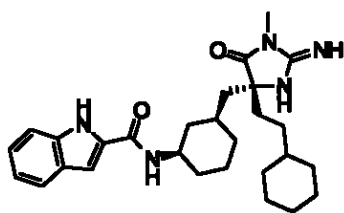
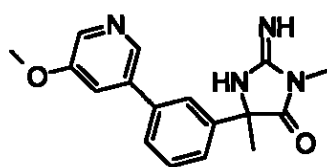




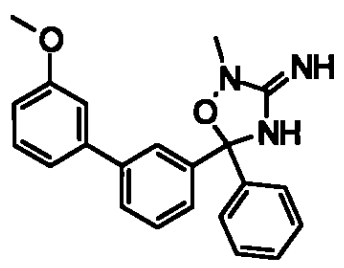
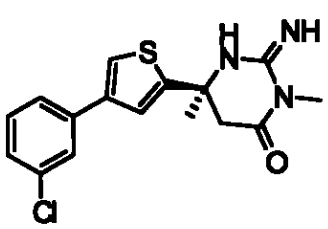
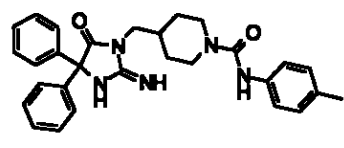
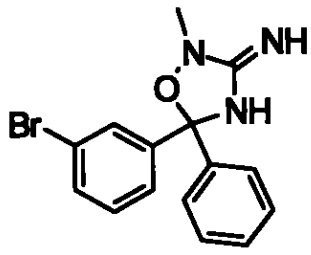
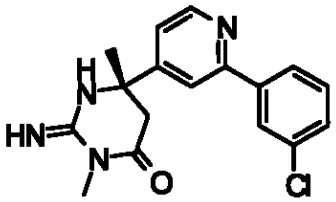
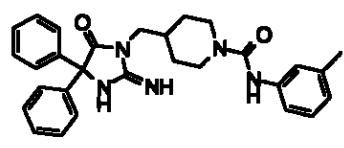
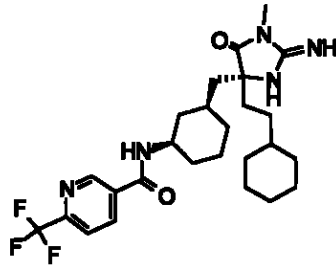
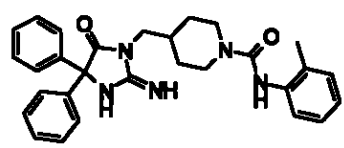
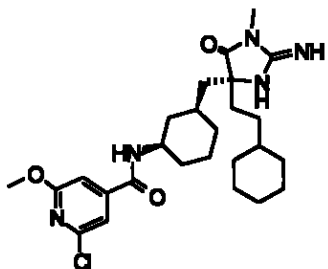
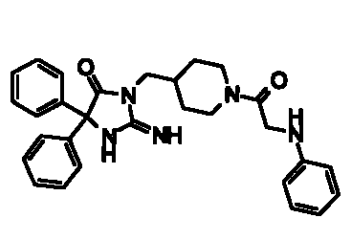
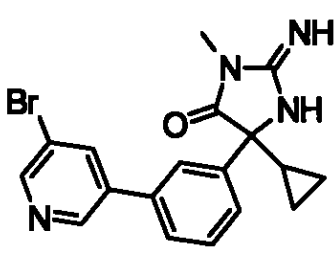
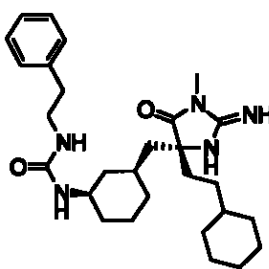
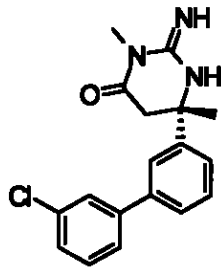
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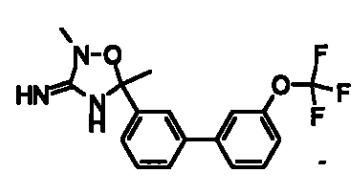
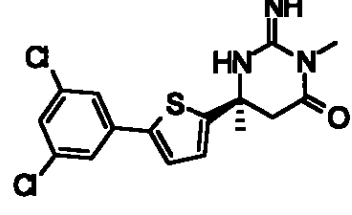
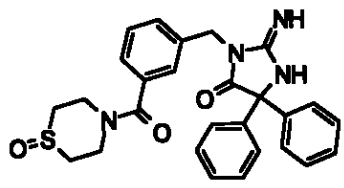
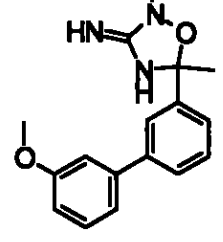
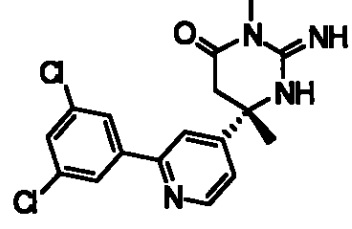
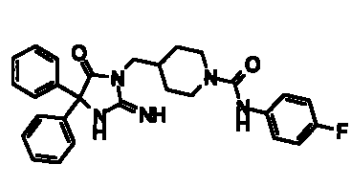
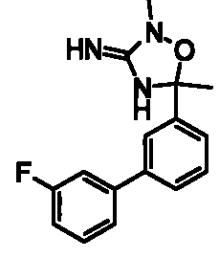
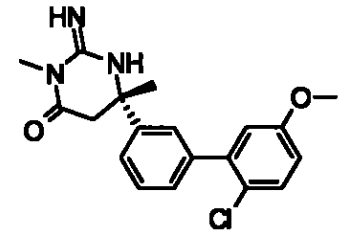
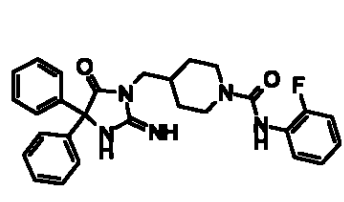
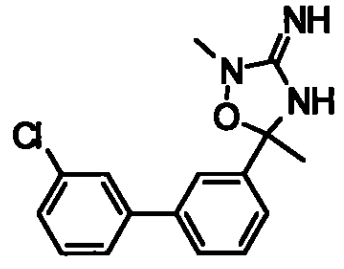
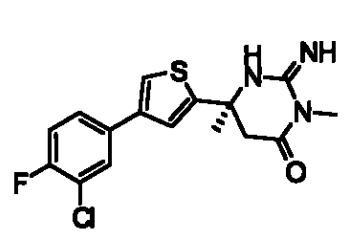
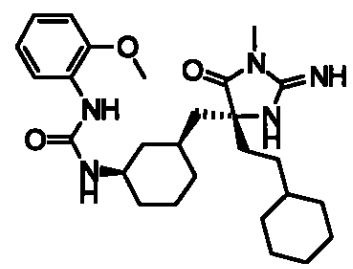
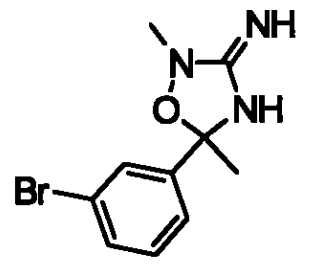
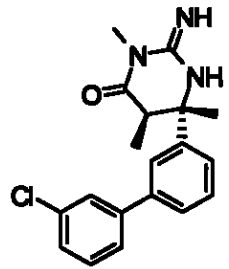
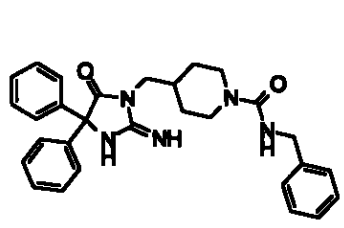
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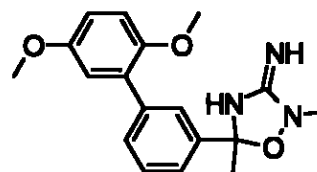
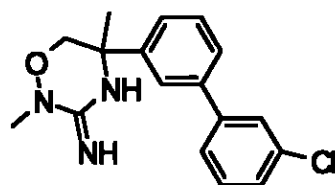
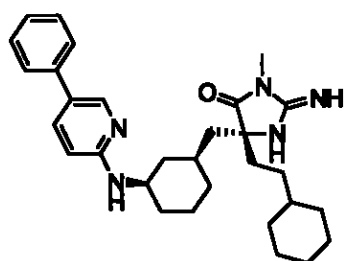
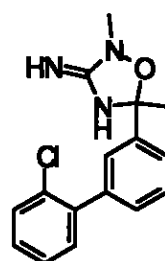
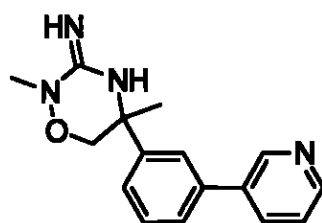
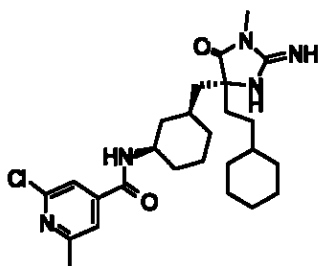
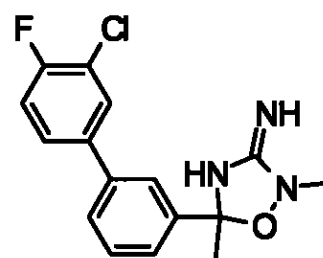
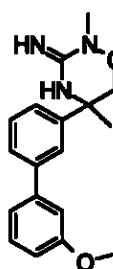
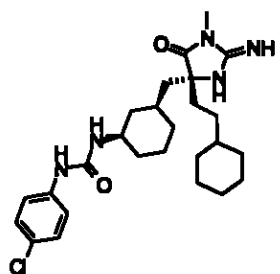
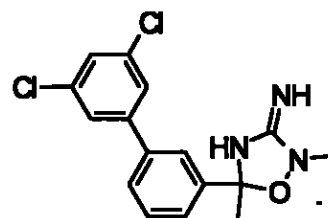
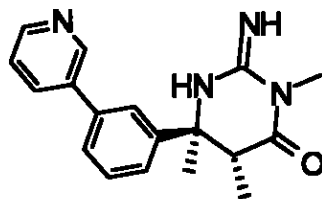
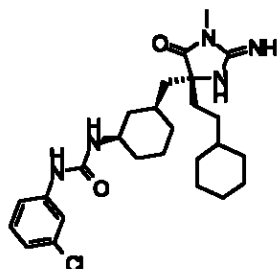
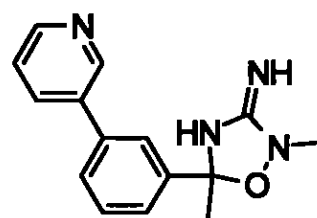
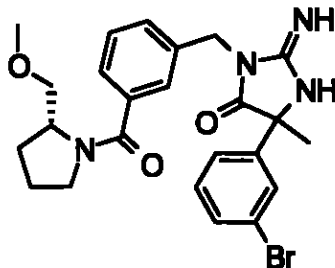
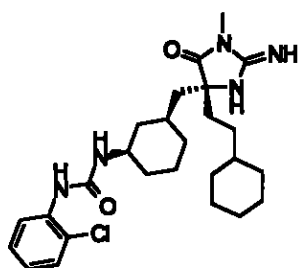
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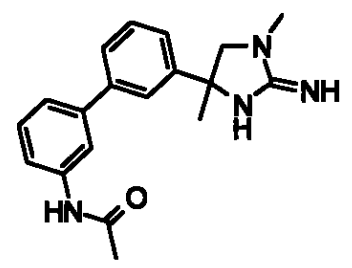
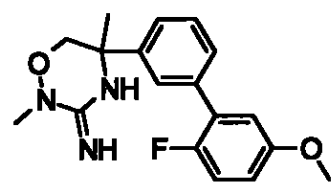
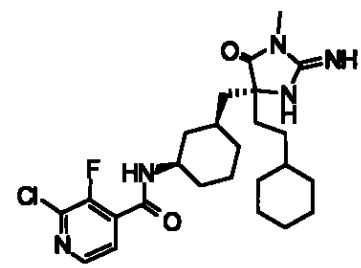
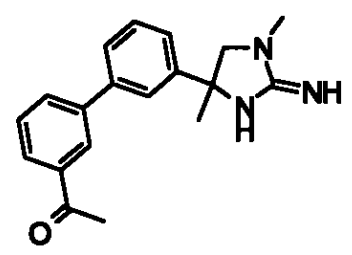
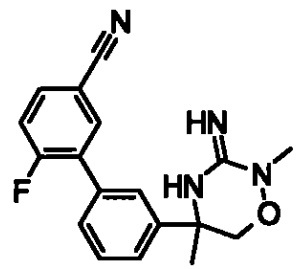
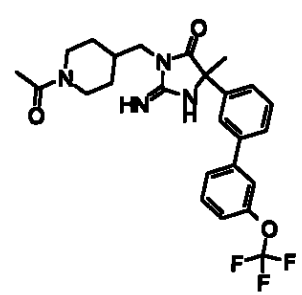
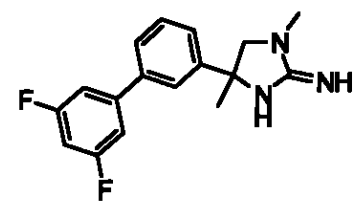
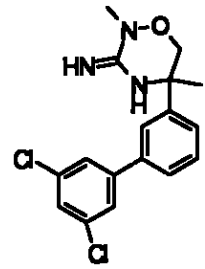
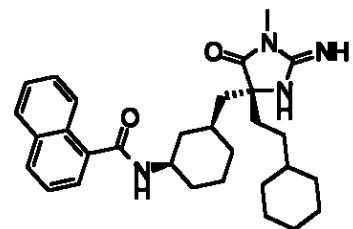
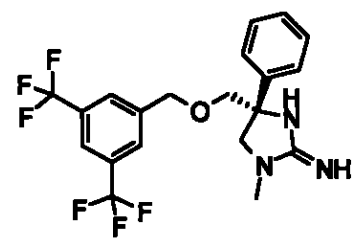
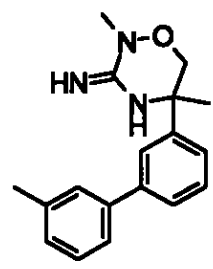
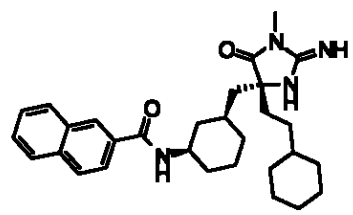
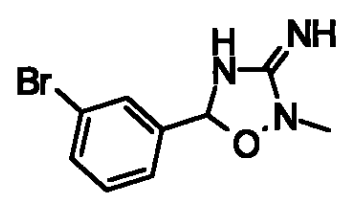
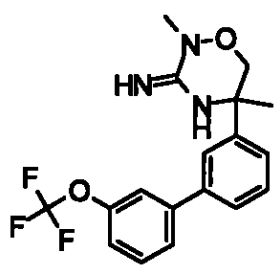
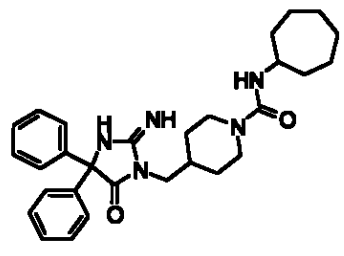
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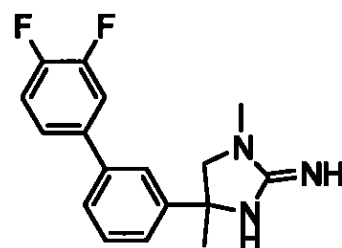
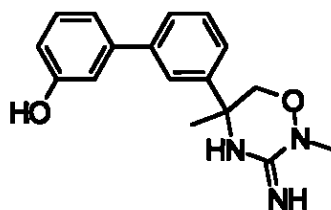
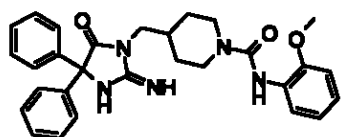
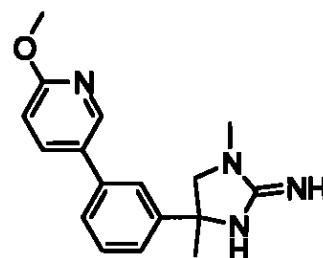
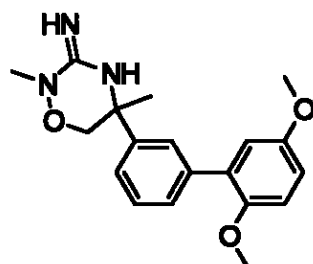
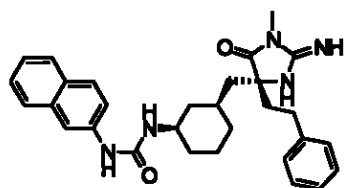
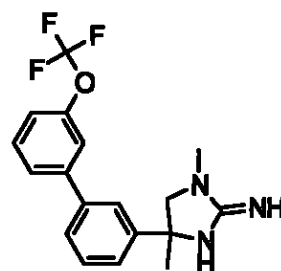
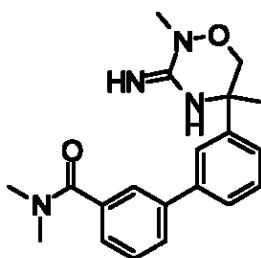
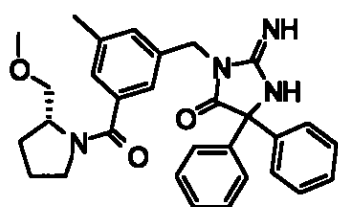
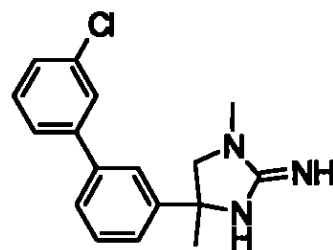
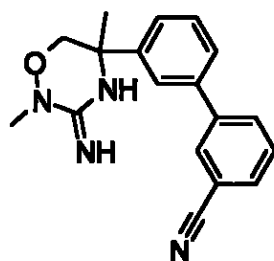
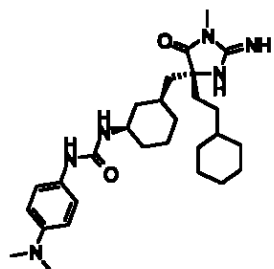
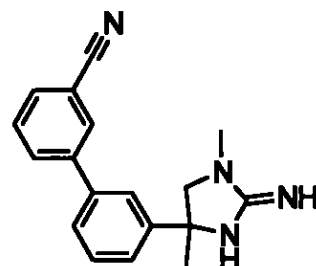
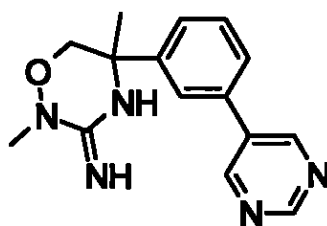
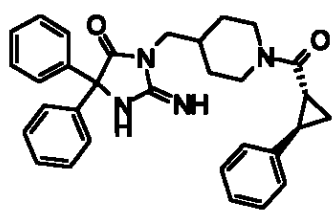


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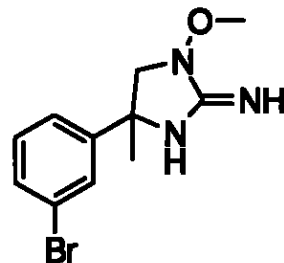
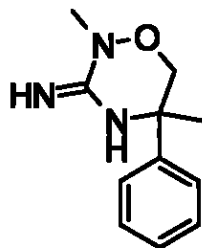
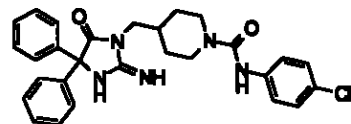
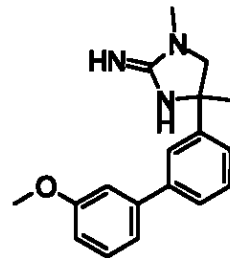
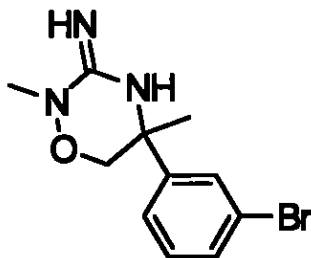
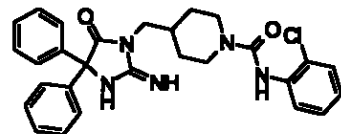
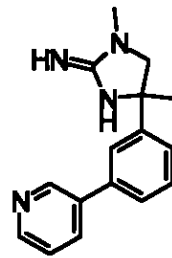
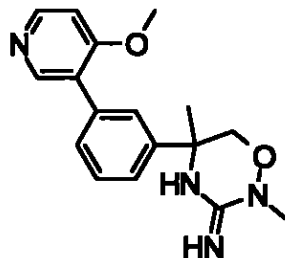
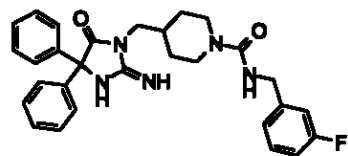
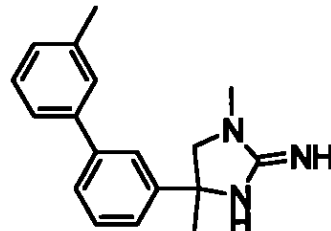
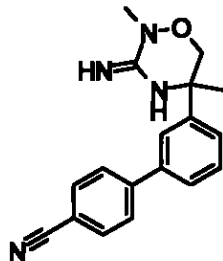
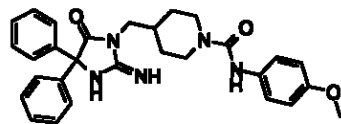
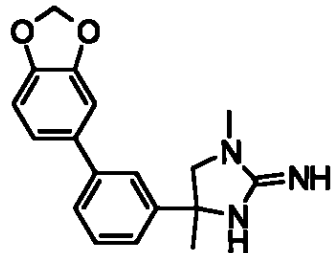
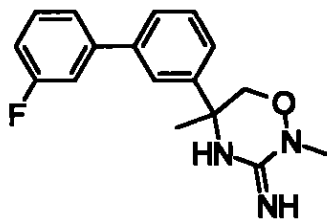
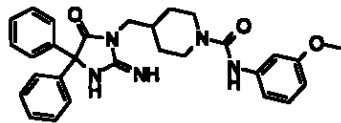


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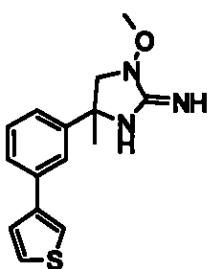
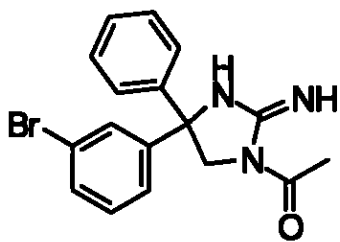
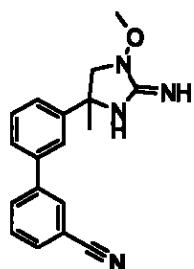
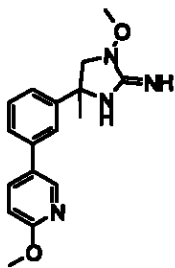
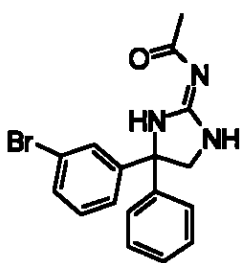
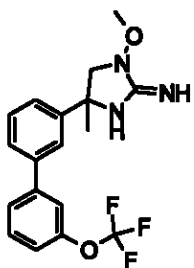
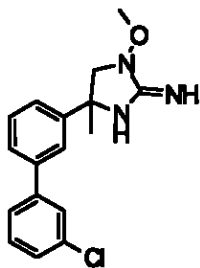
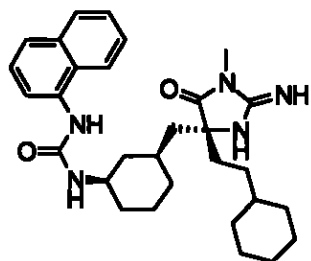
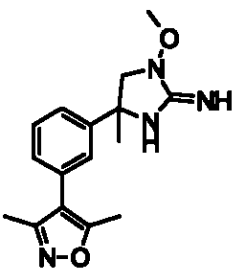
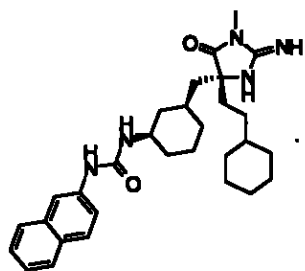




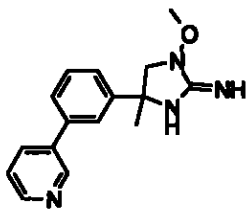
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2. Una composición farmacéutica que comprende una cantidad eficaz de un compuesto de la reivindicación 1 y un vehículo eficaz para uso farmacéutico.
3. Un método para inhibir aspartil proteasa que comprende la administración a un paciente que necesita tal tratamiento, de una cantidad eficaz de un compuesto de la reivindicación 1.
4. Un método para tratar enfermedades cardiovasculares, enfermedades cognitivas y neurodegenerativas, y los métodos para inhibir el Virus de Inmunodeficiencia Humana, plasmepsina, catépsina D y enzimas protozoales que comprende la administración a un paciente que necesita de tal tratamiento, una cantidad eficaz de un compuesto de la reivindicación 1.
5. El método de la reivindicación 4 en el cual se trata una enfermedad cognitiva o neurodegenerativa.
6. El método de la reivindicación 5 en el cual se trata la enfermedad de Alzheimer.
7. Una composición farmacéutica que comprende una cantidad eficaz de un compuesto de la reivindicación 1, y una cantidad eficaz de un inhibidor de colinesterasa o un agonista m_1 muscarínico o un antagonista m_2 en un vehículo eficaz para uso farmacéutico.
8. Un método para tratar una enfermedad cognitiva o neurodegenerativa que comprende la administración a un paciente que necesita tal tratamiento de una cantidad eficaz de un compuesto de la reivindicación 1 en combinación con una cantidad eficaz de un inhibidor de colinesterasa.
9. El método de la reivindicación 8 en el cual se trata la enfermedad de Alzheimer.

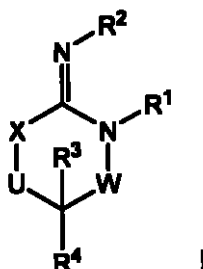
10. Un método para tratar una enfermedad cognitiva o neurodegenerativa que comprende la administración a un paciente que necesita tal tratamiento de una cantidad eficaz de un compuesto de la reivindicación 1 en combinación con una cantidad eficaz de un inhibidor de gamma secretasa, un inhibidor de HMG-CoA reductasa o un agente anti-inflamatorio no-esteroidal.
11. El método de la reivindicación 10 en el cual se trata la enfermedad de Alzheimer.
12. El método de la reivindicación 10 en el cual dicho inhibidor de HMG-CoA reductasa es atorvastatina, lovastatina, simvastatina, pravastatina, fluvastatina o rosuvastatina.
13. El método de la reivindicación 10 en el cual dicho agente anti-inflamatorio no-esteroidal es ibuprofeno, relafeno o naproxeno.
14. Una composición farmacéutica que comprende una cantidad eficaz de un compuesto de la reivindicación 1, y una cantidad eficaz de un inhibidor de gamma secretasa; un inhibidor de HMG-CoA reductasa o un agente anti-inflamatorio no-esteroidal.
15. Un método para tratar una enfermedad cognitiva o neurodegenerativa que comprende la administración a un paciente que necesita tal tratamiento, de una cantidad eficaz de al menos un compuesto de la reivindicación 1 en combinación con una cantidad eficaz de uno o más compuestos seleccionados del grupo integrado por un inhibidor de colinesterasa, agonista m_1 muscarínico o antagonista m_2 , inhibidor de gamma secretasa, un inhibidor de HMG-CoA reductasa y agente anti-inflamatorio no-esteroidal.

p.: SHERING CORPORATION *

PHARMACOEPIA DRUG DISCOVERY, INC.

RESUMEN

Se revelan compuestos de fórmula I



o su estereoisómero, tautómero, o sal o solvato aceptable para uso farmacéutico, en la cual

W es un enlace, -C(=S)-, -S(O)-, -S(O)₂-, -C(=O)-, -O-, -C(R⁶)(R⁷)-, -N(R⁵)- o -C(=N(R⁵))-;

X es -O-, -N(R⁵)- o -C(R⁶)(R⁷)-; siempre que cuando X sea -O-, U no sea -O-, -S(O)-, -S(O)₂-, -C(=O)- o -C(=NR⁵)-;

U es un enlace, -S(O)-, -S(O)₂-, -C(O)-, -O-, -P(O)(OR¹⁵)-, -C(=NR⁵)-, -(C(R⁶)(R⁷))_b- o -N(R⁵)-; donde b es 1 o 2; siempre que cuando W sea -S(O)-, -S(O)₂-, -O-, o -N(R⁵)-, U no sea -S(O)-, -S(O)₂-, -O-, o -N(R⁵)-; siempre que cuando X es -N(R⁵)- y W es -S(O)-, -S(O)₂-, -O-, o -N(R⁵)-, entonces U no es un enlace;

y R¹, R², R³, R⁴, R⁵, R⁶, y R⁷ son según se definieron en la memoria descriptiva;

y composiciones farmacéuticas que comprenden los compuestos de fórmula I.

Además se revela el método para inhibir la aspartil proteasa, y en particular, los métodos para tratar enfermedades cardiovasculares, enfermedades cognitivas y neurodegenerativas, y los métodos para inhibir el Virus de Inmunodeficiencia Humana, plasmepsina, cathepsina D y enzimas protozoales.

Además se revelan métodos para tratar enfermedades cognitivas y neurodegenerativas que utilizan los compuestos de fórmula I en combinación con un inhibidor de colinesterasa o un agonista m₁ muscarínico o antagonista m₂.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

LEE, William, Y.
SCHERING-PLOUGH CORPORATION
Patent Department, K-8-1 1990
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530
ETATS-UNIS D'AMERIQUEDate of mailing (day/month/year)
29 May 2007 (29.05.2007)Applicant's or agent's file reference
CN06136-01International application No.
PCT/US2005/020448

IMPORTANT NOTIFICATION

International filing date (day/month/year)
09 June 2005 (09.06.2005)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

PHARMACOEPIA DRUG DISCOVERY, INC.
3000 Eastpark Boulevard
Cranbury, NJ 08512
United States of America

State of Nationality

US

State of Residence

US

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

PHARMACOEPIA, INC.
3000 Eastpark Boulevard
Cranbury, NJ 08512
United States of America

State of Nationality

US

State of Residence

US

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☒ the designated Offices concerned
☐ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Taylor Sean

Facsimile No. +41 22 338 82 70

Facsimile No. +41 22 338 90 90

Telephone No. +41 22 338 74 07

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-050189- -00000-0000

Fecha: 2007-06-12 16:49:14 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYI Evo: 378 FASENACIONAL
Act. 411 PRESENTACION Folios: 827



Industria y Comercio
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

12 JUN. 2007

Fecha

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@slc.gov.co
www.slc.gov.co
Bogotá, D.C., Colombia

821

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RAISBECK J. IAN
Apoderado(a) y/o Representante de
SCHERING CORPORATION
PHARMACOPEDIA, INC.

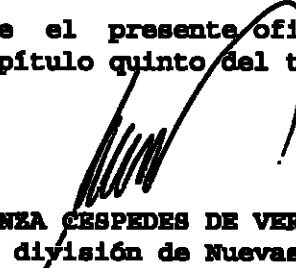
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	Solicitud internacional	PCT/US2005/020446
	Fecha inicio fase nacional	13/07/2007
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	8911

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486. Cuando se trate de documentos otorgados en el extranjero, deben legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 27 JUL 2007
adpa11