# Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

# PATENTE DE INVENCIÓN

21 **EXPEDIENTE No.** 03-108298

54 **TÍTULO** "Inhibidores de proteasa VIH, composiciones que contienen los mismos, sus usos farmacéuticos y materiales para su síntesis"

51 **CLASIFICACIÓN INTERNACIONAL** A61K 31/425

71 **SOLICITANTE** Agouron Pharmaceuticals, Inc.

**DOMICILIO** La Jolla, CA 92037, Estados Unidos de Amer.

74 **APODERADO** Ramiro Castro Duque

22 **BOGOTÁ, D. C.,**

Qf

# PETITORIO

AS 92 859

Industria y Comercio
SUPERINTENDENCIA

03 108298 00

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03108298 00000000 Folios: 298
Fecha (AMD): 2003-12-10 17:01:16
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

## FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

## PCT

## ENTRADA EN FASE NACIONAL

**1 SOLICITUD DE:**

☒ Patente de Invención ☐ Patente de Modelo de Utilidad

☐ Capítulo I ☒ Capítulo II

| | | |
|---|---|---|
| **2 SOLICITANTE (71)** | Nombre **AGOURON PHARMACEUTICALS, INC.**<br>Dirección 10350 North Torrey Pines Road, La Jolla, CA 92037, Estados Unidos de Américа<br>Nacionalidad o Domicilio Estados Unidos<br>Lugar de Constitución Estados Unidos<br>Teléfono: Fax:<br>E-mail | **IDENTIFICACION**<br>CC ☐ NIT ☐<br>CE ☐ Otro ☐<br>Cual_____<br>Número _____ |
| **3 REPRESENTANTE O APODERADO** | Nombre RAMIRO CASTRO DUQUE<br>Dirección Cra 7 Ne 16-56 Piso 9<br>Teléfono 380-2200 Fax 380-2700<br>E-mail | **IDENTIFICACION**<br>CC ☒ NIT ☐<br>CE ☐ Otro ☐<br>Cual_____<br>Número 170 322 TP 1003 |
| **4 INVENTOR (ES) (72)** | Nombre EN HOJA ANEXA<br>Dirección<br>Nacionalidad o Domicilio: Estados Unidos de Américа (Respectivamente) | |

**5 PCT (86)**
Solicitud Internacional No PCT/US02/18548 Fecha 11-06-2002
Publicación Internacional No. WO 02/100845 A1 Fecha 19-12-2002

**Título (54):** INHIBIDORES DE PROTEASA VIH, COMPOSICIONES QUE CONTIENEN LOS MISMOS, SUS USOS FARMACEUTICOS Y MATERIALES PARA SU SÍNTESIS

**7 Clasificación Internacional (51)** A61K31/415

| **8 Prioridad** SI ☒ NO ☐ | (33) País de Origen | (32) Fecha | (31) Número de Solicitud |
|---|---|---|---|
| | US | 11-06-2001 | 60/297,460 |
| | US | 12-06-2001 | 60/297,729 |

**9 Comprobante de pago No.** 03-61471 **Fecha** 09-12-2003

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

2020-F06 (01-11-15)

X
2

**10 ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud $400.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Fotocopia Autenticada
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar 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 12x12
- [ ] 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.
- [x] Otros Tarjeta de propietarios.

**11 FIGURA CARACTERÍSTICA.**

**12 Solicito la concesión de la patente.**

**NOMBRE: RAMIRO CASTRO DUQUE**

**FIRMA**

C.C 170.322 de Bogotá T.P. 1003 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página

**Drigard & Castro**
Abogados

Apartado 3692
Cra 7 16-56
Bogotà - Colombia S A
Tel Conm 3802200
Tel./Fax (57 1) 2827976
(57 1) 3802700
E Mail bncas@brigardycastro com co

3 3

**AS: 92.859**

## LISTA DE INVENTORES

STACIE S CANON-KOCH
5940 La Jolla, Messa Drive, La Jolla, CA 92137
Estados Unidos de América

THERESE N ALEXANDER
6557 Thornwood Street,
San Diego, CA 92111
Estados Unidos de América

MARK BARVIAN
1225 Olivia Avenue,
Ann Arbor, MI 48104
Estados Unidos de América

GARY BOLTON
4800 Hillway Ct ,
Ann Arbor, MI 48105
Estados Unidos de América

FREDRICK E BOYER
482 Pleasant Ridge Drive,
Canton Township, MI 48188
Estados Unidos de América

BENJAMIN J BURKE
5761 Campanile Way,
San Diego, CA 92115
Estados Unidos de América

TOD HOLLER
2381 Placid Way,
Ann Arbor, MI 48105
Estados Unidos de América

TANYA M. JEWELL
12604 Torrey Bluff
Drive #400, San Diego, CA 92130
Estados Unidos de América

VARA PRASAD JOSYULA
3129 Fawn Meadow Court,
Ann Arbor, MI 48105
Estados Unidos de América

DAVID J KUCERA
14099 Recuerdo Drive,
Del Mar, CA 92014
Estados Unidos de América

JEFF MACHAK
12980 Easton Court,
Shelby Township, MI 48315
Estados Unidos de América

LENNERT J MITCHELL
520 N Woodlawn Avenue,
Chula Vista, CA 91910
Estados Unidos de América

SEAN T MURPHY
7716 Dover Drive, Ypsilanti,
MI 48197
Estados Unidos de América

SIEGFRIED H REICH
311 Glenmont Drive,
Solana Beach, CA 92075
Estados Unidos de América

DONALD J SKALITZKY
4269 Taos Drive,
San Diego, CA 92117
Estados Unidos de América

JOHN H TATLOCK
13153 Dressage Lane,
San Diego, CA 92130
Estados Unidos de América

MICHAEL D VARNEY
738 Barbara Avenue,
Solana Beach, CA 92075
Estados Unidos de América

SCOTT C VIRGIL
3950 Mahaila Avenue,
Apt S23, San Diego, CA 92122
Estados Unidos de América

STEPHEN T WORLAND
727 Hoska Drive,
Del Mar, CA 92014
Estados Unidos de América

MICHAEL MELNICK
3613 Weeburn Court,
Ann Arbor, MI 48108
Estados Unidos de América

**Brigard & Castro**
Abogados

Apartado 3692
Cra 7 16-56
Bogotá - Colombia S A
Tel Conm 3802200
Tel./Fax (57 1) 2827976
(57 1) 3802700

E Mail bncas@brigardycastro com co

4

92 859

MARIA A LINTON
11320 Red Cedar Drive,
San Diego, CA 92131
Estados Unidos de América

STEPHEN E WEBBER
3531 Milikan Avenue,
San Diego, CA 92122
Estados Unidos de América

5

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03108298 00000000 Folios: 298
Fecha (AMD): 2003-12-10 17:01:16
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 01.471
FECHA : NOVIEMBRE 7 DE 2003

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

| DEPOSITANTE | TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PGO | Vr. PAGO |
|---|---|---|---|---|---|---|
| BRIGARD & CASTRO LTDA | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 1374303 | 07/11/2003 | 15,620,000.00 |

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

| CANT. | RENTISTICO | CONCEPTO | TOTAL CONCEPTO |
|---|---|---|---|
| 1 | 50005-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE IN | 400,000.00 |
| | | TOTAL : $ | 400,000.00 |

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

92 359

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

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 December 2002 (19.12.2002)

PCT

(10) International Publication Number
WO 02/100845 A1

(51) International Patent Classification[7] C07D 277/06
A61K 31/425 C07D 417/12, 403/12, 207/16, A61P 31/18

(21) International Application Number: PCT/US02/18548

(22) International Filing Date: 11 June 2002 (11.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data
60/297,460 11 June 2001 (11.06.2001) US
60/297,729 12 June 2001 (12.06.2001) US

(71) Applicant (*for all designated States except US*) AGOURON PHARMACEUTICALS, INC. [US/US], 10350 North Torrey Pines Road, La Jolla, CA 92037 (US).

(72) Inventors: CANON-KOCH, Stacie, S., 5940 La Jolla Mesa Drive, La Jolla, CA 92137 (US). ALEXANDER, Therese, N., 6557 Thornwood Street, San Diego, CA 92111 (US) BARVIAN, Mark, 1225 Olivia Avenue, Ann Arbor, MI 48104 (US) BOLTON, Gary, 4800 Hillway Court, Ann Arbor, MI 48105 (US). BOYER, Fredrick, E., 482 Pleasant Ridge Drive Canton Township, MI 48188 (US) BURKE, Benjamin, J., 5761 Campanile Way, San Diego, CA 92115 (US) HOLLER, Ted, 2381 pLACID wAY, aNN aRBOR, mi 48105 (US) JEWELL, Tanya, M., 12604 Torrey Bluff Drive #400, San Diego, CA 92130 (US) PRASAD JOSYULA, Vara, 3129 Fawn Meadow Court, Ann Arbor, MI 48105 (US) KUCERA, David, J., 14099 Recuerdo Drive, Del Mar, CA 92014 (US). MACHAK, Jeff, 12980 Easton Court, Shelby Township, MI 48315 (US) MITCHELL, Lennert, J., 520 N Woodlawn Avenue, Chula Vista, CA 91910 (US) MURPHY, Sean, T., 7716 Dover Drive, Ypsilanti, MI 48197 (US) REICH, Siegfried, H 311 Glenmont Drive, Solana Beach, CA 92075 (US). SHALITZKY, Donald, J., 4269 Taos Drive, San Diego CA 92117 (US). TATLOCh., John, H., 13153 Dressage Lane, San Diego, CA 92130 (US) VARNEY, Michael, D., 738 Barbara Avenue, Solana Beach, CA 92075 (US). VIRGIL, Scott, C., 3950 Mahala Avenue, Apt. S23, San Diego, CA 92122 (US). WORLAND, Stephen, T., 727 Hoska Drive, Del Mar, CA 92014 (US). MELNICh., Michael, 3613 Weeburn Court, Ann Arbor, MI 48108 (US). LINTON, Maria A., 11320 Red Cedar Drive, San Diego, CA 92131 (US) WEBBER, Stephen E. 3531 Milikan Avenue, San Diego, CA 92122 (US)

(74) Agents: MANDRA, Raymond, R. et al., Fitzpatrick, Cella, Harper & Scinto, 30 Rockefeller Plaza, New York, NY 10112-3801 (US).

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

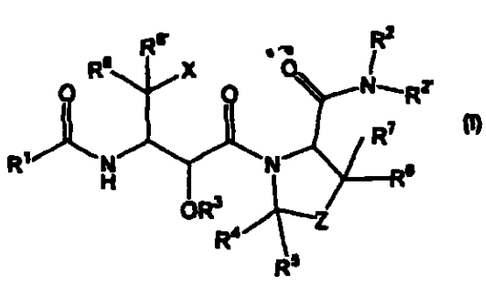
(84) Designated States (*regional*). ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published
— *with international search report*

(48) Date of publication of this corrected version
20 March 2003

*[Continued on next page]*

(54) Title: HIV PROTEASE INHIBITORS, COMPOSITIONS CONTAINING THE SAME, THEIR PHARMACEUTICAL USES AND MATERIALS FOR THEIR SYNTHESIS



(I)

(57) Abstract: Compounds of formula (I) where the formula variables are as defined herein, are disclosed that advantageously inhibit or block the biological activity of the HIV protease. These compounds, as well as pharmaceutical compositions containing these compounds, are useful for treating patients or hosts infected with the HIV virus. Intermediates and synthetic methods for preparing such compounds are also described.

WO 02/100845 A1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATI N TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 December 2002 (19.12.2002)

PCT

(10) International Publication Number
WO 02/100845 A1

(51) International Patent Classification⁷: C07D 277/06, A61K 31/425, C07D 417/12, 403/12, 207/16, A61P 31/18

(21) International Application Number: PCT/US02/18548

(22) International Filing Date: 11 June 2002 (11.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/297,460 11 June 2001 (11.06.2001) US
60/297,729 11 June 2001 (11.06.2001) US

(71) Applicant (*for all designated States except US*): AGOURON PHARMACEUTICALS, INC. [US/US], 10350 North Torrey Pines Road, La Jolla, CA 92037 (US).

(72) Inventors: CANON-KOCH, Stacie, S., 5940 La Jolla Mesa Drive, La Jolla, CA 92137 (US) ALEXANDER, Therese, N., 6557 Thornwood Street, San Diego, CA 92111 (US). BARVIAN, Mark, 1225 Olivia Avenue, Ann Arbor, MI 48104 (US). BOLTON, Gary, 4800 Hillway Court, Ann Arbor, MI 48105 (US). BOYER, Fredrick, E., 482 Pleasant Ridge Drive, Canton Township, MI 48188 (US) BURKE, Benjamin, J., 5761 Campanile Way, San Diego, CA 92115 (US) HOLLER, Ted, 2381 pLACID wAY, aNN aRBOR, mi 48105 (US). JEWELL, Tanya, M., 12604 Torrey Bluff Drive #400, San Diego, CA 92130 (US). PRASAD JOSYULA, Vara, 3129 Fawn Meadow Court, Ann Arbor, MI 48105 (US). KUCERA, David, J., 14099 Recuerdo Drive, Del Mar, CA 92014 (US). MACHAK, Jeff; 12980 Easton Court, Shelby Township, MI 48315 (US). MITCHELL, Lennert, J., 520 N Woodlawn Avenue, Chula Vista, CA 91910 (US). MURPHY, Sean, T., 7716 Dover Drive, Ypsilanti, MI 48197 (US). REICH, Siegfried, H., 311 Glenmont Drive, Solana Beach, CA 92075 (US) SKALITZKY, Donald, J., 4269 Taos Drive San Diego, CA 92117 (US). TATLOCK, John, H., 13153 Dressage Lane San Diego, CA 92130 (US) VARNEY, Michael, D., 738 Barbara Avenue, Solana Beach, CA 92075 (US). VIRGIL, Scott, C., 3950 Mahala Avenue, Apt. S23, San Diego, CA 92122 (US). WORLAND, Stephen, T., 727 Hoska Drive, Del Mar, CA 92014 (US). MELNICK, Michael, 3613 Westburn Court, Ann Arbor, MI 48108 (US). LINTON, Maria A., 11320 Red Cedar Drive, San Diego, CA 92131 (US) WEBBER, Stephen E., 3531 Mikkan Avenue, San Diego, CA 92122 (US).

(74) Agents: MANDRA, Raymond, R. et al., Fitzpatrick, Cella, Harper & Scinto, 30 Rockefeller Plaza, New York, NY 10112-3801 (US).

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

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published
— *with international search report*

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

WO 02/100845 A1

(54) Title: HV PROTEASE INHIBITORS, COMPOSITIONS CONTAINING THE SAME, THEIR PHARMACEUTICAL USES AND MATERIALS FOR THEIR SYNTHESIS

(57) Abstract: Compounds of formula (I) where the formula variables are as defined herein, are disclosed that advantageously inhibit or block the biological activity of the HIV protease. These compounds, as well as pharmaceutical compositions containing these compounds, are useful for treating patients or hosts infected with the HIV virus. Intermediates and synthetic methods for preparing such compounds are also described

# HIV PROTEASE INHIBITORS, COMPOSITIONS CONTAINING THE SAME, THEIR PHARMACEUTICAL USES AND MATERIALS FOR THEIR SYNTHESIS

## BACKGROUND OF THE INVENTION

### Field of the Invention

This invention relates to novel compounds as useful as HIV protease inhibitors and to the use of such compounds as antiviral agents for treatment of HIV infected individuals. This invention also relates to methods of preparation of these compounds and to intermediates that are useful in the preparation thereof

### Related Background Art

Acquired Immune Deficiency Syndrome (AIDS) causes a gradual breakdown of the body's immune system as well as progressive deterioration of the central and peripheral nervous systems. Since its initial recognition in the early 1980's, AIDS has spread rapidly and has now reached epidemic proportions within a relatively limited segment of the population. Intensive research has led to the discovery of the responsible agent, human T-lymphotropic retrovirus III (HTLV-III), now more commonly referred to as the human immunodeficiency virus or HIV

HIV is a member of the class of viruses known as retroviruses. The retroviral genome is composed of RNA, which is converted to DNA by reverse transcription. This retroviral DNA is then stably integrated into a host cell's chromosome and, employing the replicative processes of the host cells, produces new retroviral particles and advances the infection to other cells. HIV appears to have a particular affinity for the human T-4 lymphocyte cell, which plays a vital role in the body's immune system HIV infection of these white blood cells depletes this white cell population. Eventually, the immune system is rendered inoperative and ineffective against various opportunistic diseases such as, among others, pneumocystic carinii pneumonia, Kaposi's sarcoma, and cancer of the lymph system

Although the exact mechanism of the formation and working of the HIV virus is not understood, identification of the virus has led to some progress in controlling the disease. For example, the drug azidothymidine (AZT) has been found effective for inhibiting the reverse transcription of the retroviral genome of the HIV virus, thus giving a measure of control, though not a cure, for patients afflicted with AIDS. The search continues for drugs that can cure or at least provide an improved measure of control of the deadly HIV virus

Retroviral replication routinely features post-translational processing of polyproteins. This processing is accomplished by virally encoded HIV protease enzyme This yields mature polypeptides that will subsequently aid in the formation and function of infectious virus If this molecular processing is stifled, then the normal production of HIV is terminated. Therefore, inhibitors of HIV protease may function as anti-HIV viral agents.

HIV protease is one of the translated products from the HIV structural protein pol gene. This retroviral protease specifically cleaves other structural polypeptides at discrete sites to release these newly activated structural proteins and enzymes, thereby rendering the virion replication-competent. As such, inhibition of the HIV protease by potent compounds may prevent proviral integration of infected T-lymphocytes during the early phase of the HIV-1 life cycle, as well as inhibit viral proteolytic processing during its late stage. Additionally, the protease inhibitors may have the advantages of being more readily available, longer lived in virus, and less toxic than currently available drugs, possibly due to their specificity for the retroviral protease.

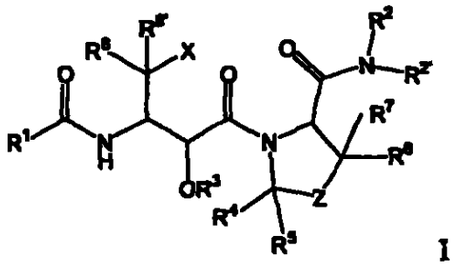
Related inhibitors of HIV proteases have been described in, e.g , U.S Patent No. 5,962,640, U.S. Patent No. 5,932,550, Australian Patent No. 705193, Canadian Patent Application No 2,179,935, European Patent Application No. 0 751 145, and Japanese Patent

Application No.100867489. Other related HIV protease inhibitors have been described in K. Yoshimura, et al., *Proct. Natl. Acad. Sci USA*, 96, 8675-8680 (1999) and T. Mimoto, et al., *J Med. Chem.*, 42, 1789-1802 (1999).

On-going treatment of HIV-infected individuals with compounds that inhibit HIV protease has led to the development of mutant viruses that possess proteases that are resistant to the inhibitory effect of these compounds. Thus, to be effective, new HIV protease inhibitors must be effective not only against wild-type strains of HIV, but must also demonstrate efficacy against the newly emerging mutant strains that are resistant to the commercially available protease inhibitors. Accordingly, there continues to be a need for new inhibitors targeting the HIV protease in both wild type and mutant strains of HIV.

## SUMMARY OF THE INVENTION

This invention relates to compounds useful for inhibiting the activity of HIV-protease of Formula I.



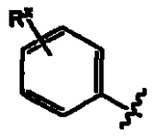
I

wherein

$R^1$ is a 5- or 6-membered mono-cyclic carbocyclic or heterocyclic group, wherein said carbocyclic or heterocyclic group is saturated, partially unsaturated or fully unsaturated and is unsubstituted or substituted by one or more suitable substituents,

$R^2$ is a substituted alkyl group, a substituted or unsubstituted alkenyl group, a substituted or unsubstituted alkynyl group, a substituted phenyl group, a substituted phenylalkyl group, a substituted or unsubstituted phenylalkenyl group or a substituted or unsubstituted phenylalkynyl group,

$R^2$ is H or a substituted or unsubstituted $C_1$-$C_4$ alkyl group;

X is  , wherein $R^x$ is H or one or more suitable substituents;

Z is S, O, SO, $SO_2$, $CH_2$ or CFH,

$R^3$ is H or a substituted or unsubstituted $C_1$-$C_4$ alkyl group;

$R^4$, $R^5$, $R^6$ and $R^7$ are independently selected from H or a $C_1$-$C_6$ alkyl group; and

$R^8$ and $R^{8'}$ are independently selected from H, halo, a $C_1$-$C_4$ aliphatic group or a $C_1$-$C_4$ halo-substituted aliphatic group,

where any of said substituted alkyl, alkenyl or alkynyl groups are substituted by one or more suitable substituents

provided that said 5- or 6-membered mono-cyclic heterocycloalkyl, heterocycloalkenyl or heteroaryl group contains at least two heteroatoms when $R^2$ is a substituted phenyl group, a substituted phenylalkyl group, a substituted or unsubstituted phenylalkenyl group or a substituted or unsubstituted phenylalkynyl group; or

provided that said alkyl, alkenyl or alkynyl moiety of said substituted phenylalkyl, phenylalkenyl or phenylalkynyl group is substituted by one or more substituents selected from halo or keto; or

provided that said substituted phenyl group or phenyl moiety of said substituted phenylalkyl, phenylalkenyl or phenylalkynyl group is substituted by one or more suitable substituents other than halo or methyl

The present invention relates to compounds of Formula I below, and prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts and solvates thereof that inhibit the protease encoded by human immunodeficiency virus (HIV) type 1 (HIV-1) or type 2 (HIV-2), as well as mutant strains thereof These compounds are useful in the treatment of infection by HIV and the treatment of the acquired immune deficiency syndrome (AIDS). The compounds, their pharmaceutically acceptable salts, and the pharmaceutical compositions of the present invention can be used alone or in combination with other antivirals, immunomodulators, antibiotics or vaccines Compounds of the present invention can also be converted to prodrugs, by derivatization, according to conventional techniques Methods of treating AIDS, methods of treating HIV infection and methods of inhibiting HIV protease are disclosed.

## DETAILED DESCRIPTION OF INVENTION AND PREFERRED EMBODIMENTS

In accordance with a convention used in the art, $\sim\!\!\!\!\diagup$ is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure.

As used herein, the term "aliphatic" represents a saturated or unsaturated, straight- or branched-chain hydrocarbon, containing 1 to 10 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below. The term "aliphatic" is intended to encompass alkyl, alkenyl and alkynyl groups.

As used herein, the term "alkyl" represents a straight- or branched-chain saturated or unsaturated hydrocarbon, containing 1 to 10 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below Exemplary alkyl substituents include, but are not limited to methyl (Me), ethyl (Et), propyl, isopropyl, butyl, isobutyl, t-butyl, and the like. The term "lower alkyl" refers to an alkyl group containing from 1 to 6 carbon atoms

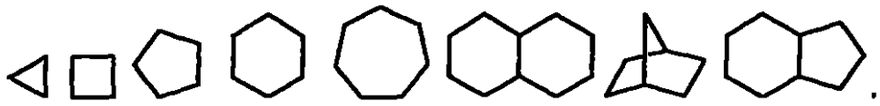
The term "alkenyl" represents a straight- or branched-chain hydrocarbon, containing one or more carbon-carbon double bonds and having 2 to 10 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below Exemplary alkenyl substituents include, but are not limited to ethenyl, propenyl, butenyl, allyl, pentenyl and the like

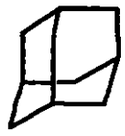
The term "alkynyl" represents a straight- or branched-chain hydrocarbon, containing one or more carbon-carbon triple bonds and having 2 to 10 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below An alkynyl moiety may also contain one or more carbon-carbon double bonds Exemplary alkynyl substituents include, but are not limited to ethynyl, butynyl, propynyl (propargyl) isopropynyl, pentynyl, hexynyl and the like.

The term "carbocyclic" represents a saturated, partially saturated, or fully unsaturated (aromatic) cyclic hydrocarbon group containing from 3 to 14 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described herein below. The term "carbocyclic" is intended to encompass mono-, bi- and tri-cyclic saturated, partially saturated, or fully unsaturated hydrocarbon groups; for example, cycloalkyl, cycloalkenyl and

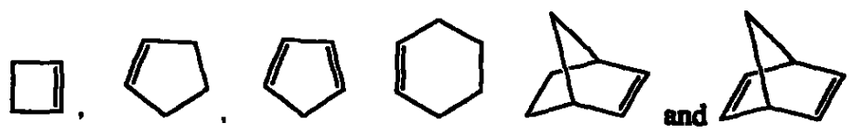
aryl groups. The term "carbocyclic" is also intended to encompass bi- and tri-cyclic hydrocarbon groups which contain any combination of ring moieties that are saturated, partially saturated, or fully unsaturated (aromatic). Partially saturated carbocycles include, for example, dihydro-arenes (e.g , indanyl) or tetrahydro-arenes (e.g. tetrahydronaphthalene), wherein any one or more points of saturation may occur in any ring moiety of the carbocycle. In addition, it is understood that bonding between any bi- or tri-cyclic carbocyclic group and any other substituent or variable group may be made at any suitable position of the carbocycle. The term "carbocyclic-aliphatic" group is intended to encompass aliphatic groups having a carbocyclic substituent (e.g., phenylmethyl- (benzyl), phenylethyl-, cyclopropylmethyl-, etc.), wherein the carbocyclic moiety and the aliphatic moiety thereof may be independently substituted by one or more suitable substituents.

"Cycloalkyl" represents a group comprising a non-aromatic monocyclic, bicyclic, or tricyclic hydrocarbon containing from 3 to 14 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below. Exemplary cycloalkyls include monocyclic rings having from 3-8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Illustrative examples of cycloalkyl groups include the following:

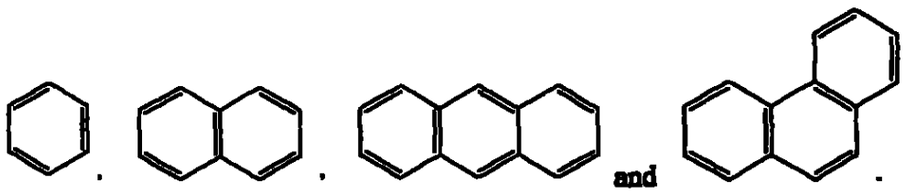


and 

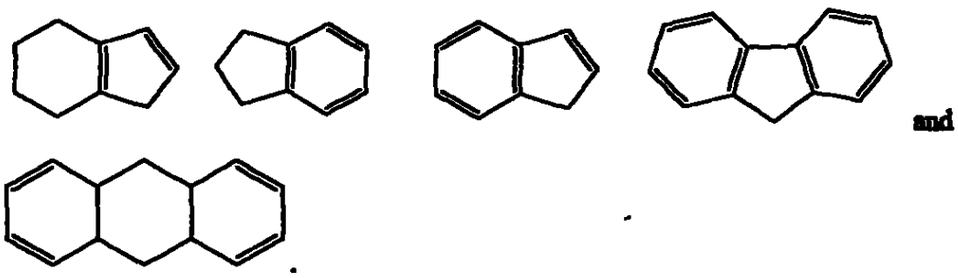
"Cycloalkenyl" represents a group comprising a non-aromatic monocyclic, bicyclic, or tricyclic hydrocarbon containing from 4 to 14 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below and contains at least one carbon-carbon double bond. Exemplary monocyclic cycloalkenyls include groups having from 4-8, preferably 5-6, carbon atoms, such as cyclopentenyl, cyclopentadienyl, cyclohexenyl, cycloheptenyl and the like. Illustrative examples of cycloalkenyl groups include the following:



"Aryl" represents a group comprising an aromatic, monovalent monocyclic, bicyclic, or tricyclic radical containing from 6 to 18 carbon ring atoms, which may be unsubstituted or substituted by one or more of the substituents described below Illustrative examples of aryl groups include the following·

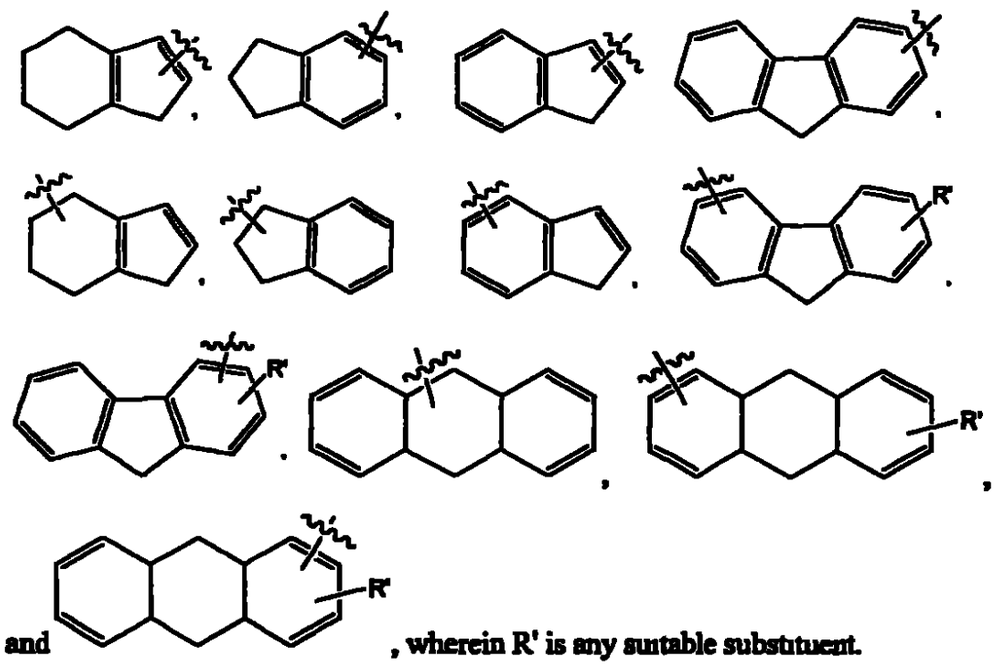


The term "carbocyclic" also to encompasses mixed bi- and tri-cyclic cycloalkyl/cycloalkenyl/aryl groups, which may be unsubstituted or substituted by one or more of the substituents described below. Illustrative examples of such mixed bi-and tri-cyclic groups include the following



It is understood that bonding or substitution of any bi-cyclic or tri-cyclic carbocyclic or heterocyclic group described herein may be at any suitable position on any ring.

Illustrative examples of such bonding in mixed bi-and tri-cyclic carbocyclic groups include the following.

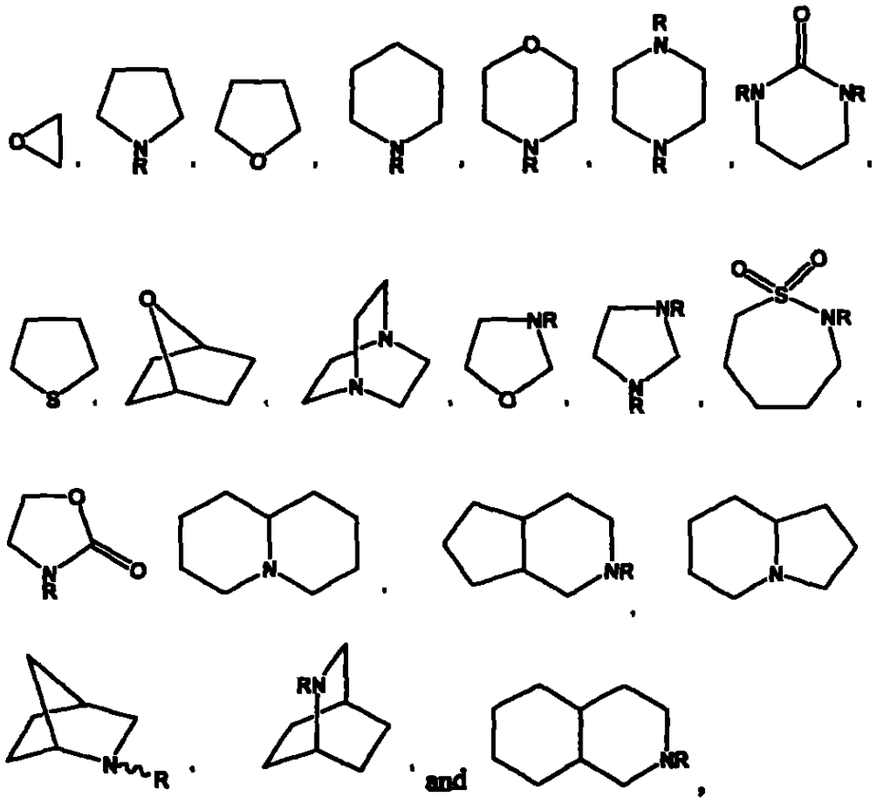



and , wherein R' is any suitable substituent.

The term "heterocyclic" represents a saturated, partially saturated, or fully unsaturated (aromatic) cyclic group containing from 3 to 18 ring atoms, which includes 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, and which may be unsubstituted or substituted by one or more of the substituents described herein below. The term "heterocyclic" is intended to encompass mono-, bi- and tri-cyclic saturated, partially saturated, or fully unsaturated heteroatom-containing cyclic groups; for example, heterocycloalkyl, heterocycloalkenyl and heteroaryl groups. The term "heterocyclic" is also intended to encompass bi- and tri-cyclic groups which contain any combination of ring moieties that are saturated, partially saturated, or fully unsaturated (aromatic). Partially saturated heterocycles include, for example, dihydroheteroarenes (e.g., dihydroindole) or tetrahydro-heteroarenes (e.g. tetrahydroquinoline), wherein any one or more points of saturation may occur in any ring moiety of the heterocycle. In addition, it is understood that bonding between any bi- or tri-cyclic heterocyclic group and any other substituent or variable group may be made at any suitable position of the heterocycle (i.e., there is no restriction that a substituent or variable group must be bonded to the heteroatom-containing moiety of a bi- or tri-cyclic heterocyclic group). The term "heterocyclic-aliphatic" group is intended to encompass aliphatic groups having a heterocyclic substituent (e.g., pyridylmethyl-, thiazolylmethyl-,

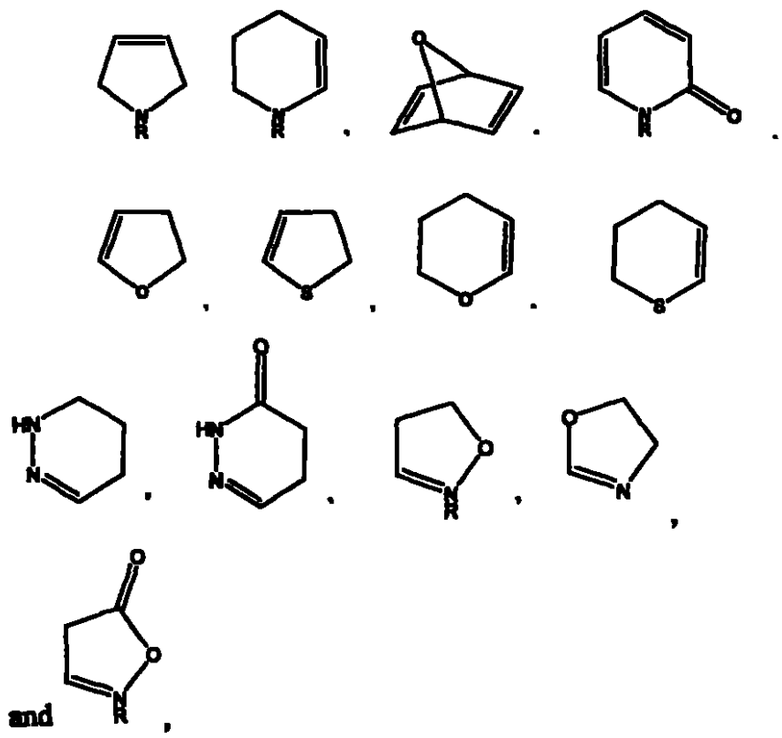
tetrahydrofuranylmethyl-, etc ) wherein the heterocyclic moiety and the aliphatic moiety thereof may be independently substituted by one or more suitable substituents

"Heterocycloalkyl" represents a group comprising a saturated monovalent monocyclic, bicyclic, or tricyclic radical, containing 3 to 18 ring atoms, which includes 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, and which may be unsubstituted or substituted by one or more of the substituents described below. Illustrative examples of heterocycloalkyl groups include, but are not limited to, azetidinyl, pyrrolidyl, piperidyl, piperazinyl, morpholinyl, tetrahydro-2H-1,4-thiazinyl, tetrahydrofuryl, tetrahydropyranyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, azabicylo[3.2.1]octyl, azabicylo[3.3.1]nonyl, azabicylo[4.3 0]nonyl, oxabicylo[2.2.1]heptyl, 1,5,9-triazacyclododecyl, and the like. Illustrative examples of heterocycloalkyl groups include the following:



wherein R is H, alkyl, hydroxyl or represents a compound according to Formula I, and the bond depicted as " ∿∿∿ ", represents bonding to either face of the bi-cyclic moiety (i.e., endo or exo).

The term "heterocycloalkenyl" is used herein to represent a non-aromatic, monovalent monocyclic, bicyclic, or tricyclic radical, containing 4 to 18 ring atoms, which may include from 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, and which may be unsubstituted or substituted by one or more of the substituents described below and which contains at least one carbon-carbon or carbon-heteroatom double bond. Exemplary monocyclic heterocycloalkenyls include groups having from 4-8, preferably 5-6, ring atoms Illustrative examples of heterocycloalkenyl groups include, but are not limited to, dihydrofuryl, dihydropyranyl, isoxazolinyl, dihydropyridyl, tetrahydropyridyl, and the like. Illustrative examples of heterocycloalkenyl groups include the following:

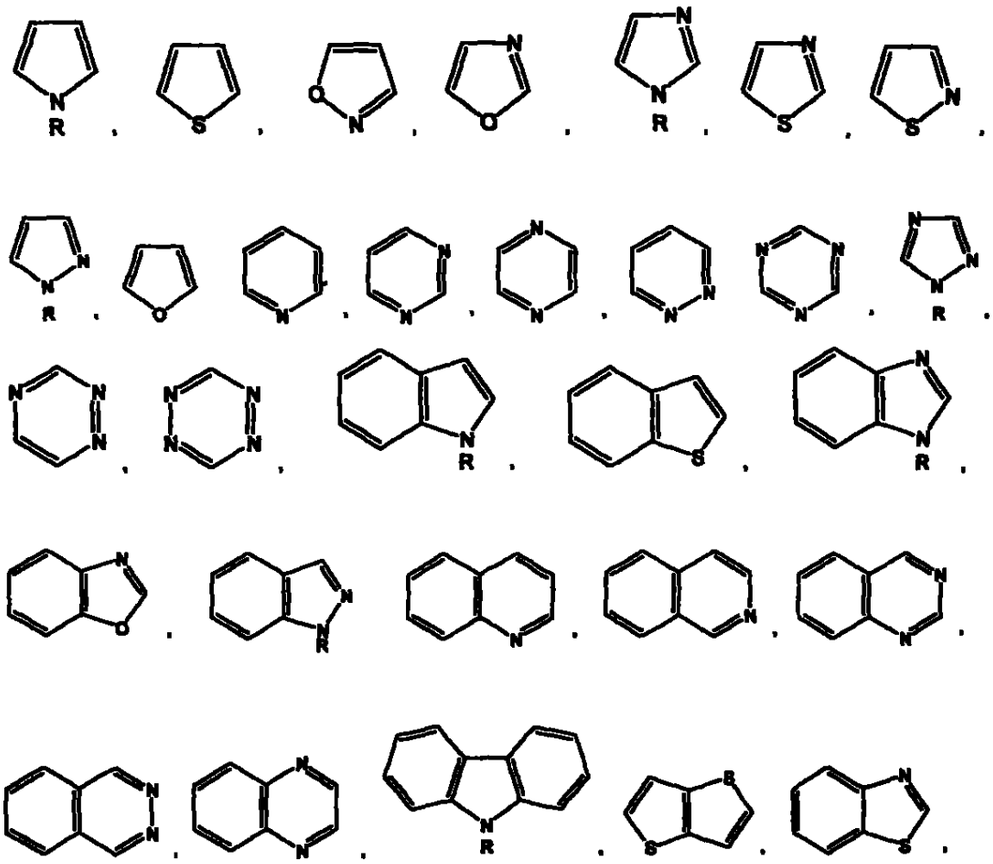


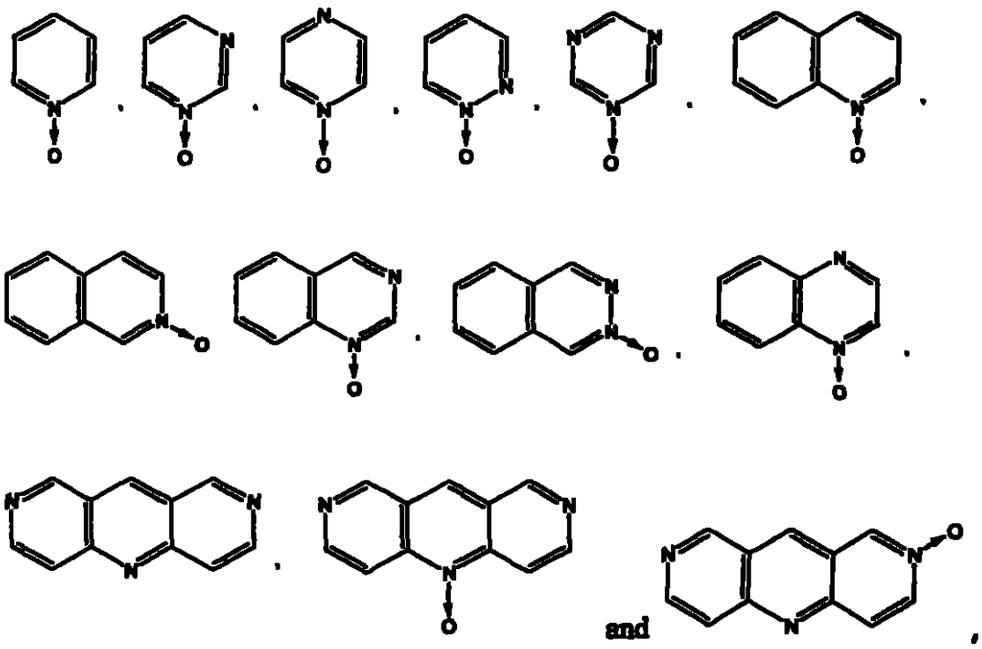
and ,

wherein R is H, alkyl, hydroxyl or represents a compound according to Formula L.

"Heteroaryl" represents a group comprising an aromatic monovalent monocyclic, bicyclic, or tricyclic radical, containing 5 to 18 ring atoms, including 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, which may be unsubstituted or substituted by one or more of the substituents described below As used herein, the term "heteroaryl" is also intended to encompass the N-oxide derivative (or N-oxide derivatives, if the heteroaryl group contains more than one nitrogen such that more than one N-oxide derivative may be formed) of the nitrogen-containing heteroaryl groups described herein. Illustrative examples of

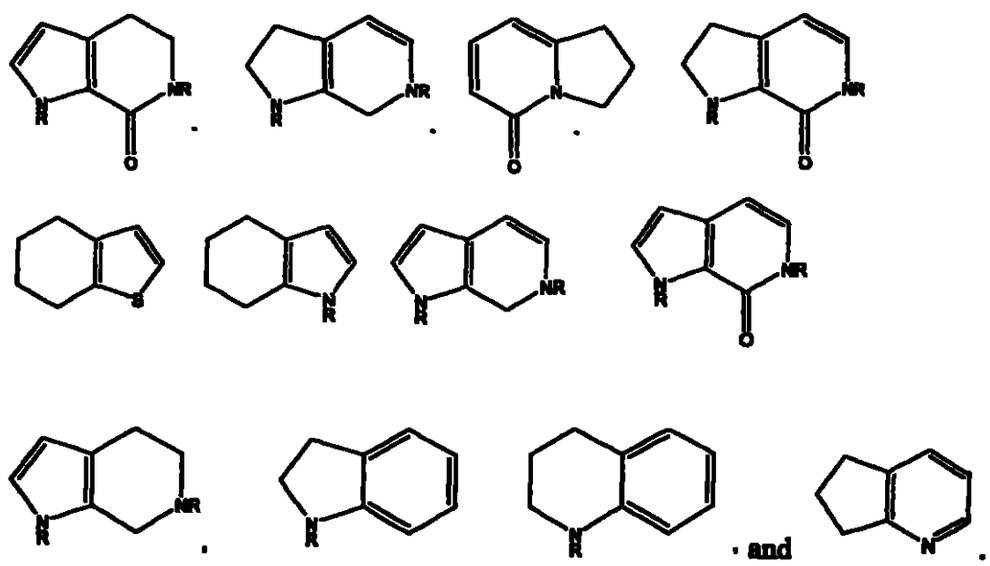
heteroaryl groups include, but are not limited to, thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl, thiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, benzo[b]thienyl, naphtho[2,3-b]thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathienyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxyalinyl, quinzolinyl, benzothiazolyl, benzimidazolyl, tetrahydroquinolinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, and phenoxazinyl. Illustrative examples of N-oxide derivatives of heteroaryl groups include, but are not limited to, pyridyl N-oxide, pyrazinyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, triazinyl N-oxide, isoquinolyl N-oxide, and quinolyl N-oxide Further examples of heteroaryl groups include the following moieties:



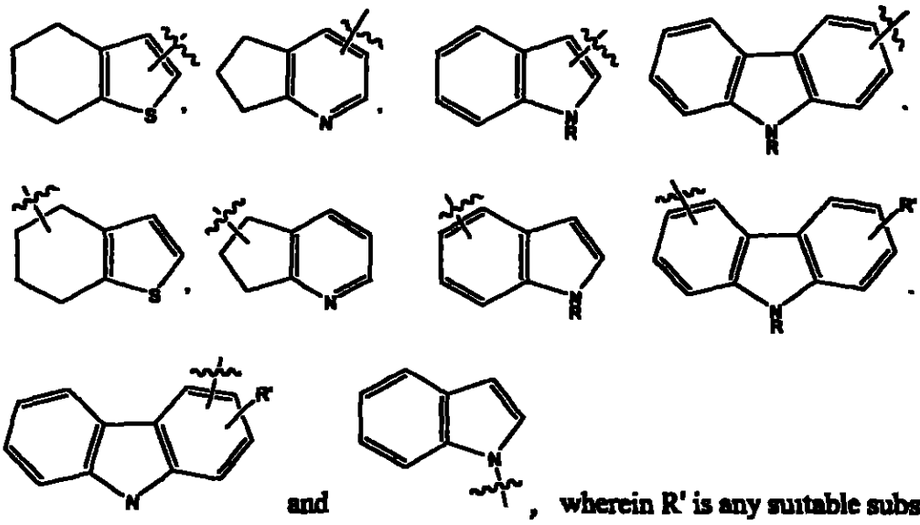


wherein R is H, alkyl, hydroxyl or represents a compound according to Formula I.

The term "heterocyclic" also to encompasses mixed bi- and tri-cyclic heterocycloalkyl/heterocycloalkenyl/heteroaryl groups, which may be unsubstituted or substituted by one or more of the substituents described below. Illustrative examples of such mixed bi-and tri-cyclic heterocyclic groups include the following



Illustrative examples of such bonding in mixed bi-and tri-cyclic heterocyclic groups include the following:



and , wherein R' is any suitable substituent.

In the compounds of this invention, the alkyl, alkenyl and alkynyl groups may be optionally substituted by one or more suitable substituents independently selected from phenyl, nitro, amino, cyano, halogen, hydroxyl, alkoxy. haloalkoxy, aryloxy, cycloalkyloxy, cycloalkylalkyloxy, cycloalkenyloxy, cycloalkenylalkyloxy, heterocycloalkoxy, heterocycloalkylalkyloxy, heterocycloalkenyloxy, heterocycloalkenylalkyloxy, heteroaryloxy, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyoxycarbonyl, carboxyl, carbamoyl, formyl, keto (oxo), thioketo, sulfo, alkylamino, alkenylamino, alkynylamino, cycloalkylamino, cycloalkenylamino, arylamino, heterocycloalkylamino, heterocycloalkenylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, alkenylaminocarbonyl, alkynylaminocarbonyl, cycloalkylaminocarbonyl, cycloalkenylamino, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heterocycloalkenylcarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl,

alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino, cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, haloalkylthio, arylthio and heteroarylthio groups, wherein any of the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl moieties present in the above substituents may be further substituted. The alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl moieties of any of the above substituents may be optionally substituted by one or more groups independently selected from alkyl (except for alkyl), haloalkyl, aryl, nitro, amino, alkylamino, dialkylamino, halogen, hydroxyl, alkoxy, haloalkoxy, aryloxy, mercapto, alkylthio, haloalkylthio or arylthio groups.

In the compounds of this invention the substituted carbocyclic or heterocyclic groups may be optionally substituted by one or more suitable substituents independently selected from alkyl, haloalkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, nitro, amino, cyano, halogen, hydroxyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, alkylenedioxy, aryloxy, cycloalkyloxy, cycloalkylalkyloxy, cycloalkenyloxy, cycloalkenylalkyloxy, heterocycloalkoxy, heterocycloalkylalkyloxy, heterocycloalkenyloxy, heterocycloalkenylalkyloxy, heteroaryloxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyoxycarbonyl, carboxyl, carbamoyl, formyl, keto (oxo), thioketo, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino, cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino,

heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, haloalkylthio, arylthio and heteroarylthio groups, wherein any of the alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents may be further substituted Preferred "suitable substituents" include alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halogen, hydroxyl, alkoxy, alkylenedioxy, aryloxy, cycloalkoxy, heteroaryloxy, alkylthio, haloalkylthio and carboxyl. The alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of any of the above substituents may be optionally substituted by one or more groups independently selected from: alkyl, haloalkyl, nitro, amino, alkylamino, dialkylamino, halogen, hydroxyl, alkoxy, haloalkoxy, mercapto, alkylthio, haloalkylthio or arylthio groups.

For example, in the compounds of this invention, the substituted phenyl or phenyl moiety of $R^2$ may comprise at least one substituent (other than halo or methyl) selected from haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkoxyalkyl, alkylcarbonylalkyl, haloalkoxyalkyl, aryloxyalkyl, alkylthioalkyl, haloalkylthioalkyl, arylthioalkyl, cyanoalkyl, aminoalkyl, alkylaminoalkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, nitro, amino, cyano, hydroxyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, alkylenedioxy, aryloxy, cycloalkyloxy, cycloalkylalkyloxy, cycloalkenyloxy, cycloalkenylalkyloxy, heterocycloalkoxy, heterocycloalkylalkyloxy, heterocycloalkenyloxy, heterocycloalkenylalkyloxy, heteroaryloxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyoxycarbonyl, carboxyl, carbamoyl, formyl, keto (oxo), thioketo, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino, cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino,

alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, haloalkylthio, arylthio and heteroarylthio groups, wherein any of the alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents may be further substituted. Preferred "suitable substituents" include alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halogen, hydroxyl, alkoxy, alkylenedioxy, aryloxy, cycloalkoxy, heteroaryloxy, alkylthio, haloalkylthio and carboxyl. The alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of any of the above substituents may be optionally substituted by one or more groups independently selected from: alkyl, haloalkyl, nitro, amino, alkylamino, dialkylamino, halogen, hydroxyl, alkoxy, haloalkoxy, mercapto, alkylthio, haloalkylthio or arylthio groups.

If the substituents themselves are not compatible with the synthetic methods of this invention, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions used in these methods. The protecting group may be removed at a suitable point in the reaction sequence of the method to provide a desired intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, *Protecting Groups in Chemical Synthesis* (3rd ed.), John Wiley & Sons, NY (1999), which is incorporated herein by reference in its entirety. In some instances, a substituent may be specifically selected to be reactive under the reaction conditions used in the methods of this invention. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful in an intermediate compound in the methods of this invention or is a desired substituent in a target compound.

In the *compounds* of this invention, $R^2$ and $R^2$, independently or taken together, may be a suitable nitrogen protecting group. As indicated above, nitrogen protecting groups are well known in the art and any nitrogen protecting group that is useful in the methods of preparing the compounds of this invention or may be useful in the HIV protease inhibitory compounds of this invention may be used. Exemplary nitrogen protecting groups include alkyl, substituted alkyl, carbamate, urea, amide, imide, enamine, sulfenyl, sulfonyl, nitro, nitroso, oxide, phosphinyl, phosphoryl, silyl, organometallic, boronic acid and boronic acid groups. Examples of each of these groups, methods for protecting nitrogen moieties using these groups and methods for removing these groups from nitrogen moieties are disclosed in

T. Greene and P. Wuts, *supra*. Preferably, when $R^2$ and/or $R^{2'}$ are independently suitable nitrogen protecting groups, suitable $R^2$ and $R^{2'}$ substituents include, but are not limited to, carbamate protecting groups such as alkyloxycarbonyl (e.g., Boc: t-butyloxycarbonyl) and aryloxycarbonyl (e.g., Cbz: benzyloxycarbonyl, or FMOC fluorene-9-methyloxycarbonyl), alkyloxycarbonyls (e.g., methyloxycarbonyl), alkyl or arylcarbonyl, substituted alkyl, especially arylalkyl (e.g., trityl (triphenylmethyl), benzyl and substituted benzyl), and the like. When $R^2$ and $R^{2'}$ taken together are a suitable nitrogen protecting group, suitable $R^2/R^{2'}$ substituents include phthalimido and a stabase (1,2-bis (dialkylsilyl))ethylene).

The terms "halogen" and "halo" represent chloro, fluoro, bromo or iodo substituents. "Heterocycle" is intended to mean a heteroaryl or heterocycloalkyl group. "Acyl" is intended to mean a -C(O)-R radical, where R is a substituted or unsubstituted alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group. "Acyloxy" is intended to mean an -OC(O)-R radical, where R is a substituted or unsubstituted alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group. "Thioacyl" is intended to mean a -C(S)-R radical, where R is a substituted or unsubstituted alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group. "Sulfonyl" is intended to mean an $-SO_2-$ biradical. "Sulfenyl" is intended to mean an -SO- biradical. "Sulfo" is intended to mean an $-SO_2H$ radical. "Hydroxy" is intended to mean the radical -OH. "Amine" or "amino" is intended to mean the radical $-NH_2$. "Alkylamino" is intended to mean the radical $-NHR_a$, where $R_a$ is an alkyl group. "Dialkylamino" is intended to mean the radical $-NR_aR_b$, where $R_a$ and $R_b$ are each independently an alkyl group, and is intended to include heterocycloalkyl groups, wherein $R_a$ and $R_b$, taken together, form a heterocyclic ring that includes the amine nitrogen. "Alkoxy" is intended to mean the radical $-OR_a$, where $R_a$ is an alkyl group. Exemplary alkoxy groups include methoxy, ethoxy, propoxy, and the like. "Lower alkoxy" groups have alkyl moieties having from 1 to 4 carbons. "Alkoxycarbonyl" is intended to mean the radical $-C(O)OR_a$, where $R_a$ is an alkyl group. "Alkylsulfonyl" is intended to mean the radical $-SO_2R_a$, where $R_a$ is an alkyl group. "Alkylenedioxy" is intended to mean the divalent radical $-OR_aO-$ which is bonded to adjacent atoms (e.g., adjacent atoms on a phenyl or naphthyl ring), wherein $R_a$ is a lower alkyl group. "Alkylaminocarbonyl" is intended to mean the radical $-C(O)NHR_a$, where $R_a$ is an alkyl group. "Dialkylaminocarbonyl" is intended to mean the radical $-C(O)NR_aR_b$, where $R_a$ and $R_b$ are each independently an alkyl group. "Mercapto" is intended to mean the radical -SH. "Alkylthio" is intended to mean the radical $-SR_a$, where $R_a$ is an alkyl group. "Carboxy" is

intended to mean the radical -C(O)OH. "Keto" or "oxo" is intended to mean the diradical =O. "Thioketo" is intended to mean the diradical =S. "Carbamoyl" is intended to mean the radical -C(O)$NH_2$. "Cycloalkylalkyl" is intended to mean the radical –alkyl-cycloalkyl, wherein alkyl and cycloalkyl are defined as above, and is represented by the bonding arrangement present in the groups -$CH_2$-cyclohexane or -$CH_2$-cyclohexene. "Arylalkyl" is intended to mean the radical –alkylaryl, wherein alkyl and aryl are defined as above, and is represented by the bonding arrangement present in a benzyl group. "Aminocarbonylalkyl" is intended to mean the radical –alkylC(O) $NH_2$ and is represented by the bonding arrangement present in the group -$CH_2CH_2C(O)NH_2$ "Alkylaminocarbonylalkyl" is intended to mean the radical –alkylC(O)$NHR_a$, where $R_a$ is an alkyl group and is represented by the bonding arrangement present in the group -$CH_2CH_2C(O)NHCH_3$. "Alkylcarbonylaminoalkyl is intended to mean the radical –alkylNHC(O)-alkyl and is represented by the bonding arrangement present in the group -$CH_2NHC(O)CH_3$. "Dialkylaminocarbonylalkyl" is intended to mean the radical –alkylC(O)$NR_aR_b$, where $R_a$ and $R_b$ are each independently an alkyl group. "Aryloxy" is intended to mean the radical -$OR_c$, where $R_c$ is an aryl group. "Heteroaryloxy" is intended to mean the radical -$OR_d$, where $R_d$ is a heteroaryl group. "Arylthio" is intended to mean the radical -$SR_c$, where $R_c$ is an aryl group. "Heteroarylthio" is intended to mean the radical -$SR_d$, where $R_d$ is a heteroaryl group

If an inventive compound is a base, a desired salt may be prepared by any suitable method known in the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, pyranosidyl acid, such as glucuronic acid or galacturonic acid, alpha-hydroxy acid, such as citric acid or tartaric acid, amino acid, such as aspartic acid or glutamic acid, aromatic acid, such as benzoic acid or cinnamic acid, sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

If an inventive compound is an acid, a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary); an alkali metal or alkaline earth metal hydroxide; or the like. Illustrative examples of suitable salts include organic salts derived from amino acids such as glycine and arginine; ammonia, primary, secondary, and

tertiary amines, and cyclic amines, such as piperidine, morpholine, and piperazine, as well as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

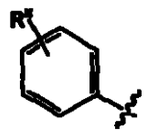
Specific embodiments of the compounds of this invention comprising the compounds depicted by Formula I may also be described. For example, this invention relates to compounds useful for inhibiting the activity of HIV-protease of Formula I, above, wherein.

$R^1$ is a 5- or 6-membered monocyclic cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group, where said cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group is unsubstituted or substituted with one or more substituents independently selected from alkyl, haloalkyl, amino, cyano, halogen, hydroxyl, alkoxy, haloalkoxy, alkylenedioxy, di-haloalkylenedioxy, aryloxy, cycloalkoxy, cycloalkylalkoxy, cycloalkenyloxy, cycloalkenylalkoxy, heterocycloalkoxy, heterocycloalkylalkoxy, heterocycloalkenyloxy, heterocycloalkenylalkoxy, heteroaryloxy, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylamino, dialkylamino, keto, alkylsulfonyl, arylsulfonyl, alkylcarbonylamino, alkylthio, haloalkylthio and arylthio, wherein any of the alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents may be further substituted by one or more groups independently selected from alkyl, haloalkyl, aryl, nitro, amino, alkylamino, dialkylamino, halogen, hydroxyl, alkoxy, haloalkoxy, aryloxy, mercapto, alkylthio, haloalkylthio and arylthio groups;

$R^2$ is a substituted alkyl group, a substituted or unsubstituted alkenyl group, or a substituted or unsubstituted alkynyl group, wherein said alkyl, alkenyl or alkynyl group is a straight or branched chained group, and

where said substituted alkyl, alkenyl or alkynyl group is substituted by one or more substituents independently selected from amino, cyano, halogen, hydroxyl, alkoxy, haloalkoxy, aryloxy, cycloalkoxy, cycloalkylalkoxy, cycloalkenyloxy, cycloalkenylalkoxy, heterocycloalkoxy, heterocycloalkylalkoxy, heterocycloalkenyloxy, heterocycloalkenlalkoxy, heteroaryloxy, alkylamino, dialkylamino, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylthio, haloalkylthio, arylthio and heteroarylthio groups, wherein any of the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl moieties present in the above substituents may be further substituted by one or more groups independently selected from alkyl, haloalkyl, halogen, hydroxyl, alkoxy, haloalkoxy, alkylthio and haloalkylthio groups,

$R^2$ is H, methyl, ethyl or propyl, where said methyl, ethyl or propyl is unsubstituted or substituted by halo or hydroxyl;

X is  , wherein $R^x$ is H or one or more substituents independently selected from halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl, alkylenedioxy, dihaloalkylenedioxy, alkylamino, dialkylamino, alkylthio and haloalkylthio;

Z is S, O, SO, $SO_2$, $CH_2$ or CFH;

$R^3$ is H,

$R^4$, $R^5$, $R^6$ and $R^7$ are independently selected from H or methyl; and

$R^8$ and $R^{8'}$ are independently selected from H, halogen, methyl, monohalo-methyl, dihalo-methyl and tri-halomethyl,

or a prodrug, pharmaceutically active metabolite or pharmaceutically active salt or solvate thereof.

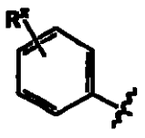
In more specific embodiments, this invention relates to compounds of Formula I, above, wherein:

$R^1$ is phenyl, pyrrolyl, pyrrolidinyl, isoxazolyl, pyrazolyl, thiazolyl, tetrahydrofuranyl, furanyl, thienyl or tetrahydropyridazinyl, where said phenyl, pyrrolyl, pyrrolidinyl, isoxazolyl, pyrazolyl, thiazolyl, tetrahydrofuranyl, furanyl, thienyl or tetrahydropyridazinyl is unsubstituted or substituted with one or more substituents independently selected from alkyl, haloalkyl, halogen, and hydroxyl,

$R^2$ is a substituted alkyl group, a substituted or unsubstituted $C_1$-$C_6$ alkenyl group, or a substituted or unsubstituted $C_1$-$C_6$ alkynyl group, wherein said alkyl, alkenyl or alkynyl group is a straight or branched chained group, and

where said substituted alkyl, alkenyl or alkynyl group is substituted by one or more substituents independently selected from cyano, halogen and alkylamino;

$R^{2'}$ is H, methyl or ethyl;

X is  , wherein $R^x$ is H, halogen, or alkoxy;

Z is S, O, $CH_2$ or CFH,

$R^3$, $R^4$, $R^5$, $R^8$ and $R^{8'}$ are each H; and

$R^6$ and $R^7$ are independently selected from H or methyl;

or a prodrug, pharmaceutically active metabolite or pharmaceutically active salt or solvate thereof

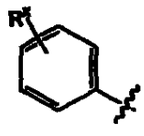
In preferred specific embodiments, this invention relates to compounds of Formula I, above, wherein:

$R^1$ is phenyl, where said phenyl is substituted with one or more substituents independently selected from alkyl, halogen or hydroxyl,

$R^2$ is a $C_1$-$C_6$ alkenyl group or a $C_1$-$C_6$ alkynyl group, wherein said alkenyl or alkynyl group is a straight or branched chained group, and

where said alkenyl or alkynyl group is unsubstituted or is substituted by one or more halogen substituents,

$R^{2'}$ is H;

X is  , wherein $R^x$ is H,

Z is S,

$R^3$, $R^4$, $R^5$, $R^8$ and $R^{8'}$ are each H; and

$R^6$ and $R^7$ are each methyl,

or a prodrug, pharmaceutically active metabolite or pharmaceutically active salt or solvate thereof.

More specifically, this invention relates to compounds useful for inhibiting the activity of HIV-protease of Formula I, above, wherein

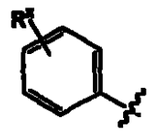
$R^1$ is a 5- or 6-membered mono-cyclic cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group, where said cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group is unsubstituted or substituted with one or more substituents independently selected from alkyl, haloalkyl, amino, cyano, halogen, hydroxyl, alkoxy, haloalkoxy, alkylenedioxy, dihaloalkylenedioxy, aryloxy, cycloalkoxy, cycloalkylalkoxy, cycloalkenyloxy, cycloalkenylalkoxy, heterocycloalkoxy, heterocycloalkylalkoxy, heterocycloalkenyloxy, heterocycloalkenylalkoxy, heteroaryloxy, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylamino, dialkylamino, alkylsulfonyl, arylsulfonyl, alkylcarbonylamino, alkylthio, haloalkylthio and arylthio, wherein

any of the alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents are substituted by one or more groups independently selected from alkyl, haloalkyl, aryl, nitro, amino, alkylamino, dialkylamino, halogen, hydroxyl, alkoxy, haloalkoxy, aryloxy, mercapto, alkylthio, haloalkylthio and arylthio groups;

$R^2$ is a substituted phenyl group, a substituted phenylalkyl group, a substituted or unsubstituted phenylalkenyl group or a substituted or unsubstituted phenylalkynyl group,

where said alkyl, alkenyl or alkynyl moiety of said phenylalkyl, phenylalkenyl or phenylalkynyl group is a straight or branched chain moiety;

$R^7$ is H, methyl, ethyl or propyl, where said methyl, ethyl or propyl is unsubstituted or substituted with halo or hydroxyl;

X is  , wherein $R^x$ is H or one or more substituents independently selected from halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl, alkylenedioxy, di-haloalkylenedioxy, alkylamino, dialkylamino, alkylthio and haloalkylthio;

Z is S, O, SO, $SO_2$, $CH_2$ or CFH;

$R^3$ is H;

$R^4$, $R^5$, $R^6$ and $R^7$ are independently selected from H or methyl; and

$R^8$ and $R^9$ are independently selected from H, halogen, methyl, monohalo-methyl, dihalo-methyl and tri-halomethyl,

provided that said 5- or 6-membered mono-cyclic heterocycloalkyl, heterocycloalkenyl or heteroaryl group contains at least two heteroatoms; or

provided that said alkyl, alkenyl or alkynyl moiety of said substituted phenylalkyl, phenylalkenyl or phenylalkynyl group is substituted by one or more substituents selected from halo or keto; or

provided that said substituted phenyl group or phenyl moiety of said substituted phenylalkyl, phenylalkenyl or phenylalkynyl group is substituted by one or more substituents other than halo or methyl, where said one or more substituents is independently selected from haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkoxyalkyl, alkylcarbonylalkyl, haloalkoxyalkyl, aryloxyalkyl, alkylthioalkyl, haloalkylthioalkyl, arylthioalkyl, cyanoalkyl, aminoalkyl, alkylaminoalkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, nitro, amino, cyano, hydroxyl, alkoxy, haloalkoxy, alkenyloxy,

alkynyloxy, alkylenedioxy, aryloxy, cycloalkoxy, cycloalkylalkoxy, cycloalkenyloxy, cycloalkenylalkoxy, heterocycloalkoxy, heterocycloalkylalkoxy, heterocycloalkenoxy, heterocycloalkenylalkoxy, heteroaryloxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyoxycarbonyl, carboxyl, carbamoyl, formyl, keto, thioketo, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino, cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, haloalkylthio, arylthio and heteroarylthio groups, wherein any of the alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl moieties present in the above substituents are unsubstituted or substituted by one or more groups independently selected from alkyl, haloalkyl, halogen, hydroxyl, alkoxy, haloalkoxy, alkylthio and haloalkylthio groups,

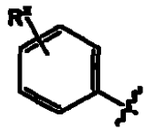
or a prodrug, pharmaceutically active metabolite or pharmaceutically active salt or solvate thereof If the phenyl group or phenyl moiety of $R^2$ contains more than one substituent, the substituents may be the same or different, and may be independently selected from the above-described substituents

More specifically, this invention relates to compounds useful for inhibiting the activity of HIV-protease of Formula I, above, wherein.

$R^1$ is phenyl, pyrrolyl, pyrrolidinyl, isoxazolyl, pyrazolyl, thiazolyl, tetrahydrofuranyl, furanyl, thienyl or tetrahydropyridazinyl, where said phenyl, pyrrolyl, pyrrolidinyl, isoxazolyl, pyrazolyl, thiazolyl, tetrahydrofuranyl, furanyl, thienyl or tetrahydropyridazinyl is unsubstituted or substituted with one or more substituents independently selected from alkyl, haloalkyl, halogen, and hydroxyl,

$R^2$ is a substituted phenylalkyl group, where said alkyl moiety of said substituted phenylalkyl group is a straight or branched chain alkyl moiety;

$R^{2'}$ is H, methyl, ethyl or propyl, where said methyl, ethyl or propyl is unsubstituted or substituted with hydroxyl;

X is  , wherein $R^x$ is H, halogen, or alkoxy;

Z is S, O, $CH_2$ or CFH;

$R^3$, $R^4$, $R^5$, $R^6$ and $R^{6'}$ are each H; and

$R^6$ and $R^7$ are independently selected from H or methyl;

provided that $R^1$ is selected from isoxazolyl, pyrazolyl, thiazolyl or tetrahydropyridazinyl, where said is isoxazolyl, pyrazolyl, thiazolyl or tetrahydropyridazinyl is unsubstituted or substituted with one or more substituents independently selected from alkyl, haloalkyl, halogen, and hydroxyl when $R^2$ is a substituted or unsubstituted phenylalkyl group or

provided that $R^1$ is selected from phenyl, pyrrolyl, pyrrolidinyl, isoxazolyl, pyrazolyl, thiazolyl, tetrahydrofuranyl, furanyl, thienyl or tetrahydropyridazinyl when $R^2$ is a substituted phenylalkyl group and said phenyl moiety of said substituted phenylalkyl group comprises one or more substituents other than halo or methyl, where said one or more substituents is independently selected from haloalkyl, amino, hydroxyl, alkoxy, haloalkoxy, alkylenedioxy, di-haloalkylenedioxy, cycloalkylalkyloxy, dialkylamino, alkylsulfonyl and alkylthio,

or a prodrug, pharmaceutically active metabolite or pharmaceutically active salt or solvate thereof.

In preferred embodiments, this invention relates to compounds of Formula I, above, wherein

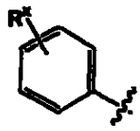
$R^1$ is phenyl, where said phenyl is substituted with one or more substituents independently selected from methyl, halogen or hydroxyl;

$R^2$ is a substituted phenylalkyl group, where said alkyl moiety of said substituted phenylalkyl group is a straight or branched chain alky moiety;

where said phenyl moiety of said substituted phenylalkyl group comprises one or more substituents other than halo or methyl, where said one or more substituents is independently

selected from trifluoromethyl, amino, hydroxyl, $C_1$-$C_4$alkoxy, alkylenedioxy, di-fluoro-alkylenedioxy, cyclopropylmethoxy, di-methyl-amino, methanesulfonyl and methylthio;

$R^2$ is H, methyl or ethyl;

X is  , wherein $R^x$ is H,

Z is S or O, and

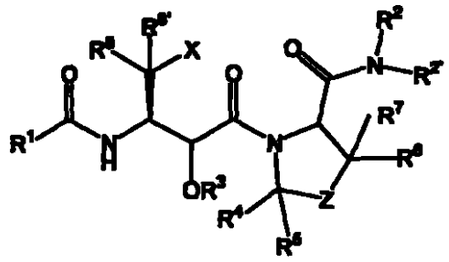
$R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$ and $R^{8'}$ are each H;

or a prodrug, pharmaceutically active metabolite or pharmaceutically active salt or solvate thereof.

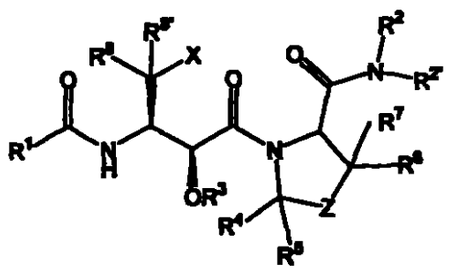
All compounds of this invention contain at least one chiral center and may exist as single stereoisomers (e.g., single enantiomers or single diastereomers), any mixture of stereoisomers (e.g., any mixture of enantiomers or diastereomers) or racemic mixtures thereof. All such single stereoisomers, mixtures and racemates are intended to be encompassed within the broad scope of the present invention Compounds identified herein as single stereoisomers are meant to describe compounds that are present in a form that contains at least 90% of a single stereoisomer of each chiral center present in the compounds. Where the stereochemistry of the chiral carbons present in the chemical structures illustrated herein is not specified, the chemical structure is intended to encompass compounds containing either stereoisomer of each chiral center present in the compound. Preferably, however, the inventive compounds are used in optically pure, that is, stereoisomerically pure, form or substantially optically pure (substantially stereoisomerically pure) form. As used herein, the term "stereoisomeric" purity (or "optical" purity) refers to the "enantiomeric" purity and/or "diastereomeric" purity of a compound Compounds that are substantially enantiomerically pure contain at least 90% of a single isomer and preferably contain at least 95% of a single isomer of each chiral center present in the enantiomer. Compounds that are substantially diastereomerically pure contain at least 90% of a single isomer of each chiral center present in the diastereomer, and preferably contain at least 95% of a single isomer of each chiral center. More preferably, the substantially enantiomerically and diastereomerically pure compounds in this invention contain at least 97.5% of a single isomer and most preferably contain at least 99% of a single isomer of each chiral center in the compound. The term "racemic" or "racemic mixture" refers to a mixture of equal amounts of enantiomeric

compounds, which encompasses mixtures of enantiomers and mixtures of enantiomeric diastereomers. The compounds of this invention may be obtained in stereoisomerically pure (i.e., enantiomerically and/or diastereomerically pure) or substantially stereoisomerically pure (i.e., substantially enantiomerically and/or diastereomerically pure) form. Such compounds may be obtained synthetically, according to the procedures described herein using optically pure or substantially optically pure materials. Alternatively, these compounds may be obtained by resolution/separation of a mixture of stereoisomers, including racemic mixtures, using conventional procedures. Exemplary methods that may be useful for the resolution/separation of stereoisomeric mixtures include chromatography and crystallization/re-crystallization. Other useful methods may be found in "*Enantiomers, Racemates, and Resolutions*," J. Jacques et al., 1981, John Wiley and Sons, New York, NY, the disclosure of which is incorporated herein by reference. Preferred stereoisomers of the compounds of this invention are described herein.

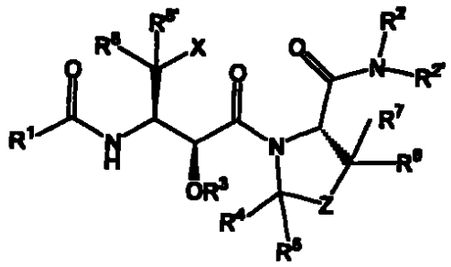
Especially preferred embodiments of this invention comprise compounds, wherein the stereogenic centers (chiral carbons) have the following designated stereochemistry:



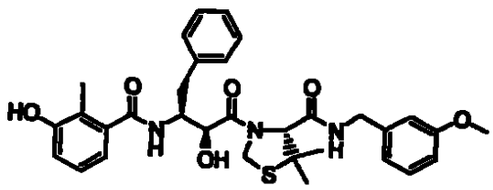
More preferably, at least two of the stereogenic centers have the following designated stereochemistry

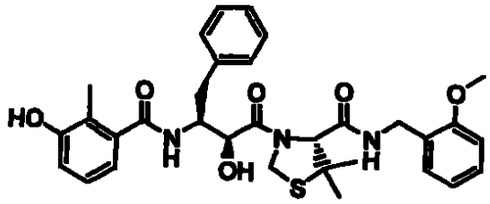


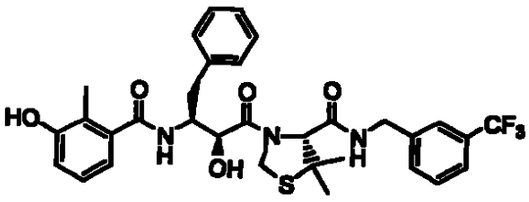
Even more preferably, at least three of the stereogenic centers have the following designated stereochemistry:

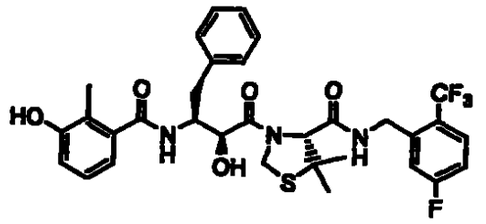


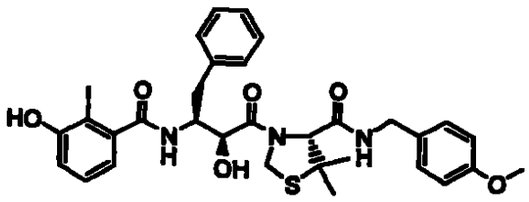
Exemplary compounds of this invention include:

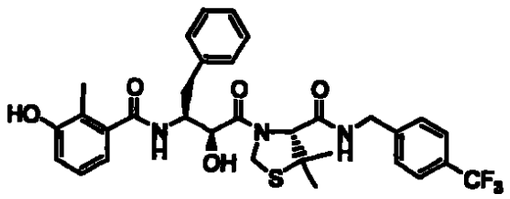


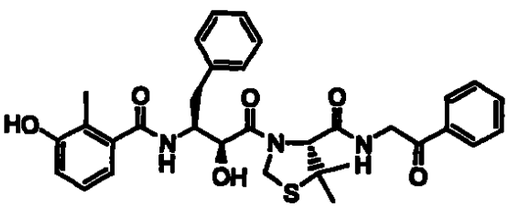


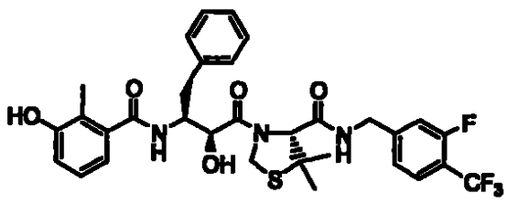


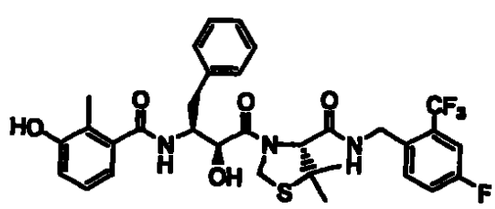


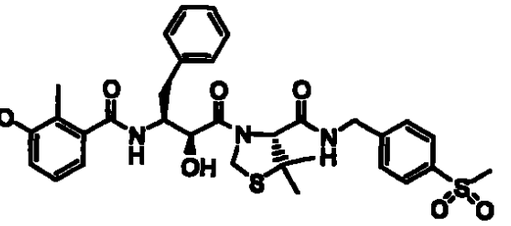


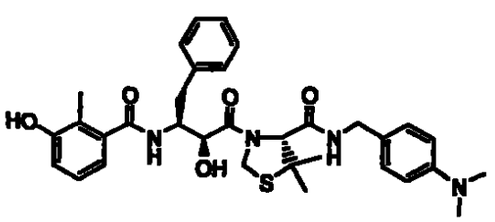


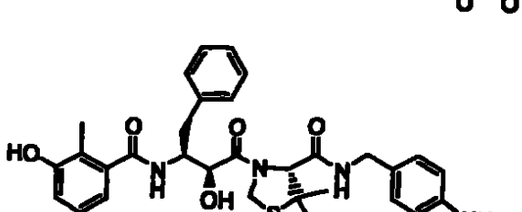






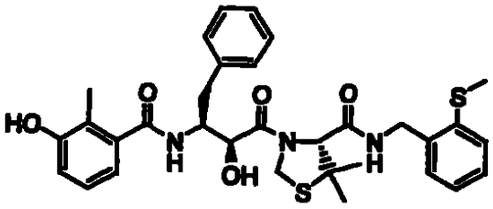


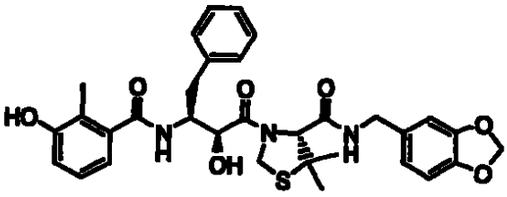


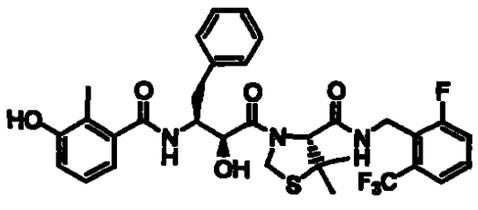


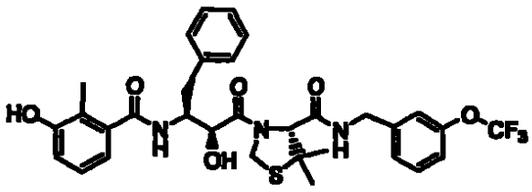


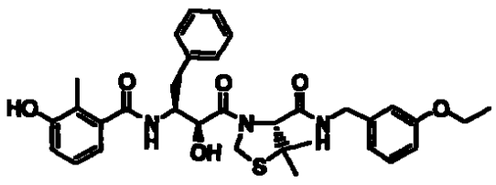


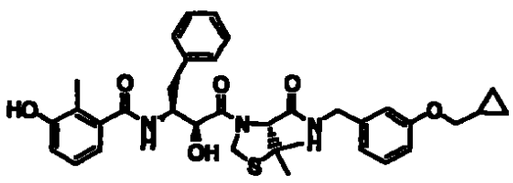


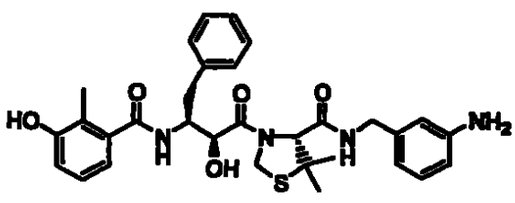


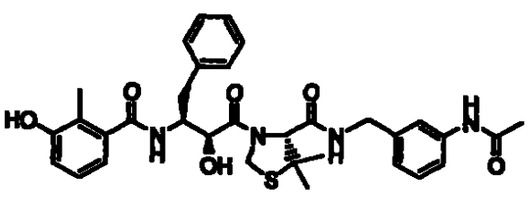


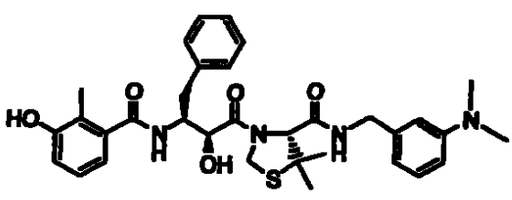


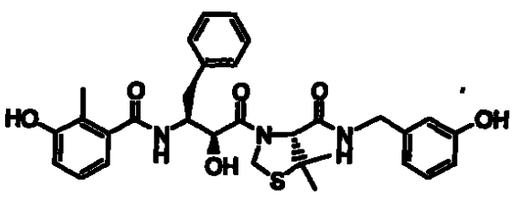


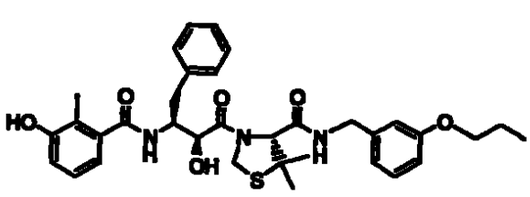


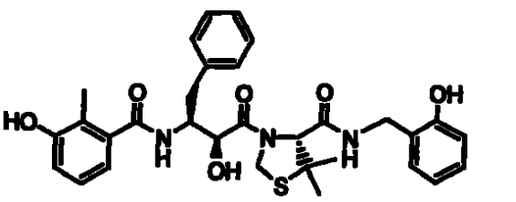


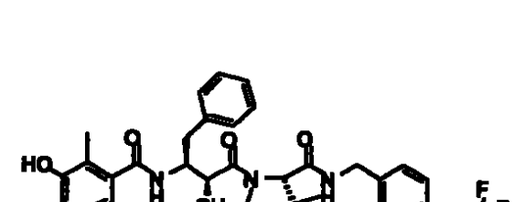


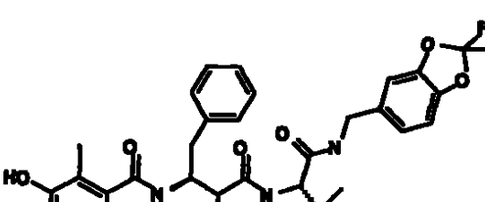


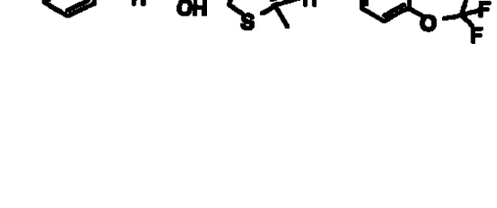


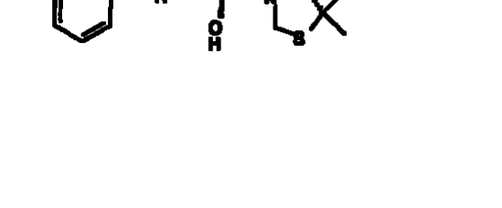


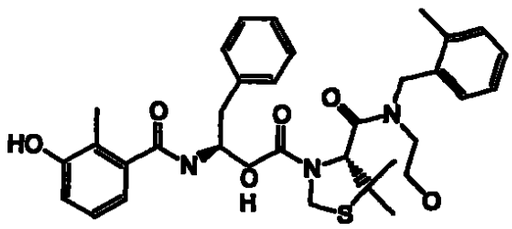


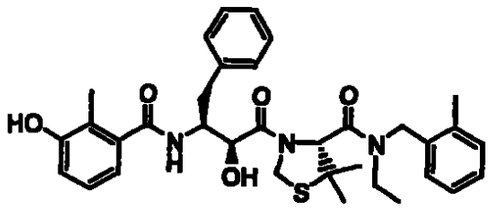


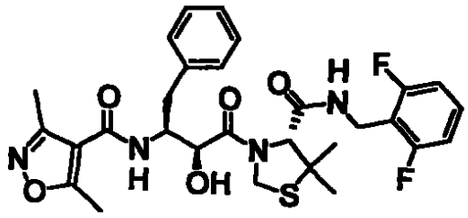


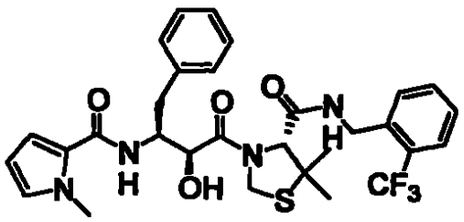


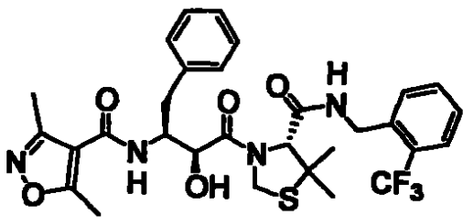


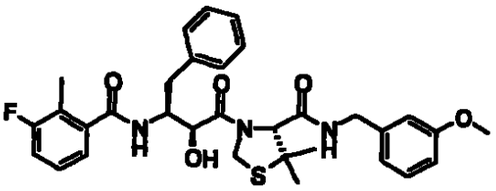


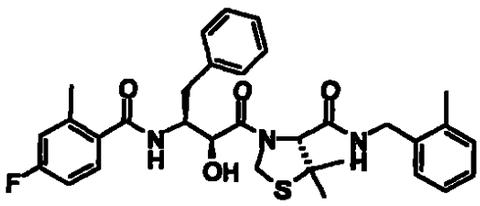




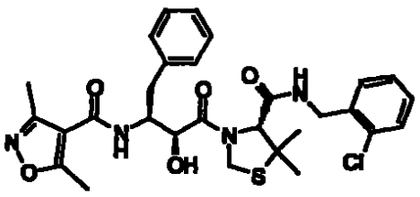


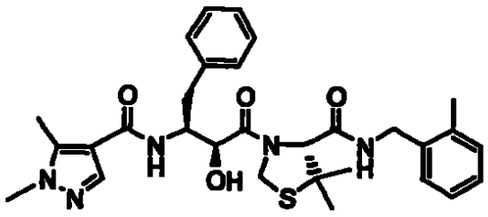


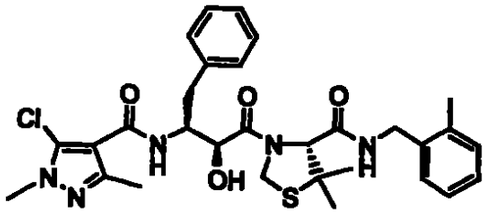


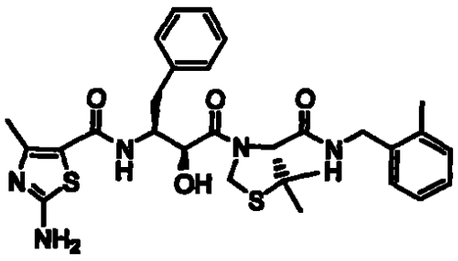


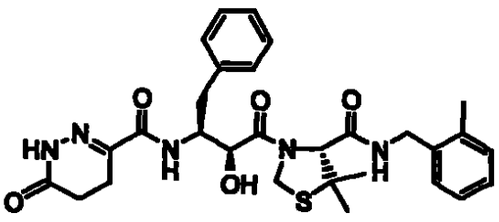
China

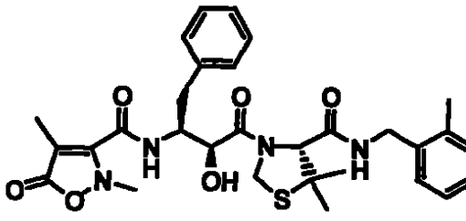


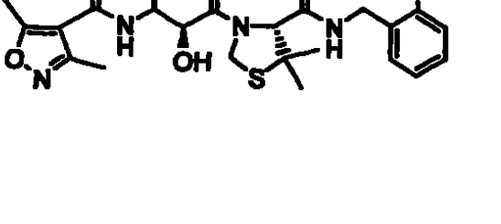


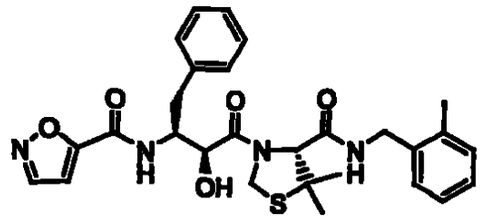


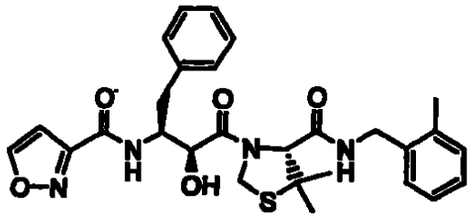


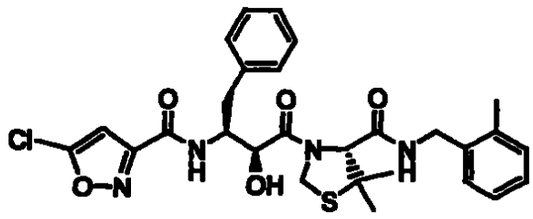


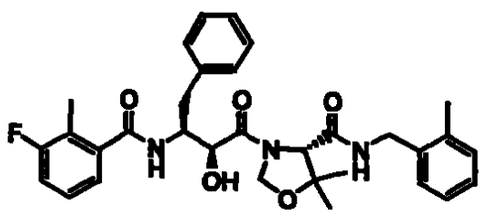


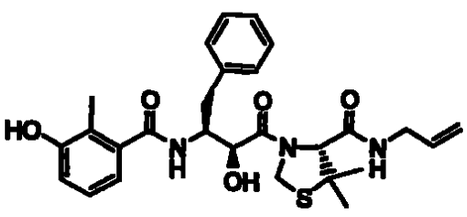


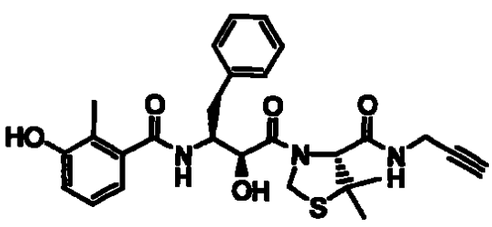


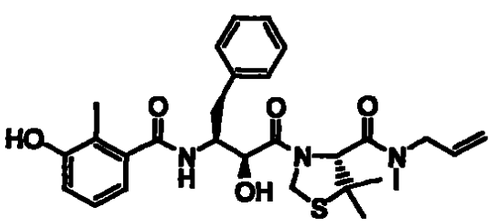


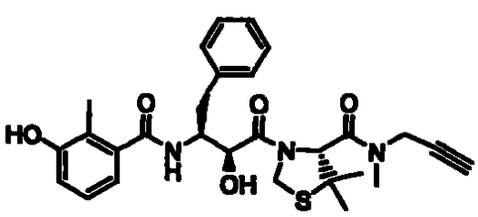


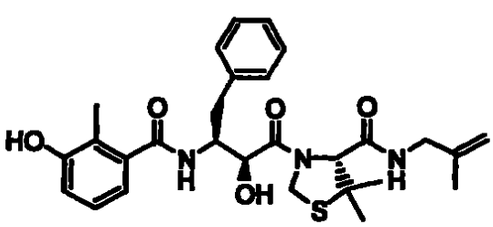


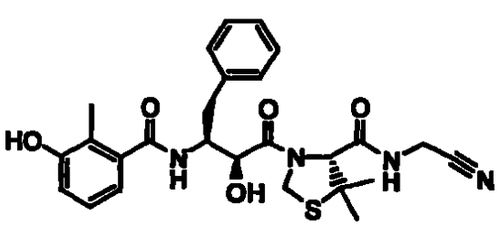


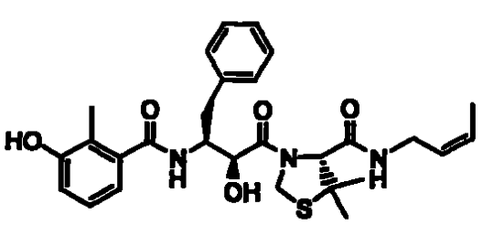


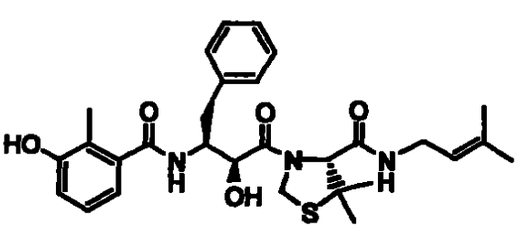


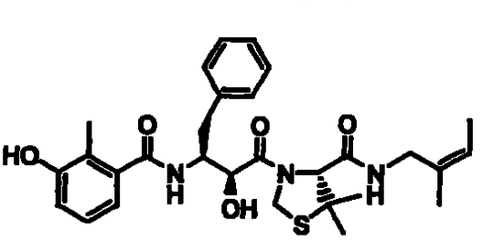


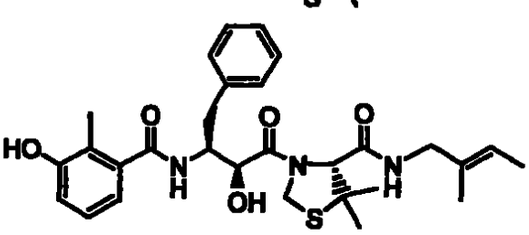


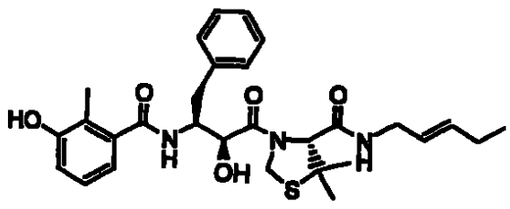


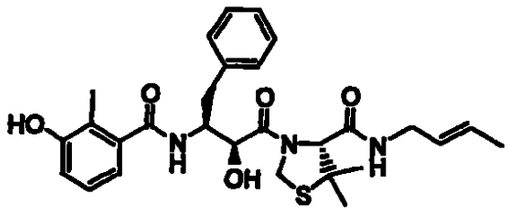


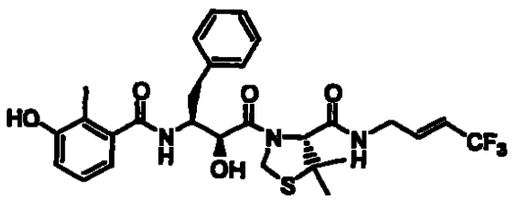


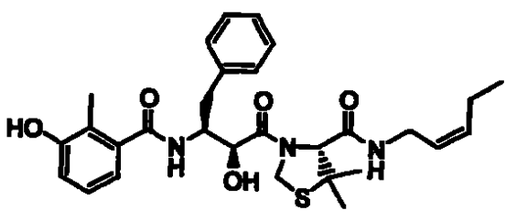


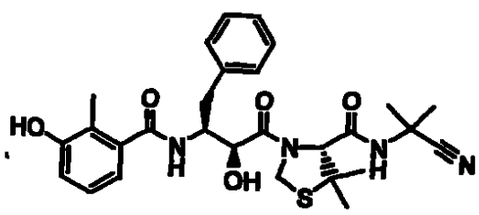


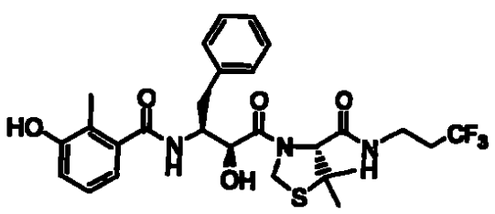


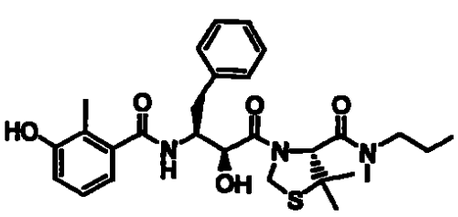


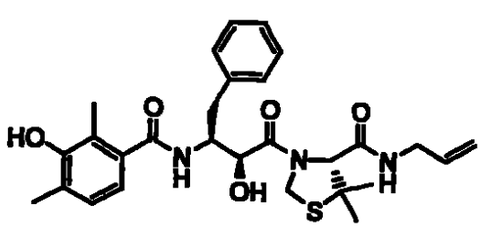


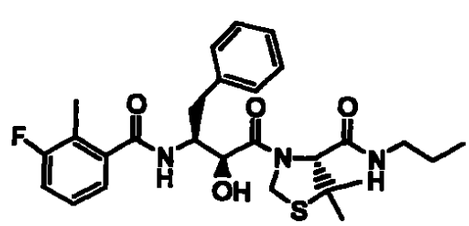


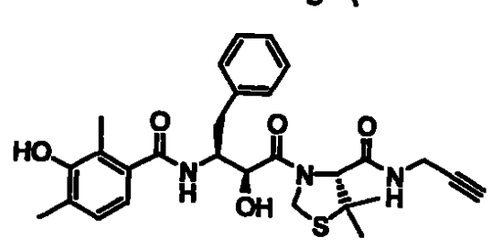


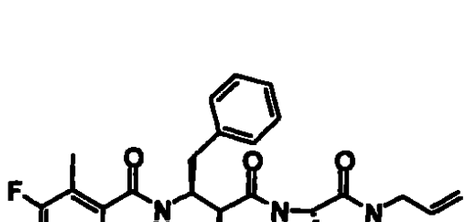


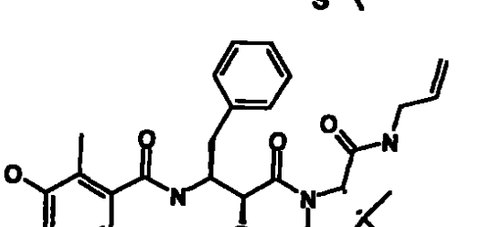


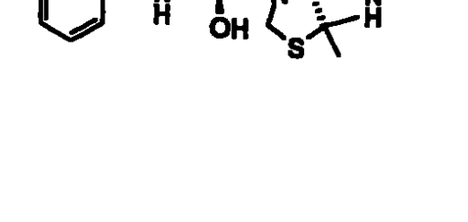


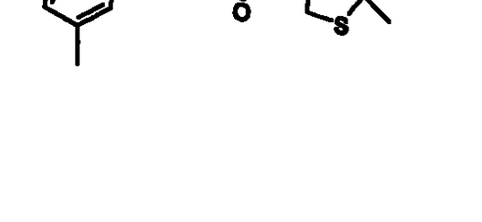


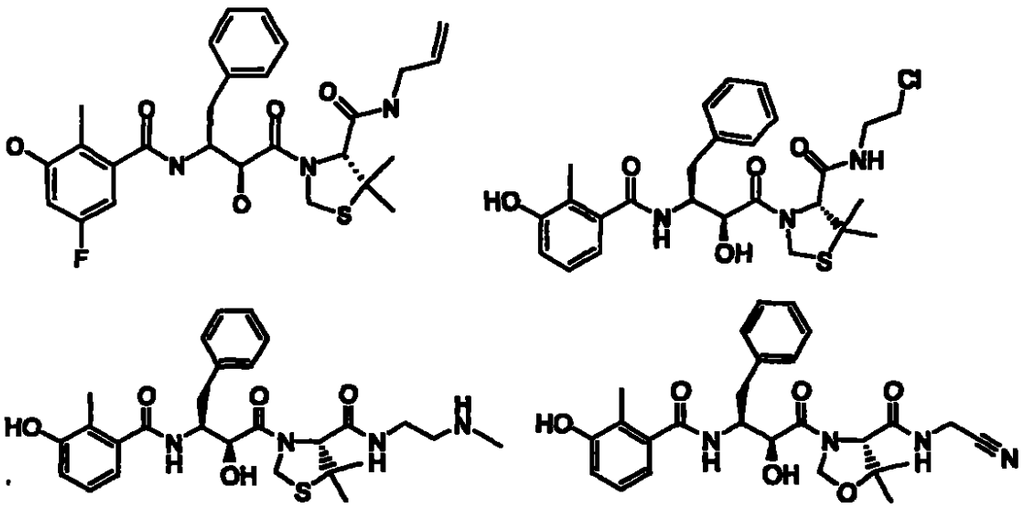






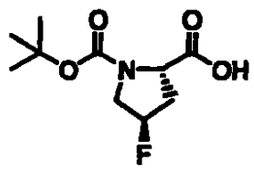




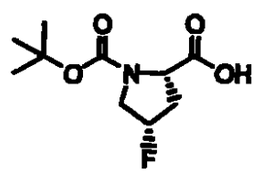


and the prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts and solvates thereof.

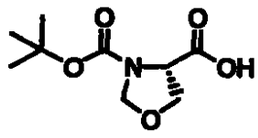
The invention is also directed to the intermediates of Formula II, which are useful in the synthesis of certain compounds of Formula I



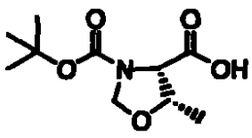
20a



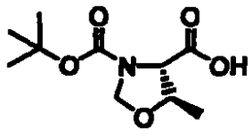
20b



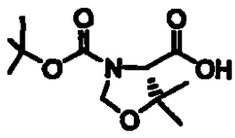
20c



20d



20e

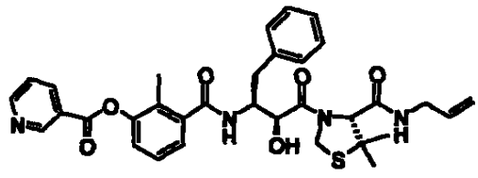


20f

The HIV protease inhibitor compounds of this invention include prodrugs, the pharmaceutically active metabolites, and the pharmaceutically acceptable salts and solvates thereof. In preferred embodiments, the compounds of Formula I, prodrugs, pharmaceutically acceptable salts, and pharmaceutically active metabolites and solvates thereof demonstrate an HIV-protease inhibitory activity, corresponding to $K_i$ of at least 100 nM, an $EC_{50}$ of at least 10 mM or an $IC_{50}$ of at least 10 mM. Preferably, the compounds of this invention demonstrate an HIV-protease inhibitory activity, corresponding to a $K_i$ of at least 10 nM, an

$EC_{50}$ of at least 1mM or an $IC_{50}$ of at least 1 mM More preferably, the compounds of this invention demonstrate an HIV-protease inhibitory activity against mutant strains of HIV, corresponding to a $K_i$ of at least 100 nM, an $EC_{50}$ of at least 10 mM or an $IC_{50}$ of at least 10 mM. Even more preferably, the compounds of this invention demonstrate protease inhibitory activity against mutant strains corresponding to a $K_i$ of at least 10 nM, an $EC_{50}$ of at least 1 mM or an $IC_{50}$ of at least 1 mM.

A "prodrug" is intended to mean a compound that is converted under physiological conditions or by solvolysis or metabolically to a specified compound that is pharmaceutically active. A prodrug may be a derivative of one of the compounds of this invention that contains a moiety, such as for example $-CO_2R$, $-PO(OR)_2$ or -C=NR, that may be cleaved under physiological conditions or by solvolysis. Any suitable R substituent may be used that provides a pharmaceutically acceptable solvolysis or cleavage product. A prodrug containing such a moiety may be prepared according to conventional procedures by treatment of a compound of this invention containing, for example, an amido, carboxylic acid, or hydroxyl moiety with a suitable reagent. A "pharmaceutically active metabolite" is intended to mean a pharmacologically active compound produced through metabolism in the body of a specified compound. Prodrugs and active metabolites of compounds of this invention of the above-described Formulas may be determined using techniques known in the art, for example, through metabolic studies See, e.g., "Design of Prodrugs," (Bundgaard, ed.), 1985, Elsevier Publishers B.V., Amsterdam, The Netherlands The following is an example of a prodrug that can be converted to the compound of this invention under physiological conditions, by solvolysis or metabolically:



A "pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of a specified compound and that is not biologically or otherwise undesirable. Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides,

acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycollates, tartrates, methane-sulfonates (mesylates), propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates. A "solvate" is intended to mean a pharmaceutically acceptable solvate form of a specified compound that retains the biological effectiveness of such compound. Examples of solvates include compounds of the invention in combination with water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or ethanolamine. In the case of compounds, salts, or solvates that are solids, it is understood by those skilled in the art that the inventive compounds, salts, and solvates may exist in different crystal forms, all of which are intended to be within the scope of the present invention and specified formulas.

The present invention is also directed to a method of inhibiting HIV protease activity, comprising contacting the protease with an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate thereof. For example, HIV protease activity may be inhibited in mammalian tissue by administering a compound of Formula I or a pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate thereof. More preferably, the present method is directed at inhibiting HIV-protease activity "Treating" or "treatment" is intended to mean at least the mitigation of a disease condition in a mammal, such as a human, that is alleviated by the inhibition of the activity of HIV proteases The methods of treatment for mitigation of a disease condition include the use of the compounds in this invention in any conventionally acceptable manner, for example, as a prophylactic. The activity of the inventive compounds as inhibitors of HIV protease activity may be measured by any of the suitable methods known to those skilled in the art, including *in vivo* and *in vitro* assays. Examples of suitable assays for activity measurements are escribed herein. Administration of the compounds of the Formula I and their pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates may be performed according to any of the generally accepted modes of administration available to those skilled in the art. Illustrative examples of suitable modes of administration include oral, nasal, parenteral, topical, transdermal, and rectal

An inventive compound of Formula I or a pharmaceutically acceptable salt, prodrug, active metabolite, or solvate thereof may be administered as a pharmaceutical composition in any pharmaceutical form recognizable to the skilled artisan as being suitable Suitable pharmaceutical forms include solid, semisolid, liquid, or lyophilized formulations, such as tablets, powders, capsules, suppositories, suspensions, liposomes, and aerosols. Pharmaceutical compositions of the invention may also include suitable excipients, diluents, vehicles, and carriers, as well as other pharmaceutically active agents, depending upon the intended use or mode of administration. Acceptable methods of preparing suitable pharmaceutical forms of the pharmaceutical compositions may be routinely determined by those skilled in the art. For example, pharmaceutical preparations may be prepared following conventional techniques of the pharmaceutical chemist involving steps such as mixing, granulating, and compressing when necessary for tablet forms, or mixing, filling, and dissolving the ingredients as appropriate, to give the desired products for oral, parenteral, topical, intravaginal, intranasal, intrabronchial, intraocular, intraaural, and/or rectal administration.

The present invention includes pharmaceutical compositions useful for inhibiting HIV protease, comprising an effective amount of a compound of this invention, and a pharmaceutically acceptable carrier. Pharmaceutical compositions useful for treating infection by HIV, or for treating AIDS or ARC, are also encompassed by the present invention, as well as a method of inhibiting HIV protease, and a method of treating infection by HIV, or of treating AIDS or ARC Additionally, the present invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention in combination with a therapeutically effective amount of an HIV infection/AIDS treatment agent selected from:

1) an HIV/AIDS antiviral agent,
2) an anti-infective agent, and
3) an immunomodulator.

The present invention also includes the use of a compound of the present invention as described above in the preparation of a medicament for (a) inhibiting HIV protease, (b) preventing or treating infection by HIV, or (c) treating AIDS or ARC.

The present invention further includes the use of any of the HIV protease inhibiting compounds of the present invention as described above in combination with one or more HIV

infection/AIDS treatment agents selected from an HIV/AIDS antiviral agent, an anti-infective agent, and an immunomodulator for the manufacture of a medicament for (a) inhibiting HIV protease, (b) preventing or treating infection by HIV, or (c) treating AIDS or ARC, said medicament comprising an effective amount of the HIV protease inhibitor compound and an effective amount of the one or more treatment agents

Solid or liquid pharmaceutically acceptable carriers, diluents, vehicles, or excipients may be employed in the pharmaceutical compositions. Illustrative solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, pectin, acacia, magnesium stearate, and stearic acid Illustrative liquid carriers include syrup, peanut oil, olive oil, saline solution, and water. The carrier or diluent may include a suitable prolonged-release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. When a liquid carrier is used, the preparation may be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid (e.g., solution), or a nonaqueous or aqueous liquid suspension. A dose of the pharmaceutical composition contains at least a therapeutically effective amount of the active compound (i.e., a compound of Formula I or a pharmaceutically acceptable salt, prodrug, active metabolite, or solvate thereof), and preferably is made up of one or more pharmaceutical dosage units. The selected dose may be administered to a mammal, for example, a human patient, in need of treatment mediated by inhibition of HIV protease activity, by any known or suitable method of administering the dose, including: topically (for example, as an ointment or cream), orally, rectally (for example, as a suppository), parenterally (by injection) or continuously by intravaginal, intranasal, intrabronchial, intraaural, or intraocular infusion A "therapeutically effective amount" is intended to mean the amount of an inventive agent that, when administered to a mammal in need thereof, is sufficient to effect treatment for disease conditions alleviated by the inhibition of the activity of one or more variant of the HIV protease. The amount of a given compound of the invention that will be therapeutically effective will vary depending upon factors such as the particular compound, the disease condition and the severity thereof, the identity of the mammal in need thereof, which amount may be routinely determined by artisans.

The compounds of this invention are also useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants that are excellent screening tools for more powerful

antiviral compounds Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HIV protease, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes

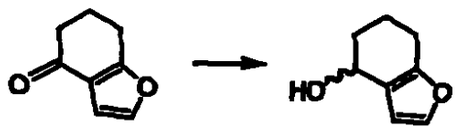
## GENERAL SYNTHETIC METHODS

Preferably, the inventive compounds are prepared by the methods of the present invention, including the General Methods shown below. When stereochemistry is not specified in chemical structures, either stereocenter may be utilized. The following abbreviations also apply: Boc (*tert*-butoxycarbonyl), Ac (acetyl), Cbz (benzyloxycarbonyl), DMB (2,4-dimethoxybenzyl), TBS (*tert*-butyldimethylsulyl), TBDPS (*tert*-butyldiphenylsilyl), Ms (methanesulfonate), Ts (toluenesulfonate), Bn (benzyl), and Tr (triphenylmethyl)

All reactions were performed in septum-sealed flasks under a slight positive pressure of argon unless otherwise noted. All commercial reagents and solvents were used as received from their respective suppliers with the following exceptions: Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Dichloromethane ($CH_2Cl_2$) was distilled from calcium hydride prior to use. Flash chromatography was performed using silica gel 60 (Merck art. 9385) $^1$H NMR spectra were recorded at 300 MHz utilizing a Varian UNITY*plus* 300 spectrometer. Chemical shifts are reported in ppm (δ) downfield relative to internal tetramethylsilane, and coupling constants are given in Hertz. Infrared absorption spectra were recorded using a Perkin-Elmer 1600 series FTIR spectrometer Elemental analyses were performed by Atlantic Microlab, Inc , Norcross, GA Melting points are uncorrected.

All P2' amine variants mentioned in General Methods A-E described hereinbelow were either purchased and used directly or synthesized as follows.

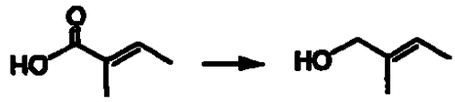
**METHOD A: REPRESENTATIVE PROCEDURE FOR REDUCTION OF KETONES TO ALCOHOLS.**



1 2

6,7-Dihydro-4-(5H)-benzofuranone (1) (1 00 g 7.34 mmol) was dissolved in methanol (55 mL). The mixture was cooled to 0 °C and $NaBH_4$ (0.31 g, 8.08 mmol) was added in portions The reaction was stirred for 2 h at 0 °C at which time the methanol was evaporated. The residue was dissolved in EtOAc and poured into $NaHCO_3$ (saturated aqueous) and extracted with EtOAc (3 x 10 mL) The combined organic extracts were washed with brine (10 mL), passed over a short plug of $Na_2SO_4$, and concentrated *in vacuo* to give 2 (1.01 g, 99%, as a mixture of isomers) as a pale yellow, thick oil, which was of sufficient quality to be advanced to the next step without further purification. Rf (50% EtOAc/hexanes): 0.53.

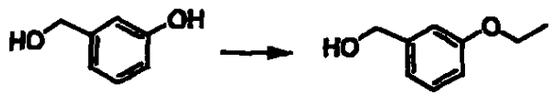
**METHOD B: REPRESENTATIVE PROCEDURE FOR REDUCTION OF ACIDS TO ALCOHOLS**



1 2

Tiglic acid (1) (20.0 g, 0.200 mol) was dissolved in ether (80ml) and added dropwise over 30 min to a suspension of $LiAlH_4$ (15.0 g, 0.417 mol) in ether (80 ml) at 0 °C and the reaction mixture was allowed to warm to room temperature. After 3 h the mixture was re-cooled to 0 °C and quenched slowly by the addition of $H_2O$ (15 ml), 15% NaOH (15 ml) and $H_2O$ (15 ml) The reaction mixture was filtered to remove the granular precipitate and washed thoroughly with ether. The filtrate was washed successively with 1N HCl, $NaHCO_3$ (saturated aqueous), and brine The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give (*E*)-2-methyl-but-2-en-1-ol (2) as a clear oil (12.8g, 74%).

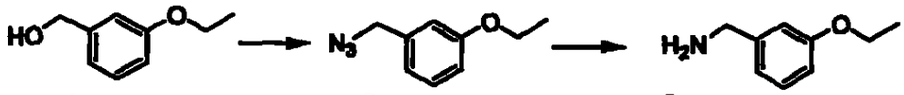
**METHOD C: REPRESENTATIVE PROCEDURE FOR ALKYLATION OF PHENOLS ALCOHOLS.**



1 2

3-Hydroxybenzylalcohol (1) (0.500 g 4 03 mmol) was dissolved in DMF (2 mL) at ambient temperature. Ethyl bromide (0.900 mL, 12.1 mmol) and finely crushed $K_2CO_3$ (2.78 g, 20.1 mmol) were added and the reaction mixture was stirred for 5 h. The DMF was then removed *in vacuo* and the residue was partitioned between EtOAc and $H_2O$, and extracted with EtOAc (3 x 10 mL). The organic layers were washed with brine (10 mL) and passed over a short plug of $Na_2SO_4$ The solvents were removed *in vacuo* to give alcohol 2 (0 55 g, 90%) as a pale yellow, thick oil, which was of sufficient quality to be advanced to the next step without further purification. Rf (40% EtOAC/hexanes). 0 69.

**METHOD D: REPRESENTATIVE PROCEDURE FOR CONVERSION OF ALCOHOLS TO AMINES.**



1 2 3

3-Ethoxy-phenyl-methanol (1) (1.23 g 8.08 mmol) was dissolved in $CH_2Cl_2$ (10 mL) at ambient temperature and diphenylphosphoryl azide (2.67 g, 9.70 mmol) and 1,8-diazabicyclo [5.4 0] undec-7-ene (1.45 mL, 9 70 mmol) were added The mixture was stirred for 5 h at which time the $CH_2Cl_2$ was removed *in vacuo* and the crude residue was partitioned between EtOAc and $H_2O$ and extracted with EtOAc (3 x 10 mL) The combined organic layers were washed with brine (10 mL), passed over a short plug of $Na_2SO_4$, and concentrated *in vacuo* to give a yellow oil that was loaded directly onto a flash silica gel column and was quickly eluted with 10% EtOAc/hexanes. The solvents were removed *in vacuo* to give azide 2 (1.43 g, 84%) as a colorless oil. Rf (30% EtOAc/hexanes) 0 79

1-Azidomethyl-3-ethoxy-benzene (2) (1.19 g 6.71 mmol) was dissolved in MeOH (15 mL) and palladium 10% on activated carbon, wet (20% in weight) was added. The reaction was hydrogenated for 30 min at 40 PSI in a Parr Hydrogenator The black suspension was then filtered through compacted celite and the methanol was removed *in vacuo* to give amine

3 (0.88 g, 88%) as a pale yellow, thick oil, which was of sufficient quality to be advanced to the coupling reactions without further purification.

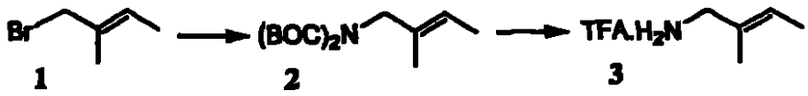
**METHOD E: REPRESENTATIVE PROCEDURE FOR CONVERSION OF ALCOHOLS TO BROMIDES.**




1 2

Cis-2-penten-1-ol (1) (1.00 g, 11.6 mmol) and carbon tetrabromide (3 85 g, 13.9 mmol) were dissolved in $CH_2Cl_2$ (75 mL). The mixture was cooled to 0 °C and triphenylphosphine (3.65 mL, 13.9 mmol) dissolved in $CH_2Cl_2$ (50 mL) was added dropwise. . The mixture was allowed to warm to room temperature and was stirred overnight. The $CH_2Cl_2$ was removed *in vacuo* and the crude residue was loaded directly onto a flash silica gel column and eluted quickly with 20% EtOAc/hexanes. The solvents were removed *in vacuo* to give bromide 2 (1.53 g, 88%) as a colorless volatile oil. Rf (30% EtOAC/hexanes): 0 89.

**METHOD F: REPRESENTATIVE PROCEDURE FOR CONVERSION OF BROMIDES TO AMINES.**

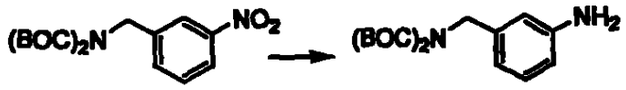



1 2 3

A mixture of bromide 1 (3.00 g, 20.1 mmol), di-tert-butyl-iminodicarboxylate (4.8 g, 22 mmol), and $K_2CO_3$ (3.10 g, 80.4 mmol) in DMF (30ml) was stirred at ambient temperature overnight. The mixture was partitioned between 1N HCl and EtOAc. The organic layer was washed with $H_2O$ and brine, then dried over $NaSO_4$. Concentration *in vacuo* affored a yellow oil which upon purification by flash column chromatography (hexanes to 5% EtOAc/Hexane gradient) yielded protected amine 2 as a clear oil (2.0g, 35%).

A mixture of the diBOC amine 2 (2.0 g, 7.0 mmol), trifluoroacetic acid (2.7 ml, 35 mmol) and $CH_2Cl_2$ (40 ml) was stirred at ambient temperature overnight. The reaction mixture was concentrated *in vacuo* to give the TFA salt of (*E*)-2-methyl-but-2-enylamine (3)

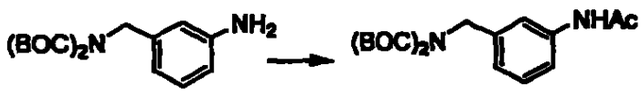
**METHOD G: REPRESENTATIVE PROCEDURE FOR REDUCTION OF AROMATIC NITRO GROUPS BY HYDROGENATION.**




1 2

Compound 1 (2.04, 5.79 mmol) was dissolved in EtOAc (20 mL) and palladium 10% on activated carbon, wet (20% in weight) was added. The reaction was hydrogenated for 4h at 45 PSI in a Parr Hydrogenator. The black suspension was then filtered through compacted celite and the methanol was removed *in vacuo* to give aniline 2 (1.65 g, 88%) as a pale yellow, thick oil, which was of sufficient quality to be advanced to the acetylation reaction without further purification.

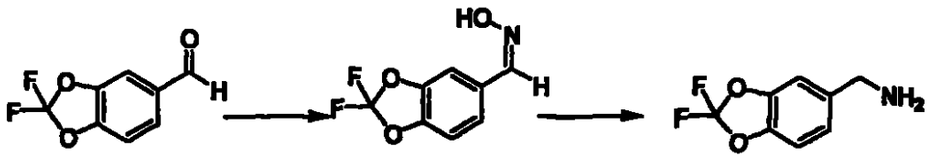
**METHOD H: REPRESENTATIVE PROCEDURE FOR ACETYLATION OF ANILINES.**




1 2

Aniline 1 (1.65 g, 5.12 mmol) was dissolved in $CH_2Cl_2$ (25 mL) at ambient temperature. Acetyl chloride (0 48 g, 6 14 mmol) and *N,N*-Diisopropylethylamine (0.79 g, 6.14 mmol) were added, and the reaction was stirred overnight. The $CH_2Cl_2$ was removed *in vacuo* and the crude residue was partitioned between EtOAc and 5% $KHSO_4$ and extracted with EtOAc (3 x 10 mL) The combined organic extracts were washed with $NaHCO_3$( saturated aqueous, 10 mL), brine (10 mL), and dried over $Na_2SO_4$. The solvents were removed *in vacuo* to give an orange oil which was of sufficient quality to be advanced to the next step without further purification. Rf (50% EtOAC/hexanes): 0 42

**METHOD I: REPRESENTATIVE PROCEDURE FOR REDUCTION OF ALDEHYDES TO AMINES.**

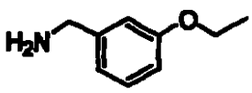


1 2 3

Hydroxyl amine hydrochloride (758 mg, 10.7 mmol) and pyridine (2 16 mL) was added to a solution of 2,2-difluoro-5-formyl benzodioxole (1) (2 00 g, 10.7 mmol) in MeOH (10 mL). After 18 hours the MeOH was removed *in vacuo*. The reaction mixture was diluted with EtOAc and was washed sequentially with $H_2O$, 10% w/v $CuSO_4$, and brine and then dried over $MgSO_4$. The solution was concentrated *in vacuo*. The hydroxy imine was purified by column chromatography using 20% EtOAc/Hexanes to give 1.37 g (64% yield) of a white solid. Imine was then subjected to LAH reduction as described above to provide amine 3.

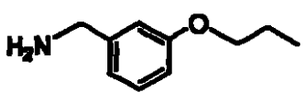
The following amines were synthesized for the corresponding example numbers:

**Example A26**



Amine was generated by alkylation of 3-hydroxybenzyl alcohol with ethyl bromide as describe in method C above followed by conversion of the alcohol to the amine as described in method D above provided desired amine.

**Example A43**

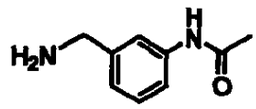


Amine was generated as described above for Example A43 using propylbromide as the alkylating agent.

30

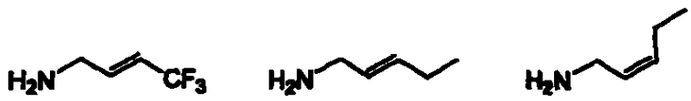
29

**Example A33**



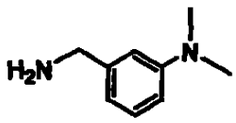
Amine was generated from displacement of bromide in 3-nitrobenzylbromide with di BOC amine as described in method F above. Reduction of the nitro moiety to the aniline (method G above) followed by acetylation (method H above) and BOC removal (method F above) provided desired amine.

**Example A36, Example A37 and Example A40**



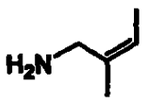
Amines were generated from conversion of the corresponding primary alcohols as described in method E above Displacement of the bromide with di BOC amine and deprotection with TFA (method F above) provided the desired amines.

**Example A39**



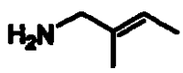
Amine was generated from 3-dimethylaminobenzyl alcohol as described in method D above.

**Example A34**



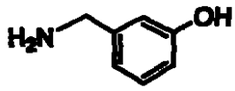
Amine was generated by reduction of the corresponding methyl ester to the primary alcohol (Wipf, *J Org. Chem.* 1994, *59*, 4875-86.). Conversion to the bromide (method E above) followed by displacement with diBOC amine and deprotection (method F above) provided desired amine

**Example A35**



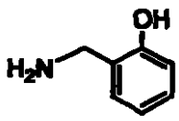
Amine was generated from the corresponding carboxylic acid. Reduction of the acid as described in method B above followed by bromide displacement as described in method E above gave the primary bromide. Conversion of the bromide to the primary amine followed the procedure described in method F above

**Example A42**



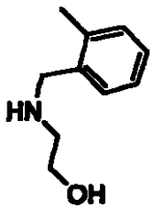
Amine was generated from 3-benzyloxybenzyl alcohol. Conversion to the azide and reduction of both the azide and benzyl protecting group were accomplished using method D as described above with longer hydrogenation time.

**Example A44**



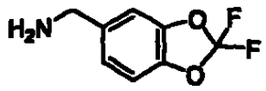
Amine was generated by $LiAlH_4$ reduction of 2-cyanophenol (Ludeman, S.M., et. al. *J. Med. Chem* 1975, *18*, 1252-3.)

**Example A50**



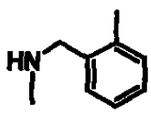
Amine was generated from the condensation of o-tolualdehyde with 2-aminoethanol followed by reduction with sodium borohydride (*Tetrahedron Assym.* 1997, *8*, 2367-74.).

**Example A48**



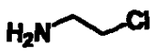
Amine was generated from the corresponding aldehyde by the reductive amination procedure described in method I above.

**Example A7**



Amine was generated by a reductive amination with the corresponding aldehyde (*Arch. Pharm.* 1987, *320*, 647-54.).

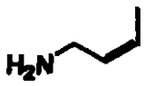
**Example A49**



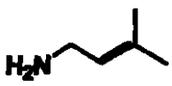
Amine was generated on the thiazolidine core as follows

Diphenylchlorophosphate (1.0 ml, 4.2 mmol) followed by triethylamine (0 59 ml, 4.2 mmol) were added to a cooled 0 °C solution of BOC-DMTA 1 (1.0 g, 3 8 mmol) in EtOAc (10 ml). The mixture was stirred for 1 h and at which time triethylamine (0.59 ml, 4.2 mmol) and ethanolamine (0.25 ml, 4.2 mmol) were added The reaction was left to stir overnight at ambient temperature and then partitioned between 1N HCl and EtOAc. The organic layer was washed with $NaHCO_3$(saturated aqueous) and brine. The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo* to a pale yellow oil 2. The oil was stirred with thionyl chloride (2 ml) for 45 min at room temperature. The mixture was concentrated *in vacuo* and the residual oil was partitioned between 1N NaOH and EtOAc. The organic layer was extracted with 1N HCl (2 x 20 ml). The combined aqueous layers were made basic with 1N NaOH and then extracted with EtOAc (3 x 60 ml) The organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated *in vacuo* to give (R)-5,5-Dimethyl-thiazolidine-4-carboxylic acid (2-chloro-ethyl)-amide 3 as a clear oil (0.39 g, 55%).

The following amines were prepared as described.



Example A31



Example A32



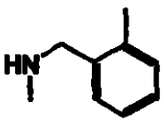
Example A38

The above amines were prepared according to Carlsen, H. J., *J Heterocycle Chem* 1997, *34*, 797-806.



Example A41

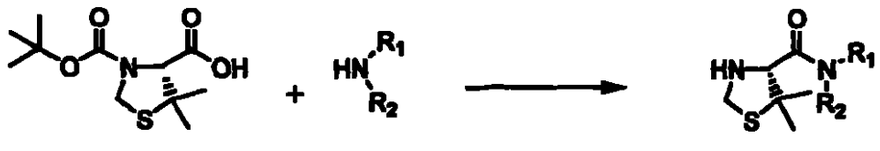
The above amine was prepared according to O'Brien, P. M., *J Med. Chem.* 1994, *37*, 1810-1822.



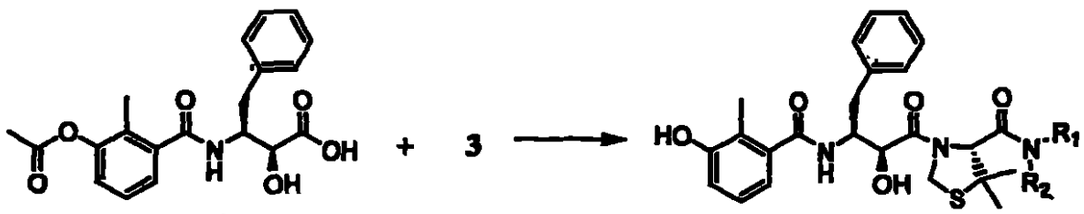
Example A7

The above amine was prepared according to Weinheim, G. *Arch. Pharm.* 1987, *320*, 647-654.

**General Method A**

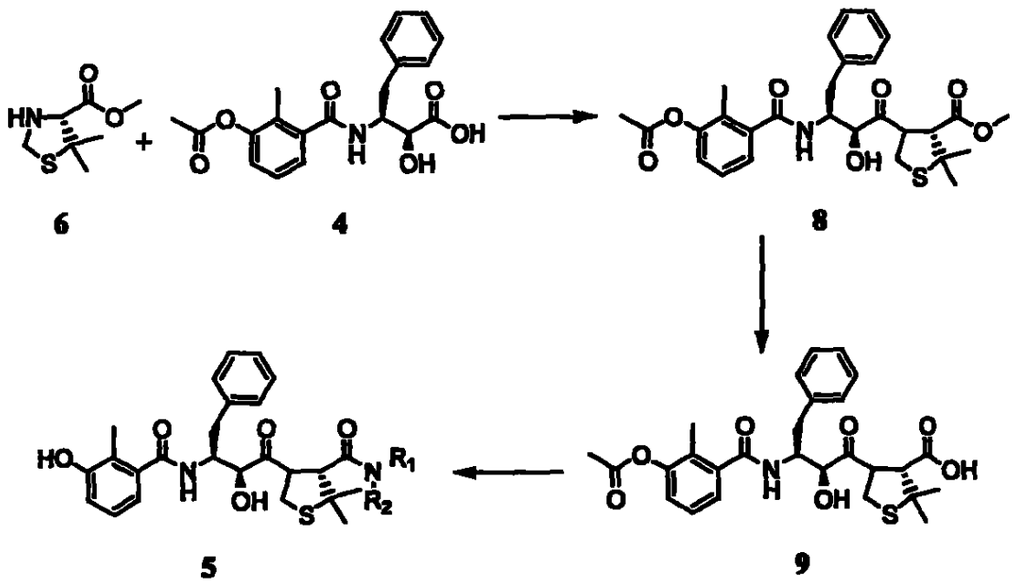


1 2 3



4 5

The synthesis of compounds with the general structure 5 is as follows. The boc-protected thiazolidine carboxylic acid 1 is coupled to the requisite amines 2 to yield amino amides 3 using a two step process. The process includes treatment of 1 with 2 in the presence of either diphenylchlorophosphate or HATU, followed by exposure to methane sulfonic acid. Final compounds 5 are obtained by a DCC-mediated coupling of 3 and 4 followed by deprotection of the P2 phenol. Final compounds were purified either by flash chromatography or preparative HPLC.

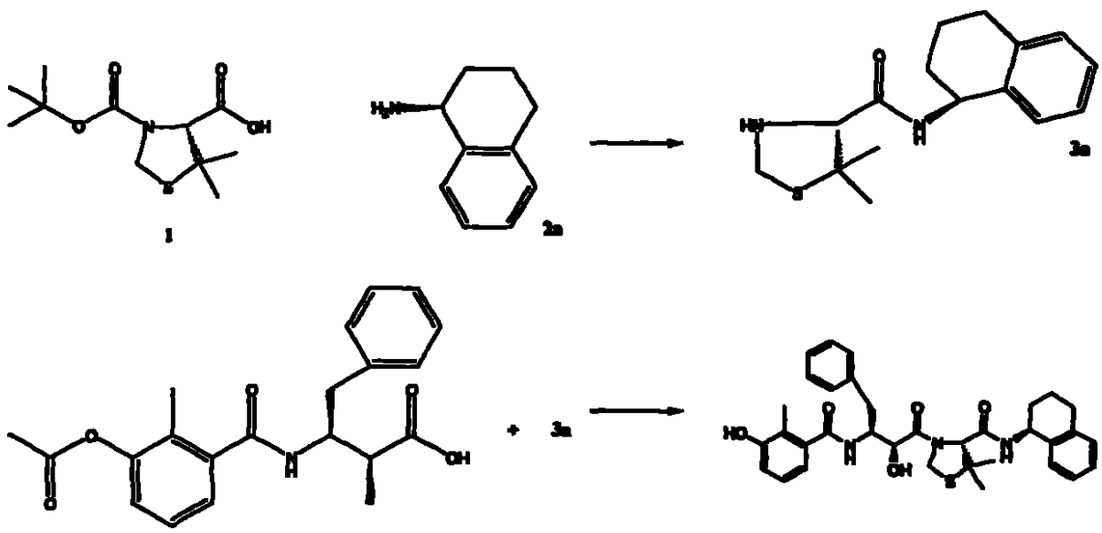


6 4 8

9 5

An alternative approach to the general structure 5 is as follows The thiazolidine ester 6 is coupled to acid 7 under carbodiimide reaction conditions, resulting in product 8 which is converted to acid 9 by mild base hydrolysis. Acid 9 is combined with various amines, using diphenylphosphoryl azide, followed by cleavage of the P2 acetate to yield final compounds 5. The products were purified by either flash chromatography or preparative HPLC

**Specific Method A.**

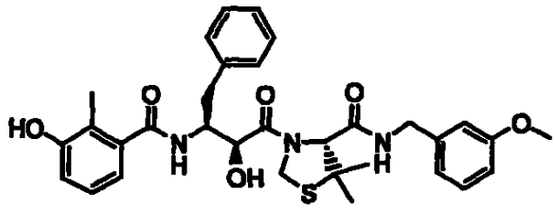


**Example A1:3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (1,2,3,4-tetrahydro-naphthalen-1-yl)-amide**

The title compound was prepared as follows (R)-5,5-Dimethyl-thiazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 1 (0.3 g, 1.15 mmol) was dissolved in EtOAc (3 mL) and cooled to 0 °C. Diphenyl chlorophosphate (0.26 mL, 1.26 mmol) was added followed by TEA (0.18 mL, 1.26 mmol) The reaction was stirred at 0 °C for 1h, and treated with (S)-1,2,3,4-Tetrahydro-1-naphthylamine (0.19 g, 1 26 mmol). The reaction mixture was stirred at room temperature overnight, then partitioned between 1N HCl (5 mL) and EtOAc (10 mL). The organic layer was washed with saturated $NaHCO_3$, brine, dried over $Na_2SO_4$ and concentrated to a light yellow oil. The resulting crude oil was dissolved in EtOAc (5 mL) and the cooled to 0 °C. Methanesulfonic acid (0.36 mL, 5.32 mmol) was added and the solution was stirred at 0 °C for 15 minutes, then at room temperature for 1h. The mixture was re-cooled to 0 °C and quenched with 5% $Na_2CO_3$ (5 mL) then extracted with EtOAc (10 mL). The organic layer was washed with brine, dried over $Na_2SO_4$ and concentrated in vacuo to give 3a as a yellow oil. The yellow oil 3a (0.34 g, 1.15 mmol) was dissolved in EtOAc (12 mL). AMB-AHPBA 4 (0.40 g, 1.09 mmol) was added followed by HOBt (0.15 g, 1 09 mmol). The mixture was stirred at room temperature 1h, then cooled to 0 °C DCC (0.24 g, 1.15 mmol) was slowly added as solution in EtOAc (6 mL) The mixture was warmed to room temperature and

stirred overnight The mixture was filtered and the filtrate was washed with 1N HCl (10 mL), saturated $NaHCO_3$ (10 mL), brine (10 mL), dried over $Na_2SO_4$ and concentrated to give a crude white solid (contaminated with DCU). The DCU was removed by flash chromatography (30% to 50% EtOAc in hexanes) to provide a white solid, which was dissolved in MeOH (2 mL) and treated with 4N HCl in 1,4-dioxane (0.26 mL, 1 1 mmol). The reaction was stirred at room temperature overnight then partitioned between 1N HCl (10 mL) and EtOAc (10 mL) The organic layer was washed with saturated $NaHCO_3$, dried over $Na_2SO_4$ and concentrated to a residue which was purified by flash chromatography (60% EtOAc in hexanes) to provide the title compound as a white solid mp = 125-126 °C; IR ($cm^{-1}$) 3320, 2932, 1704, 1644, 1530, 1454, 1361, 1284, $^1H$ NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.28 (d, $J$ = 8.6, 1H), 8.21 (d, $J$ = 8 8, 1H), 7.35-6.91 (m, 10H), 6 76 (d, $J$ = 8.0, 1H), 6.54 (d, $J$ = 7.5, 1H), 5.34 (d, $J$ = 6.0, 1H), 5.13 (d, $J$ = 9.0, 1H), 5.02 (d, $J$ = 9.0, 1H), 4 60-4 30 (m, 4H), 2.81-2.68 (m, 4H), 1.81 (s, 3H), 1 78-1.60 (m, 4H), 1 48 (s, 3H), 1.45 (s, 3 H); Anal. Calcd for $C_{34}H_{39}N_3O_5S$•1.5 $H_2O$. C, 64.95; H, 6 73, N, 6.68. Found: C, 64.88; H, 6.31; N, 6.18

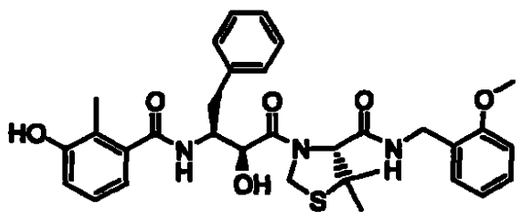
**Example A2: (R)-3-((2S,3R)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 3-methoxy-benzylamide**




White solid· mp 108-110 °C; IR (neat, $cm^{-1}$) 3310, 2965, 1644, 1586, 1531, 1455, 1359, 1284, $^1H$ NMR (DMSO-$d_6$) δ 9.37 (s, 1H), 8.40 (t, $J$ = 6.0, 1H), 8.09 (d, $J$ = 8.1, 1H), 7.31-6.52 (m, 12H), 5.49 (d, $J$ = 6.0, 1H), 5.12 (d, $J$ = 9.3, 1H), 5.00 (d, $J$ = 9.3, 1H), 4.44-4.35 (m, 3H), 4.42 (s, 1H), 4 09 (dd, $J$ = 15.0, 6 0, 1H), 3.69 (s, 3H), 2 87-2 67 (m, 2H), 1.82 (s, 3H), 1.49 (s, 3H), 1 34 (s, 3 H); Anal Calcd for $C_{32}H_{37}N_3O_6S$•0 75 $H_2O$: C, 63.50; H, 6.41, N, 6.94. Found. C, 63.60; H, 6.23; N, 6 80.

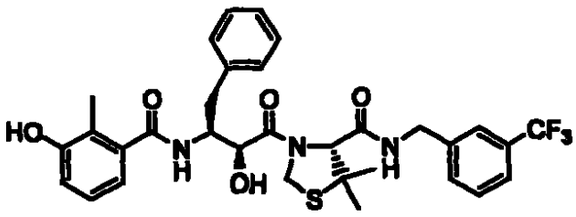
The following examples were prepared by the specific method outlined above using the requisite amine 2.

**Example A3: (R)-3-(2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methoxy-benzylamide**



White solid: mp = 123-125 °C; IR ($cm^{-1}$) 3318, 2965, 1644, 1525, 1495, 1464, 1286, 1246, 1120, 1030; $^1H$ NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.26 (t, $J$ = 5.9, 1H), 8.14 (d, $J$ = 8.0, 1H), 7.39-7.13 (m, 6H), 6 95-6.76 (m, 5H), 6.53 (d, $J$ = 7.5, 1H), 5.49 (d, $J$ = 6.0, 1H), 5.13 (d, $J$ = 9.0, 1H), 5.01 (d, $J$ = 9.0, 1H), 4.47 (s, 1H), 4 41-4.16 (m, 4H), 3 78 (s, 3H), 2.90-2.62 (m, 2H), 1.81 (s, 3H), 1.49 (s, 3H). 1.32 (s, 3H); Anal. Calcd for $C_{32}H_{37}N_3O_6S$·0.75 $H_2O$: C, 63.50; H, 6.41; N, 6.94. Found. C, 63.68; H, 6.20; N, 6 54.

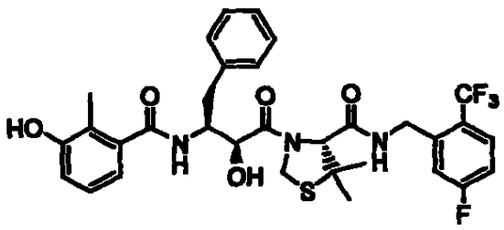
**Example A4: 3-(2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 3-trifluoromethyl-benzylamide**



White solid: mp = 108-110 °C; IR ($cm^{-1}$) 3308, 3065, 1646, 1540, 1456, 1362, 1329, 1284, 1165, 1125, 1074; $^1H$ NMR (DMSO-$d_6$) δ 9.38 (s, 1H), 8.56 (t, $J$ = 6.0, 1H), 8.12 (d, $J$ = 8.2, 1H), 7.65 (s, 1H), 7 60-7.47 (m, 3H), 7.28-7.13 (m, 5H), 6 96-6 92 (m, 1H), 6 77 (d, $J$ = 8.0,

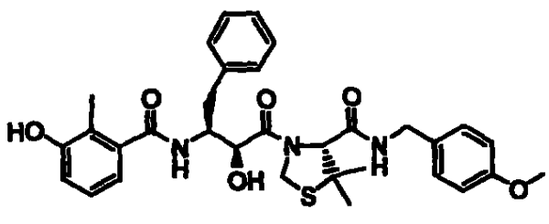
1H), 6 53 (d, $J$ = 7 5, 1H), 5.45 (d, $J$ = 6.0, 1H), 5.14 (d, $J$ = 9.2, 1H), 5 00 (d, $J$ = 9.2, 1H), 4.53-4 41 (m, 4H), 4.22 (dd, $J$ = 16.0, 6 0, 1H), 2.86-2.66 (m, 2H), 1.81 (s, 3H), 1.49 (s, 3H), 1.31 (s, 3 H); Anal. Calcd for $C_{32}H_{34}F_3N_3O_5S$: C, 61.04, H, 5.44; N, 6.67. Found : C, 61.03; H, 5.56, N, 6.51.

**Example A5: 3-(2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methyanoyl]amino} -4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxlic acid fluoro trifluoromethyl-benzylamide**



$^1$H NMR (DMSO-$d_6$) δ 9.33 (s, 1H), 8.69 (t, $J$ = 5.6, 1H), 8.12-6.56 (m, 11H), 5.50 (d, $J$ = 6.0, 1H), 5.22 (d, $J$ = 9.3, 1H), 5.06 (d, $J$ = 9.3, 1H), 4.60-4.36 (m, 5H), 4.50 (s, 1H), 2.89-2.67 (m, 2H), 1.83 (s, 3H), 1.55 (s, 3H), 1 39 (s, 3H), Anal. Calcd for $C_{32}H_{31}N_3O_5SF_4$: C, 59.34; H, 5.14; N, 6.49; S, 4.95 Found C, 59.06; H, 5.31, N, 6.22; S, 4 66

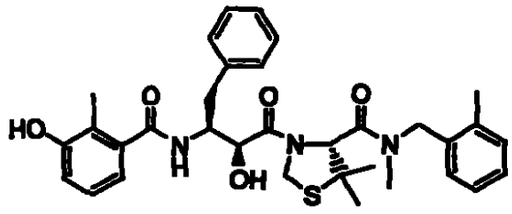
**Example A6: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 4-methoxy-benzylamide**



IR (neat cm$^{-1}$) 3335, 2920, 1641, 1516, 1463, 1374, 1285, 1249, 1172, 1118, $^1$H NMR (DMSO-$_{d6}$) δ 9.38 (s, 1H), 8.37 (t, $J$ = 5.5, 1H), 8 12 (d, $J$ = 8.2, 1H), 7.33-7.13 (m, 7H), 6.94

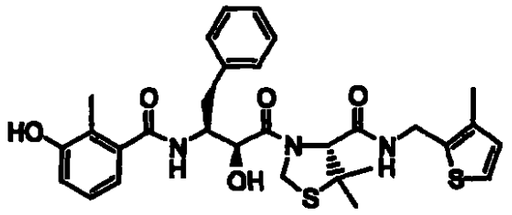
(t, $J$ = 7.7, 1H), 6.84-6.79 (m, 3H), 6.54 (d, $J$ = 7 0, 1H), 5 48 (d, $J$ = 6.6, 1H), 5 12 (d, $J$ = 9.2, 1H), 5.00 (d, $J$ = 9.2, 1H), 4.49-4 42 (m, 3H), 4 32 (dd, $J$ = 6.2, 14 8, 6., 1H), 4.09 (dd, $J$ = 14.8, 5.3, 1H), 3.67 (s, 3H), 2.87-2.68 (m, 2H), 1.82 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3H); HRMS (ESI) $m/z$ calcd for $C_{32}H_{37}N_3O_6SNa$ $(M + Na)^+$ 614.2301, found 614.2305; Anal. Calcd for $C_{32}H_{37}N_3O_6S \cdot 0.75\ H_2O$· C, 63 50, H, 6.41; N, 6 94. Found: C, 63.65; H, 6 43; N, 6.74.

**Example A7: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiiazolidine-4-carboxylic acid methyl-(2-methyl-benzyl)-amide**



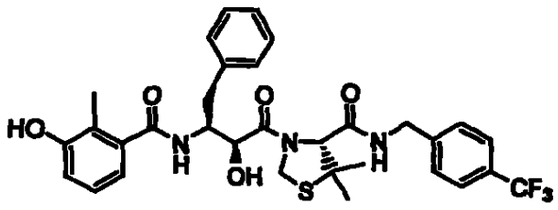
$^1$H NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.44 (t, $J$ = 7.98, 1 H), 8.13-8.07 (m, 2H), 7.34-7.13 (m, 9H), 6.93 (t, $J$ = 7.9, 1H), 6.78 (d, $J$ = 7.7, 1H), 6.53 (d, $J$ = 7 1, 1H), 5.58 (d, $J$ = 6 8, 1H), 5.45 (d, $J$ = 7.0, 1H), 5.12 (dd $J$ = 7.8 8.2 1H), 4.51-4.31(m, 6H), 2.86-2.67 (m, 2H), 2.19 (s, 3H), 1.81 (s, 3H), 1.51 (s, 3H), 1.34 (s, 3H); Anal. Calcd for $C_{33}H_{39}N_3O_5S \cdot 0\ 37\ H_2O$. C, 66.45; H, 6 72, N, 7.15. Found: C, 66.34; H, 7.28, N, 7 45.

**Example A8: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiiazolidine-4-carboxylic acid methyl-(3-methyl-thiophen-2-ylmethyl)-amide**



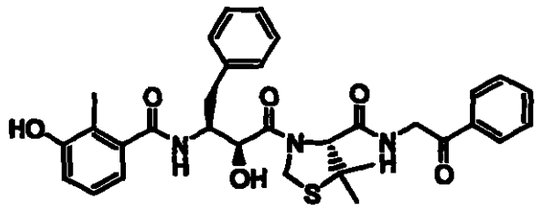
IR (neat or KBr $cm^{-1}$) 3150, 3000, 2942, 2187, 1712, 1600, 1567, 1505; $^1H$ NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.44 (t, $J$ = 7.98, 1 H), 8.13-8.07 (m, 2H), 7.34-7.13 (m, 5H), 6.93 (t, $J$ = 7.9, 1H), 6.78 (d, $J$ = 7 7, 1H), 6.53 (d, $J$ = 7 1, 1H), 5 45 (d, $J$ = 7.0, 1H), 5.12 (dd, $J$ = 7.8, 8.2 1H), 4.51-4.31(m, 4H), 2.86-2 67 (m, 2H), 2 19 (s, 3H), 1.81 (s, 3H), 1.51 (s, 3H), 1.34 (s, 3H), Anal. Calcd for $C_{30}H_{35}N_3O_5S_2$: calculated C, 61.94 H, 6.06 N, 7.22 Found C, 62 38 H, 6.23, N, 7.17.

**Example A9: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 4-trifluoromethyl-benzylamide**



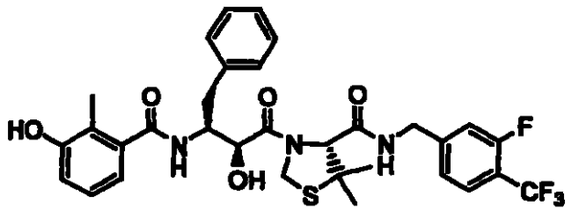

IR (neat $cm^{-1}$) 3343, 2931, 1543, 1530, 1454, 1326, 1122; $^1H$ NMR (DMSO-$d_6$) δ 9.38 (s, 1H), 8.57 (t, $J$ = 5.0, 1H), 8.15 (d, $J$ = 8 4, 1H), 7.59 (d, $J$ = 8 2, 2H), 7.50 (d, $J$ = 8.2, 2H), 7.28-7.13 (m, 5H), 6.93 (t, $J$ = 7.5, 1H), 6.77 (d, $J$ = 7.7, 1H), 6.54 (d, $J$ = 7 3, 1H), 5.50 (s br, 1H), 5.15 (d, $J$ = 9.2, 1H), 5.02 (d, $J$ = 9.2, 1H), 4.47-4 21 (m, 5H), 2.85-2 67 (m, 2H), 1.81 (s, 3H), 1.51 (s, 3H), 1 34 (s, 3H), ), HRMS (ESI) $m/z$ calcd for $C_{32}H_{34}F_3N_3O_5SNa$ $(M + Na)^+$ 652.2063, found 652.2044, Anal. Calcd for $C_{32}H_{34}F_3N_3O_5S \cdot 0.25\ H_2O$· C ,60.60; H, 5.48, N, 6.63. Found: C, 60.50; H, 5.29, N, 6.48.

**Example A10: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (2-oxo-2-phenyl-ethyl)-amide**



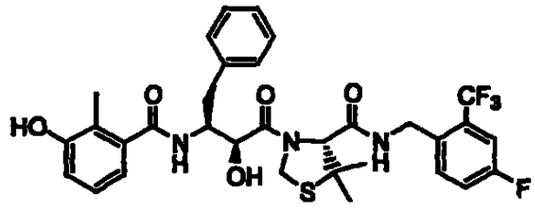
$^1$H NMR (DMSO-$d_6$) δ 9.39 (s, 1H), 8.36 (t, $J$ = 4.8, 1H), 8 15 (d, $J$ = 8 1, 1H), 7.98 (d, $J$ = 7 4, 1H), 7.65 (m, 1H), 7.52 (m, 2H), 7.32-7 11 (m, 6H), 6.93 (t, $J$ = 7.9, 1H), 6.76 (d, $J$ = 7.9, 1H), 6.54 (d, $J$ = 7.5, 1H), 5 42 (d, $J$ = 6 4, 1H), 5.08 (d, $J$ = 9.3, 1H), 5.02 (d, $J$ = 9.0, 1H), 4.78-4.30 (m, 5H), 2.84-2.66 (m, 2H), 1 81 (s, 3H), 1.57 (s, 3H), 1.45 (s, 3H); HRMS (ESI) $m/z$ calcd for $C_{32}H_{35}N_3O_6SNa$ $(M + Na)^+$ 612.2139, found 612.2141.

**Example A11: 3-(2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl-amino}-4-phenyl-butanoyl-5,5-dimethyl-thiazolidine-4-carboxylic acid 3-fluoro-4-trifluoromethyl-benzylamide**



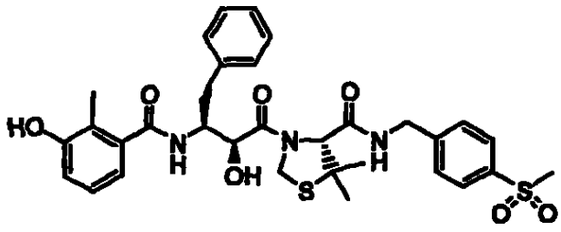
$^1$H NMR (DMSO-$d_6$) δ 9.34 (s, 1H), 8.62 (t, $J$ = 5.9, 1H), 8.09-6.54 (m, 11H), 5 45 (s br, 1H), 5 18 (d, $J$ = 9.2, 1H), 5.03 (d, $J$ = 9.2, 1H), 4.55-4 00 (m, 5H), 4 45 (s, 1H), 2.86-2.49 (m, 2H), 1.82 (s, 3H), 1.53 (s, 3H), 1.36 (s, 3H); Anal. Calcd for $C_{32}H_{33}N_3O_5SF_4$ C, 59.34; H, 5.14; N, 6.49, S,4.95. Found: C, 59.14; H, 5.29, N, 6.21; S, 4.67

**Example A12: 3-(2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methylmoyl-amino}-4-phenyl-butanoyl)-5,5-dimehtyl-thiazolidine-4-carboxylic acid -2-trifluoromethyl-4-fluoro-benzylamide**



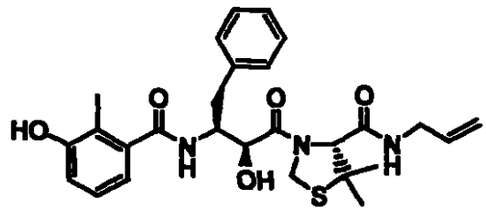
$^1$H NMR (DMSO-$d_6$) δ 9 33 (s, 1H), 8.65 (t, $J$ = 5.9, 1H), 8.12-6.54 (m, 11H), 5 45 (d, $J$ = 6.9, 1H), 5.18 (d, $J$ = 9 2, 1H), 5.05 (d, $J$ = 9.2, 1H), 4.59-4.34 (m, 5H), 4.50 (s, 1H), 2.85-2.67 (m, 2H), 1.82 (s, 3H), 1.53 (s, 3H), 1.37 (s, 3H); Anal. Calcd for $C_{32}H_{33}N_3O_5SF_4$· C, 59.34; H, 5 14; N, 6.49; S, 4.95. Found: C, 59.26; H, 5.35; N, 6.23; S, 4.69.

**Example A13: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 4-methanesulfonyl-benzamide**



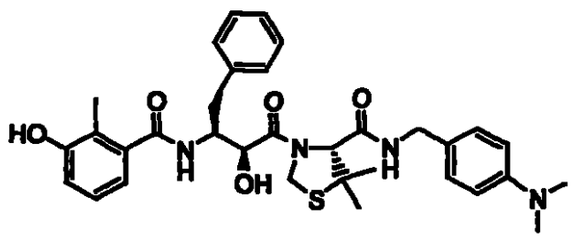
$^1$H NMR (DMSO-$d_6$) δ 9 38 (s, 1H), 8.37 (t, $J$ = 5.5, 1H,), 8.12 (d, 1H, $J$ = 8.2, 1H,), 7.33-7.13 (m, 7H), 6.94 (t, 1H, $J$ = 7.7, 1H,), 6.84-6 79 (m, 3H), 6.54 (d, 1H, $J$ = 7.3, 1H), 5.48 (d, $J$ = 6.6, 1H), 5.12 (d, $J$ = 9 2, 1H,), 5.00 (d, 1H, $J$ = 9.2, 1H), 4.49-4.42 (m, 3H), 4 32 (dd, $J$ = 14 8, 6.2, 1H,), 4.09 (dd, 1H, $J$ = 14.8, 5.3, 1H), 3.47 (s, 3H), 2 87-2.68 (m, 2H), 1.82 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3 H); Anal. Calcd for $C_{32}H_{37}N_3O_7S_2$: C, 60.07; H, 5 83; N, 6 57. Found C, 60.25; H, 6 13, N, 6 74.

**Example A14: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid allylamide**



IR (neat $cm^{-1}$) 3342, 2966, 1637, 1531, 1460, 1366, 1284, 1108; $^1H$ NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.13-8.07 (m, 2H), 7.34-7.13 (m, 5H), 6.93 (t, $J$ = 7.9, 1H), 6.78 (d, $J$ = 7.7, 1H), 6.53 (d, $J$ = 7.0, 1H), 5.82-5.70 (m. 1H), 5 46 (d, $J$ = 6.6, 1H), 5.23-4.97 (m, 4H), 4.40 (m, 3H), 3.81-3.59 (m, 2H), 2.86-2.67 (m, 2H), 1.81 (s, 3H), 1.50 (s, 3H), 1.35 (s, 3H), HRMS (ESI) *m / z* calcd for $C_{27}H_{33}N_3O_5S$ Na $(M + Na)^+$ 534.2039, found 534.2062; Anal. Calcd for $C_{27}H_{33}N_3O_5S$: C, 63.38; H, 6.50; N, 8.21. Found. C, 63.68; H, 6.57; N, 8.29.

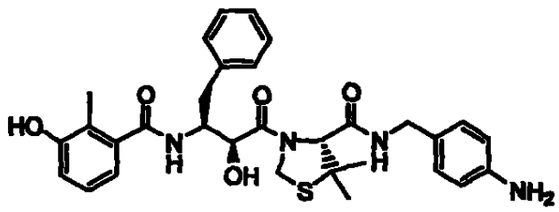
**Example A15: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 4-dimethylamino-benzylamide**



IR (neat $cm^{-1}$) 3331, 2931, 1643, 1519, 1455, 1349, 1284, $^1H$ NMR (DMSO-$d_6$) δ 9.37 (s, 1H), 8.26 (m, 1H), 8.12 (d, $J$ = 7 1, 1H), 7.38-6.92 (m, 8H), 6.78 (t, $J$ = 7.9, 1H), 6.60 (d, $J$ = 8.6, 1H), 6.55 (d, $J$ = 7.3, 1H), 6.42 (d, $J$ = 8.2, 1H), 5.46 (d, $J$ = 6.0, 1H), 5.11 (d, $J$ = 9.3, 1H), 5.00 (d, $J$ = 9.3, 1H), 4 45 (m, 3H), 4.25 (m, 1H), 4 03 (m, 1H), 2.80 (s, 3H), 2.87-2.73

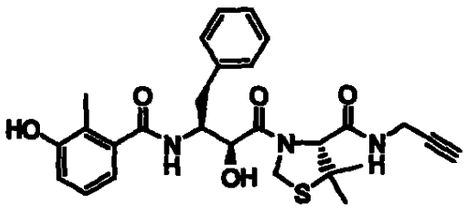
(m, 2H), 1 82 (s, 3H), 1.48 (s, 3H), 1 32 (s, 3 H); HRMS (ESI) *m / z* calcd for $C_{33}H_{40}N_4O_5SNa$ $(M + Na)^+$ 627.2612, found 627.2607.

**Example A16: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 4-amino-benzylamide**



Pale yellow solid: mp = 107-109 °C; IR ($cm^{-1}$) 3378, 2919, 1631, 1518, 1453, 1382, 1281, 1121; $^1H$ NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.21 (t, *J* = 6.0, 1H), 7 40-7.10 (m, 6H), 8.12 (d, *J* = 8 1, 1H), 6 92 (d, *J* = 8.4, 2H), 6.77 (d, *J* = 7.2, 1H), 6.54 (d, *J* = 7.2, 1H), 6.44 (d, *J* = 8.4, 2H), 5 44 (d, *J* = 6.0, 1H), 5.10 (d, *J* = 9.2, 1H), 4.99 (d, *J* = 9.2, 1H), 4.90 (s, 2H), 4.50-4.32 (m, 3H), 4.22-3.93 (m, 2H), 2.90-2.60 (m, 2H), 1.81 (s, 3H), 1.47 (s, 3H), 1.31 (s, 3 H); Anal Calcd for $C_{31}H_{36}N_4O_5S$•0.25 $H_2O$: C, 64.06, H, 6.33, N, 9.64. Found: C, 64 17, H, 6.38; N, 9 60

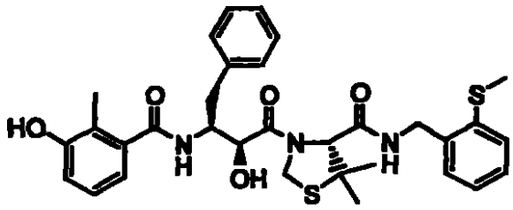
**Example A17: 3-(2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid prop-2-ynylamide**



$^1H$ NMR (DMSO-$d_6$) δ 9.33 (s, 1H), 8.38 (t, *J* = 5.5, 1H), 8.08(d, *J* = 8.3, 1H), 7 35-6.53 (m, 8H), 5.46 (d, *J* = 6.6, 1H), 5.10 (d, *J* = 9.2, 1H), 5.02 (d, *J* = 9.2, 1H), 4.44-4.40 (m, 1H), 4.40 (s, 1H), 3.85 (m, 3H), 3.08 (t, *J* = 2.5, 1H), 2.88-2 68 (m, 2H), 1.82 (s, 3H), 1 51 (s, 3H), 1.37

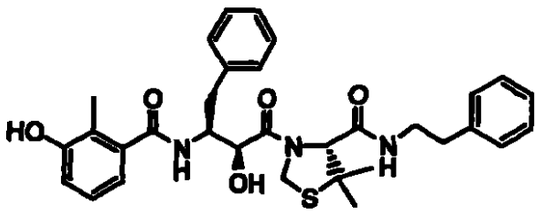
(s, 3H); Anal. Calcd for $C_{27}H_{31}N_3O_5S$: C, 63.63; H, 6 13; N, 8.24; S, 6.29. Found: C, 63.50, H, 6.33; N, 7.81; S, 5.68.

**Example A18: 3-(2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoylamino}-4-phenyl-butanoyl)]-5,5-dimethyl-thiazolidine-4-carboxylic acid (2-methylsulfanyl-phenyl)-amide**



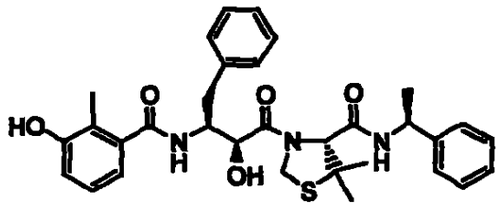
$^1$H NMR (DMSO-$d_6$) δ 9.33 (s, 1H), 8.41 (t, $J$ = 5.7, 1H), 8.10 (d, $J$ = 8.3, 1H) 8.09-6.54 (m, 12H), 5.46 (d, $J$ = 6.6, 1H), 5.14 (d, $J$ = 9.2, 1H), 5.04 (d, $J$ = 9.2, 1H), 4.50-4.02 (m, 4H), 4.50 (s, 1H), 2.89-2.69 (m, 2H), 2.51 (s, 3H), 1.84 (s, 3H), 1 53 (s, 3H), 1.39 (s, 3H); Anal. Calcd for $C_{32}H_{37}N_3O_5S_2$: C, 63.24; H, 6.14, N, 6.91. Found: C, 63.01; H, 6.30; N, 6.53.

**Example A19: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid phenethyl-amide**



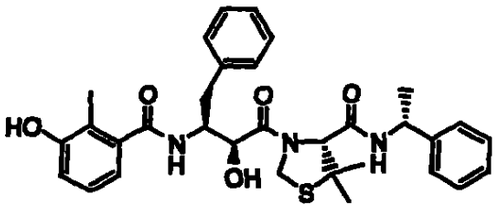
$^1$H NMR (DMSO-$d_6$) δ 9.41 (s, 1H), 8.38 (t, $J$ = 4.8, 1H), 8.16 (d, $J$ = 8.1, 1H), 8 01 (d, $J$ = 7.4, 1H), 7.64 (m, 1H), 7.52 (m, 2H), 7.32-7.11 (m, 6H), 6 93 (t, $J$ = 7.9, 1H), 6.76 (d, $J$ = 7.9, 1H), 6.54 (d, $J$ = 7.5, 1H), 5.42 (d, $J$ = 6.4, 1H), 5.10 (d, $J$ = 9.3, 1H), 5.05 (d, $J$ = 9.0, 1H), 4.80-4.32 (m, 5H), 2.84-2.66 (m, 4H), 1.80 (s, 3H), 1.56 (s, 3H), 1.45 (s, 3H); Anal. Calcd for $C_{32}H_{37}N_3O_5S$: C, 66.76, H, 6.48, N, 7.30 Found C, 66 50, H, 6.56; N, 7.23

**Example A20: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid ((S)-1-phenyl-ethyl)-amide**



White solid: mp 114-115 °C; IR (neat, $cm^{-1}$) 3306, 2971, 1643, 1531, 1451, 1372, 1284, 1211, 1107; $^1H$ NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.45 (d, $J$ = 8.2, 1H), 8.19 (d, $J$ = 8.2, 1H), 7.32-7.18 (m, 10H), 6.96-6.91 (m, 1H), 6.76 (d, $J$ = 8.1, 1H), 6.54 (d, $J$ = 7.5, 1H), 5.36 (d, $J$ = 7.2, 1H), 5.08 (d, $J$ = 9.7, 1H), 5.01 (d, $J$ = 9.7, 1H), 4.95-4.85 (m, 2H), 4.48 (s, 1H), 4.45-4.30 (m, 1H), 2.80-2.60 (m, 2H), 1.79 (s, 3H), 1.47 (s, 3H), 1.36 (d, $J$ = 7.2, 3H), 1.30 (d, $J$ = 7.0, 3H); Anal Calcd for $C_{32}H_{37}N_3O_5S \cdot 0.25\ H_2O$ C, 66.24; H, 6.51; N, 7.24. Found C, 66.30, H, 6.56; N, 6.89.

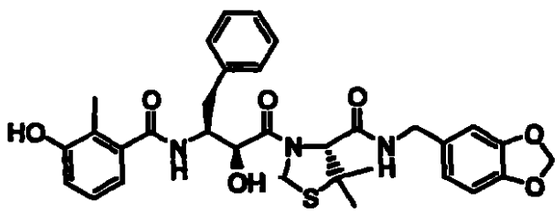
**Example A21: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid ((R)-1-phenyl-ethyl)-amide**



White solid: mp 114-115 °C; IR (neat, $cm^{-1}$) 3299, 1643, 1583, 1520, 1454, 1377, 1284, 1104; $^1H$ NMR (DMSO-$d_6$) δ 9.35 (s, 1H), 8.36 (d, $J$ = 8.2, 1H), 8.15 (d, $J$ = 8.2, 1H), 7.44-7.13 (m, 10H), 6.96-6.91 (m, 1H), 6.75 (d, $J$ = 8.1, 1H), 6.52 (d, $J$ = 6.7, 1H), 5.38 (d, $J$ = 6.9, 1H), 5.15 (d, $J$ = 9.7, 1H), 4.99 (d, $J$ = 9.7, 1H), 5.28-4.74 (m, 1H), 4.52(s, 1H), 4.49-4.35 (m,

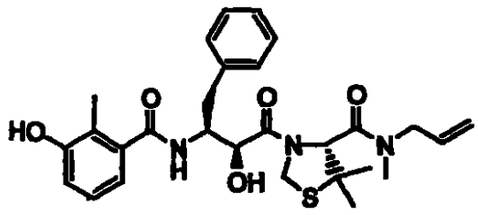
2H), 2.80-2 60 (m, 2H), 1 79 (s, 3H), 1.50 (s, 3H), 1 38 (s, 3H), 1.34 (d, $J$ = 7.0, 3H); Anal Calcd for $C_{32}H_{37}N_3O_5S$•0.25 $H_2O$: C, 66.24; H, 6.51, N, 7.24. Found: C, 66.38, H, 6.52; N, 7.30

**Example A22: 3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide**



IR (neat or KBr $cm^{-1}$) 3302, 2922, 2351, 2333, 1768, 1750, 1646, 1537; $^1H$ NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.44 (s, 1H), 8.13 (d, $J$ = 7.9 1H), 7.34-7.13 (m, 5H), 6.99-6.77 (m, 4H), 6.78 (d, $J$ = 7.7, 1H), 5.93 (d, $J$ = 7.1, 2H), 5.15 (d, $J$ = 7.0, 1H), 5.08 (d, $J$ = 7.8, 1H), 4.43 (d, $J$ =9.32, 2H), 4.34 (m, 2H), 4.12(d, $J$ = 6.18, 1H), 4.08 (d, $J$ = 6.08, 1H), 2.86-2.67 (m, 2H), 2.55 (s, 1H), 1.81 (s, 3H), 1.51 (s, 3H), 1 39 (s, 3H), Anal Calcd $C_{32}H_{35}N_3O_7S$•0.65 TFA•1.0 $H_2O$: C, 57.31 H, 5.44 N, 6.02. Found. C, 57.58 H, 5.47 N, 5.85.

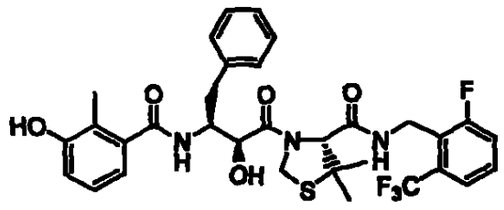
**Example A23: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid allyl-methyl-amide**



IR (neat, $cm^{-1}$) 3380, 2943, 1637, 1460, 1284, $^1H$ NMR (DMSO-$d_6$) δ 9.37 (s, 1H), 8 24 (d, $J$ = 8.4, 1H), 7.34-7.15 (m, 5H), 6.94 (t, $J$ = 7.5, 1H), 6.77 (d, $J$ = 7.7, 1H), 6.53 (d, $J$ = 7 5,

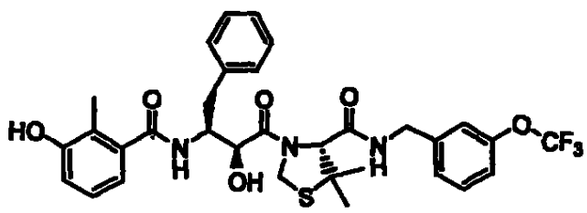
1H), 5.99 (m, 1H), 5 70-5.65 (m, 1H), 5.49-5.00 (m, 5H), 4.30-3.85 (m, 4H), 3.08 (s, 3H), 2 78-2.65 (m, 2H), 1.80 (s, 3H), 1.58 (s, 3H), 1.38 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{28}H_{35}N_3O_5SNa$ $(M + Na)^+$ 548.2190, found 548.2178.

**Example A24: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid fluoro-trifluoromethyl-benzylamide**



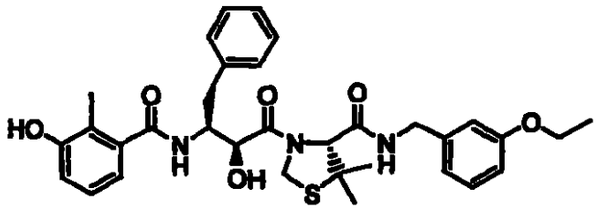
$^1H$ NMR (DMSO-$d_6$) $\delta$ 9.34 (s, 1H), 8.32 (t, $J$ = 6.0, 1H), 8.20 (d, $J$ = 8.4, 1H), 7.70-7.56 (m, 3H), 7 37 (d, $J$ = 6.9, 2H), 7.27 (t, $J$ = 7.5, 2H), 7.18 (t, $J$ = 7.4, 1H), 6.97 (t, $J$ = 7.0, 1H), 6.79 (d, $J$ = 7.0, 1H), 6.58 (d, $J$ = 6 6, 1H), 5.15 (d, $J$ = 9.0, 1H), 5.02 (d, $J$ = 9.0, 1H), 4.60-4.48 (m, 3H), 4.48-4.32 (m, 2H), 2.88-2 65 (m, 2H), 1.83 (s, 3H), 1.48 (s, 3H), 1.34 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{32}H_{33}N_3O_5SF_4Na$ $(M + Na)^+$ 670.1969, found 670.1999, Anal. Calcd for $C_{32}H_{33}N_3O_5S$ $F_4$•1 $H_2O$, 0.3 TFA. C, 55 94; H, 5.08, N, 6.00 Found: C, 55 74; H, 4.98, N, 5.94.

**Example A25: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 3-trifluoromethoxy-benzylamide**



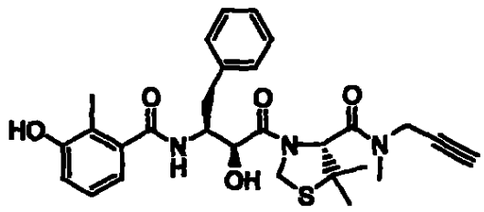
White solid. mp = 102-105 °C; IR ($cm^{-1}$) 3306, 2966, 1644, 1586, 1520, 1216, 1166; $^1H$ NMR (DMSO-$d_6$) δ 9.38 (s, 1H), 8.53 (t, $J$ = 6.0, 1H), 8.12 (d, $J$ = 8.1, 1H), 7 40-7.13 (m, 9H), 6.96-6.91 (m, 1H), 6.77 (d, $J$ = 8.2, 1H), 6.54 (d, $J$ = 7.7, 1H), 5.48 (d, $J$ = 6 4, 1H), 5.13 (d, $J$ = 9.2, 1H), 5.00 (d, $J$ = 9.2, 1H), 4 46-3 97 (m, 5H), 2.87-2.67 (m, 2H), 1.81 (s, 3H), 1.50 (s, 3H), 1.30 (s, 3H); Anal. Calcd for $C_{32}H_{34}F_3N_3O_6S \cdot 0.25\ H_2O$: C, 59.11; H, 5.35; N, 6.46. Found: C, 58.91; H, 5.40; N, 6.30.

**Example A26: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 3-ethoxy-benzylamide**



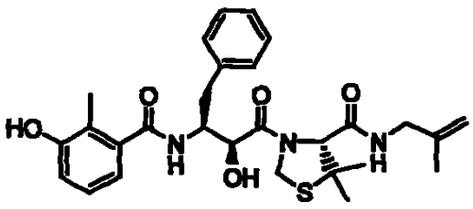
White solid. mp = 105-107 °C; IR ($cm^{-1}$) 3322, 3063, 2978, 1643, 1585, 1538, 1454, 1354, 1265, 1159, 1050, $^1H$ NMR (DMSO-$d_6$) δ 9 38 (s, 1H), 8 40 (t, $J$ = 5.6, 1H), 8 11 (d, $J$ = 8.2, 1H), 7.30-6.70 (m, 11H), 6.53 (d, $J$ = 7.5, 1H), 5 48 (d, $J$ = 5.9, 1H), 5.11 (d, $J$ = 8.9, 1H), 5 00 (d, $J$ = 8.9, 1H), 4.50-4.20 (m, 4H), 4.07 (dd, $J$ = 15 0, 5.3, 1H), 3.94 (dd, $J$ = 14.0, 6.9, 2H), 2 90-2 62 (m, 2H), 1.81 (s, 3H), 1 49 (s, 3H), 1.34 (s, 3 H), 1.25 (t, $J$ = 6.9, 3H), Anal. Calcd for $C_{33}H_{39}N_3O_6S \cdot 0.75\ H_2O$: C, 64.01; H, 6.59, N, 6.79. Found: C, 63 89; H, 6.27; N, 6.44.

**Example A27: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid methyl-prop-2-ynyl-amide**



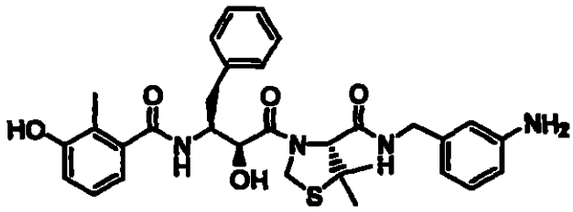
IR (neat, $cm^{-1}$) 3378, 1643, 1461, 1279, 1108, $^1H$ NMR (DMSO-$d_6$) δ 9.37 (s, 1H), 8.21 (d, $J$ = 9.2, 1H), 7.33-7.13 (m, 5H), 6.94 (t, $J$ = 7.7, 1H), 6.78 (d, $J$ = 8.1, 1H), 6.52 (d, $J$ = 7.0, 1H), 5 45 (d, $J$ = 6 8, 1H), 5.16 (d, $J$ = 9 2, 1H), 5 02 (d, $J$ = 9 2, 1H), 4.98 (s, 1H), 4.47-4.13 (s, 3H), 4.03-3 92 (m, 1H), 3.17 (s, 3H), 2.88 (s, 1H), 2.79-2.50 (m, 2H), 1 80 (s, 3H), 1.57 (s, 3H), 1.36 (s, 3H); Anal. Calcd for $C_{28}H_{33}N_3O_5S \cdot 0\ 6H_2O$· C, 62.95; H, 6 45; N, 7 86 Found· C, 62.95; H, 6 39; N, 7.69

**Example A28: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (2-methyl-allyl)-amide**



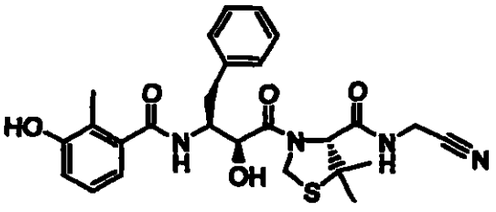
$^1H$ NMR (DMSO-$d_6$) δ 9.33, (s, 1H), 8 18-7.79 (m, 2H), 7.39-7.12 (m, 5H), 6.92 (t, $J$ = 8 1, 1H), 6.75 (d, $J$ = 8.1, 1H), 6.53 (d, $J$ = 7 0, 1H), 5.09 (d, $J$ = 9 2, 1H), 4 96 (d, $J$ = 9.2, 1H), 4.70 (s, 1H), 4.43 (s, 1H), 4.40 (br s, 2H) 3.81-3 49 (m, 4H), 2.85-2.65 (m, 2H), 1.82 (s, 3H), 1.63 (s, 3H), 1.49 (s, 3H), 1.35 (s, 3H); Anal Calcd for $C_{28}H_{35}N_3O_5S$ C, 63.97, H, 6.71; N, 7.99 Found. C, 63.85; H, 6.92, N, 7 65

**Example A29: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 3-amino-benzylamide**



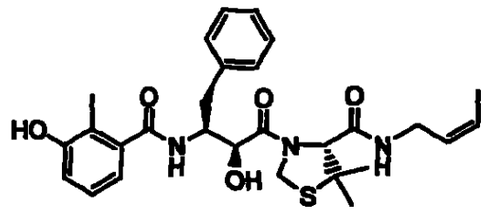
IR (neat, $cm^{-1}$) 3401, 2943, 1643, 1525, 1461, 1373, $^1H$ NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.28 (t, $J$ = 8.0, 1H), 8.12 (d, $J$ = 8.9, 1H), 7.33-6.37 (m, 12H), 5.45 (d, $J$ = 7.0, 1H), 5.10 (d, $J$ = 8.9, 1H), 4.99 (d, $J$ = 8 9, 1H), 4.50-4.35 (m, 3H), 4.30-3.90 (m 2H), 2.90-2.70 (m, 2H), 2.06 (s, 2H), 1.81 (s, 3H), 1.48 (s, 3H), 1.33 (s, 3H); Anal. Calcd for $C_{31}H_{36}N_4O_5S$•0.5 $H_2O$: C, 63.57; H, 6.37; N, 9.57 Found: C, 63.59; H, 6.38; N, 9.58.

**Example A30: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid cyanomethylamide**



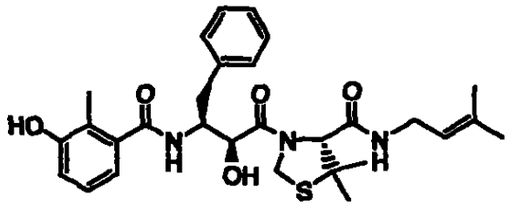
$^1H$ NMR (DMSO-$d_6$) δ 9.34 (s, 1H), 8.65 (s, 1H), 8 15 (m, 1H), 7.42-7 19 (m, 5H), 6.94 (t, $J$ = 7.9, 1H), 6.81 (d, $J$ = 7.9, 1H), 6.62 (d, $J$ = 7.9, 1H), 5.22 (d, $J$ = 9 7, 1H), 5.05 (d, $J$ = 9.7, 1H), 4 61-4.36 (m, 4H), 3.01-2 71 (m, 4H), 1.84 (s, 3H), 1.47 (s, 3H), 1.34 (s, 3H), Anal Calcd for $C_{26}H_{30}N_4O_5S$: C, 61.16; H, 5.92, N, 10.97. Found· C, 61.24, H, 6.14; N, 10.62.

**Example A31: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (Z)-but-2-enylamide**



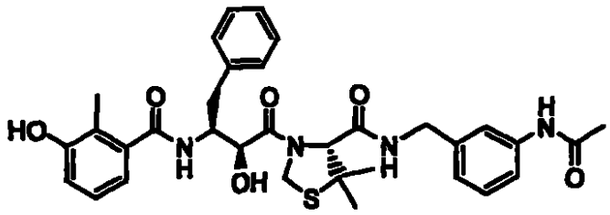
$^1$H NMR (DMSO-$d_6$) δ 9.37 (s, 1H), 8.35 (m, 1H), 8.12 (m, 1H), 7 15-6.98 (m, 6H), 6.77 (d, $J$ = 7 7, 1H), 6.68 (d, $J$ = 7.5, 1H), 5.60-5.33 (m, 3H), 5.18 (d, $J$ = 9.2, 1H), 5.02 (d, $J$ = 9.2, 1H), 4.52-4.39 (m, 3H), 3.79-3.68 (m, 2H), 2.92-2.62 (m, 2H), 1.80 (s, 3H), 1.61 (d, $J$ = 6.9, 3H), 1.51 (s, 3H), 1.38 (s, 3H); Anal. Calcd for $C_{28}H_{35}N_3O_5S$: C, 63.97, H, 6.71; N, 7.99. Found· C, 63.73; H, 6.75; N, 7.83.

**Example A32: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (3-methyl-but-2-enyl)-amide**



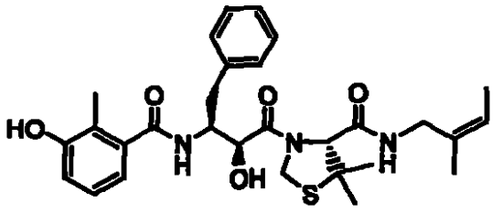
$^1$H NMR (DMSO-$d_6$) δ 9.33 (s, 1H), 8.19 (d, $J$ = 8 6, 1H), 7.96 (s br, 1H), 7.39-7.18 (m, 5H), 6.91 (t, $J$ = 7.6, 1H), 6.79 (d, $J$ = 7.9, 1H), 6.55 (d, $J$ = 7.1, 1H), 5.41 (m br, 1H), 5.21 (m, 2H), 5 02 (d, $J$ = 9.1, 1H), 4.57-4 37 (m, 3H), 3.79-3.61 (m, 2H), 2 90-2.71 (m, 2H), 1.81 (s, 3H), 1.63 (s, 6H), 1.52 (s, 3H), 1.40 (s, 3H); Anal. Calcd for $C_{29}H_{37}N_3O_5S$· C, 64.54; H, 6.91; N, 7.79. Found: C, 64.75; H, 6 82; N, 7 43.

**Example A33: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 3-acetylamino-benzylamide**



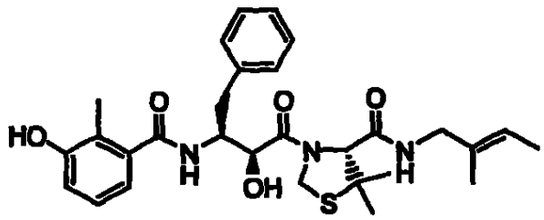
White solid: mp = 145-147 °C; IR (neat, $cm^{-1}$) 3378, 2919, 1637, 1514, 1461, 1361; $^1H$ NMR (DMSO-$d_6$) δ 9.87 (s, 1H), 9.36 (s, 1H), 8.45-8.40 (m, 1H), 8.12 (d, *J* = 7.9, 1H). 7.49-6 91 (m, 10H), 6.77 (d, *J* = 7.9, 1H), 6.55 (d, *J* = 7.9, 1H), 5 49 (d, *J* = 7.0, 1H), 5.10 (d, *J* = 9.3, 1H), 5.00 (d, *J* = 9.3, 1H), 4.44-3.95 (m, 5H), 2.90-2 62 (m, 2H), 2.00 (s, 3H), 1.80 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3H); Anal Calcd for $C_{32}H_{38}N_4O_6S \cdot 1.5\ H_2O$· C, 61.38; H, 6.40; N, 8.68. Found C, 61.49; H, 6.14; N, 8.35.

**Example A34: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid ((Z)-2-methyl-but-2-enyl)-amide**



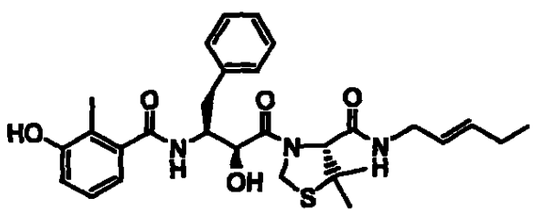
$^1H$ NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.16 (d, *J* = 8 4, 1H), 8.00 (t, *J* = 5.3, 1H), 7.36-7.13 (m, 5H), 6.94 (t, *J* = 7.7, 1H), 6.77 (d, *J* = 8.1, 1H), 6 53 (d, *J* = 7.3, 1H), 5.37 (d, *J* = 5.7, 1H), 5.24 (m, 1H), 5.12 (d, *J* = 9.0, 1H), 5.00 (d, *J* = 9.0, 1H), 4.48-4.39 (m, 3H), 3.71 (d, *J* = 3.7, 2H), 2.82-2.65 (m, 2H), 1.80 (s, 3H), 1.61 (m, 6H), 1.49 (s, 3H), 1.35 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{29}H_{37}N_3O_5SNa$ $(M + Na)^+$ 562 2346, found 562.2360, Anal. Calcd for $C_{29}H_{37}N_3O_5S$: C, 64 54; H, 6.91; N, 7.79. Found: C, 64.33; H, 6 92; N, 7.60.

**Example A35 (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid ((E)-2-methyl-but-2-enyl)-amide**



$^1$H NMR (DMSO-$d_6$) δ 9.37(s, 1H), 8.11 (d, $J$ = 8.2, 1H), 7.96 (t, $J$ = 5.5, 1H), 7.34-7 13 (m, 5H), 6.94 (t, $J$ = 7.7, 1H), 6.77 (d, $J$ = 8.1, 1H), 6.53 (d, $J$ = 7.3, 1H), 5.44 (d, $J$ = 6.6, 1H), 5.34 (d, $J$ = 6 6, 1H), 5.10 (d, $J$ = 9.0, 1H), 4.98 (d, $J$ = 9.1, 1H), 4.47-4.36 (m, 3H), 3.71 (dd, $J$ = 14.7, 6.6, 1H), 3 46 (dd, $J$ = 14.5, 4.8, 1H), 2.85-2.67 (m, 2H), 1.81 (s, 3H), 1.50 (m, 9H), 1.35 (s, 3H); HRMS (ESI) $m/z$ calcd for $C_{29}H_{37}N_3O_5SNa$ $(M+Na)^+$ 562.2346, found 562.2220.

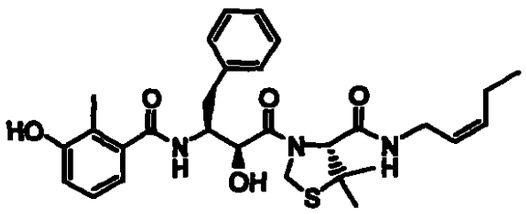
**Example A36: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (E)-pent-2-enylamide**



White solid· mp = 113-115 °C; IR (neat, cm$^{-1}$) 3315, 2964, 1643, 1584, 1530, 1454, 1371, 1283, 1104, 969; $^1$H NMR (DMSO-$d_6$) δ 9.35 (s, 1H), 8.11 (d, $J$ = 8.2, 1H), 8 02 (t, $J$ = 5.6, 1H), 7.33-7.13 (m, 5H), 6.96-6 90 (m, 1H), 6.76 (d, $J$ = 8.2, 1H), 6.52 (d, $J$ = 7 5, 1H), 5.66-5.56 (m, 1H), 5.43(d, $J$ = 6 8, 1H), 5.38-5.31 (m, 1H), 5 10 (d, $J$ = 8.9, 1H), 4.99 (d, $J$ = 8.9, 1H), 4.47-4.39 (m, 2H), 4.38 (s, 1H), 3:72-3.53 (m, 2H), 2 84-2.66 (m, 2H), 1 98-1.83 (m,

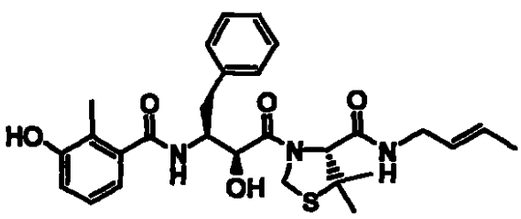
2H), 1.80 (s, 3H), 1 48 (s, 3H), 1.34 (s, 3H), 0.87 (t, $J$ = 7.3, 3H); Anal. Calcd for $C_{29}H_{37}N_3O_5S$•0 5 $H_2O$. C, 63.48; H, 6.98; N, 7.66 Found: C, 63.30; H, 7.00, N, 7.28.

**Example A37: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (Z)-pent-2-enylamide**



White solid: mp = 112-113 °C; IR (neat, $cm^{-1}$) 3320, 2965, 1659, 1643, 1538, 1455, 1372, 1285, 1210, 1105, 1048; $^1H$ NMR (DMSO-$d_6$) δ 9.35 (s, 1H), 8.11 (d, $J$ = 7 9, 1H), 8.03 (t, $J$ = 5.3, 1H), 7.35-7.13 (m, 5H), 6.96-6.90 (m, 1H), 6.76 (d, $J$ = 8.1, 1H), 6.53 (d, $J$ = 7.3, 1H), 5.42 (d, $J$ = 6.7, 1H), 5.37-5.35 (m, 1H), 5.29-5.23 (m, 1H), 5.09 (d, $J$ = 9.2, 1H), 4.99 (d, $J$ = 9.2, 1H), 4.45-4.38 (m, 2H), 4.36 (s, 1H), 3.80-3.62 (m, 2H), 2.84-2.70 (m, 2H), 2.07-1.97 (m, 2H), 1.80 (s, 3H), 1.48 (s, 3H), 1.34 (s, 3H), 0 90 (t, $J$ = 7.5, 3H); Anal. Calcd for $C_{29}H_{37}N_3O_5S$•0 5 $H_2O$: C, 63.48, H, 6 98, N, 7.66. Found: C, 63.60, H, 6.92, N, 7.48.

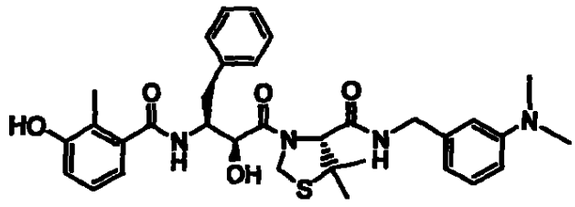
**Example A38: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (E)-but-2-enylamide**



$^1H$ NMR (DMSO-$d_6$) δ 9.39 (s, 1H), 8.19 (m br, 1H), 8.03 (m br, 1H), 7.40-7.16 (m, 5H), 6.94 (t, $J$ = 7.1, 1H), 6.79 (d, $J$ = 7.7, 1H), 6.55 (d, $J$ = 7.5, 1H), 5.64-5.31 (m, 3H), 5.19 (d, $J$ = 9.2, 1H), 5 02 (d, $J$ = 9.2, 1H), 4.55-4.38 (m, 3H), 3 80-3.69 (m, 2H), 2.84-2 70 (m, 2H),

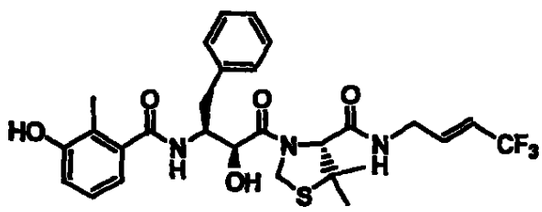
1.80 (s, 3H), 1 61 (s br, 3H), 1.51 (s, 3H), 1.39 (s, 3H). Anal. Calcd for $C_{28}H_{35}N_3O_5S$ C, 63.73; H, 7.07, N, 7.96 Found. C, 63.41; H, 7.23, N, 7. 71.

**Example A39: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 3-dimethylamino-benzylamide**



White solid. mp = 105-106 °C; IR (neat, $cm^{-1}$) 2219, 2966, 1732, 1644, 1585, 1531, 1494, 1454, 1373, 1264, 1047; $^1H$ NMR (DMSO-$d_6$) δ 9.37 (s, 1H), 8.33 (t, $J$ = 6.1, 1H), 8 08 (d, $J$ = 8.1, 1H), 7 32-6.52 (m, 12H), 5.54 (d, $J$ = 6.0, 1H), 5.10 (d, $J$ = 9.2, 1H), 4.99 (d, $J$ = 9.2, 1H), 4.43-4.31 (m, 4H), 4.03 (dd, $J$ = 15.3, 5.3, 1H), 2.84 (s, 6H), 2.84-2.67 (m, 2H), 1.81 (s, 3H), 1.49 (s, 3H), 1.35 (s, 3H). Anal. Calcd for $C_{33}H_{40}N_4O_5S$•0.1 $H_2O$ C, 65.35; H, 6.68; N, 9.24. Found: C, 65 49; H, 6.67; N, 9.30.

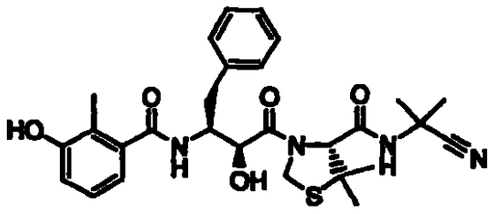
**Example A40: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid ((E)-4,4,4-trifluoro-but-2-enyl)-amide**



White foam; IR (neat, $cm^{-1}$) 3332, 1661, 1641, 1584, 1531, 1443, 1280, 1119; $^1H$ NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.32 (t, $J$ = 5.6, 1H), 8 15 (d, $J$ = 8.4, 1H), 7.35-7.12 (m, 5H), 7.00-6.90 (m, 1H), 6 77 (d, $J$ = 7 3, 1H), 6.52 (d, $J$ = 7 3, 1H), 6 49-6 40 (m, 1H), 6.08-6.00

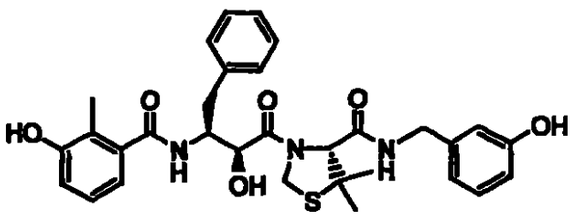
(m, 1H), 5.49(d, $J$ = 6.4, 1H), 5.15 (d, $J$ = 9.2, 1H), 5.01 (d, $J$ = 9.2, 1H), 4.50-4.40 (m, 2H), 4.38 (s, 1H), 4.10-3.90 (m, 1H), 3.80-3.70 (m, 1H), 2.90-2.60 (m, 2H), 1.80 (s, 3H), 1.51 (s, 3H), 1.34 (s, 3H); Anal. Calcd for $C_{28}H_{32}F_3N_3O_5S$: C, 58.02; H, 5.56; N, 7.25. Found: C, 58.37, H, 5.70, N, 6.91.

**Example A41: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (1-cyano-1,1-dimethyl-methyl)-amide**



$^1$H NMR (DMSO-$d_6$) δ 9.39 (s, 1H), 8.31-8.12 (m, 2H), 7.38-7.17 (m, 5H), 6.97 (t, $J$ = 7.3, 1H), 6.79 (d, $J$ = 7 7, 1H), 6.59 (d, $J$ = 7.4, 1H), 5.41 (m br, 1H), 5.21 (d, $J$ = 9.2, 1H), 5.00 (d, $J$ = 9.2, 1H), 4.58-4.35 (m, 3H), 2.85-2.62 (m, 2H), 1.81 (s, 3H), 1.62 (s, 6H), 1.47 (s, 3H), 1.39 (s, 3H); Anal. Calcd for $C_{28}H_{34}N_4O_5S$: C, 62.43, H, 6.36; N, 10.40. Found: C, 62.12; H, 6.55; N, 10.13.

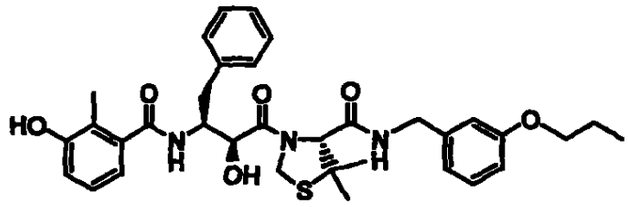
**Example A42: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 3-hydroxy-benzylamide**



$^1$H NMR (DMSO-$d_6$) δ 9.37 (s, 1H), 9.30 (s, 1H), 8.35 (t, $J$ = 5.9, 1H), 8 11 (d, $J$ = 8.1, 1H), 7.33-7.15 (m, 5H), 7.04 (t, $J$ = 7.7, 1H), 6.94 (t, $J$ = 7.9, 1H), 6 77 (d, $J$ = 8.1, 1H), 6.70-6.54

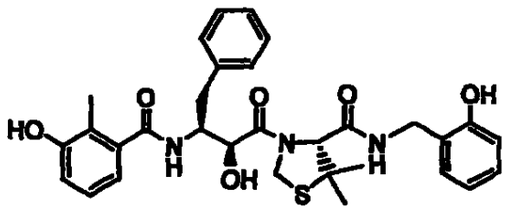
(m, 4H), 5 49 (s br, 1H), 5.11 (d, $J$ = 9 2, 1H), 5 00 (d, $J$ = 9.3, 1H), 4.43 (m, 3H), 4.27 (dd, $J$ = 15.2, 6 0, 1H), 4.07 (dd, $J$ = 15.0, 5.5, 1H), 2.88-2.67 (m, 2H), 1 82 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H), Anal Calcd for $C_{31}H_{35}N_3O_6S \cdot H_2O$· C, 62.50; H, 6 26; N, 7 05 Found· C, 62.66; H, 6.19, N, 6.83.

**Example A43: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 3-propoxy-benzylamide**



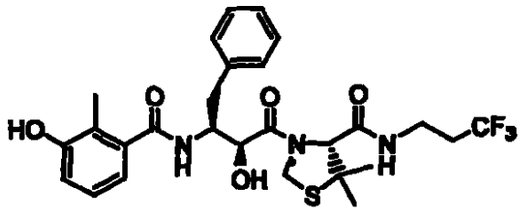
White foam; IR ($cm^{-1}$) 3319, 2966, 1644, 1585, 1531, 1454, 1373, 1264, 1047, $^1H$ NMR (DMSO-$d_6$) δ 9.37 (s, 1H), 8.40 (t, $J$ = 5.8, 1H), 8.10 (d, $J$ = 8.4, 1H), 7.31-6.71 (m, 11H), 6.53 (d, $J$ = 7 3, 1H), 5.46 (d, $J$ = 6 4, 1H), 5.12 (d, $J$ = 9.2, 1H), 5.00 (d, $J$ = 9.2, 1H), 4.50-4.20 (m, 4H), 4.11-3.83 (m, 3H), 2.90-2.62 (m, 2H), 1.81 (s, 3H), 1.72-1.60 (m, 2H), 1.49 (s, 3H), 1.34 (s, 3H), 0.92 (t, $J$ = 7.3, 3H). Anal Calcd for $C_{34}H_{41}N_3O_6S \cdot 0.25\ H_2O$: C, 65.42; H, 6.70, N, 6.73. Found: C, 65.49, H, 6.67, N, 6 70.

**Example A44: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-hydroxy-benzylamide**



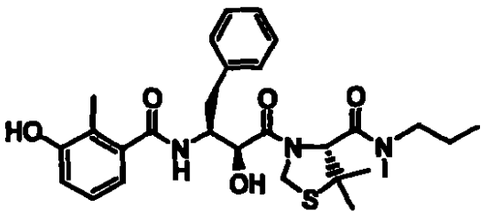
$^1$H NMR (DMSO-$d_6$) δ 9.50 (s, 1H), 9.36 (s, 1H), 8 33 (t, $J$ = 5.5, 1H), 8.14 (d, $J$ = 8.2, 1H), 7.32-7.12 (m, 6H), 7.04-6.91 (m, 2H), 6.76 (m, 2H), 6.68 (t, $J$ = 7.5, 1H), 6.54 (d, $J$ = 7.5, 1H), 5.46 (d, $J$ = 6.6, 1H), 5.13 (d, $J$ = 9.2, 1H), 5.01 (d, $J$ = 9.3, 1H), 4.47 (m, 3H), 4.28-4.19 (m, 2H), 2.86-2.67 (m, 2H), 1.82 (s, 3H), 1.49 (s, 3H), 1.32 (s, 3H); HRMS (ESI) $m/z$ calcd for $C_{31}H_{36}N_3O_6S$ $(M+H)^+$ 578.2325, found 578.2325

**Example A45: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (3,3,3-trifluoro-propyl)-amide**



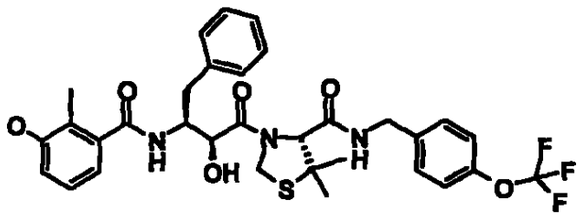
$^1$H NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.20 (t, $J$ = 5.5, 1H), 8.13 (d, $J$ = 8 2, 1H), 7.34-7.13 (m, 5H), 6.93 (t, $J$ = 7.7, 1H), 6.76 (d, $J$ = 8.1, 1H), 6 08 (d, $J$ = 7.5, 1H), 5.44 (d, $J$ = 6.8, 1H), 5.10 (d, $J$ = 9.2, 1H), 5.05 (d, $J$ = 9.2, 1H), 4.48-4.38 (m, 2H), 4.35 (s, 1H), 3.32-3.25 (m, 2H), 2.75-2.70 (m, 2H), 2.44-2.35 (m, 2H), 1 80 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H); HRMS (ESI) $m/z$ calcd for $C_{27}H_{33}N_3O_5SF_3$ $(M+H)^+$ 568.2093, found 568.2118.

**Example A46: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid methyl-propyl-amide**



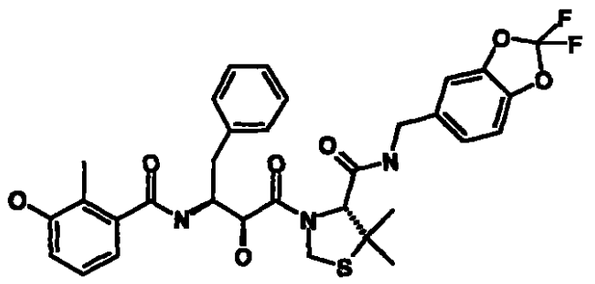
White solid mp = 108-110 °C, IR ($cm^{-1}$) 3325, 2964, 1637, 1522, 1456, 1372, 1284, $^1H$ NMR (DMSO-$d_6$) δ 9.35 (s, 1H), 8.22 (d, $J$ = 8.6, 1H), 7.34-7.12 (m, 5H), 6.96-6.90 (m, 1H), 6 77-6.75 (m, 1H), 6.53-6.50 (m, 1H), 5.46 (d, $J$ = 6 4, 1H), 5.18-4.70 (m, 3H), 4.48-4.20 (m, 2H), 3.31 (s, 3H), 2.90-2.50 (m, 2H), 1.80 (s, 3H), 1.80-1.77 (m, 2H), 1.56 (s, 3H), 1.56-1.36 (m, 2H), 1.37 (s, 3H), 0.79 (t, $J$ = 7 5, 3H) Anal. Calcd for $C_{28}H_{37}N_3O_5S$•1 0 $H_2O$: C, 61.63; H, 7.20, N, 7.60. Found· C, 62.03; H, 6.93; N, 7.33

**Example A47: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 4-trifluoromethoxy-benzylamide**



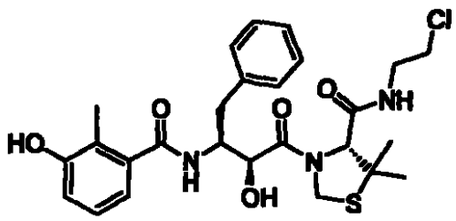
White solid: $^1H$ NMR (DMSO) δ 9.37 (s, 1H), 8 51 (t, $J$ = 5 9, 1H), 8.13 (d, $J$ = 7.3, 1H), 7.39 (d, $J$ = 8 6, 1H), 7.32-7.10 (m, 8H), 7 00-6.90 (m, 1H), 6.76 (d, $J$ = 8.2, 1H), 6.53 (d, $J$ = 7 3, 1H), 5 49 (d, $J$ = 6.6, 1H), 5.14 (d, $J$ = 9.3, 1H), 5 00 (d, $J$ = 9.3, 1H), 4.49-4.37 (m, 4H), 4.17 (dd, $J$ = 15 0, 5.7, 1H), 2 90-2 64 (m, 2H), 1.81 (s, 3H), 1 49 (s, 3H), 1.32 (s, 3H); HRMS (ESI) $m/z$ calcd for $C_{32}H_{35}N_3O_6F_3S$ $(M + H)^+$ 646 2199, found 646.2184.

**Example A48: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (2,2-difluoro-benzo[1,3]dioxol-5-ylmethyl)-amide**



$^1$H NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.55 (t, $J$ = 5.8, 1H), 8.14 (d, $J$ = 8.4, 1H), 7.29-7.11 (m, 8H), 6.94 ( t, $J$ = 7.8, 1H), 6.77 (d, $J$ = 7.9, 1H), 6.54 (d, $J$ = 7.4, 1H), 5.58 (d, $J$ = 8.2, 1H), 5.17 (d, $J$ = 9.2, 1H), 5.02 (d, $J$ = 9.2, 1H), 4.49-4.39 (m, 3H), 4.43 (s, 1H), 4.21 (dd, $J$ = 5 4, 15.3, 1H), 2 83 (m, 1H), 2.71 (dd, $J$ = 13.5, 10.7, 1H), 2.20 (s, 3H), 1.51 (s, 3H), 1.34 (s, 3H); HRMS (ESI) $m/z$ calcd for $C_{32}H_{34}F_2N_3O_7S$ $(M+H)^+$ 642.2086, found 642.2099; Anal. Calcd for $C_{32}H_{33}F_2N_3O_7S$. C, 59.90; H, 5.18; N, 6.55. Found: C, 60 01; H, 5.27; N, 6 29

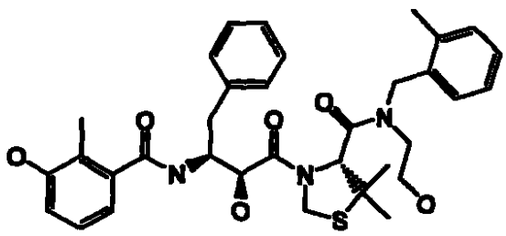
**Example A49: (R)-3-[(2S,3S)-2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (2-chloro-ethyl)-amide**



$^1$H NMR (DMSO-$d_6$) δ 9.40 (s, 1H), 8.31 (t, 1H, $J$ = 5.5), 8.17 (d, 1H, $J$ = 8.4), 7.37-7.16 (m, 5H), 6.96 (t, 1H, $J$ = 7.9), 6.79 (d, 1H, $J$ = 8.1), 6 55 (d, 1H, $J$ = 7.5), 5.47 (d, 1H, $J$ = 6 8), 5 11 (d, 1H, $J$ = 9.3), 5.03 (d, 1H, $J$ = 9.3), 4.50 – 4.45 (m, 2H), 4.41 (s, 1H), 3 64-3.58 (m, 2H), 3.46-3.34 (m, 2H), 2.86-2.69 (m, 2H), 1.82 (s, 3H), 1.53 (s, 3H), 1.40 (s, 3H). Exact mass calculated for $C_{26}H_{33}N_3O_5SCl$ $(M+H)^+$ 534 1829, found 534.1841.

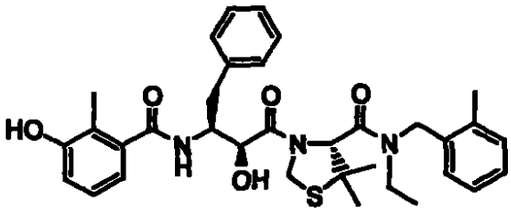
45

**Example A50: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (2-hydroxy-ethyl)-(2-methyl-benzyl)-amide**



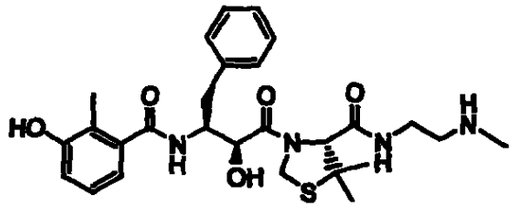
$^1$H NMR (DMSO-$d_6$) δ 9.38 (s, 1H), 8.29 (d, $J$ = 8.4, 1H), 7 42-6 87 (m, 10H), 6.78 (d, $J$ = 7.1, 1H), 6.55 (d, $J$ = 6.8, 1H), 5.44 (d, $J$ = 6.8, 1H), 5.26 (d, $J$ = 10.0, 1H), 5.08 (s, 1H), 5.04 (d, $J$ = 9.2, 1H), 4.82-4 67 (m, 2H), 4.55-4.24 (m, 3H), 3.67 (m, 2H), 3.47 (m, 2H), 2.78 (m, 2H), 2.24 (s, 3H), 1.82 (s, 3H), 1 61 (s, 3H), 1.45 (s, 3H), HRMS (ESI) $m/z$ calcd for $C_{34}H_{42}N_3O_6S$ $(M+H)^+$ 620.2794, found 620.2798; Anal Calcd for $C_{34}H_{41}N_3O_6S \cdot 1\ H_2O$ : C, 64 03, H, 6.80, N, 6 59. Found: C, 63.66; H, 6 40; N, 6.59.

**Example A51: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid methyl-(2-ethyl-benzyl)-amide**



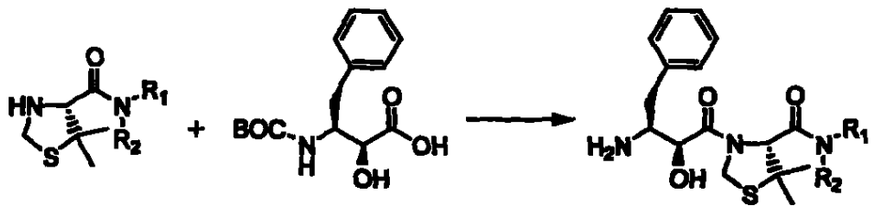
White solid: $^1$H NMR (DMSO-$d_6$) δ 9 40 (s, 1H), 8.45 (t, $J$ = 7.99, 1H), 8 10 (d, $J$ = 8.1, 1H), 7.41-6 91 (m, 12H), 6 62 (d, $J$ = 7.8, 1H), 5.41 (d, $J$ = 6.8, 1H), 5.12 (dd, $J$ = 8 1, 7.8, 1H), 4.44-4.35 (m, 3H), 4.42 (s, 1H), 2.91-2.67 (m, 2H), 2 54- 2.21 (q, $J$ = 6 89, 2H), 2.1 (s, 3H), 1.88 (s, 3H), 1.56 (t, $J$ = 6.90, 3H), 1.49 (s, 3H), 1.34 (s, 3 H), Anal. ($C_{34}H_{41}N_3O_5S$•0.75 $H_2O$) calculated C (62.34), H (6 43), N (6.23), found C (62 72), H (6.52), N (5 97). HRMS (ESI) $m/z$ calcd for 604.2845, found 604.2845

**Example A52: 3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (2-methylamino-ethyl)-amide**

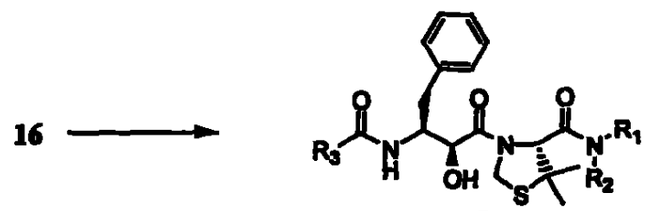


White solid: $^1$H NMR (DMSO-$d_6$) δ 9.40 (s, 1H), 8.45-8.01 (m, 1H), 7.41-7.13 (m, 12H), 6 98 (t, $J$ = 7.8, 1H), 6.78 (d, $J$ = 6.85, 1H), 6.55 (d, $J$ = 6.99, 1H), 5.41 (m, 1H), 5.12-4.98 (m, 2H), 4.44-4.35 (m, 2H), 3.15 (m, 2H), 2.91-2.67 (m, 2H), 1.84 (s, 3H), 1.66 (q, $J$ = 8.2, 4H), 1.34 (s, 3H); Anal. ($C_{27}H_{36}N_4O_5S$•0.50 $H_2O$) calculated C (60.31), H (6.94), N (10.42), found C (60 59), H (6.50), N (8.08). HRMS (ESI) *m/z* calcd for 556.2771, found 556.2770.

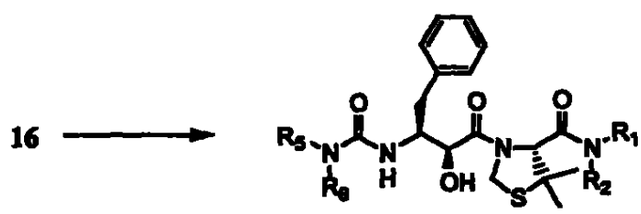
**General Method B**



3 15 16



17

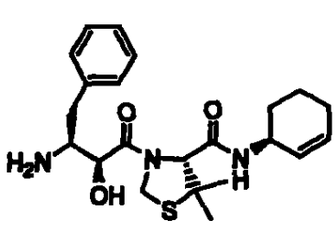


19

Amides of the general structure 3 (synthesized in the same manor as in the Methods A section) are coupled to boc-protected acid 15, and exposed to methane sulfonic acid to yield amines 16 Subjecting amines 16 to the reaction conditions depicted yielded a series of amides 17 and ureas 19

Synthesis of amines of the general type 16.

**16a**



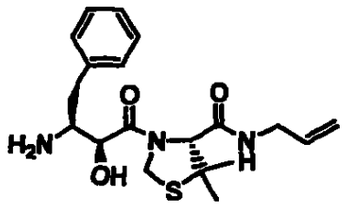
The title compound was prepared as follows. (R)-5,5-Dimethyl-thiazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 1 (1.95 g, 7 47 mmol) was dissolved in EtOAc (25 mL) and cooled to 0 °C. Diphenyl chlorophosphate (1.71 mL, 8.23 mmol) was added followed by TEA (1.14 mL, 8.23 mmol) The reaction was stirred at 0 °C for 1h, and

treated with (S)-Cyclohex-2-enylamine (0 8 g, 8.23 mmol). The reaction mixture was stirred at room temperature overnight, then partitioned between 1N HCl (25 mL) and EtOAc (30 mL) The organic layer was washed with saturated $NaHCO_3$, brine, dried over $Na_2SO_4$ and concentrated to a yellow oil. The resulting oil (2.54 g, 7.47 mmol) was dissolved in EtOAc (30 mL) and then cooled to 0 °C Methanesulfonic acid (2.27 mL, 33.62 mmol) was added and the solution was stirred at 0 °C for 15 minutes, then at room temperature for 4h. The mixture was re-cooled to 0 °C and quenched with 10% $Na_2CO_3$ (30 mL) then extracted with EtOAc (30 mL). Organic layer was washed with brine, dried over $Na_2SO_4$ and concentrated in vacuo to give a yellow oil 3. The resulting yellow oil (1.86 g, 7.74 mmol) was dissolved in EtOAc (77 mL) BOC-AHPBA 4 (2.29 g, 7.74 mmol) was added followed by HOBt (1.05g, 7.74 mmol). The mixture was stirred at room temperature 1h, then cooled to 0 °C DCC (1.60 g, 7.74 mmol) was slowly added as solution in EtOAc (30 mL). The mixture was allowed to gradually warm to room temperature and stirred overnight. The mixture was filtered and the filtrate was washed with 1N HCl (40 mL), saturated $NaHCO_3$ (40 mL), brine (40 mL), dried over $Na_2SO_4$ and concentrated to give a crude white solid (contaminated with DCU). The DCU was removed by flash chromatography (30% to 50% EtOAc in hexanes) to provide a white solid (4 g, 7.73 mmol), which was dissolved in EtOAc (30 mL) and then cooled to 0 °C. Methanesulfonic acid (2.35 mL, 34.76 mmol) was added and the solution was stirred at 0 °C for 15 minutes, then at room temperature for 3h The mixture was re-cooled to 0 °C and quenched with 10% $Na_2CO_3$ (35 mL) then extracted with EtOAc (30 mL) Organic layer was washed with brine, dried over $Na_2SO_4$ and concentrated in vacuo to give a material which was recrystalized from 60% EtOAc in hexanes to provide the titled compound (2 41g, 80%) as a white solid. $^1H$ NMR (DMSO-$d_6$) δ 8.21 (d, $J$ = 8.1, 1H), 7.31-7.17 (m, 5H), 5 80 (d, $J$ = 5.6, 1H), 5 52-5 48 (m, 2H), 5 30-5.25 (m, 2H), 4.89 (s, 2H), 4.26 (s, 1H), 4 21-4 00 (m, 3H), 3.15-2.70 (m, 2H), 2.50-2 00 (m, 2H), 2.00-1.00 (m, 4H), 1.49 (s, 3H), 1.31 (s, 3H); Anal. Calcd for $C_{22}H_{31}N_3O_3S$: C, 63.28, H, 7 48; N, 10.06. Found C, 63.40; H, 7.20, N, 9.98

**The following amines a-h were prepared by the specific method outlined above using the requisite amine.**

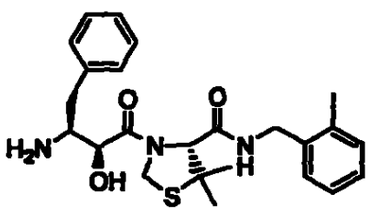
47

16a

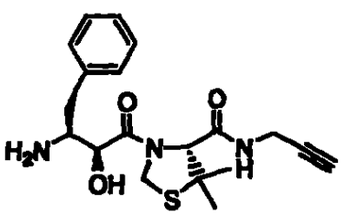


$^1$H NMR (DMSO-$d_6$) δ 8.36 (t, $J$ = 6.0, 1H), 7.36-7.14 (m, 5H), 5.70 (m, 1H), 5.34 (s br, 1H), 5.12 (d, $J$ = 17.0, 1H), 4.96-4 88 (m, 3H), 4.34 (s, 1H), 4.10 (d, $J$ = 7.0, 1H), 3.80-3.55 (m, 2H), 3.06 (d, $J$ = 13.0, 1H), 2.87 (t, $J$ = 9 0, 1H), 2.38 (dd, $J$ = 13.0, 10.0, 1H), 1.52 (s, 3H), 1.33 (s, 3H)

16b

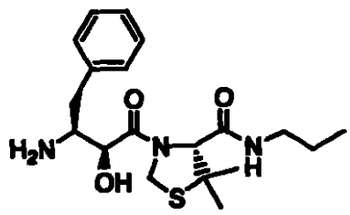


16c



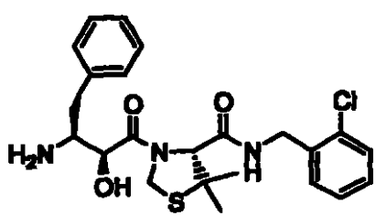
$^1$H NMR (DMSO-$d_6$) δ 8.69 (t, $J$ = 5.3, 1H), 7.34-7.14 (m, 5H), 5.34 (s br, 1H), 4.90 (s, 2H), 4.29 (s, 1H), 4.08 (d, $J$ = 7.0, 1H), 3.90-3.70 (m, 2H), 3.07 (dd, $J$ = 13 4, 2.5, 1H), 2.96 (t, $J$ = 2.6, 1H), 2.88, (ddd, $J$ = 9 8, 8.0, 2.8, 1H), 2.37 (dd, $J$ = 13 2, 9 9, 1H), 1.50 (s, 3H), 1.32 (s, 3H).

16d



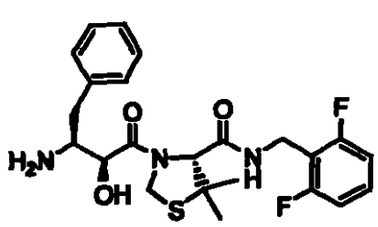
$^1$H NMR (DMSO-$d_6$) δ 8.13 (t, $J$ = 5.4, 1H), 7.35-7.15 (m, 5H), 5.28 (d, $J$ = 8.1, 1H), 4.79 (m, 2H), 4.27 (s, 1H), 4 07 (t, $J$ = 7 1, 1H), 3.10-2.71 (m, 4H), 2.37 (dd, $J$ = 13.2, 9.9, 1H), 1.49 (s, 3H), 1.34 (m, 2H), 1.33 (s, 3H), 0.77 (t, $J$ = 7.4, 3H)

16e



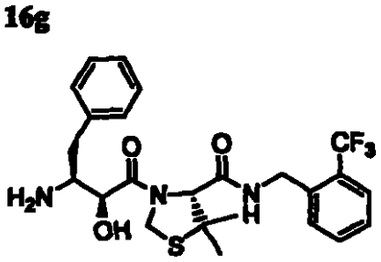
Isolated yield. 84%, MS (APCI, m/z): 461, 463 (M+H)

16f



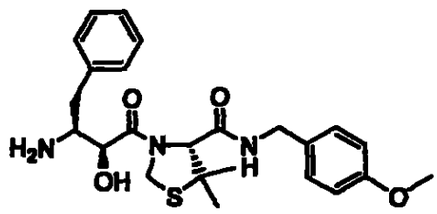
Isolated yield: 93%; MS (APCI, m/z)· 464 (M+H).

16g



Isolated yield. 86%; MS (APCI, m/z): 496 (M+H).

16h



Isolated yield: 87 %. MS-APCI (*m/z*+): 458.

**Synthesis of final products of the general type 17 from 16a-h,**
**General Methods:**

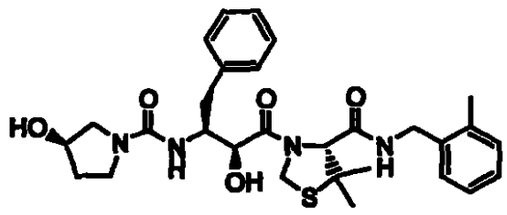
Amide formation - To a solution of acid, amine 16 and HOBT in $CH_2Cl_2$ was added EDC and the solution stirred overnight at room temperature The solution was concentrated in vacuo and the residue dissolved in ethyl acetate and a small portion of water. The solution was washed with saturated $NH_4Cl$ or 0 5N HCl (2x), saturated $NaHCO_3$ (2x), brine (1x), dried with $MgSO_4$ and concentrated in vacuo The resulting residue subjected to flash silica gel chromatography or preparative HPLC to afford the desired product.

Urea formation #1 - The corresponding amine and isocyanate (1.1-1 2 eq.) were taken in dichloromethane and stirred at room temperature under nitrogen (1.5 hr to overnight) The solvent was then removed in vacuo and the resulting residue subjected to flash silica gel chromatography or preparative HPLC to afford the desired product.

Urea formation #2 - The corresponding amine was dissolved in $CH_2Cl_2$ and treated with diisopropylethylamine (1.5 eq.) and phosgene (1 eq., 20% soln. in toluene) at –78 °C. The resulting solution was warmed to room temperature and treated with the amine of general structure 16. The resulting residue subjected to flash silica gel chromatography or preparative HPLC to afford the desired product.

Specific Urea Synthesis

**Example B1: 3-(2-hydroxy-3-{[1-(3-hydroxy-pyrrolidin-yl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid-2-methyl-benzylamide**

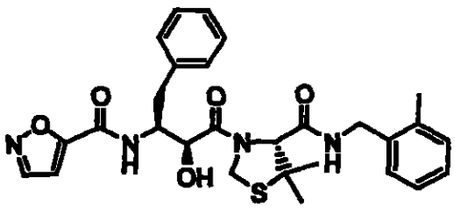


(R)-Pyrrolidin-3-ol (0.21 g, 2.40 mmol) was dissolved in dry $CH_2Cl_2$ (15 mL) and cooled to –78 °C under argon with magnetic stirring. To this solution was added Diisopropylethylamine (0.63 mL, 3.63 mmol) followed by Phosgene as a 20% solution in toluene (1.2 mL, 2.40 mmol). The resulting yellow solution was stirred for 20 min at –78 °C then allowed to warm to room temperature. The solution was concentrated and re-dissolved in dry $CH_2Cl_2$ (5 mL) and THF (5 mL). To this was added Diisopropylethylamine (0.31 mL, 1.81 mmol) followed by 16e. The result was stirred for 16h at 23 °C then diluted with EtOAc (50 mL) The mixture was washed sequentially with 10% citric acid (1 x 50 mL), saturated $NaHCO_3$ (1 x 50 mL), $H_2O$ (1 x 50 mL). The organics were dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (5% MeOH in EtOAc) to yield the title compound (0.12 g, 18%) as a white foam.

$^1$H NMR (DMSO-$d_6$) δ 8.38 (t, $J$ = 5.7, 1H), 7.34-7.09 (m, 10H), 5.99 (d, $J$ = 8.3, 1H), 5.04 (d, $J$ = 9.5, 1H), 4.96 (d, $J$ = 9.5, 1H), 4 49 (s, 1H), 4.48-4 38 (m, 3H), 4.22-3.83 (m, 4H), 3.29-3.04 (m, 3H), 2.77-2.70 (m, 2H), 2.28 (s, 3H), 1.52 (s, 3H), 1.32 (s, 3H), 1.82-1 69 (m, 2H); HRMS (ESI) $m/z$ calcd for $C_{29}H_{38}N_4O_5SNa$ $(M + Na)^+$ 577.2455, found 577.2440; Anal. Calcd for $C_{29}H_{38}N_4O_5S \cdot 2H_2O$ C, 58 96; H, 7.17, N, 9.48; S, 5.43. Found: C, 58.90; H, 6.40; N, 9.23; S, 5.24.

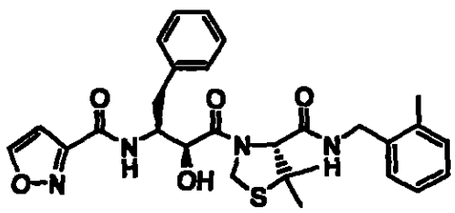
The following examples were prepared by the corresponding specific method outlined above using the requisite P2 fragment.

**Example B2: Isoxazole-5-carboxylic acid {(1S,2S)-1-benzyl-3-[(R)-5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide**



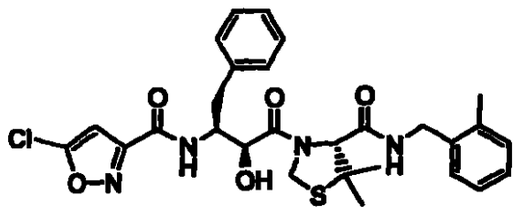
White solid; mp = 82-84 °C; IR (neat, $cm^{-1}$) 3313, 2967, 1656, 1538, 1454, 1372, 1283, 1211, 1108, 916; $^1H$ NMR (DMSO-$d_6$) δ 8.91 (d, $J$ = 8.6, 1H), 8.67 (d, $J$ = 2.0, 1H), 8.35 (t, $J$ = 5.0, 1H), 7.31-7.08 (m, 9H), 7.03 (d, $J$ = 2.0, 1H), 5.63 (d, $J$ = 6.9, 1H), 5.02 (d, $J$ = 8.6, 1H), 4.97 (d, $J$ = 8.6, 1H), 4.60-4.30 (m, 4H), 4.14-4.00 (m, 1H), 2.90-2.75 (m, 2H), 2.23 (s, 3H), 1.49 (s, 3H), 1.28 (s, 3H); HRMS (ESI) $m/z$ calcd for $C_{28}H_{32}N_4O_5SNa$ $(M + Na)^+$ 559.1986, found 559 1994, Anal Calcd for $C_{28}H_{32}N_4O_5S \cdot 0.5H_2O$ C, 61.63, H, 6.10; N, 10.27. Found C, 61 40, H, 5.91; N, 9.97.

**Example B3: Isoxazole-3-carboxylic acid {(1S,2S)-1-benzyl-3-[(R)-5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide**



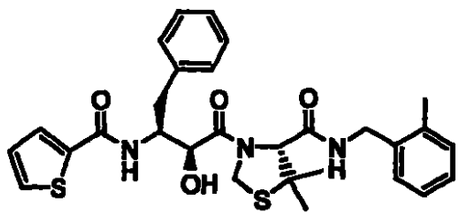
White solid; IR (neat, $cm^{-1}$) 3436, 1643, 1537, 1425, 1378, $^1H$ NMR (DMSO-$d_6$) δ 9.03 (s, 1H), 8.66 (d, $J$ = 8.7, 1H), 8.32 (t, $J$ = 5.3, 1H), 7.30-7 11 (m, 9H), 6.79 (s, 1H), 5.67 (d, $J$ = 6 8, 1H), 4.97 (s, 2H), 4.47-4.32 (m, 4H), 4.09 (dd, $J$ = 15.0, 5.0, 1H), 2.84 (m, 2H), 2.24 (s, 3H), 1.49 (s, 3H), 1.34 (m, 3H); HRMS (ESI) $m/z$ calcd for $C_{28}H_{32}N_4O_5SNa$ $(M + Na)^+$ 559.1986, found 559.1980

**Example B4: 5-Chloro-isoxazole-3-carboxylic acid {(1S,2S)-1-benzyl-3-[(R)-5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide**



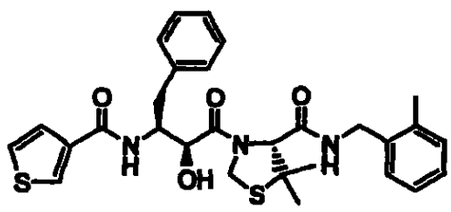
White solid; IR (neat, $cm^{-1}$) 3320, 2969, 1657, 1547, 1434, 1372, 1266; $^1H$ NMR (DMSO-$d_6$) δ 8.74 (d, $J$ = 8.2, 1H), 8.29 (t, $J$ = 5.5, 1H), 7.28-7.08 (m, 9H), 6.90 (s, 1H), 5.72 (d, $J$ = 7.1, 1H), 4.96 (s, 2H), 4.44 (m, 3H), 4.32 (dd, $J$ = 15.2, 6.0, 1H), 4.09 (dd, $J$ = 15.2, 4.6, 1H), 2.85 (m, 2H), 2.83 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H); HRMS (ESI) $m/z$ calcd for $C_{28}H_{31}N_4O_5SClNa$ $(M + Na)^+$ 593.1596, found 593.1569.

**Example B5: (R)-3-{(2S,3S)-2-Hydroxy-4-phenyl-3-[(1-thiophen-2-yl-methanoyl)-amino]-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide**



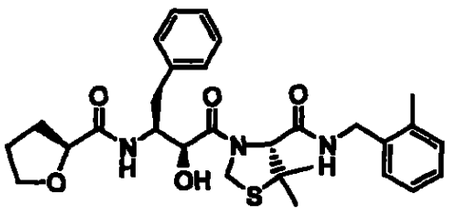
White solid mp = 98-101 °C, IR (neat, $cm^{-1}$) 3416, 1644, 1538, 1455, 1372, 1291, 1107, $^1H$ NMR (DMSO-$d_6$) δ 8.56 (d, $J$ = 8.0, 1H), 8.38 (t, $J$ = 4.8, 1H), 7.85 (d, $J$ = 3.5, 1H), 7.69 (d, $J$ = 4.8, 1H), 7.36-7.08 (m, 10H), 5.38 (d, $J$ = 7.2, 1H), 5.10 (d, $J$ = 8.8, 1H), 4.98 (d, $J$ = 8.8, 1H), 4.54-4.20 (m, 5H), 2.90-2.70 (m, 2H), 2.25 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H); HRMS (ESI) $m/z$ calcd for $C_{29}H_{33}N_3O_4S_2Na$ $(M + Na)^+$ 574.1805, found 574.1818, Anal. Calcd for $C_{29}H_{33}N_3O_4S_2 \cdot 0.75H_2O$: C, 61.62; H, 6 15; N, 7.43. Found. C, 61.31; H, 5.97, N, 7.28.

**Example B6: (R)-3-{(2S,3S)-2-Hydroxy-4-phenyl-3-[(1-thiophen-3-yl-methanoyl)-amino]-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide**



White solid mp = 98-100 °C; IR (neat, $cm^{-1}$) 3312, 3086, 2966, 1644, 1538, 1455, 1372, 1286, 1109; $^1H$ NMR (DMSO-$d_6$) δ 8.42-8 34 (m, 2H), 8.14 (m, 1H), 7.54-7.06 (m, 11H), 5.74 (d, $J$ = 9.3, 1H), 5.35 (d, $J$ = 6 8, 1H), 4.99 (d, $J$ = 9.3, 1H), 4.53 (d, $J$ = 3 0, 1H), 4 50 (s, 1H), 4.42 (dd, $J$ = 15.0, 7.0, 1H), 4.40-4 30 (m, 1H), 4.15 (dd, $J$ = 15.0, 5 0, 1H), 2 90-2.70 (m, 2H), 2.26 (s, 3H), 1.50 (s, 3H), 1.35 (s, 3H); HRMS (ESI) $m/z$ calcd for $C_{29}H_{33}N_3O_4S_2Na$ $(M + Na)^+$ 574 1805, found 574.1789; Anal. Calcd for $C_{29}H_{33}N_3O_4S_2 \cdot 1H_2O$: C, 61.14; H, 6.19; N, 7.38. Found C, 60.74, H, 5 90, N, 7.15.

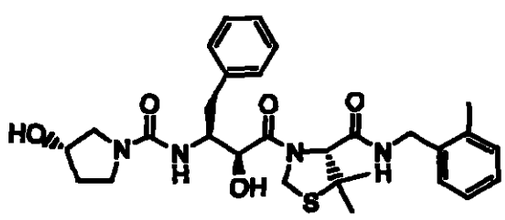
**Example B7: (R)-3-{(2S,3S)-2-Hydroxy-4-phenyl-3-[((S)-1-tetrahydro-furan-2-yl-methanoyl)-amino]-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide**



White solid: mp = 82-84 °C; IR (neat, $cm^{-1}$) 3314, 2969, 1651, 1531, 1456, 1372, 1109, 1071; $^1H$ NMR (DMSO-$d_6$) δ 8.35 (t, $J$ = 6.0, 1H), 7 60 (d, $J$ = 9.2 , 1H), 7.31-7 09 (m, 9H), 5.45 (d, $J$ = 6.8, 1H), 4.97 (d, $J$ = 9.5, 1H), 4 93 (d, $J$ = 9.5, 1H), 4.46 (s, 1H), 4 41-4 07 (m, 4H), 3.77-3.65 (m, 3H), 2.78-2.64 (m, 2H), 2.26 (s, 3H), 2.00-1.80

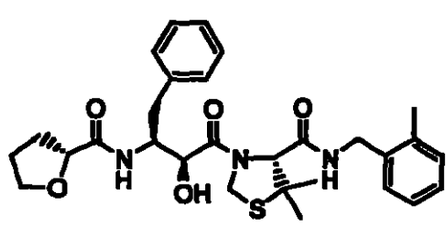
(m, 1H), 1.60 (m, 1H), 1.49 (s, 3H), 1.44-1.38 (m, 2H), 1 34 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{29}H_{37}N_3O_5SNa$ $(M + Na)^+$ 562.2346, found 562.2345; Anal. Calcd for $C_{29}H_{37}N_3O_5S \cdot 0.5\ H_2O$: C, 63.48; H, 6.98; N, 7.66. Found: C, 63.61; H, 6.85; N, 7.58.

**Example B8: 3-(2-hydroxy-3-{[1-(3-hydroxy-pyrrolidin-yl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid-2-methyl-benzylamide**



$^1H$ NMR (DMSO-$d_6$) δ 8.38 (t, $J$ = 5.5, 1H), 7.34-7.09 (m, 10H), 5.99 (d, $J$ = 8.2, 1H), 5.04 (d, $J$ = 9.5, 1H), 4.96 (d, $J$ = 9.5, 1H), 4.49 (s, 1H), 4.48-4.38 (m, 3H), 4.35-4.16 (m, 3H), 4.00 (m, 1H), 3.29-3.04 (m, 3H), 2.78-2.70 (m, 2H), 2.28 (s, 3H), 1.83-1.65 (m, 2H), 1.52 (s, 3H), 1.36 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{29}H_{38}N_4O_5SNa$ $(M + Na)^+$ 577.2455, found 577.2473; Anal. Calcd for $C_{29}H_{38}N_4O_5S \cdot 2H_2O$ C, 58.96; N, 9.48 Found: C, 58.68; N, 9.11.

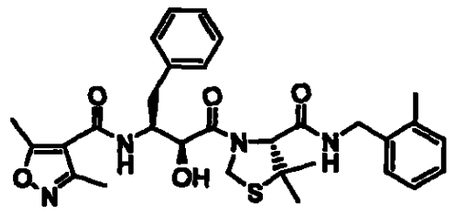
**Example B9: (R)-3-{(2S,3S)-2-Hydroxy-4-phenyl-3-[((R)-1-tetrahydro-furan-2-yl-methanoyl)-amino]-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide**



White solid; IR (neat, $cm^{-1}$) 3324, 2959, 2873, 1724, 1651, 1526, 1455, 1372, 1289, 1073; $^1H$ NMR (DMSO-$d_6$) δ 8 35 (t, $J$ = 4.9, 1H), 7.77 (d, $J$ = 8.9, 1H), 7.52-7.09 (m,

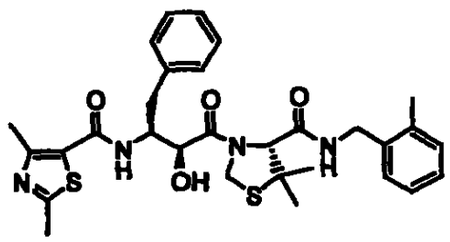
9H), 5.51 (d, $J$ = 6.6, 1H), 4.97-4.89 (m, 2H), 4.52-3.66 (m, 8H), 2.90-2.60 (m, 2H), 2.25 (s, 3H), 1.99-1.63 (m, 4H), 1.48 (s, 3H), 1.33 (s, 3H), HRMS (ESI) $m/z$ calcd for $C_{29}H_{37}N_3O_5SNa$ $(M+Na)^+$ 562.2346, found 562.2366. Anal. Calcd for $C_{29}H_{37}N_3O_5S \cdot 0.25\ H_2O$. C, 64.01; H, 6.95, N, 7.72. Found. C, 64.20, H, 6 90, N, 7.82.

**Example B10: 3,5-Dimethyl-isoxazole-4-carboxylic acid {(1S,2S)-1-benzyl-3-[(R)-5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide**



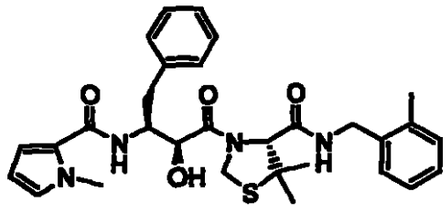
Isolated yield 92%; 1H-NMR (400 MHz, dmso-$d_6$)· δ 8.38 (t, 1H), 8.13 (d, 1H), 7.04 – 7.35 (m, 10H), 5.52 (d, 1H), 5.09 (d, 1H), 5.0 (d, 1H), 4.53 (m, 1H), 4.5 (s, 1H), 4.48 (m, 2H), 4 17 (dd, 1H), 2.87 (dd, 1H), 2.7 (q, 1H), 2.26 (s, 6H), 2.09 (s, 3H), 1.52 (s, 3H), 1.35 (s, 3H) ; IR (KBr in cm-1): 3313, 1643, 1521, 743; MS (APCI, m/z): 565 (M+H), 519, 265, C30H36N4O5S1 0.69 $H_2O$ Calculated· C62 43, H6.53, N9 71, Observed: C63.81, H6 43, N9 92; HPLC . Rf (min ) 20.167, Purity. 98%.

**Example B11: 2,4-Dimethyl-thiazole-5-carboxylic acid {1-benzyl-3-[5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide**



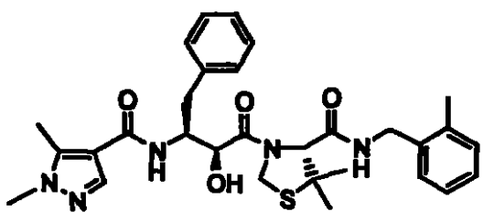
Isolated yield: 80%; 1H-NMR (400 MHz, dmso-$d_6$): δ 8 35 (t, 1H), 8.14 (d, 1H), 7.0 – 7.35 (m, 10H), 5.48 (d, 1H), 5.04 (d, 1H), 5.0 (d, 1H), 4.52 (m, 1H), 4.4 (s, 1H), 4.35 (m, 2H), 4.14 (dd, 1H), 2.78 (d, 2H), 2 57 (s, 3H), 2.30 (s, 3H), 2.26 (s, 3H), 1.48 (s, 3H), 1.35 (s, 3H) ; IR (KBr in cm-1): 3310, 1641, 1534, 743; MS (APCI, m/z): 581 (M+H), 317, 265, 259, $C_{30}H_{36}N_4O_4S_{2.0.39}H_2O$ Calculated: C61.30, H6.31, N9.53, Observed: C62.04, H6.25, N9.65; HPLC : Rf (min.) 19.613; Purity: 98%.

**Example B12: (R)-3-{(2S,3S)-2-Hydroxy-3-[(1-methyl-1H-pyrrole-2-carbonyl)-amino]-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide**



Isolated yield: 82%; 1H-NMR (400 MHz, dmso-$d_6$): δ 8.35 (t, 1H), 7.91 (d, 1H), 7.35 – 7.04 (m, 10H), 6 78 (s, 2H), 5.96 (s, 1H), 5.35 (d, 1H), 5.13 (s, 1H), 5.0 (d, 1H), 4.48 (s, 2H), 4.38 (dd, 1H), 4.30 (m, 1H), 4 13 (dd, 1H), 3.7 (s, 3H), 2.8 (m, 2H), 2.26 (s, 3H), 1.52 (s, 3H), 1.35 (s, 3H) ; IR (KBr in cm-1): 3324, 1639, 1538, 735, MS (APCI, m/z): 549 (M+H), 503, 382, 285; $C_{30}H_{36}N_4O_4S_{1.2.44}H_2O$ Calculated: C60 80, H6.95, N9.45, Observed: C65.67, H6.61, N10.21; HPLC . Rf (mın ) 20.745, Purity: 100%.

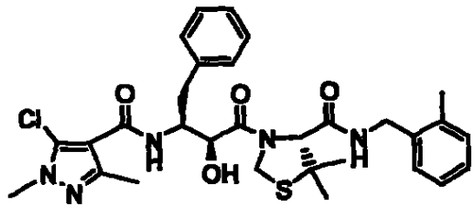
**Example B13: (R)-3-{(2S,3S)-3-[(1,5-Dimethyl-1H-pyrazole-4-carbonyl)-amino]-2-hydroxy-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide**



52

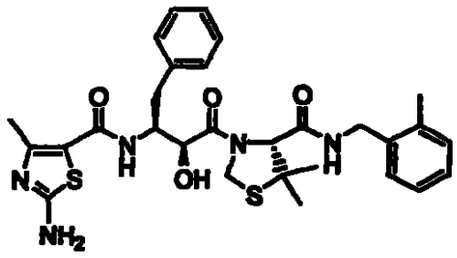
Isolated yield: 68%; 1H-NMR (400 MHz, dmso-$d_6$). δ 8.30 (t, 1H), 7 83 (d, 1H), 7.31 – 7.04 (m, 10H), 6.30 (s, 1H), 5 48 (d, 1H), 4.92 (s, 2H), 4.30 – 4 48 (m, 4H), 4.17 (dd, 1H), 3 7 (s, 3H), 2.74 (m, 2H), 2.26 (s, 3H), 2.18 (s, 3H), 1 48 (s, 3H), 1.30 (s, 3H), IR (KBr in cm-1). 3313, 1645, 1532, 744; MS (APCI, m/z): 564 (M+H), 300, 272; C30H37N5O4S1.0.5 $H_2O$ Calculated: C62.86, H6 69, N12.22, Observed C63 92, H6.62, N12.42; HPLC . Rf (min.) 19.724, Purity: 100%

**Example B14: 3-{(S)-3-[(5-Chloro-1,3-dimethyl-1H-pyrazole-4-carbonyl)-amino]-2-hydroxy-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide**



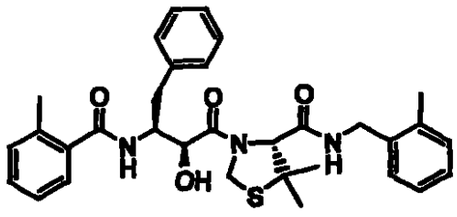
Isolated yield. 92%; 1H-NMR (400 MHz, dmso-$d_6$) δ 8.35 (t, 1H), 7.74 (d, 1H), 7.30 – 7 0 (m, 10H), 5.44 (d, 1H), 4 96 (q, 2H), 4 48 (m, 1H), 4.35 (m, 2H), 4 13 (dd, 1H), 2 74 (m, 2H), 2.22 (s, 3H), 2.09 (s, 3H), 1 48 (s, 3H), 1.26 (s, 3H); IR (KBr in cm-1): 3438, 3313, 1693, 1649, 1513, 1372, 754; MS (APCI, m/z). 598 (M+H), 334, 276, 174; C30H36N5O4S1Cl1.0.17 H2O Calculated: C59 93, H6.09, N11.65, Observed. C60.24, H6 07, N11.71; HPLC : Rf (min.) 19.829; Purity 100%.

**Example B15: 2-Amino-4-methyl-thiazole-5-carboxylic acid {(S)-1-benzyl-3-[5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide**



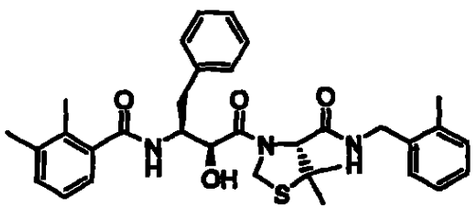
Isolated yield. 42%; 1H-NMR (400 MHz, dmso-$d_6$): δ 8.48 (brs, 1H), 8.35 (brs, 1H), 7 44 (d, 1H), 7.35 – 7.04 (m, 9H), 6.91 (s, 1H), 5.37 (d, 1H), 4.96 (q, 2H), 4.48 – 4.0 (m, 5H), 2,96 (m, 2H), 2.22 (2, 3H), 2.13 (s, 3H), 1.48 (s, 3H), 1.30 (s, 3H) ; IR (KBr in cm-1): 3307, 1625, 1495; MS (APCI, m/z)· 582 (M+H), 442, 318, C29H35N5O4S2Cl1 Calculated: C60.13, H6.5, N10.82, Observed: C59.87, H6.06, N12.04; HPLC : Rf (min.) 17 981; Purity: 98%.

**Example B16: 3-[2-Hydroxy-3-(2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide**



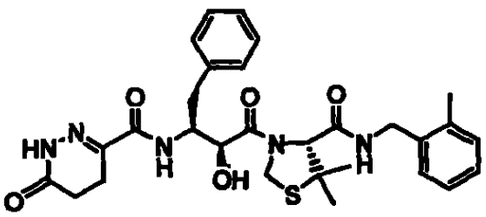
Isolated yield: 76%; 1H-NMR (400 MHz, dmso-$d_6$): δ 8.31 (t, 1H), 8.22 (d, 1H), 7.32 – 7.04 (m, 13H), 5.48 (d, 1H), 5.13 (d, 1H), 5.0 (d, 1H), 4.48 (s, 2H), 4.38 (dd, 2H), 4.09 (dd, 1H), 2 83 (d, 1H), 2.70 (t, 1H), 2.26 (s, 3H), 2.01 (s, 3H), 1.48 (s, 3H), 1.33 (s, 3H) ; IR (KBr in cm-1)· 3309, 1641, 1520, 742; MS (APCI, m/z): 560 (M+H), 514, 296, 265; C32H37N3O4S1. 0.64 H2O Calculated· C67 40, H6.59, N7.37, Observed: C68.79, H6 49, N7.52; HPLC · Rf (min.) 21.024; Purity· 98%

**Example B17: 3-[3-(2,3-Dimethyl-benzoylamino)-2-hydroxy-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide**



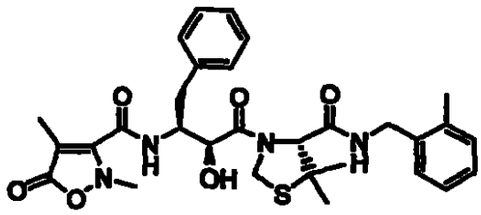
Isolated yield 72%, 1H-NMR (400 MHz, dmso-$d_6$)· δ 8.33 (t, 1H), 8.22 (d, 1H), 7.35 – 6 83 (m, 12H), 5.48 (d, 1H), 5.13 (d, 1H), 5.04 (d, 1H), 4 48 – 4.30 (m, 4H), 4.09 (dd, 1H), 2.84 (d, 1H), 2 70 (t, 1H), 2.26 (s, 3H), 2.17 (s, 3H), 1 87 (s, 3H), 1.48 (s, 3H), 1.30 (s, 3H) ; IR (KBr in cm-1) 3307, 1640, 1515, 743 , MS (APCI, m/z). 574 (M+H), 528, 310, 265; C33H39N3O4S1. 0.54 H2O Calculated C68.05, H6 76, N7.21, Observed· C69.20, H6.76, N7.34; HPLC : Rf (min.) 21 449, Purity· 99%

**Example B18: 6-Oxo-1,4,5,6-tetrahydro-pyridazine-3-carboxylic acid {1-benzyl-3-[5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide**



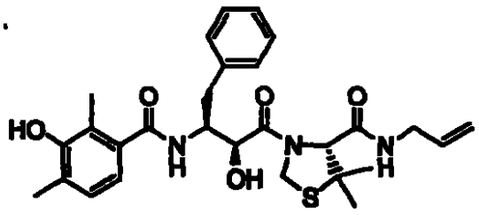
Isolated yield: 67%, 1H-NMR (400 MHz, dmso-$d_6$): δ 8.35 (t, 1H), 8.09 (d, 1H), 7.30 – 7.0 (m, 10H), 5 6 (d, 1H), 4.91 (d, 1H), 4 83 (d, 1H), 4.44 (s, 1H), 4.30 (m, 3H), 4.17 (dd, 1H), 2.78 (d, 2H), 2.61 (t, 2H), 2 30 (t, 2H), 2.22 (s, 3H), 1 48 (s, 3H), 1.30 (s, 3H) ; IR (KBr in cm-1): 3306, 1650, 1521, 742 , MS (APCI, m/z) 566 (M+H), 520, 265; C29H35N5O5S1 0.7 H2O Calculated: C60 23, H6.34, N12.11, Observed. C61.57, H6 24, N12.38, HPLC . Rf (min.) 18.455; Purity: 97%

**Example B19: 2,4-Dimethyl-5-oxo-2,5-dihydro-isoxazole-3-carboxylic acid {1-benzyl-3-[5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide**



Isolated yield: 73%; 1H-NMR (400 MHz, dmso-$d_6$)· δ 8.91 (d, 1H), 8.35 (t, 1H), 7.30 – 7.04 (m, 9H), 5.70 (d, 1H), 5.0 (d, 2H), 4 44 (s + m, 3H), 4.31 (dd, 1H), 4.13 (dd, 1H), 2.91 ( s + m, 4H), 2.65 (t, 1H), 2.22 (s, 3H), 1.52 (s, 3H), 1.48 (s, 3H), 1.30 (s, 3H) ; IR (KBr in cm-1): 3325, 2932, 1729, 1649, 1527, 742 ; MS (APCI, m/z). 581 (M+H), 539, 493, 225; C30H36N4O6S1 Calculated: C62.29, H5.61, N9.19, Observed. C62.05, H6.25, N9.65; HPLC : Rf (min.) 19.638, Purity: 100%

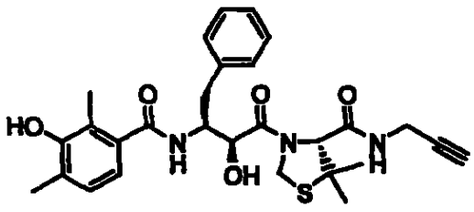
**Example B20: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2,4-dimethyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid allylamide**



$^1$H NMR (DMSO-$d_6$) δ 8.23 (s, 1H), 8.10-8.03 (m, 2H), 7.33-7.12 (m, 5H), 6 85 (d, $J$ = 7.7, 1H), 6.51 (d, $J$ = 7.7, 1H), 5.82-5.70 (m, 1H), 5.44 (d, $J$ = 6.8, 1H), 5.22-4.97 (m, 4H), 4.50-4.30 (m, 3H), 3.84-3.60 (m, 2H), 2 84-2.66 (m, 2H), 2.13 (s, 3H), 1.85 (s, 3H), 1.49 (s, 3H), 1.35 (s, 3H); HRMS (ESI) $m/z$ calcd for $C_{28}H_{36}N_3O_5S$ $(M+H)^+$

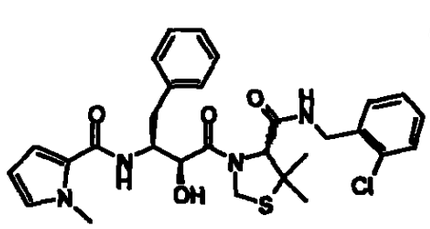
526 2376, found 526 2380, Anal. Calcd for $C_{28}H_{35}N_3O_5S \cdot 0.2$ TFA: C, 62.19; H, 6 47; N, 7 66 Found: C, 62.27, H, 6.78; N, 7.26

**Example B21: 3-(2-Hydroxy-3-{[1-(3-hydroxy-2,4-dimethyl-phenyl)-methyanoyl]-amino}-4-phenyl-butznoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid prop-2-ynylamide**



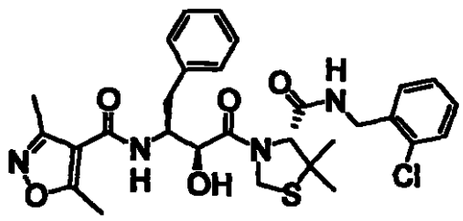
$^1$H NMR (DMSO-$d_6$) δ 8 40 (t, $J$ = 5.4, 1H), 8.22 (s, 1H), 8.02 (d, $J$ = 8.2, 1H), 7.35-6.52 (m, 7H), 5 44 (d, $J$ = 6 8, 1H), 5.10 (d, $J$ = 9.1, 1H), 5 02 (d, $J$ = 9.1, 1H), 4.46-4.40 (m, 2H), 4 40 (s, 1H), 3.86 (s br, 2H), 3 08 (t, $J$ = 1.8, 1H), 2.82-2.72 (m, 2H), 2.15 (s, 3H), 1 88 (s, 3H), 1 51 (s, 3H), 1.37 (s, 3H); HRMS (ESI) $m/z$ calcd for $C_{28}H_{34}N_3O_5S$ $(M+H)^+$ 524.2219, found 524 2219; Anal Calcd for $C_{28}H_{33}N_3O_5S \cdot 0.5H_2O$· C, 63.13; H, 6.43, N, 7.89; S, 6.02. Found· C, 62 80, H, 6.64; N, 7.71, S, 5.69.

**Example B22: 3-{2-Hydroxy-3-[(1-methyl-1H-pyrrole-2-carbonyl)-amino]-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-chloro-benzylamide**



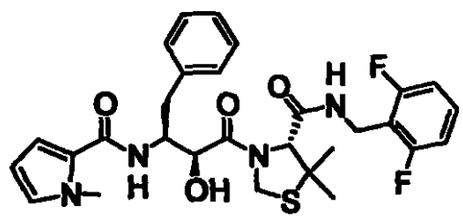

Isolated yield· 50%; 1H-NMR (400 MHz, dmso-$d^6$). 6 40-7 40 (m, 11H), 6 00 (m, 1H), 4.20-5.20 (m, 7H), 3.71, 3.54 (s 3H), 2 70-2.90 (m, 2H), 1 52 (d, $J$ = 2 0 Hz, 3H), 1 32 (d, $J$ = 2.1 Hz, 3H), MS (APCI, m/z): 570 (M+H)

**Example B23: 3,5-Dimethyl-isoxazole-4-carboxylic acid {1-benzyl-3-[4-(2-chloro-benzylcarbamoyl)-5,5-dimethyl-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide**



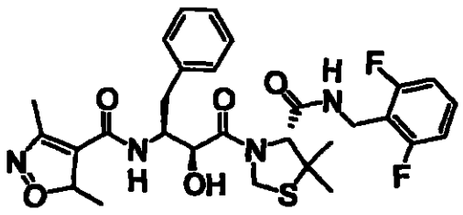
Isolated yield: 55%; 1H-NMR (400 MHz, dmso-$d^6$): 7.00-7.40 (m, 9H), 4.36-5.08 (m, 7H), 2.70-2.90 (m, 2H), 2.34, 2.25 (s, 3H), 2.18, 2.12 (s, 3H), 1.56 (d, $J$ = 8.5 Hz, 3H), 1.35 (d, $J$ = 6.2 Hz, 3H); MS (APCI, m/z): 586 (M+H); $C_{29}H_{33}ClN_4O_5S$. $0.42H_2O$ Calculated: C58.77, H5.75, N9.45, Observed: C58.37, H5.73, N9.19.

**Example B24: 3-{2-Hydroxy-3-[(1-methyl-1H-pyrrole-2-carbonyl)-amino]-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2,6-difluoro-benzylamide**



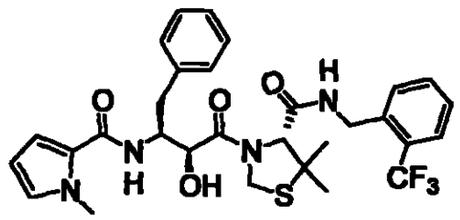
Isolated yield 75%; 1H-NMR (400 MHz, dmso-$d^6$). 6.40-7.40 (m, 10H), 6.00 (m, 1H), 4.20-5.20 (m, 7H), 3.64, 3.61 (s 3H), 2 70-2.90 (m, 2H), 1.52, 1.49 (s, 3H), 1.33, 1.29 (s, 3H); MS (APCI, m/z): 571 (M+H); $C_{29}H_{32}F_2N_4O_4S$ Calculated: C61.04, H5.65, N9.82, Observed: C60.86, H5 94, N9 71.

**Example B25: 3,5-Dimethyl-isoxazole-4-carboxylic acid {1-benzyl-3-[4-(2,6-difluoro-benzylcarbamoyl)-5,5-dimethyl-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide**



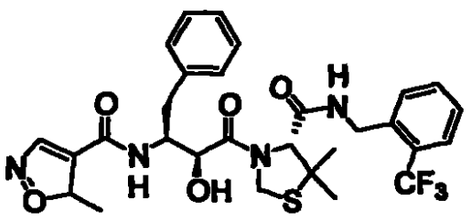
Isolated yield. 75%; 1H-NMR (400 MHz, dmso-$d^6$) 6 60-7 40 (m, 8H), 4.26-5.08 (m, 7H), 2.70-2 90 (m, 2H), 2.32, 2.28 (s, 3H), 2.16, 2.13 (s, 3H), 1 56, 1 53 (s, 3H), 1 37, 1.34 (s, 3H), MS (APCI, m/z)· 587 (M+H); $C_{29}H_{32}F_2N_4O_5S$ Calculated. C59.37, H5.50, N9.55, Observed· C59.12, H5.88, N9.50

**Example B26: 3-{2-Hydroxy-3-[(1-methyl-1H-pyrrole-2-carbonyl)-amino]-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-trifluoromethyl-benzylamide**



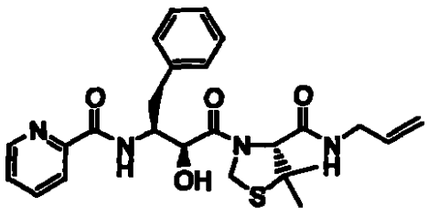
Isolated yield: 83%; 1H-NMR (400 MHz, dmso-$d^6$) 6 40-7 60 (m, 11H), 6.00 (m, 1H), 4.20-5.20 (m, 7H), 3.70, 3.54 (s 3H), 2.70-2.90 (m, 2H), 1.52 (s, 3H), 1.36, 1.29 (s, 3H); MS (APCI, m/z): 619 (M+H), $C_{30}H_{33}F_3N_4O_4S$ Calculated C59 79, H5 52, N9 30, Observed· C59.42, H5.55, N9.06.

**Example B27: 3,5-Dimethyl-isoxazole-4-carboxylic acid {1-benzyl-3-[5,5-dimethyl-4-(2-trifluoromethyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide**



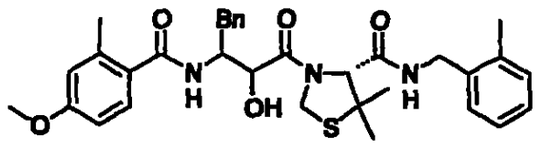
Isolated yield: 93%; 1H-NMR (400 MHz, dmso-$d^6$): 7.05-7.60 (m, 9H), 4.36-5.08 (m, 7H), 2.70-2.90 (m, 2H), 2.30, 2.21 (s, 3H), 2.15, 2.05 (s, 3H), 1.54, 1.52 (s, 3H), 1.39, 1.32 (s, 3H); MS (APCI, m/z): 619 (M+H); $C_{30}H_{33}F_3N_4O_5S$ Calculated: C58.24, H5.38, N9.06, Observed: C57.87, H5.68, N9.02.

**Example B28: N-[(1S,2S)-3-(4-Allylcarbamoyl-5,5-dimethyl-thiazolidin-3-yl)-1-benzyl-2-hydroxy-3-oxo-propyl]-nicotinamide**



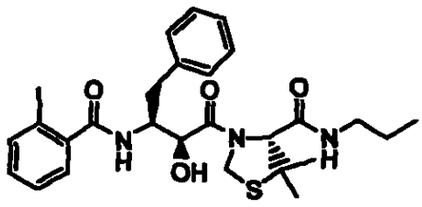
White solid. $^1$H NMR (DMSO-$d_6$) δ 8.81 (d, $J$ = 8.6, 1), 8.77 (d, $J$ = 6.2, 1H), 8.12 (m, 1H), 7.99 (m, 1H), 7.63 (m, 1H), 7.32-7.12 (m, 7H), 5.78 (m, 1H), 5.18 (m ,2H), 4.56(m ,3H), 4 40 (m, 4H), 2.87-2.67 (m, 2H), 1.49 (s, 3H), 1.34 (s, 3H); Anal. ($C_{26}H_{32}N_4O_4S$•0.5 $H_2O$•0.5 TFA) calculated C (57.65), H (6.36), N (10 19), found C (57.73), H (5.91), N (10.15). HRMS (ESI) *m/z* calcd for 483.2075, found 497.2066.

**Example B29: 3-[2-Hydroxy-3-(4-methoxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide**



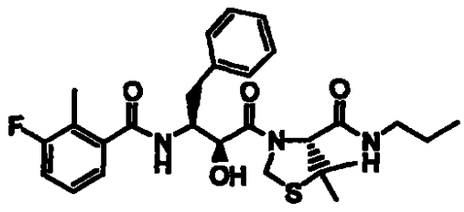
Isolated yield: 56% $^1$H NMR (400 MHz, DMSO-$d_6$)· δ 8.32 (t, 1H), 8.09 (d, 1H), 7.33-7.27 (m, 3H), 7.23-7.19 (m, 2H), 7.15-7 08 (m, 5H), 6.69 (d, 2H), 5.46 (d, 1H), 5.13 (d, 1H), 4.99 (d, 1H), 4.49 (s, 2H), 4.41-4.36 (m, 2H), 4.10 (dd, 1H), 3.71 (s,3H), 2 84-2.81 (m, 1H), 2.72 (t, 1H), 2.24 (s, 3H), 2 07 (s, 3H), 1.48 (s, 3H), 1.33 (s, 3H), MS-APCI (m/z+) 326, 590 (M+H). HPLC: Rf(min.) 21.26; Purity: 100%; $C_{33}H_{39}N_3O_5S_1$·0 4 $H_2O$: calcd. C66.40, H6.72, N7.04, found: C66.38, H6.71, N6.94.

**Example B30: (R)-3-{(2S,3S)-2-Hydroxy-4-phenyl-3-[(1-o-tolyl-methanoyl)-amino]-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid propylamide**



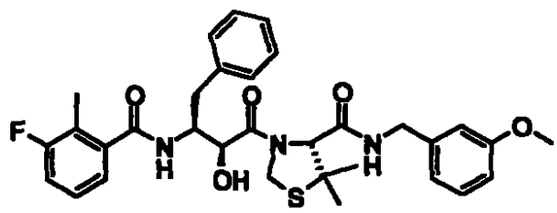
IR (neat, cm$^{-1}$) 3318, 2964, 1642, 1530, 1445, 1372, $^1$H NMR (DMSO) δ 8.21 (d, $J$ = 8 4, 1H), 7.90 (t, $J$ = 5 6, 1H), 7.35-7 07 (m, 9H), 5.45 (d, $J$ = 6 8, 1H), 5.09 (d, $J$ = 9.2, 1H), 5 00 (d, $J$ = 9.2, 1H), 4.50-4.38 (m, 2H), 4.37 (s, 1H), 3.01 (q, $J$ = 6.9, 2H), 2.90-2 60 (m, 2H), 2.02 (s, 3H), 1.49 (s, 3H), 1 44-1.35 (m, 2H), 1.34 (s, 3H), 0 82 (t, $J$ = 7.5, 3H), HRMS (ESI) $m/z$ calcd for $C_{27}H_{36}N_3O_4S$ $(M+H)^+$ 498.2424, found 498.2427.

**Example B31: (R)-3-((2S,3S)-3-{[1-(3-Fluoro-2-methyl-phenyl)-methanoyl]-amino}-2-hydroxy-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid propylamide**



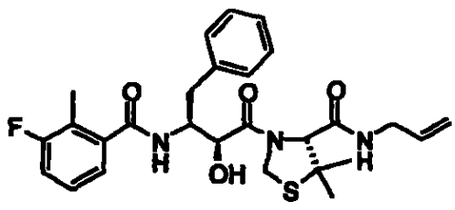
White solid: $^1$H NMR (DMSO) δ 8.34 (d, $J$ = 8.1, 1H), 7.91 (t, $J$ = 5.9, 1H), 7.40-7 10 (m, 7H), 6.93 (d, $J$ = 6.9, 1H), 5.51 (d, $J$ = 6 2, 1H), 5.08 (d, $J$ = 8.8, 1H), 5.00 (d, $J$ = 8.8, 1H), 4.50-4.39 (m, 2H), 4.38 (s, 1H), 3.00 (dd, $J$ = 12.3, 5.9, 2H), 2.90-2.60 (m, 2H), 1.89 (s, 3H), 1.49 (s, 3H), 1.40-1.34 (m, 2H), 1 34 (s, 3H), 0.82 (t, $J$ = 7.7, 3H), HRMS (ESI) $m$ / $z$ calcd for $C_{27}H_{35}N_3O_4FS$ $(M + H)^+$ 516.2332, found 516.2339.

**Example B32: (R)-3-((2S,3S)-3-{[1-(3-Fluoro-2-methyl-phenyl)-methanoyl]-amino}-2-hydroxy-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 3-methoxy-benzylamide**



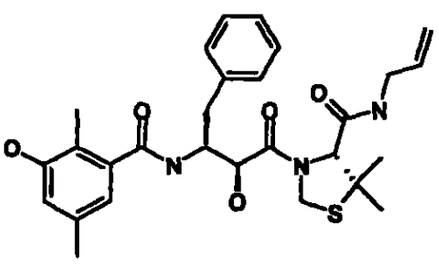
White solid: $^1$H NMR (DMSO) δ 8.43 (t, $J$ = 5 9, 1H), 8 34 (d, $J$ = 8.1, 1H), 7.31-6.72 (m, 12H), 5.57 (d, $J$ = 6.8, 1H), 5.12 (d, $J$ = 9.3, 1H), 5.01 (d, $J$ = 9.3, 1H), 4.50-4.30 (m, 4H), 4.12 (dd, $J$ = 15.7, 5.9, 1H), 3.69 (s, 3H), 2.95-2.62 (m, 2H), 1.90 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H); HRMS (ESI) $m$ / $z$ calcd for $C_{32}H_{37}N_3O_5SF$ $(M + H)^+$ 594.2434, found 594.2438.

**Example B33: (R)-3-((2S,3S)-3-{[1-(3-Fluoro-2-methyl-phenyl)-methanoyl]-amino}-2-hydroxy-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid allylamide**



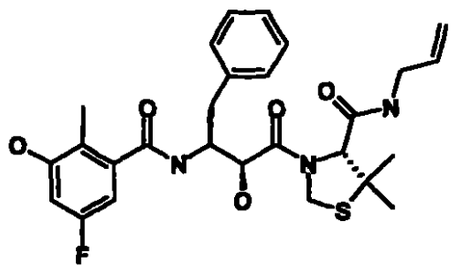
White solid. $^1$H NMR (DMSO) δ 8 34 (d, $J$ = 8 3, 1H), 8.10 (t, $J$ = 5 7, 1H), 7.40-6.90 (m, 8H), 5.81-5.69 (m, 1H), 5.54 (d, $J$ = 6.6, 1H), 5.30-4.90 (m, 4H), 4 50-4.35 (m, 3H), 3.80-3 65 (m, 2H), 2.90-2.60 (m, 2H), 1 89 (s, 3H), 1.49 (s, 3H), 1 35 (s, 3H), HRMS (ESI) $m$ / $z$ calcd for $C_{27}H_{33}N_3O_4SF$ $(M + H)^+$ 514.2182, found 514 2176

**Example B34: 3-[(2S,3S)-2-Hydroxy-3-(3-hydroxy-2,5-dimethyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid allylamide**



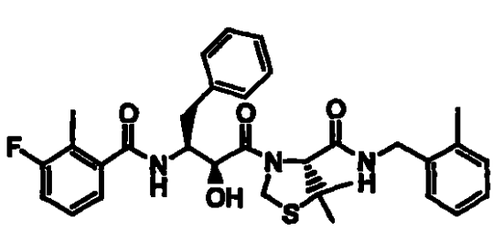
$^1$H NMR (DMSO-$d_6$) δ 9.23 (s, 1H), 8 09 (m, 2H), 7.35-7.17 (m, 5H), 6.60 (s, 1H), 6 37 (s, 1H), 5 74 (m, 1H), 5.41 (br s, 1H), 5 20 (dd, $J$ = 17.2, 1 6, 1H), 5.11 (d, $J$ = 9.2, 1H), 5 02 (dd, $J$ = 10.2, 1.5, 1H), 5.00 (d, $J$ = 9 1, 1H), 4 46-4 37 (m, 3H), 3.79 (ddd, $J$ = 15.9, 5.5, 5.3, 1H), 3 63 (ddd, $J$ = 15.9, 5.4, 5 3, 1H), 2 82 (dd, $J$ = 13.9, 0.3, 1H), 2.71 (dd, $J$ = 13.6, 10.7, 1H), 2.16 (s, 3H), 1 76 (s, 3H), 1.51 (s, 3H), 1 36 (s, 3H); Anal. Calcd for $C_{28}H_{35}N_4O_5S$•0 $3H_2O$: C, 63 32, H, 6 76, N, 7.91, Found C, 63.35, H, 6.70; N, 7.71.

**Example B35: 3-[(2S,3S)-3-(5-Fluoro-3-hydroxy-2-methyl-benzoylamino)-2-hydroxy-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid allylamide**



$^1$H NMR (DMSO-$d_6$) δ 9 94 (s, 1H), 8.23 (d, $J$ = 8.2, 1H), 8.10 (t, $J$ = 5.6, 1H), 7.33-7.17 (m, 5H), 6.58 (dd, $J$ = 10.6, 2.5, 1H), 6.32 (dd, $J$ = 8.8, 2.5, 1H), 5.78 (m, 1H), 5.54 (br s, 1H), 5.21 (dd, $J$ = 17.2, 1.7, 1H), 5.10 (d, $J$ = 9.1, 1H), 5.03 (dd, $J$ = 10.2, 1.5, 1H), 5.01 (d, $J$ = 9.1, 1H), 4.50-4.42 (m, 3H), 3.78 (ddd, $J$ = 15.9, 5.4, 5.4, 1H), 3.63 (ddd, $J$ = 15.9, 5.4, 5.3, 1H), 2.84 (dd, $J$ = 14.5, 3.3, 1H), 2.70 (dd, $J$ = 13.5, 10.3, 1H), 1.75 (s, 3H), 1.50 (s, 3H), 1.36 (s, 3H); Anal. Calcd for $C_{27}H_{32}FN_3O_5S$•0.3$H_2O$ : C, 60.61, H, 6.14; N, 7.85, Found. C, 60.63; H, 6.08; N, 8.07.

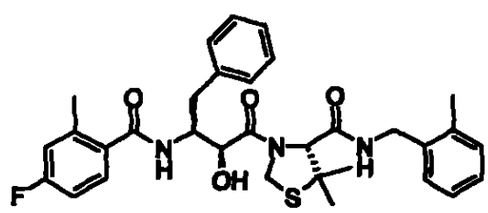
**Example B36: (R)-3-((2S,3S)-3-{[1-(3-Fluoro-2-methyl-phenyl)-methanoyl]-amino}-2-hydroxy-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide**



$^1$H NMR (DMSO) δ 8.85-8.35 (m, 2H), 7 38-6.90 (m, 12H), 5.55 (d, $J$ = 5.9, 1H), 5.12 (d, $J$ = 9.2, 1H), 5.01 (d, $J$ = 9.2, 1H), 4.58-4.32 (m, 4H), 4 10 (dd, $J$ = 15.0, 4 6, 1H), 2.92-2.62 (m, 2H), 2.24 (s, 3H), 1.90 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H); HRMS (ESI) $m/z$ calcd for $C_{32}H_{37}N_3O_4FS$ $(M+H)^+$ 578.2489, found 578.2486; Anal Calcd for

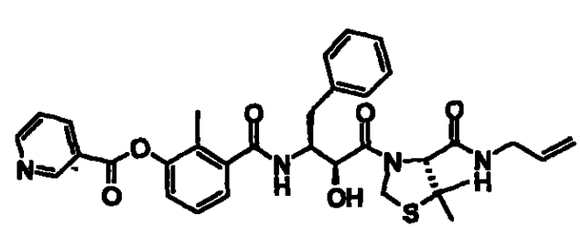
$C_{32}H_{36}N_3O_4FS \cdot 0.2$ EtOAc. C, 66.17; H, 6.37; N, 7.06. Found: C, 66.30; H, 6.54, N, 6 74

**Example B37: (R)-3-((2S,3S)-3-{[1-(4-Fluoro-2-methyl-phenyl)-methanoyl]-amino}-2-hydroxy-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide**



White solid· $^1$H NMR (DMSO) δ 8.40-8.30 (m, 2H), 7.35-6 90 (m, 12H), 5.53 (d, $J$= 6 8, 1H), 5.13 (d, $J$= 9 0, 1H), 5.00 (d, $J$= 9 0, 1H), 4 48 (s, 1H), 4.47-4 45 (m, 2H), 4.38 (dd, $J$= 15 0, 5.9, 1H), 4.10 (dd, $J$= 15.0, 4.8, 1H), 2 90-2.62 (m, 2H), 2.24 (s, 3H), 2 04 (s, 3H), 1 48 (s, 3H), 1.33 (s, 3H), HRMS (ESI) $m$ / $z$ calcd for $C_{32}H_{37}N_3O_4SF$ $(M+H)^+$ 578.2463, found 578 2489

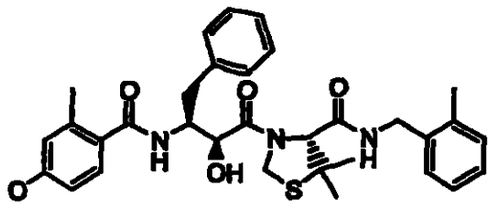
**Example B38: Nicotinic acid 3-[(1S,2S)-3-((R)-4-allylcarbamoyl-5,5-dimethyl-thiazolidin-3-yl)-1-benzyl-2-hydroxy-3-oxo-propylcarbamoyl]-2-methyl-phenyl ester**



Whute solid: $^1$H NMR (DMSO) δ 9.26 (dd, $J$= 2.0, 0.9, 1H), 8.90 (dd, $J$= 5 6, 2.0, 1H), 8.47 (dt, $J$= 7.9, 2 0, 1H), 8.40 (d, $J$= 8.2, 1H), 8.1 (t, $J$= 5.7, 1H), 7.65 (ddd, $J$= 7 9, 5 6, 0.9, 1H), 7 40-7.10 (m, 8H), 5 82-5.68 (m, 1H), 5 6 (d, $J$= 6.2, 1H), 5.30-4 90

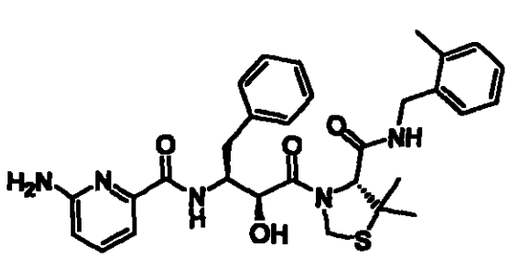
(m, 4H), 4.50-4.40 (m, 2H), 4.40 (s, 1H), 3.80-3.70 (m, 2H), 3.00-2.60 (m, 2H), 1.85 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H).

**Example B39: (R)-3-[(2S,3S)-2-Hydroxy-3-(4-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide**



White solid: $^1$H NMR (DMSO) δ 9.55 (s, 1H), 8.32 (t, $J$ = 4.9, 1H), 8.00 (d, $J$ = 8.4, 1H), 7.36-7.00 (m, 10H), 6.54-6.48 (m, 2H), 5.44 (d, $J$ = 6.6, 1H), 5.13 (d, $J$ = 9.2, 1H), 4.99 (d, $J$ = 9.2, 1H), 4.50-4.32 (m, 4H), 4 11 (dd, $J$ = 15.0, 4.8, 1H), 3.50-2 80 (m, 2H), 2.25 (s, 3H), 2.04 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H); Anal. Calcd for $C_{32}H_{37}N_3O_5S$•0.25 $H_2O$: C, 66 24, H, 6.51, N, 7.24 Found: C, 66.25; H, 6.55; N, 7.35

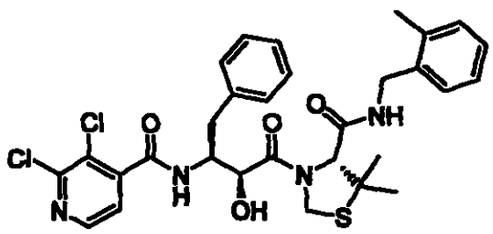
**Example B40: 6-Amino-pyridine-2-carboxylic acid {(1S,2S)-1-benzyl-3-[(R)-5,5-dimethyl-4- (2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide**



$^1$H NMR (DMSO-$d_6$) δ 8.44 (d, 1H, $J$ = 5 6), 8.36 (d, 1H, $J$ = 9.3), 7.69-7.49 (t, 1H, $J$ = 7.7), 7.34-7.06 (m, 10H), 6.61 (d, 1H, $J$ = 8.4), 6.27 (br s, 2H) 5.47 (d, 1H, $J$ = 7.1), 5 00 (m, 2H), 4.54-4.43 (m, 2H), 4.50 (s, 1H), 4.38 (dd, 1 H, $J$ = 6.4, 15 2), 4.19 (dd,

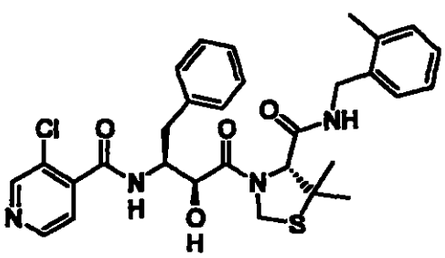
1H, $J$ = 4.6, 14 7), 2.87-2.65 (m, 2H), 2.28 (s, 3H), 1.53 (s, 3H), 1.38 (s, 3H). Exact mass calculated for $C_{30}H_{36}N_5O_4S$ $(M + H)^+$ 562.2488, found 562 2493

**Example B41: {(1S,2S)-1-Benzyl-3-[(R)-5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-2,3-dichloro-isonicotinamide**



$^1$H NMR (DMSO-$d_6$) δ 8.89 (d, 1H, $J$ = 8.42), 8 40 (t, 1H, $J$ = 5 5), 8.38 (d, 1H, $J$ = 4.8), 7.30-7.08 (m, 10H), 5.58 (d, 1H, $J$ = 7.3), 5.07 (d, 1H, $J$ = 8.8), 5.00 (d, 1H, $J$ = 8.8), 4 54-4.50 (m, 1H), 4.51 (s, 1H), 4 43-4.36 (m, 2H), 4.16 (dd, 1H, $J$ = 5.1, 15.0), 2.89-2.85 (m, 1H), 2 71-2.63 (m, 1H), 2.26 (s, 3H), 1.50 (s, 3H), 1 35s (s, 3H) Exact mass calculated for $C_{30}H_{33}N_4O_4SCl_2$ $(M + H)^+$ 615 1600, found 615 1581 Anal Calcd for $C_{30}H_{32}N_4O_4SCl_2$. C, 58 54, H, 5.24, N, 9.10 Found. C, 58.48, H, 5.10; N, 8 80.

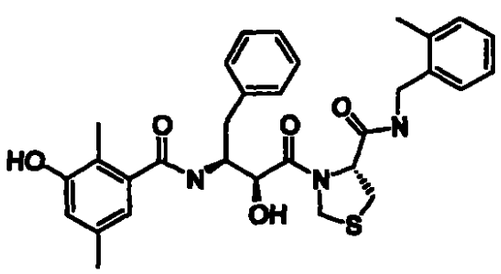
**Example B42: {(1S,2S)-1-Benzyl-3-[(R)-5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-3-chloro-isonicotinamide**



$^1$H NMR (DMSO-$d_6$) δ 8 82 (d, 1H, $J$ = 8 6), 8 62 (s, 1H), 8 52 (d, 1H, $J$ = 4 9), 8.39 (d, 1H, $J$ = 5.1), 7.29-7.09 (m, 10H), 5.54 (d, 1H, $J$ = 7.1), 5.09 (d, 1H, $J$ = 9.0), 4.99 (d,

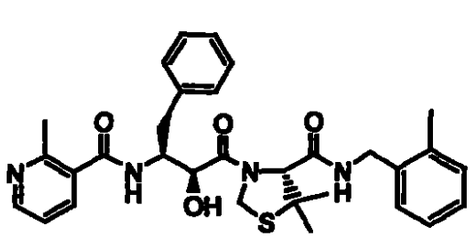
1H, $J$ = 9.0), 4.56-4.49 (m, 1H), 4.51 (s, 1H), 4.44-4.37 (m, 2H), 4.15 (dd, 1H, $J$ = 5.1, 15.0), 2.88-2.83 (m, 1H), 2.74-2.65 (m, 1H), 2.26 (s, 3H), 1.50 (s, 3H), 1.35s (s, 3H). Exact mass calculated for $C_{30}H_{33}N_4O_4SCl$ $(M)^+$ 581.1989, found 581.1983.

**Example B43: (R)-3-[(2S,3S)-2-Hydroxy-3-(3-hydroxy-2,5-dimethyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide**



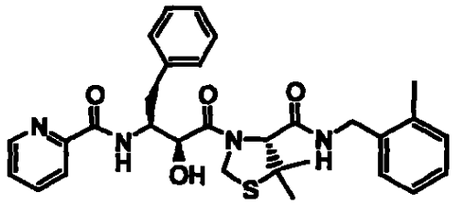
$^1$H NMR (DMSO-$d_6$) δ 9.24 (s, 1H), 8.31 (t, $J$ = 5.6, 1H), 8.10 (d, $J$ = 8.2, 1H), 7.34-7.09 (m, 9H), 6.60 (s, 1H), 6 38 (s, 1H), 5.42 (br s, 1H), 5.14 (d, $J$ = 9.1, 1H), 5.01 (d, $J$ = 9.1, 1H), 4.50 (s, 1H), 4.50-4.37 (m, 3H), 4.11 (dd, $J$ = 15.1, 4.7, 1H), 2.76 (m, 2H), 2.26 (s, 3H), 2.16 (s, 3H), 1.77 (s, 3H), 1.50 (s, 3H), 1.35 (s, 3H), HRMS (ESI) $m/z$ calcd for $C_{33}H_{40}N_3O_5S$ $(M + H)^+$ 590.2689, found 590.2676; Anal. Calcd for $C_{33}H_{39}N_3O_5S \cdot 0.3\ H_2O$. C, 66 60, H, 6 71, N, 7.06. Found. C, 66.65; H, 6 69; N, 7.05.

**Example B44: N-{(1S,2S)-1-Benzyl-3-[5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-2-methyl-nicotinamide**



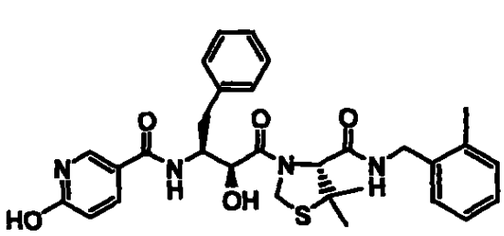
White solid $^1$H NMR (DMSO-$d_6$) δ 8.53-8.33 (m, 2H), 7.47 (d, $J$ = 7.82, 1H), 7.38-7.10 (m, 12H), 5 62 (d, $J$ = 7 94, 1H), 5.18 (dd, $J$ = 9.6, 7.6, 2H), 4.43-4 37 (m, 3H), 4 17 (dd, $J$ = 7.81, 6.99, 1H), 2.87-2.67 (m, 2H), 2.28 (s, 3H), 2.21(s, 3H), 1.49 (s 3H), 1.34 (s, 3H), Anal ($C_{31}H_{36}N_4O_4S$•1 0 $H_2O$ •1 0 MeCN) calculated C (63 95), H (6 67), N (11.30), found C (63.94), H (6 75), N (11.26). HRMS (ESI) *m/z* calcd for 561.2544, found 561 2556

**Example B45: Pyridine-2-carboxylic acid{(1S,2S)-1-benzyl-3-[5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide**



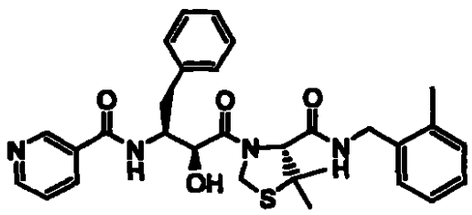
White solid: $^1$H NMR (DMSO-$d_6$) δ 8 89 (d, $J$ = 7 86,), 8 66 (d, $J$ = 4 2, 1H), 8.39 (t, $J$ = 6.54, 1H), 7 89 (m 2H), 7.32-7 12 (m, 9H), 5 68 (d, $J$ = 7.28, 1H), 5.03 (dd $J$ = 9.7, 8.3, 2H), 4 56(m 3H), 4.40 (d, $J$ = 7.5, 1H), 4.35 (d, $J$ = 7.5, 1H), 4.21 (d, $J$ = 6 7, 1H), 2 87-2 67 (m, 2H), 2.25 (s 3H), 1.49 (s, 3H), 1 34 (s, 3H), Anal ($C_{30}H_{34}N_4O_4S$•0.1 $H_2O$ •0.1 EtOAc) calculated C (65.52), H (6.33), N (10.05), found C (65 78), H (6 69), N (9 66). HRMS (ESI) *m/z* calcd for 547.2380, found 547.2373.

**Example B46: Pyridine-2-5-hydroxy-carboxylic acid{(1S,2S)-1-benzyl-3-[5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide**



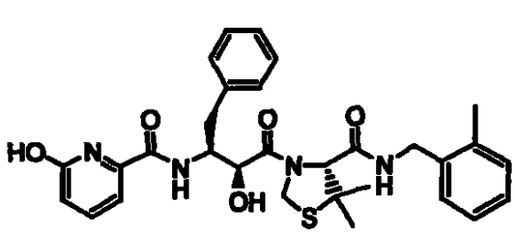
White solid: $^1$H NMR (DMSO-$d_6$) δ 8.89 (d, $J$ = 7.9, 1), 8.66 (d, $J$ = 4.2, 1H), 8.39 (t, $J$ = 6.54, 1H), 7.89 (m 2H), 7.32-7.12 (m, 9H), 5.68 (d, $J$ = 7.2, 1H), 5.03 (dd $J$ = 9.7, 8.3, 2H), 4.56(m 3H), 4.40 (d, $J$ = 7.5, 1H), 4.35 (d, $J$ = 7.5, 1H), 4.21 (d, $J$ = 6.7, 1H), 2.87-2.67 (m, 2H), 2.25 (s 3H), 1.49 (s, 3H), 1.34 (s, 3H); Anal. ($C_{30}H_{34}N_4O_5S$•0.5 $H_2O$ •0.5 EtOAc) calculated C (62.29), H (6.42), N (9.91), found C (62.53), H (6.84), N (10.10). HRMS (ESI) *m/z* calcd for 563.2325, found 563.2328.

**Example B47: N-{(1S,2S)-1-Benzyl-3-[5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-nicotinamide**



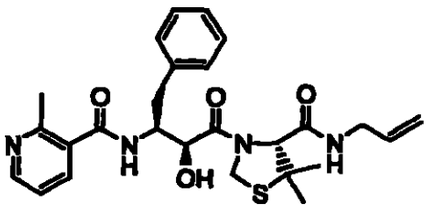
White solid $^1$H NMR (DMSO-$d_6$) δ 8.89 (d, $J$ = 7.9, 1H), 8.66 (d, $J$ = 4 2, 1H), 8 39 (t, $J$ = 6.54, 1H), 7.89 (m 2H), 7.32-7.12 (m, 9H), 5.68 (d, $J$ = 7.3, 1H), 5.03 (dd $J$ = 9.7, 8.3, 2H), 4.56(m 3H), 4.40 (d, $J$ = 7.5, 1H), 4.35 (d, $J$ = 7.5,1H), 4.21 (d, $J$ = 6.7,1H), 2.87-2.67 (m, 2H), 2.25 (s 3H), 1.49 (s, 3H), 1 34 (s, 3H); Anal ($C_{30}H_{34}N_4O_4S$•0.5 $H_2O$ •0.5 MeCN) calculated C (64.61), H (6.39), N (10 94), found C (65.02), H (6 58), N (10.90). HRMS (ESI) *m/z* calcd for 547.2372, found 547.2379.

**Example B48: N-{(1S,2S)-1-Benzyl-3-[5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-nicotinamide**



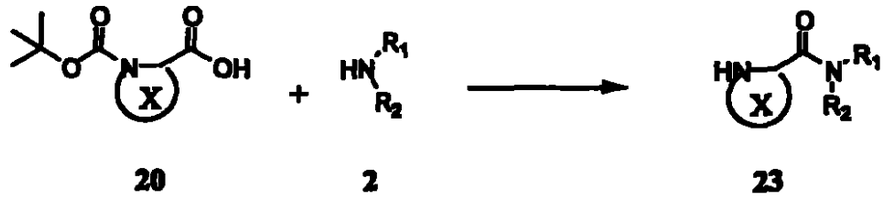
White solid $^1$H NMR (DMSO-$d_6$) δ 8.89 (d, $J$ = 7 9, 1H), 8 66 (d, $J$ = 4.2, 1H), 8.39 (t, $J$ = 6.54, 1H), 7.89 (m 2H), 7.32-7.12 (m, 9H), 5.68 (d, $J$ = 7.28, 1H), 5 03 (dd $J$ = 9 7, 8.3, 2H), 4.56(m, 3H), 4.40 (d, $J$ = 7.5, 1H), 4.35 (d, $J$ = 7.5, 1H), 4.21 (d, $J$ = 6.7, 1H), 2 87-2.67 (m, 2H), 2.25 (s 3H), 1 49 (s, 3H), 1.34 (s, 3H); Anal ($C_{30}H_{34}N_4O_5S$•1.3 $H_2O$) calculated C (61.42), H (6.32), N (9.49), found C (61.64), H (6.17), N (9.12). HRMS (ESI) *m/z* calcd for 563.2326, found 563.2328.

**Example B49: N-[(1S,2S)-3-(4-Allylcarbamoyl-5,5-dimethyl-thiazolidin-3-yl)-1-benzyl-2-hydroxy-3-oxo-propyl]-2-methyl-nicotinamide**

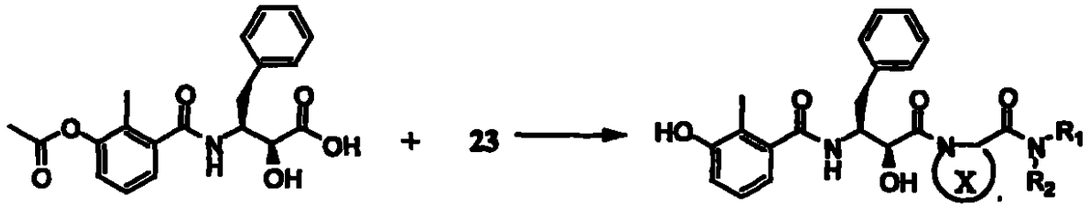


White solid $^1$H NMR (DMSO-$d_6$) δ 8 58 (m, 1H), 8.29 (d, $J$ = 7.54, 1H), 7 78 (d, $J$ = 7.88, 2H), 7 32-7.12 (m, 7H), 5.78 (m, 1H), 5 18 (dd $J$ = 9.7, 8 3, 2H), 4 56(m, 3H), 4 40 (m, 4H), 2.87-2.67 (m, 2H), 2 25 (s 3H), 1 49 (s, 3H), 1.34 (s, 3H), Anal. ($C_{26}H_{32}N_4O_4S$•0 5 $H_2O$•0.5 TFA) calculated C (57.68), H (6.66), N (8 31), found C (57 66), H (6.18), N (8.77). HRMS (ESI) *m/z* calcd for 497 2232, found 497.2223

**General Methods C**



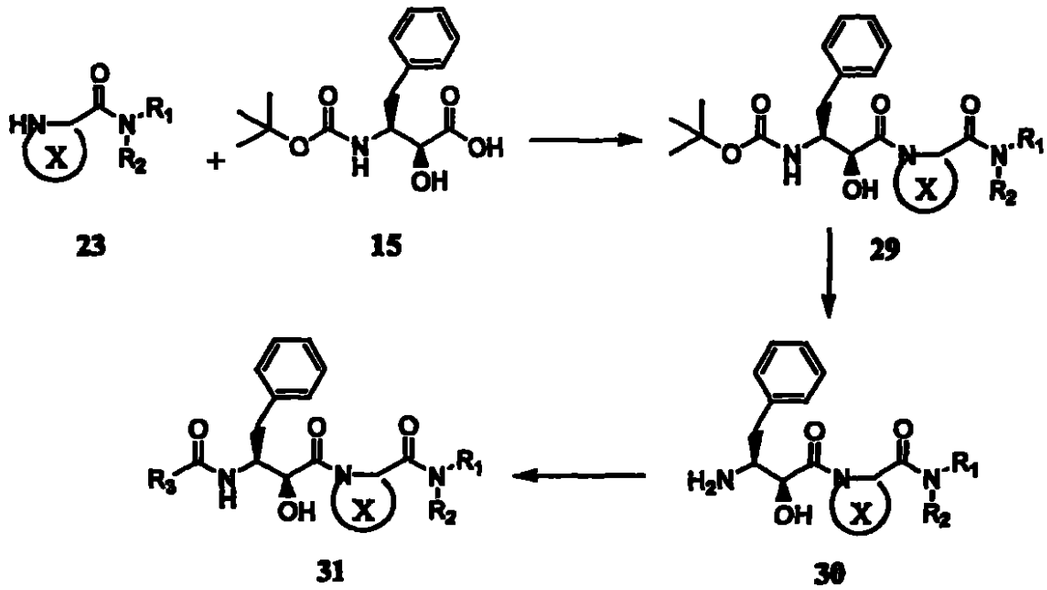
20 2 23



4 24

The synthesis of compounds with the general structure 24 is as follows. The boc-protected carboxylic acids 20a-f are coupled to the requisite amines 2 to yield amino amides 23 usng a two step process The process includes treatment of 20 with 2 in the presence of either diphenyl chlorophosphate or EDCI, followed by exposure to HCl or methane sulfonic acid. Final compounds 24 are obtained by a DCC-mediated coupling of 23 and 4 followed by deprotection of the P2 phenol. Final compounds were purified either by flash chromatography or preparative HPLC.

**Additional General Method C**



23 15 29

31 30

The synthesis of compounds of the general structure 31 (where P2 is not 2-methyl-3-hydroxy benzamide) is as follows. Amino amides of the general structure 23 were coupled to the Boc-acid intermediate 15 using DCC coupling conditions. The resulting intermediate 29 was deprotected under acidic conditions to yield amine of the general structure 30. Final compounds were obtained by modification of amine 30 by methods described in **General Methods B** section to give P2 amides and ureas.

**Methods used for synthesis of compounds with P1 variations.**

EDCI coupling – To a solution of acid, amine and HOBT in $CH_2Cl_2$ was added EDCI and the solution stirred overnight at room temperature. The solution was concentrated in vacuo and the residue dissolved in ethyl acetate and a small portion of water. The solution was washed with saturated $NH_4Cl$ (2x), saturated $NaHCO_3$ (2x), brine (1x), dried with $MgSO_4$ and concentrated in vacuo The crude used without further purification unless otherwise noted.

DCC coupling – A solution of acid, amine and HOBT was prepared in ethyl acetate To the solution was then added DCC in an EtOAc solution at 0 °C and the mixture was stirred overnight at room temperature. The mixture was filtered and the filtrate was concentrated in vacuo The residue dissolved in ethyl acetate washed with saturated $NH_4Cl$ (1x), saturated $NaHCO_3$ (1x), brine (1x), dried over $Na_2SO_4$ and concentrated in vacuo. The crude was used without further purification unless otherwise noted.

4N HCl Boc deprotection – To a solution of Boc-amine in dioxane was added 4N HCl solution in dioxane and the solution stirred overnight at room temperature. The solution was poured into saturated $NaHCO_3$ and the product was extracted into ethyl acetate. The organic solution was washed with brine, dried over $Na_2SO_4$ and concentrated in vacuo. The crude was used without further purification unless otherwise noted.

$MeSO_3H$ Boc deprotection – To a solution of Boc-amine in ethyl acetate at 0 °C was added methane sulfonic acid and the solution stirred 3-6 h at room temperature The solution was cooled to 0 °C and sufficient saturated $NaHCO_3$ was added to quench the acid. The solution was diluted with ethyl acetate, washed with saturated $NaHCO_3$

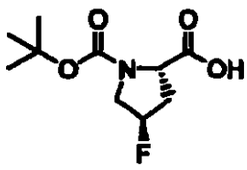
and brine, dried over $Na_2SO_4$ and concentrated in vacuo. The crude used without further purification unless otherwise noted.

KCN Phenolic acetate deprotection – A solution of phenolic acetate and KCN in ethanol was heated at 50 °C overnight. The solution was concentrated in vacuo. The residue was purified by flash chromatography eluted with 0 to 5% methanol in $CH_2Cl_2$ unless otherwise noted.

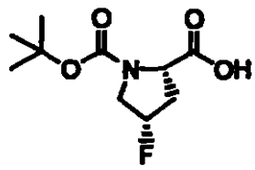
NaOMe/MeOH Phenolic acetate deprotection - 0.5 N $NaOCH_3$/MeOH Phenolic acetate deprotection –A solution of phenolic acetate in EtOAc and methanol was cooled to 0 °C in an ice bath. 0.5 N $NaOCH_3$/MeOH was then added dropwise and then stirred at 0 °C for 1.5-2 hrs following addition. Additional EtOAc was then added, the .15 N HCl (4.5 eq.) added dropwise. The phases were separated and organic phase washed with 2.5% $Na_2CO_3$ aqueous solution, then with 0.1 N HCl/brine (2:1), followed with brine, dried with $MgSO_4$ and concentrated in vacuo. The resulting residue subjected to flash silica gel chromatography to afford the desired product unless otherwise noted.

HCl/MeOH Phenolic acetate deprotection – To a solution of phenolic acetate in methanol was added 4N HCl in dioxane and the solution stirred at room temperature ca. 4 h. The solution was concentrated in vacuo. The residue was purified by flash chromatography eluted with 0 to 5% methanol in $CH_2Cl_2$ unless otherwise noted.

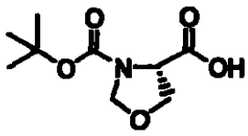
**Fragments of the General Structure 20.**



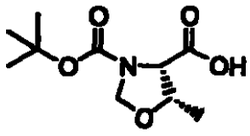
**20b**



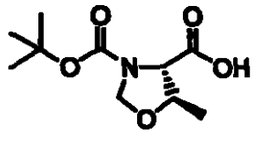
**20c**



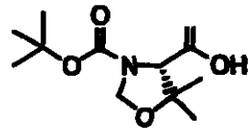
**20c**



**20d**



**20e**



**20f**

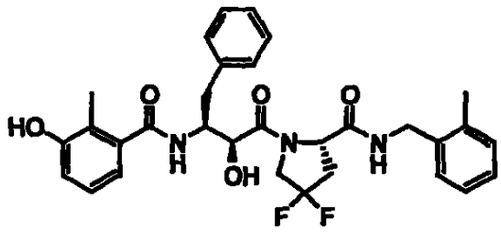
Source of Boc-carboxylic Acids 20a-f

Boc-acids **20a** and **20b** were prepared following the procedure of Demange, L.; Ménez, A.; Dugave, C. *Tet Lett* **1998**, *39*, 1169.

Boc-acids 20c, 20d, 20e and 20f were prepared following the procedure of Karanewsky, D., et al. *J Med. Chem.* 1990, *33*, 1459.

**Specific Method C**

**Example C1: (S)-4,4-Difluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-pyrrolidine-2-carboxylic acid 2-methyl-benzylamide.**

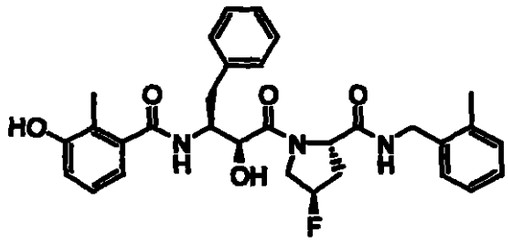


The title compound was prepared according to general methods using the corresponding Boc-protected pyrrolidinic acid (0.96 g, 3.8 mmol), o-methylbenzyl amine (0 57 mL, 4 6 mmol), HOBT (0.62 g, 4.6 mmol), EDCI (0.88 g, 4.6 mmol), $CH_2Cl_2$ (50 mL). To give the crude Boc-amide (MS-APCI (*m/z*+) 355, 255) (1.35 g, 3.8 mmol). The Boc was removed using the general 4N HCl Boc deprotection. 4N HCl in 1,4-dioxane (5 mL), 1,4-dioxane (5 mL) The result was amino amide of general structure 23 Isolated yield 0.79 g (71%, 2 steps). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.02 (t, 1H), 7.24-7.14 (m, 4H), 4 55 (t, 1H), 4 35 (dd, 1H), 4 30 (dd, 1H), 3.73 (m, 2H), 2 94 (m, 2H), 2 52 (m, 1H), 2.27 (s, 3H), $^{19}$F NMR (376 MHz, DMSO-$d_6$): δ -95.3 (dq, $J$ = 235, 15 Hz, 1F), -96.5 (dq, $J$ = 235, 12 Hz, 1F), MS-APCI (*m/z*+). 255.

Amino amide 23 (100 mg, 0.34 mmol) was coupled to carboxylic acid 4 (140 mg, 0.38 mmol) using the general DCC coupling method outlined above. HOBT (51 mg, 0.38 mmol), DCC (78 mg, 0.38 mmol), TEA (50 µL, 0 36 mmol), $CH_2Cl_2$ (10 mL). The crude was purified by chromatography eluted with 10% acetone in $CH_2Cl_2$. Isolated yield. 0.13 g (63%). MS-APCI (*m/z*+) 608 This material was subjected to the general KCN phenolic acetate deprotection conditions (130 mg, 0.21 mmol), KCN (1 mg, 15 µmol), ethanol (10 mL). The crude was precipitated from diethyl ether and

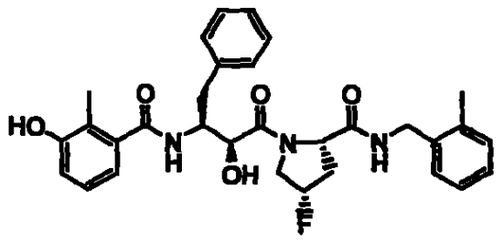
ethyl acetate with hexanes at –78 °C. Isolated yield: 0.10 g (84%). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.37 (s, 1H), 8.36 (t, 1 H), 8.16 (d, 1H), 7.32-7.09 (m, 9H), 6.93 (t, 1H), 6.76 (d, 1H), 6.54 (d, 1H), 5 49 (d, 1H), 4.66 (dd, 1H), 4.34-4.15 (m, 6H), 2.85-2.67 (m, 3H), 2.40 (m, 1H), 2.22 (s, 3H), 1.79 (s, 3H); $^{19}$F NMR (376 MHz, DMSO-$d_6$): δ -98.7 (m, 2F); MS-APCI (*m/z*+): 566; HPLC Purity: 100%; Rf (min.) 19.01; Anal. $C_{31}H_{33}N_3O_5F_2 \cdot 0.3\ H_2O$ C, H, N calcd: C65.21, H5.93, N7.36; found: C65.11, H5.90, N7.17.

**Example C2: (2S,4R)-4-Fluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-pyrrolidine-2-carboxylic acid 2-methyl-benzylamide**



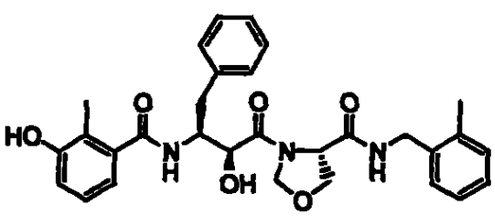
Isolated material was subjected to flash silica gel chromatography, elutng with EtOAc/hexanes (50/50) then with EtOAc EtOAc/hexanes (4.1) to afford the title compound $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9 37 (s, 1H), 8.46 (t, 1 H), 8.21 (d, 1H), 7.34 (d, 2H), 7.26 (d, 2H), 7.21 (t, 2H), 7.15-7.07 (m, 3H), 6.94 (t, 1H), 6.76 (d, 1H), 6 56 (d, 1H), 5 51 + 5.38 (bs + bs, 1H), 5 06 (d, 1H), 4.58 (t, 1H), 4.45 (dd, 1H), 4 35-4.27 (m, 2H), 4.21-4.09 (m, 3H), 3.94-3.91 + 3.84-3.81 (m +m, 1H), 2.69 (d, 2H), 2.23 (s, 3H), 2.19-2.01 (m, 1H), 1.83 (s, 3H); MS-APCI (*m/z*+). 548; HPLC· Rf(min.) 18.72; Purity: 96%. Anal $C_{31}H_{34}N_3O_5F \cdot 0\ 3\ H_2O$ calcd· 67.33, 6.31, 7.60, found: 67.37, 6.25, 7.35.

**Example C3: (2S,4S)-4-Fluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-pyrrolidine-2-carboxylic acid 2-methyl-benzylamide**



Isolated material was subjected to flash silica gel chromatography, eluting with EtOAc/hexanes (50/50) then with EtOAc to afford the title compound. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.37 (s, 1H), 8.21 (d, 1H), 7.96 (t, 1 H), 7.29 (d, 2H), 7.23 (t, 2H), 7.18-7.13 (m, 2H), 7.10-7.04 (m, 3H), 6.90 (t, 1H), 6 75 (d, 1H), 6.52 (d, 1H), 5.55 (d, 1H), 5 45 + 5.32 (bs + bs, 1H), 4.54 (d, 1H), 4.42-4.36 (m, 1H), 4.29-4.40 (m, 5H), 2.98 (t, 1H), 2.73 (t, 1H), 2.32-2.21 (m, 2H), 2.19 (s, 3H), 1.78 (s, 3H); MS-APCI (*m/z*+) 548; HPLC Rf(min.) 18.21; Purity: 99%, Anal. $C_{31}H_{34}N_3O_5F \cdot 0.5\ H_2O$ calcd. 66.89, 6.34, 7.55, found: 66.85, 6.22, 7.41

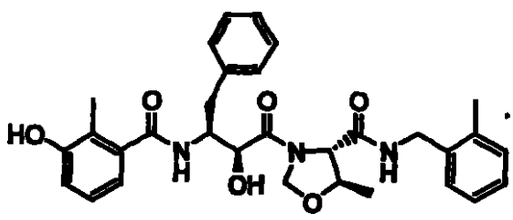
**Example C4: (S)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-oxazolidine-4-carboxylic acid 2-methyl-benzylamide**



White solid; $^1$H NMR (DMSO-$d_6$) δ 9 36 (s, 1H), 8.80 (dd, $J$ = 8 8, 4 8, 1H), 8 30 (t, $J$ = 5 5, 1H), 8.12 (d, $J$ = 8.6, 1H), 7.30-7 13 (m, 9H), 6.96 (t, $J$ = 7.9, 1H), 6.76 (d, $J$ = 7.9, 1H), 6.55 (d, $J$ = 7.2, 1H), 5.74 (d, $J$ = 8 8, 1H), 5.31 (d, $J$ = 3.8, 1H), 5.23 (d, $J$ = 4.2, 1H), 4.49 (dd, $J$ = 6 6, 6.5, 1H), 4 33-4 11 (m, 5H), 2.94-2 68 (m, 2H), 2 24 (s, 3H),

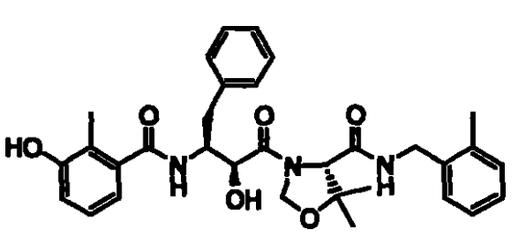
1.78 (s, 3H), HRMS (ESI) *m / z* calcd for $C_{30}H_{34}N_3O_6$ $(M+H)^+$ 532.2448, found 532.2450.

**Example C5: (4S,5R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5-methyl-oxazolidine-4-carboxylic acid 2-methyl-benzylamide**



White solid, $^1H$ NMR (DMSO-$d_6$) δ 9.38 (s, 1H), 8.51 (t, *J* = 6 0, 1H), 8.15 (d, *J* = 8.4, 1H), 7.33-7.13 (m, 9H), 6 96 (t, *J* = 7 7, 1H), 6 79 (d, *J* = 8.2, 1H), 6.58 (d, *J* = 7.3, 1H), 5.69 (d, *J* = 5.7, 1H), 5.50 (d, *J* = 4.6, 1H), 5.10 (d, *J* = 4.8, 1H), 4.39-4.22 (m, 4H), 4.11-4.01 (m, 2H), 2.90 (m, 1H), 2.74 (m, 1H), 2.27 (s, 3H), 1.82 (s, 3H), 1.37 (d, *J* = 5.9, 1H); HRMS (ESI) *m / z* calcd for $C_{31}H_{36}N_3O_6$ $(M+H)^+$ 546.2604, found 546.2595.

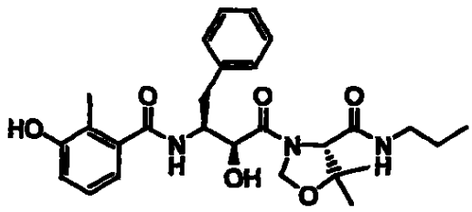
**Example C6: (S)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-oxazolidine-4-carboxylic acid 2-methyl-benzylamide**



White solid; $^1H$ NMR (DMSO-$d_6$) δ 9.34 (s, 1H), 8.32 (t, *J* = 5.8, 1H), 8.11 (*J* = 9.0, 1H), 7 31-7.10 (m, 9H), 6.93 (t, *J* = 7.9, 1H), 6.76 (d, *J* = 8.1, 1H), 6.55 (d, *J* = 6.5, 1H), 5.73 (d, *J* = 4.0, 1H), 5.46 (d, *J* = 4 1, 1H), 5.23 (d, *J* = 3.9, 1H), 4.39-4.32 (m, 2H), 4.18 (m, 3H), 2.92 (m, 1H), 2 69 (m, 1H), 2.27 (s, 3H), 1.81 (s, 3H), 1 28 (s, 3H), 1 18

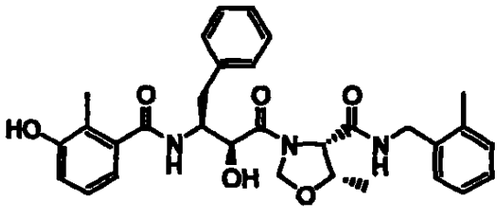
(s, 3H); HRMS (ESI) *m / z* calcd for $C_{32}H_{38}N_3O_6$ $(M + H)^+$ 560.2761, found 560.2759, Anal. Calcd for $C_{32}H_{37}N_3O_6 \cdot 0.5\ H_20$: C, 67.59, H, 6.74; N, 7.39. Found C, 67.74, H, 6.75, N, 7.16.

**Example C7: (S)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-oxazolidine-4-carboxylic acid propylamide**



$^1$H NMR (DMSO-$d_6$) δ 9 37 (s, 1H), 8 12 (d, *J* = 9.3, 1H), 7.93 (t, *J* = 5 6, 1H), 7.34-7.18 (m, 5H), 6 96 (t, *J* = 8 1, 1H), 6.79 (d, *J* = 8 1, 1H), 6.56 (d, *J* = 7.1, 1H), 5.73 (d, *J* = 6.2, 1H), 5 44 (d, *J* = 4 0, 1H), 5.24 (d, *J* = 3 8, 1H), 4.36 (m, 1H), 4 18 (m, 1H), 4 11 (s, 1H), 3.10-2.92 (m, 3H), 2.75-2 66 (m, 1H), 1.80 (s, 3H), 1 46-1.39 (m, 2H), 1.31 (s, 3H), 1 22 (s, 3H), 0.86 (t, *J* = 7.2, 3H); HRMS (ESI) *m / z* calcd for $C_{27}H_{36}N_3O_6$ $(M + H)^+$ 498.2604, found 498.2590.

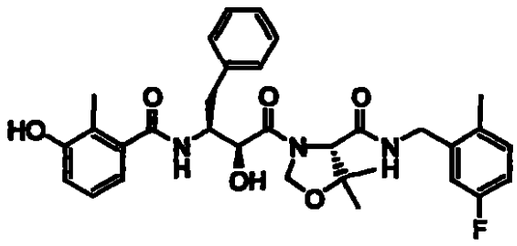
**Example C8: (4S,5S)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5-methyl-oxazolidine-4-carboxylic acid 2-methyl-benzylamide**



White solid; $^1$H NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8 26 (t, *J* = 5.5, 1H), 8 09 (d, *J* = 8 8, 1H), 7.30-7.08 (m, 9H), 6 93 (t, *J* = 7.7, 1H), 6 76 (d, *J* = 7 9, 1H), 6.56 (d, *J* = 7.5, 1H),

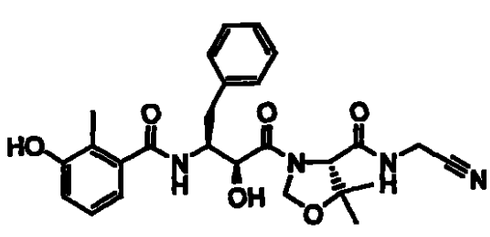
5.72 (d, $J$ = 6.4, 1H), 5.55 (d, $J$ = 3.7, 1H), 5.08 (d, $J$ = 3.8, 1H), 4.40-4.33 (m, 3H), 4.26-4.11 (m, 3H), 3.10-2.89 (m, 1H), 2.78-2 67 (m, 1H), 2.26 (s, 3H), 1 78 (s, 3H), 1.15 (d, $J$ = 6.2, 3H); HRMS (ESI) $m/z$ calcd for $C_{31}H_{36}N_3O_6$ $(M+H)^+$ 546.2604, found 546.2592.

**Example C9: (S)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-oxazolidine-4-carboxylic acid 5-fluoro-2-methyl-benzylamide**



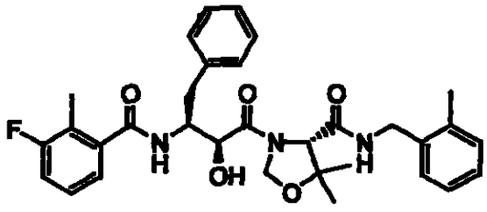
White solid; $^1$H NMR (DMSO-$d_6$) $\delta$ 9.35 (s, 1H), 8 41 (t, $J$ = 5 6, 1H), 8 12 (d, $J$ = 8.9, 1H), 7 28-7.08 (m, 8H), 6 95-6.90 (m, 1H), 6.76 (d, $J$ = 8.1, 1H), 6 55 (d, $J$ = 7.2, 1H), 5.78 (d, $J$ = 6.1, 1H), 5.47 (d, $J$ = 3.8, 1H), 5.24 (d, $J$ = 3.8, 1H), 4.40-4.25 (m, 2H), 4.20-4.10 (m, 3H), 3.00-2.60 (m, 2H), 2.22 (s, 3H), 1.77 (s, 3H), 1.30 (s, 3H), 1.19 (s, 3H), Anal. Calcd for $C_{32}H_{36}N_3O_6F$· C, 66 54, H, 6.28, N, 7.27 Found. C, 66.37; H, 6 20, N, 7.21.

**Example C10: (S)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-oxazolidine-4-carboxylic acid cyanomethyl-amide**



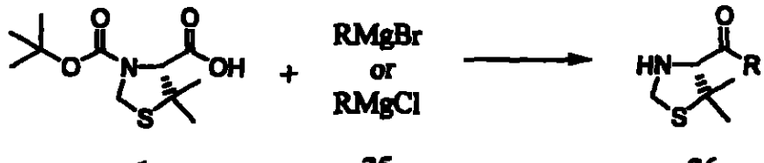
White solid; $^1$H NMR (DMSO-$d_6$) δ 9 36 (s, 1H), 8.72 (t, $J$ = 5 3, 1H), 8.11 (d, $J$ = 9.0, 1H), 7.29-7.16 (m, 5H), 6.94 (t, $J$ = 7 7, 1H), 6.76 (d, $J$ = 8 1, 1H), 6.50 (d, $J$ = 7.5, 1H), 5.85 (d, $J$ = 6.0, 1H), 5.49 (d, $J$ = 4 0, 1H), 5.23 (d, $J$ = 3.9, 1H), 4.35 (m, 1H), 4.18-4.12 (m, 3H), 4.11 (s, 1H), 2.92 (m, 1H), 2 70 (m, 1H), 1.76 (s, 3H), 1.29 (s, 3H), 1 19 (s, 3H), HRMS (ESI) $m$ / $z$ calcd for $C_{26}H_{31}N_4O_6$ (M + H)$^+$ 495.2244, found 495.2239.

**Example C11: (S)-3-((2S,3S)-3-{[1-(3-Fluoro-2-methyl-phenyl)-methanoyl]-amino}-2-hydroxy-4-phenyl-butanoyl)-5,5-dimethyl-oxazolidine-4-carboxylic acid 2-methyl-benzylamide**

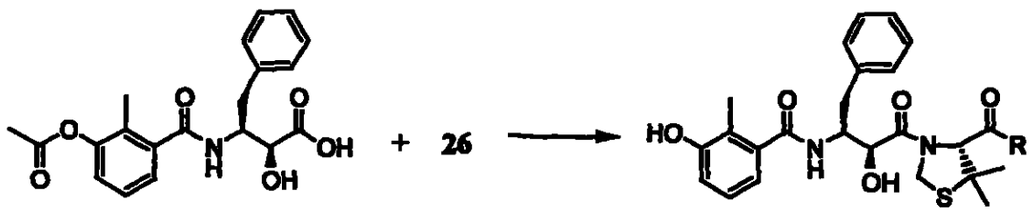


$^1$H NMR (DMSO-$d_6$) δ 8.34 (m, 2H), 7 30-7.13 (m, 11H), 6.95 (d, $J$ = 7 1, 1H), 5.82 (d, $J$ = 6 4, 1H), 5.45 (d, $J$ = 3.9, 1H), 5.23 (d, $J$ = 4.0, 1H), 4 38-4 31 (m, 2H), 4 18-4.15 (m, 3H), 2.96 (m, 1H), 2.67 (m, 1H), 2 26 (s, 3H), 1.87 (s, 3H), 1.28 (s, 3H), 1.18 (s, 3H); HRMS (ESI) $m$ / $z$ calcd for $C_{32}H_{37}N_3O_5F$ (M + H)$^+$ 562.2717, found 562 2713

**General Methods D**



1 25 26

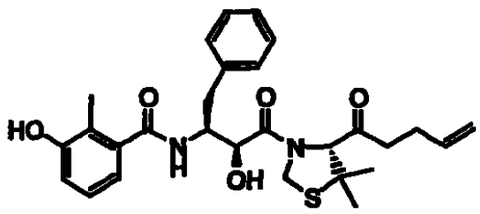


4 27

The synthesis of compounds with the general structure 27 is as follows. The boc-protected thiazolidine carboxylic acid 1 is converted to amino-ketones 26 with requisite grignard reagents 25 in the presence of oxalyl chloride. Final compounds 27 are obtained by a DCC-mediated coupling of 26 and 4 followed by deprotection of the P2 phenol. Final compounds were purified either by flash chromatography or preparative HPLC.

**Specific Method D**

Example D1: *N*-[(1S,2S)-1-Benzyl-3-((R)-5,5-dimethyl-4-pent-4-enoyl-thiazolidin-3-yl)-2-hydroxy-3-oxo-propyl]-3-hydroxy-2-methyl-benzamide

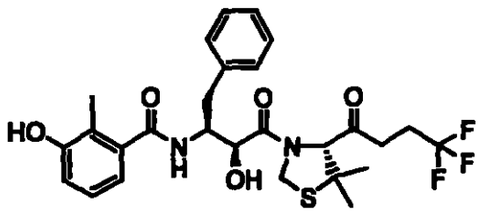



The title compound was prepared as follows. (R)-5,5-Dimethyl-thiazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 1 (1.0 g, 3.80 mmol) was dissolved in benzene (10 mL) and cooled to 0 °C with magnetic stirring. Two drops of DMF were added followed by a drop wise addition of oxalyl chloride (0.33 mL, 3 80 mmol). When gas evolution ceased, the solution was concentrated to a yellow/red residue. The material was dissolved in dry THF (10 mL) and cooled to -78 °C with magnetic stirring. The grignard reagent, 3-butenylmagnesium bromide (7.7 mL, 3.80 mmol) was added dropwise over 10 min. The result was stirred at –78 °C for 1h then at –55 °C for 30 min. The reaction was quenched at –55 °C with sat $NH_4Cl$ soln.(3 mL) and then poured into $H_2O$ (50 mL). The mixture was extracted with EtOAc (2 x 50 mL). The combined organics were washed with brine (1 x 100 mL), dried over $Na_2SO_4$, filtered, and concentrated. The result was the amino ketone 26 that was sufficiently pure to use in the subsequent step The clear oil 26 (0.24 g, 1 15 mmol) was dissolved in EtOAc (10 mL) AMB-AHPBA 4 (0.40 g, 1.09 mmol) was added followed by HOBt (0.15 g, 1.09 mmol) The mixture was stirred at room temperature 1h, then cooled to 0 °C. DCC

(0.24 g, 1.15 mmol) was slowly added as solution in EtOAc (6 mL). The mixture was warmed to room temperature and stirred overnight. The mixture was filtered and the filtrate was washed with 1N HCl (10 mL), saturated $NaHCO_3$ (10 mL), brine (10 mL), dried over $Na_2SO_4$ and concentrated to give a crude white solid (contaminated with DCU). The DCU was removed by flash chromatography (30% to 50% EtOAc in hexanes) to provide a white solid, which was dissolved in MeOH (2 mL) and treated with 4N HCl in 1,4-dioxane (0.26 mL, 1 1 mmol). The reaction was stirred at room temperature overnight then partitioned between 1N HCl (10 mL) and EtOAc (10 mL). The organic layer was washed with saturated sat. $NaHCO_3$ (1 x 25 mL) dried over $Na_2SO_4$, filtered, and concentrated to a residue which was purified by flash chromatography (60% EtOAc in hexanes) to provide the title compound as a white amorphous solid. $^1$H NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.23 (d, J = 8 1, 1H), 7.35-7.14 (m, 5H), 6.96 (t, $J$ = 7.5, 1H), 6.78 (d, $J$ = 8 2, 1H), 6.52 (d, $J$ = 7.5, 1H), 5.81-5.69 (m. 2H), 5.32 (d, $J$ = 9.7, 1H), 5.11-5 91 (m, 3H), 4 40 (m, 3H), 2.89-2.61 (m, 4H), 2.37-2.14 (m, 2H), 1.81 (s, 3H), 1.55 (s, 3H), 1.30 (s, 3H); Anal Calcd for $C_{28}H_{34}N_2O_5S$· C, 65 86; H, 6 71, N, 5.49. Found· C, 65.52; H, 6.55; N, 5 81.

The following examples were synthesized using the specific method outlined above using the appropriate grignard reagent for the desired compound.

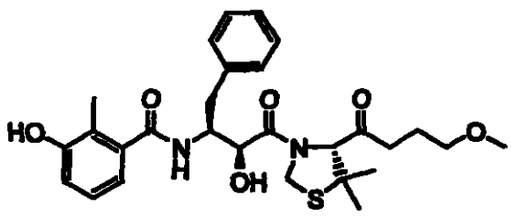
**Example D2: N-{1-Benzyl-3-[5,5-dimethyl-4-(4,4,4-trifluoro-butanoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-3-hydroxy-2-methyl-benzamide**




$^1$H NMR (DMSO-$d_6$) δ 9.34 (s, 1H), 8.16 (d, 1H, $J$ = 8.6), 7.29-6.49 (m, 8H), 5.88 (d, 1H, $J$ = 6 1), 5.33 (d, 1H, $J$ = 9.5), 5.10 (d, 1H, $J$ = 9.5), 4.56 (s br, 3H), 2 98-2.57 (m, 6H), 1.74 (s, 3H), 1.55 (s, 3H), 1.30 (s, 3H), HRMS (ESI) $m$ / $z$ calcd for

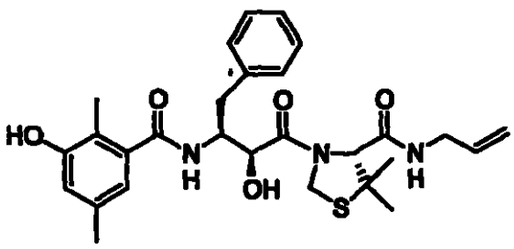
$C_{27}H_{32}N_2O_5SF_3$ $(M+H)^+$ 553.1984, found 553.1984; Anal Calcd for $C_{27}H_{31}N_2O_5SF_3 \cdot 0.5H_2O$: C, 58.59; H, 5.66; N, 5.06; S, 5.79. Found. C, 58.96; H, 6.02; N, 5.58; S, 5.33.

**Example D3: N-{1-Benzyl-2-hydroxy-3-[4-(4-methoxy-butanoyl)-5,5-dimethyl-thiazolidin-3-yl]-3-oxo-propyl}-3-hydroxy-2-methyl-benzamide**



$^1$H NMR (DMSO-$d_6$) δ 9.34 (s, 1H), 8.18 (d, 1H, $J$ = 8.2), 7.32-6.51 (m, 8H), 5.56 (d, 1H, $J$ = 7.8), 5.26 (d, 1H, $J$ = 9.5), 5.08 (d, 1H, $J$ = 9.5), 4 45-4.38 (m, 2H), 4.36 (s, 1H), 3.15 (s, 3H), 2 93-2.61 (m, 2H), 1.87-1.00 (m, 6H), 1.80 (s, 3H), 1.55 (s, 3H), 1.36 (s, 3H), HRMS (ESI) $m/z$ calcd for $C_{28}H_{37}N_2O_6S$ $(M+H)^+$ 529.2165, found 529.2372; Anal. Calcd for $C_{28}H_{36}N_2O_6S \cdot 0\ 5H_2O$: C, 62.55; H, 6.94; N, 5.21; S, 5.96. Found: C, 62.89, H, 7.32; N, 5.96; S, 5.59.

**Example D4: (R)-3-[(2S, 3S)-2-Hydroxy-3-(3-hydroxy-2,5-dimethyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid allylamide**



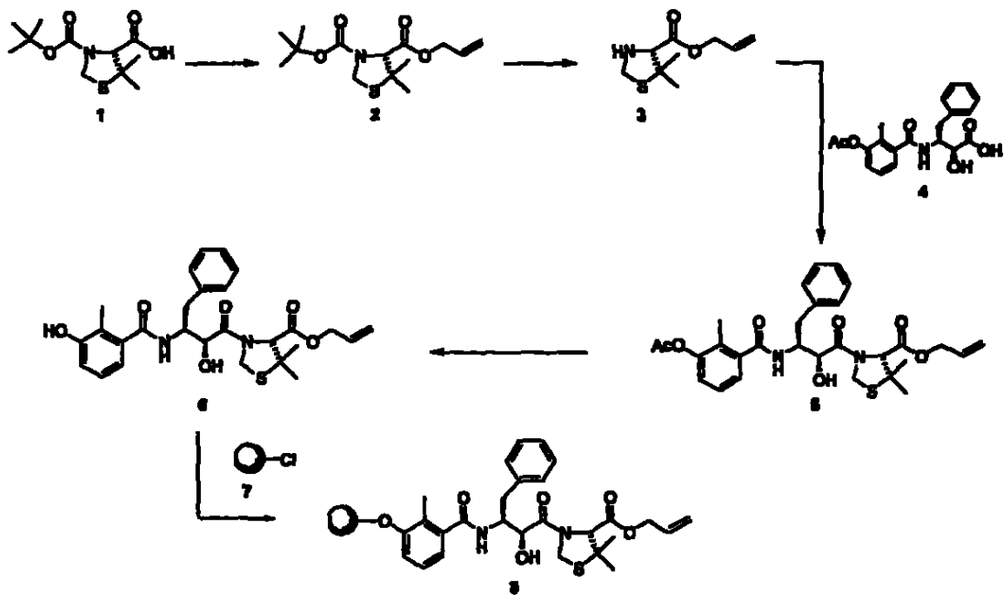
White solid: $^1$H NMR (DMSO-$d_6$) δ 9.23 (s, 1H), 8.09 (m, 2H), 7.35 – 7 17 (m, 5H), 6.60 (s, 1H), 6.37 (s, 1H), 5.82-5 68 (m, 1H), 5 41 (br s, 1H), 5.20 (dd, 1H, $J$ = 1.6, 17.2), 5.11 (d, 1H, $J$ = 9.2), 5 02 (dd, 1H, $J$ = 1.5, 10.2), 5.00 (d, 1H, $J$ = 9.1), 4 46 –

4.37 (m, 3H), 3.79 (ddd, 1H, $J$ = 5.3, 5.5, 15.9), 3.63 (ddd, 1H, $J$ = 5.4, 5.3, 15.9), 2.82 (dd, 1H, $J$ = 0.3, 13 9), 2 71 (dd, 1H, $J$ = 10.7, 13 6), 2 16 (s, 3H), 1.76 (s, 3H), 1.51 (s, 3H), 1.36 (s, 3H), HRMS (ESI) $m$ / z calcd for $C_{28}H_{36}N_3O_5S$ $(M + H)^+$ 526.6670, found 526.2376; Anal. Calcd for $C_{28}H_{35}N_3O_5S \cdot 0.3\ H_2O \cdot$ C, 63.32, H, 6.76, N, 7.91, Found: C, 63 35; H, 6 70; N, 7 71.

**Combinatorial Chemistry Approach to HIV Protease P2' Inhibitors**

General Method E

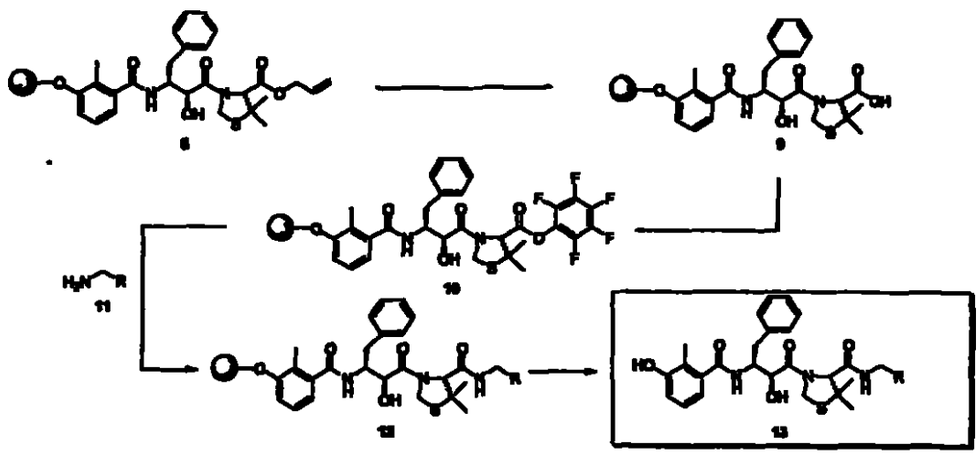
Scheme I



The combinatorial building block, 8, is prepared using the following method. The boc-protected thiazolidine carboxylic acid, 1, is treated with allyl bromide in the presence of $NaHCO_3$ to yield the boc-protected thiazolidine allyl ester, 2. Deprotection of boc-protected allyl ester, 2, with HCl (g) in EtOAc gives the HCl salt of the thiazolidine allyl ester amine, 3, which is treated with TEA and coupled to 4 in the presence of HOBT and DCC to give the building block precursor, 5. Deprotection of the building block, 5, with 4N HCl yields the phenol, 6. Loading the building block, 6, on to

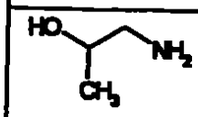
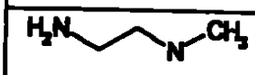
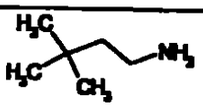
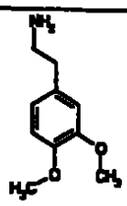
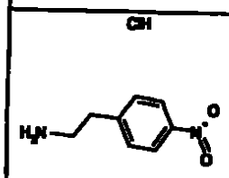
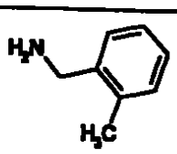
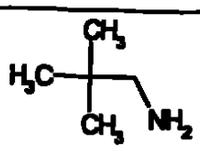
activated cross-linked trityl chloride polystyrene beads, 7, was accomplished in the following manner The polystyrene cross-linked trityl alcohol was activated to the trityl chloride, 7, by treatment with 20% acetyl chloride in anhydrous $CH_2Cl_2$ at room temperature The trityl chloride beads were combined with the phenol 6 in the presence of Hunig's base in anhydrous $CH_2Cl_2$ to yield the substrate loaded polystyrene beads 8 Intermediates were purified either by flash chromatography or preparative HPLC.

**Scheme II**

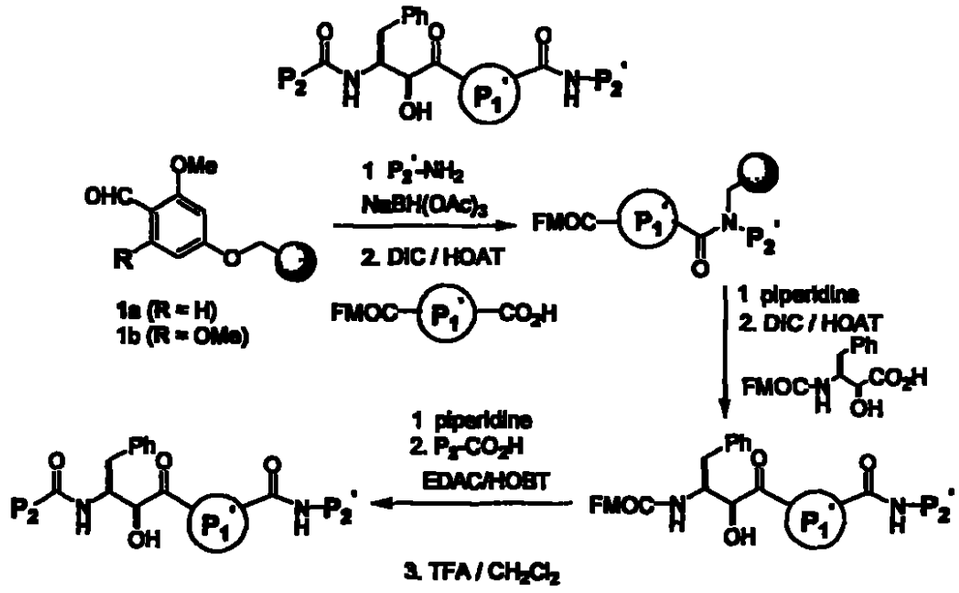


The synthesis of the HIV protease combinatorial library was carried out in the following fashion. The allyl ester was removed by treatment with $Pd[PPh_3]_4$ and NMM in anhydrous THF to give carboxylate 9, which was treated with pentafluorophenol, pentafluorophenol trifluoromethyl acetate and pyridine in DMF to yield the pentafluoro ester, 10. The pentafluoro ester 10 was treated with various primary amines in a 96-well plate format to give amides 12 The final products were cleaved from the polystyrene crowns with TFA to give products 13. Each product was analyzed by LCMS and HPLC. The following table typifies compounds synthesized by this combinatorial method.

Table 1

| P2' | Expected Mass (LCMS) | Observed Mass | % Inhibition |
|---|---|---|---|
|  | 529 | 552($Na^+$) | 38 |
|  | 528 | 529($MH^+$) | 4 |
|  | 591 | 614($Na^+$) | 18 |
|  | 555 | 578($Na^+$) | 19 |
|  | 635 | 658($Na^+$) | 5 |
|  | 656 | 656($MH^+$) | 8 |
|  | 575 | 598($Na^+$) | 86 |
|  | 541 | 564($Na^+$) | 63 |
|  | 529 | 552($Na^+$) | 49 |

**Scheme 3: Solid Phase Synthesis Of HIV Protease Inhibitors (AG 1776 Analogs)**




The solid phase combinatorial synthesis of HIV protease inhibitors was performed using the IRORI Directed Sorting Technology. Commercial 4-formyl-3-methoxyphenoxymethyl polystyrene resin 1a (PS-MB-CHO, Argonaut Technologies) or 4-formyl-3,5-dimethoxyphenoxymethyl polystyrene resin 1b (PL-FDMP resin, Polymer Laboratories) was loaded into individual MiniKans.

Step A. Reductive Amination With $P_2$' Amines

To separate flasks containing sorted MiniKans was added DCM (3 mL/MiniKan). The appropriate primary $P_2$' amine (3 eq), sodium triacetoxyborohydride (5 eq), and acetic acid (3 eq) were added, and the mixtures were placed under argon, agitated with periodic venting at room temperature for 1 –2 hours, and allowed to react overnight. For resin 1a, the filtrates were poured off and the MiniKans were washed with DCM, MeOH (2x), DCM (2x), $Et_3N$/DCM (1:3, 3x), DCM (2x), MeOH (3x), and DCM (4x). For resin 1b, a washing sequence of DCM, MeOH (2x), DCM (2x), $Et_3N$/DCM (1:3, 3x), DCM (2x), DMF, 1M NaOH/DMF (1:5, 3x), DMF (3x), MeOH (3x), and DCM (3x) was used. The MiniKans were dried under vacuum and taken on in Step B.

Step B. Peptide Coupling With $P_1$' Amino Acids

To separate flasks containing the sorted MiniKans was added DMF (3 mL/MiniKan) The appropriate FMOC-protected amino acid (2 5 eq) and 1-hydroxy-7-azabenzotriazole (HOAT) (3 eq) were added and mixed until dissolved, and 1,3-diisopropylcarbodiimide (DIC) (3 eq) was added. The containers were placed under argon and agitated at room temperature overnight. The filtrates were poured off, and the MiniKans were washed with DMF (3x), MeOH (3x), DCM (2x), and DMF (2x). The MiniKans were taken directly on to Step C.

Step C. FMOC Deprotection

A container of MiniKans in DMF and piperidine (25%) with a total reaction volume of 3 mL/MiniKan was agitated under argon at room temperature for 45 minutes. The filtrate was removed, and the reaction procedure was repeated. The MiniKans were filtered and washed with DMF (3x), MeOH (2x), DCM (3x), and DMF, and taken directly on to Step D.

Step D. Peptide Coupling With FMOC-APNS

FMOC-Allophenylnorstatine (APNS) (3 eq) was added to the flask of MiniKans in DMF (3 mL/MiniKan) After dissolution, HOAT (3.5 eq) and DIC (3.5 eq) were added The mixture was placed under argon and agitated at room temperature overnight. The reaction was filtered and the MiniKans were washed with DMF (3x), MeOH (3x), DCM (3x), and DMF. FMOC deprotection was carried out as in Step C, and the MiniKans were washed with DMF (3x), MeOH (2x), DCM (3x), dried under vacuum and taken on to Step E or F.

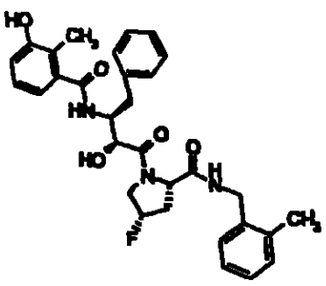
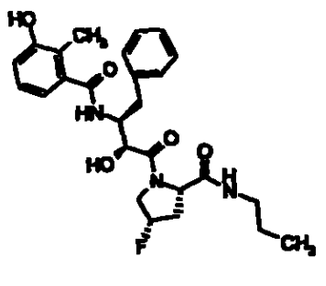
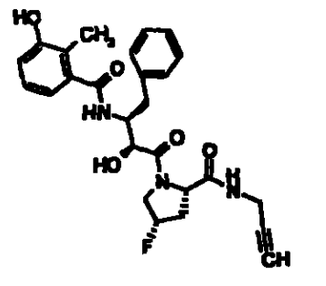
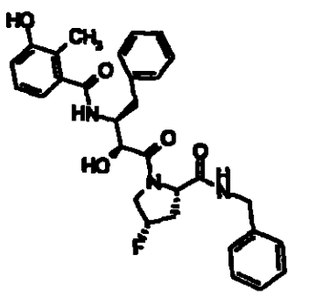
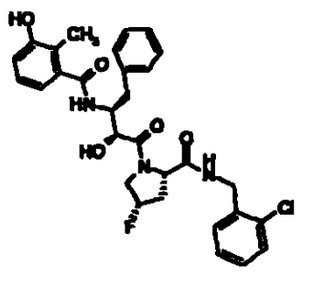
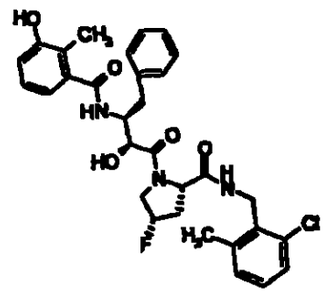
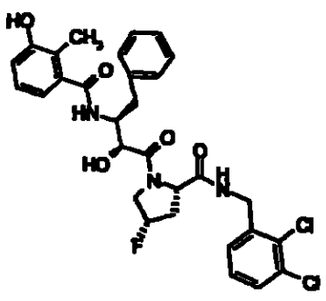
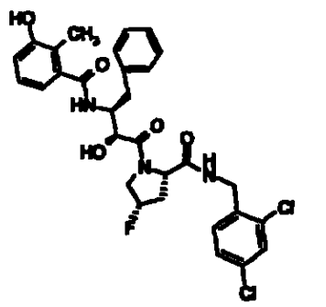
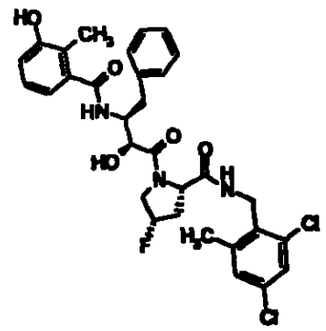
Step E Peptide Coupling With $P_2$ Acids

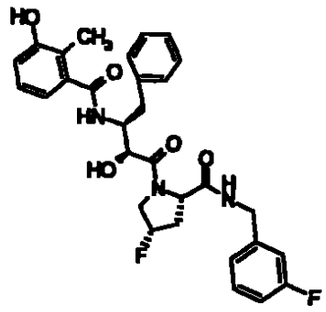
To separate flasks containing the sorted MiniKans in DMF (3 mL/MiniKan) was added the appropriate $P_2$ acid (3 eq), HOBT hydrate (4 eq), and (3-(dimethylamino)propyl)ethylcarbodiimide hydrochloride (EDAC) (3.5 eq) The reaction was agitated under argon at room temperature for 3 hours. After filtration, the MiniKans were washed with DMF (3x), MeOH (3x), and DCM (3x), dried under vacuum, and taken on to Step G.

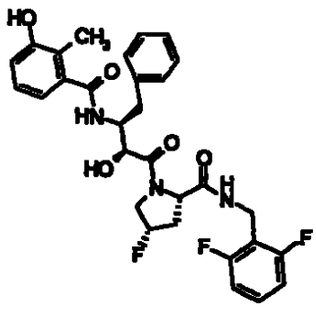
Step F. Cleavage and Processing Of The HIV Analogs

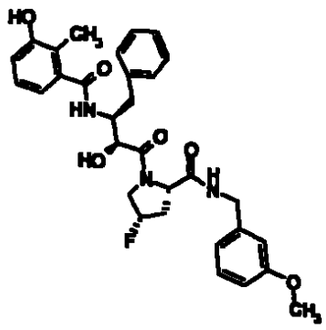
The individual MinKans were sorted into cleavage racks and a solution of 25% TFA in DCM (3 mL/MinKan) was added. The racks were agitated for 1.5 hours. The individual filtrates and DCM rinses were collected, concentrated, and purified by HPLC to provide the final compounds.

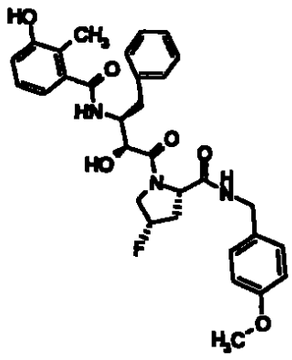
Table 2

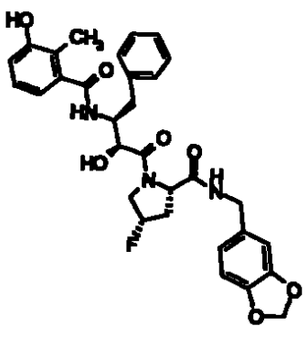










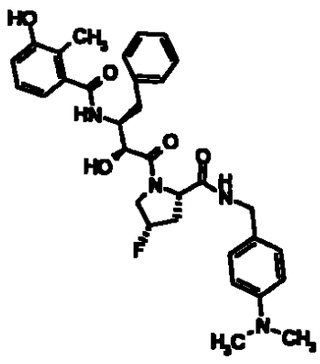


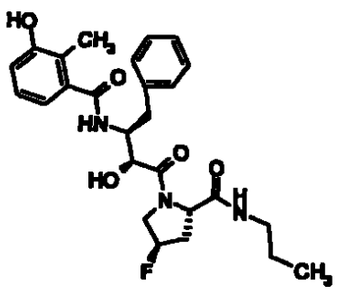


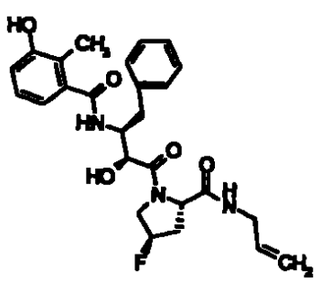


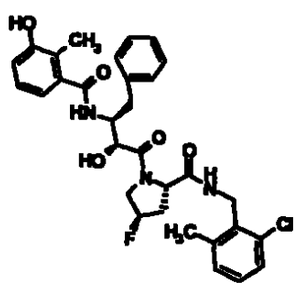


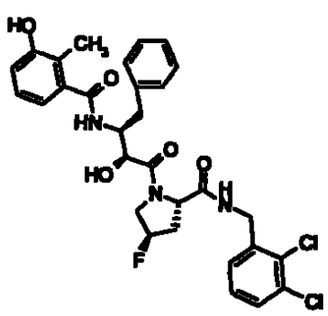


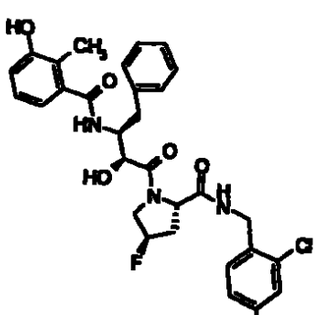


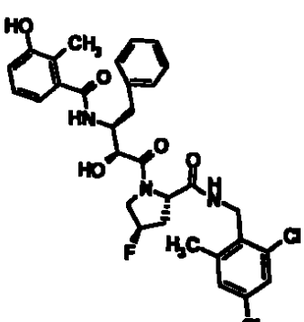


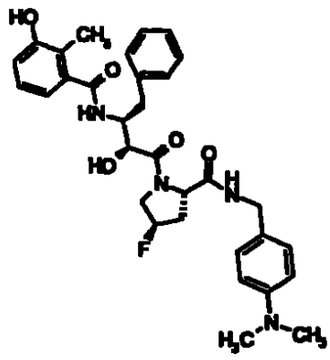
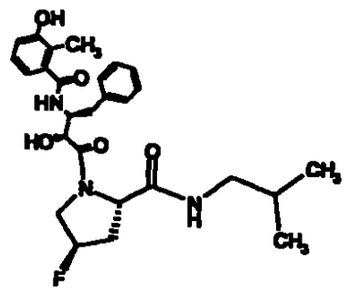
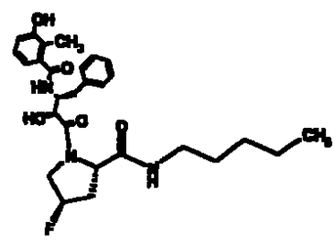
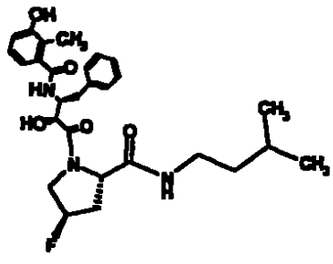
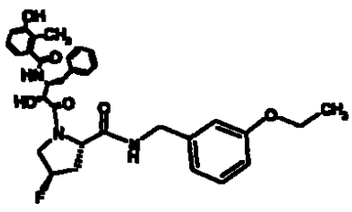
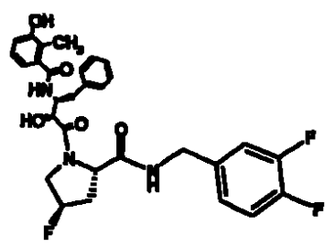
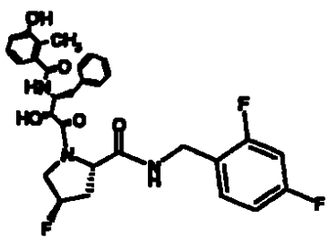
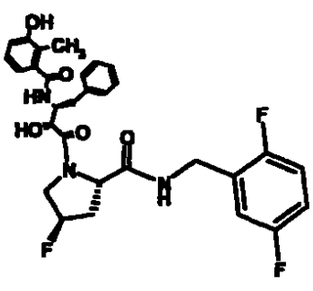
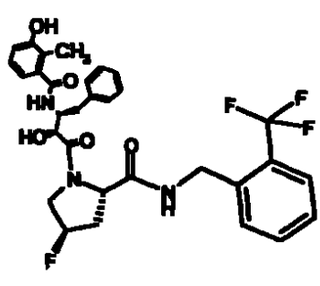
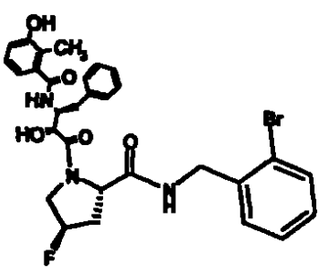
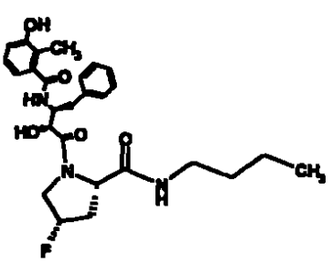
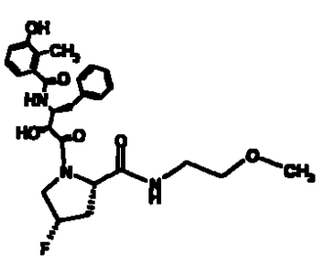
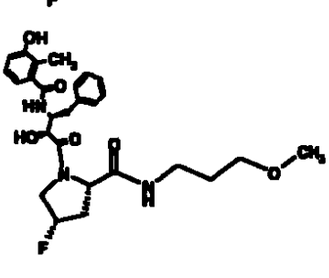
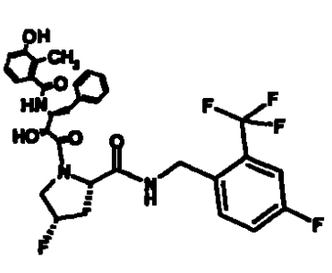
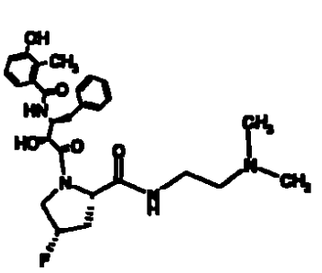


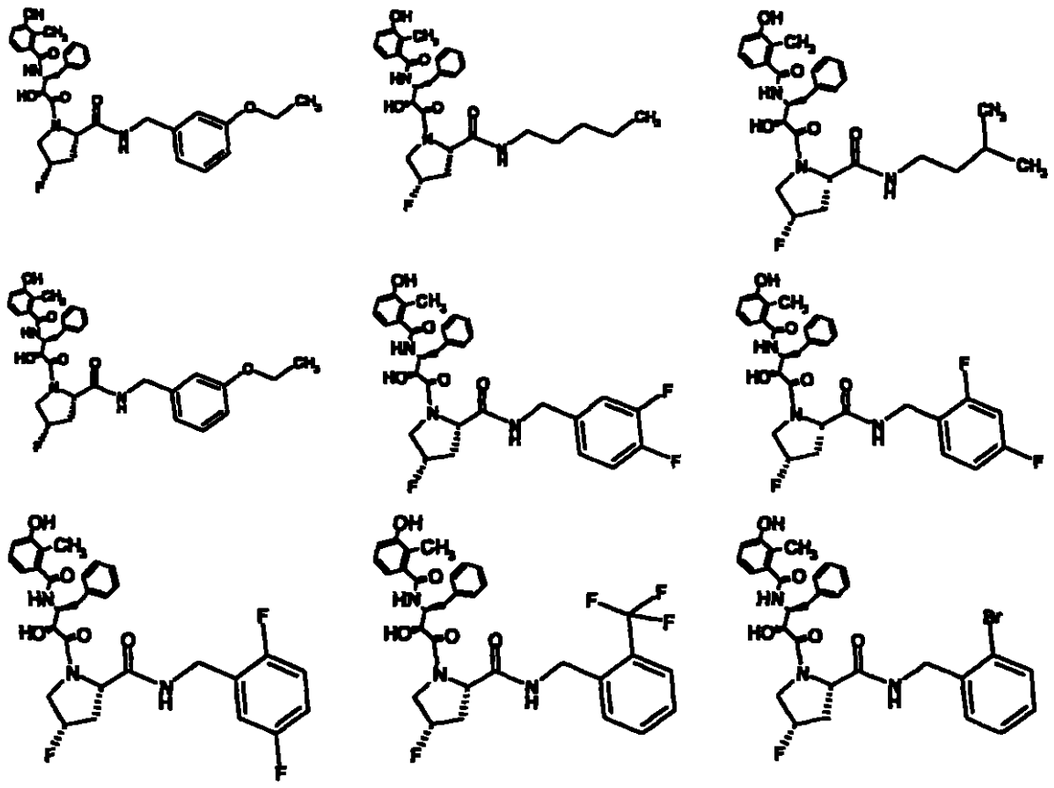




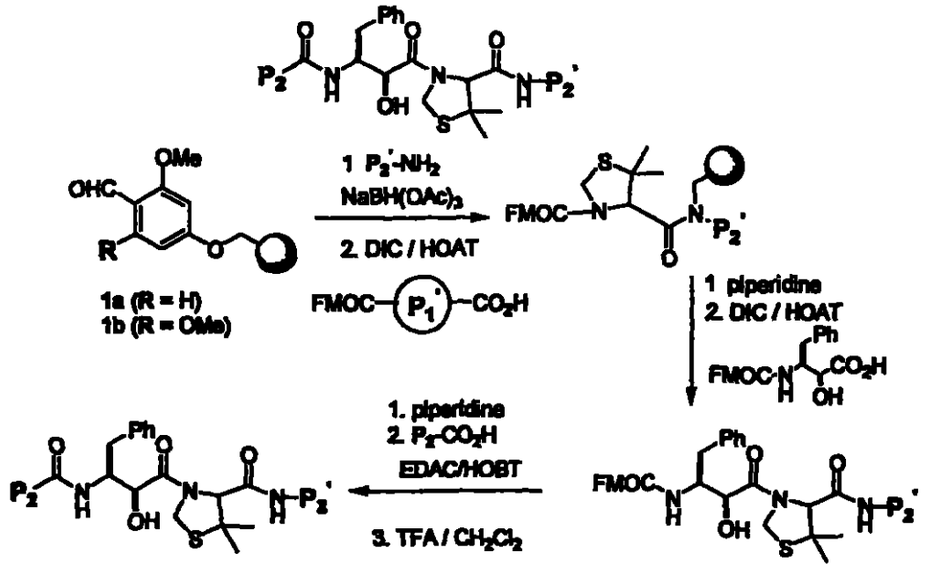






**Scheme 3: Solid Phase Synthesis Of HIV Protease Inhibitors**



**Scheme 3 Experimental**

The solid phase combinatorial synthesis of HIV protease inhibitors was performed using the IRORI Directed Sorting Technology. Commercial 4-formyl-3-methoxyphenoxymethyl polystyrene resin 1a (PS-MB-CHO, Argonaut Technologies) or 4-formyl-3,5-dimethoxyphenoxymethyl polystyrene resin 1b (PL-FDMP resin, Polymer Laboratories) was loaded into individual MiniKans.

Step A. Reductive Amination With $P_2$' Amines

To separate flasks containing sorted MiniKans was added DCM (3 mL/MiniKan). The appropriate primary $P_2$' amine (3 eq), sodium triacetoxyborohydride (5 eq), and acetic acid (3 eq) were added, and the mixtures were placed under argon, agitated with periodic venting at room temperature for 1 –2 hours, and allowed to react overnight. For resin 1a, the filtrates were poured off and the MiniKans were washed with DCM, MeOH (2x), DCM (2x), $Et_3N$/DCM (1:3, 3x), DCM (2x), MeOH (3x), and DCM (4x). For resin 1b, a washing sequence of DCM, MeOH (2x), DCM (2x), $Et_3N$/DCM (1:3, 3x), DCM (2x), DMF, 1M NaOH/DMF (1:5, 3x), DMF (3x), MeOH (3x), and DCM (3x) was used. The MiniKans were dried under vacuum and taken on in Step B

Step B. Peptide Coupling With $P_1$' Amino Acids

To separate flasks containing the sorted MiniKans was added DMF (3 mL/MiniKan). The appropriate FMOC-protected amino acid (2.5 eq) and 1-hydroxy-7-azabenzotriazole (HOAT) (3 eq) were added and mixed until dissolved, and 1,3-diisopropylcarbodiimide (DIC) (3 eq) was added The containers were placed under argon and agitated at room temperature overnight. The filtrates were poured off, and the MiniKans were washed with DMF (3x), MeOH (3x), DCM (2x), and DMF (2x). The MiniKans were taken directly on to Step C.

Step C. FMOC Deprotection

A container of MiniKans in DMF and piperidine (25%) with a total reaction volume of 3 mL/MiniKan was agitated under argon at room temperature for 45 minutes. The filtrate was removed, and the reaction procedure was repeated. The MiniKans were filtered and washed with DMF (3x), MeOH (2x), DCM (3x), and DMF, and taken directly on to Step D.

Step D Peptide Coupling With FMOC-APNS

FMOC-Allophenylnorstatine (APNS) (3 eq) was added to the flask of MiniKans in DMF (3 mL/MiniKan). After dissolution, HOAT (3.5 eq) and DIC (3 5 eq) were added. The mixture was placed under argon and agitated at room temperature overnight. The reaction was filtered and the MiniKans were washed with DMF (3x), MeOH (3x), DCM (3x), and DMF. FMOC deprotection was carried out as in Step C, and the MiniKans were washed with DMF (3x), MeOH (2x), DCM (3x), dried under vacuum and taken on to Step E or F.

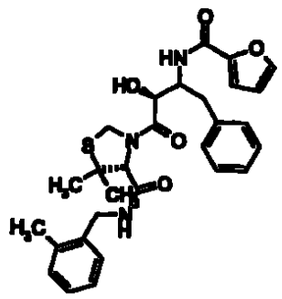
Step E. Peptide Coupling With $P_2$ Acids

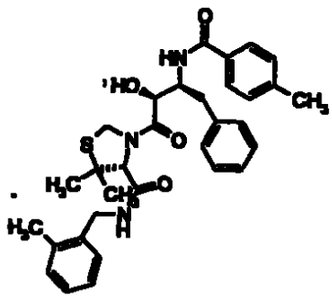
To separate flasks containing the sorted MiniKans in DMF (3 mL/MiniKan) was added the appropriate $P_2$ acid (3 eq), HOBT hydrate (4 eq), and (3-(dimethylamino)propyl)ethylcarbodiimide hydrochloride (EDAC) (3.5 eq) The reaction was agitated under argon at room temperature for 3 hours. After filtration, the MiniKans were washed with DMF (3x), MeOH (3x), and DCM (3x), dried under vacuum, and taken on to Step G

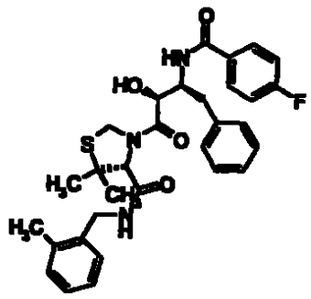
Step F. Cleavage and Processing Of The HIV Analogs

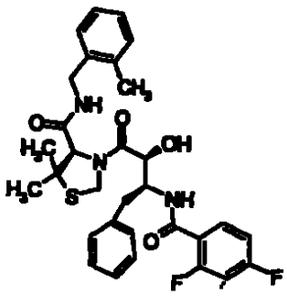
The individual MiniKans were sorted into cleavage racks and a solution of 25% TFA in DCM (3 mL/MiniKan) was added. The racks were agitated for 1.5 hours. The individual filtrates and DCM rinses were collected, concentrated, and purified by HPLC to provide the final compounds.

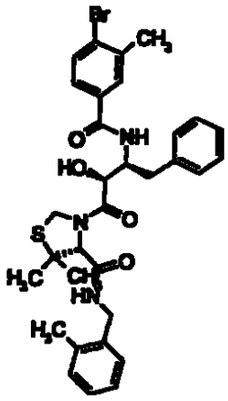
Table 3

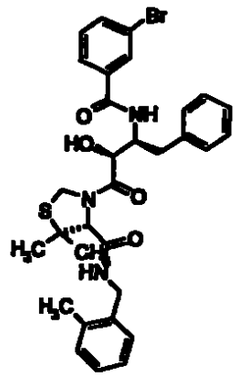


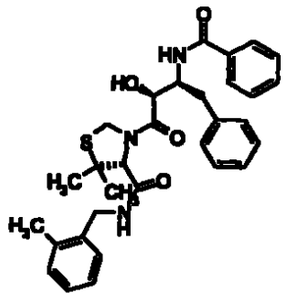


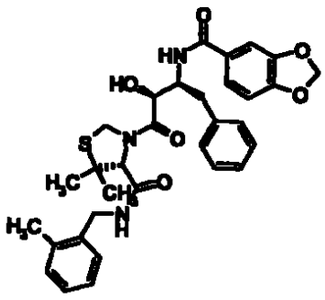


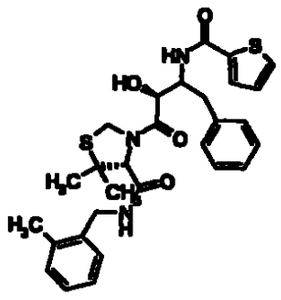


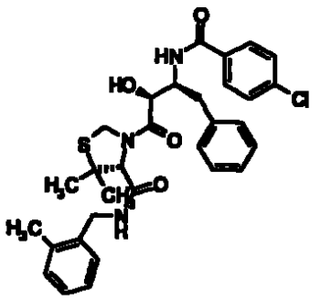


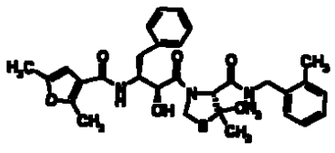


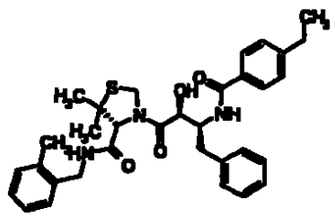


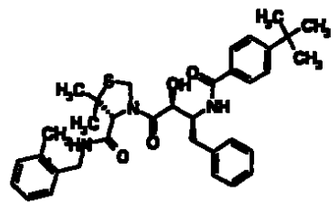
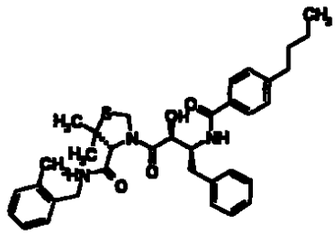
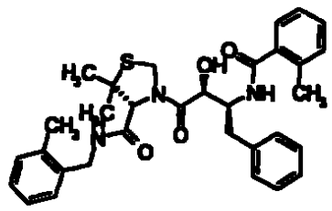
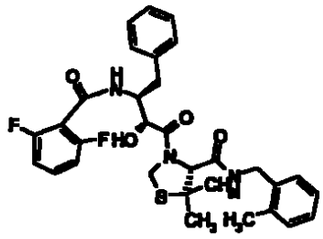
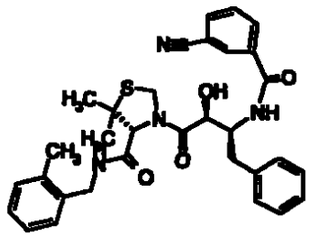
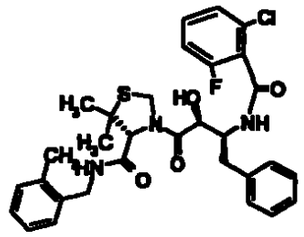
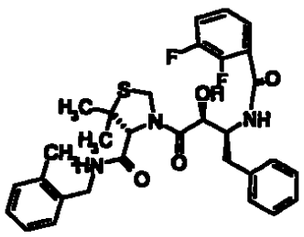
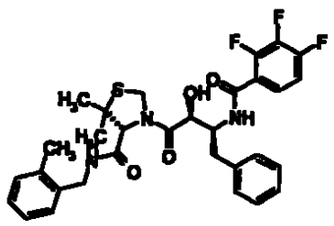
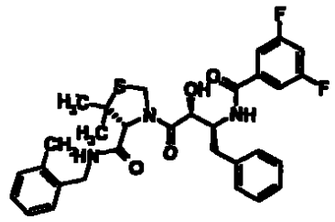
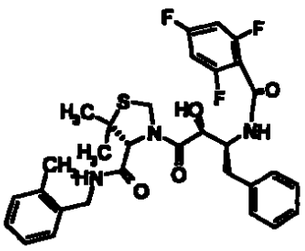
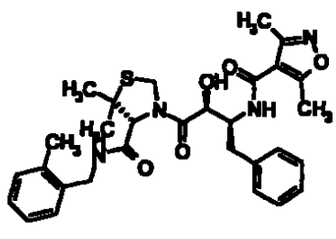
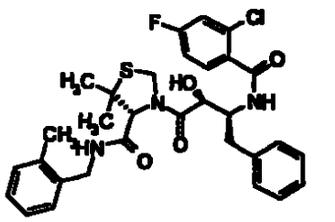
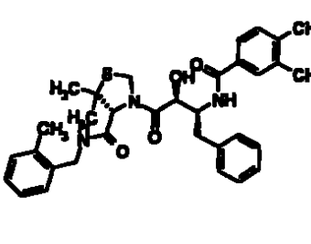
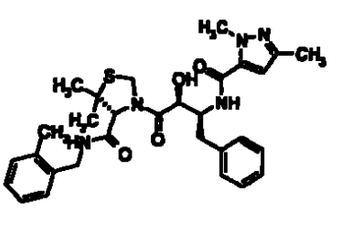
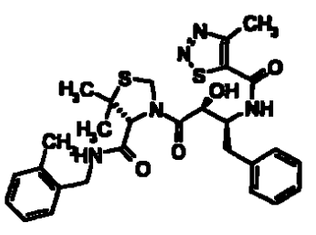
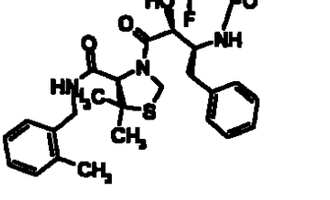
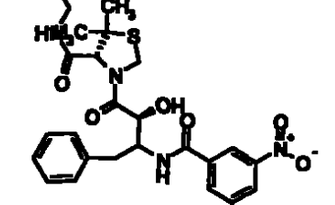
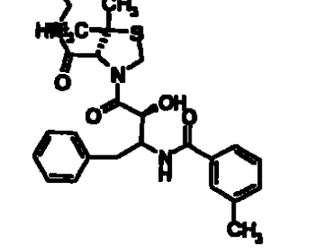


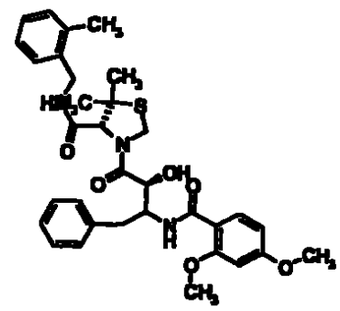
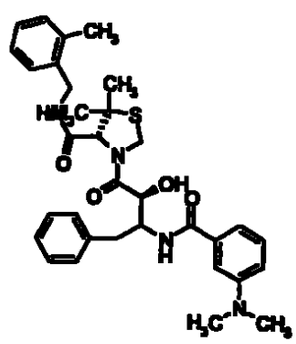
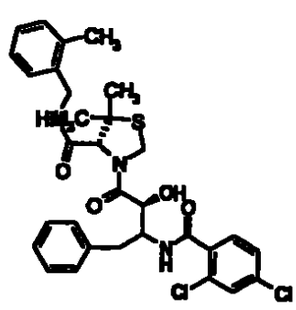
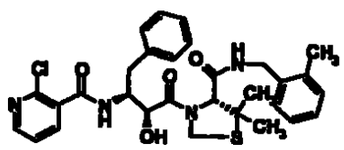
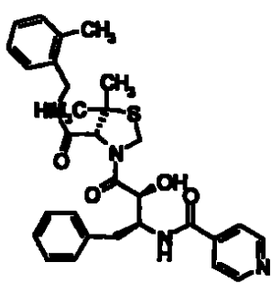
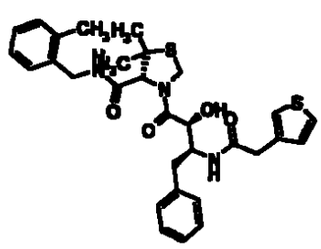
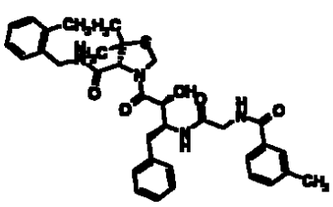
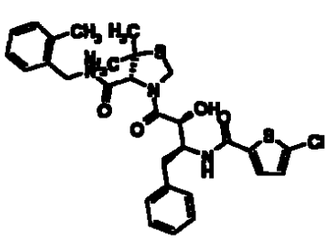
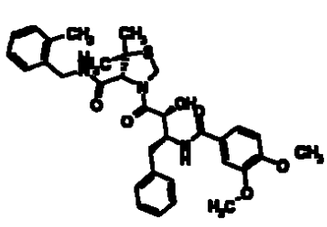
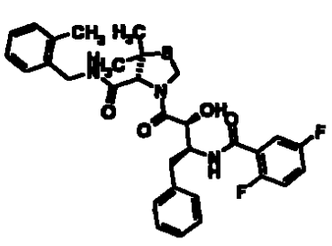
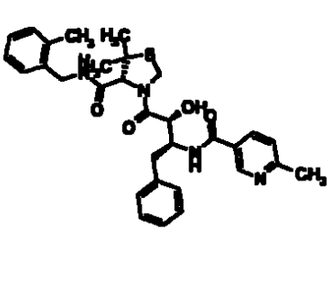
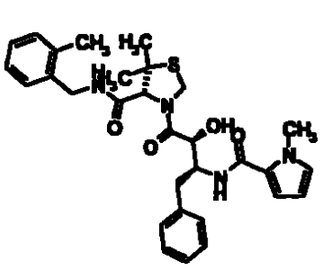
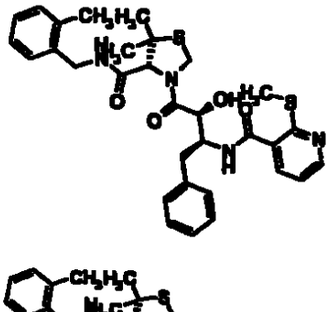
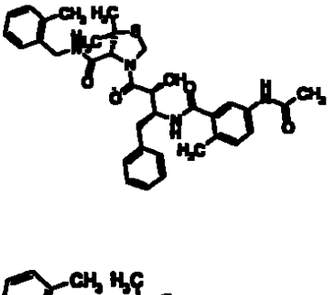
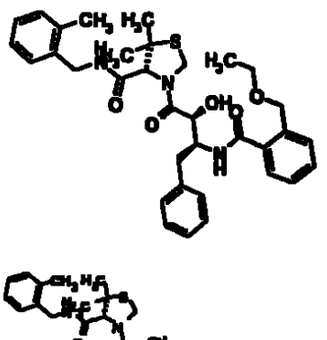
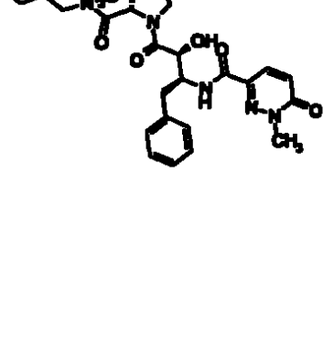
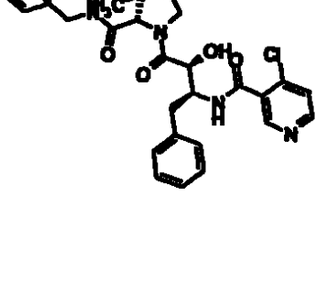
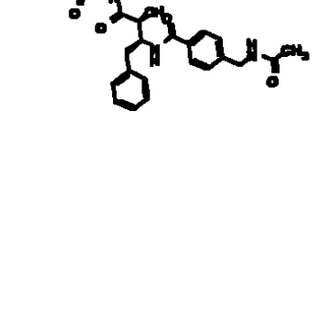








## BIOLOGICAL EVALUATION

Cells and Virus

T-cell lines, CEM-SS, and MT-2, and viruses HIV-1 RF and HIV-1 NL4-3 (pNL4-3) were obtained from the National Institutes of Health (AIDS Research and Reference Reagent Program, Bethesda, MD). HIV-1 NL4-3(I84V/L90M) was derived from a clinical isolate that exhibited the protease inhibitor-resistance associated substitutions I84V and L90M, by cloning of an reverse transcriptase-polymerase chain reaction amplified fragment into the unique Age I and Spe I restriction sites of pNL4-3.

Cytopathic effect (CPE) inhibition assays

The ability of compounds to protect cells against HIV infection was measured by the MTT dye reduction method, essentially as described (See Pauwels, R. Balzarini, J. Baba, M. Snoeck, R. Schols, D. Herdewijn, P. Desmyter, J. and De Clercq, E. 1988, "Rapid and automated tetrazolium-based colorimetric assay for the detection of anti-HIV compounds,". *J Virol. Methods.*, 20. 309-321 and Weislow, O.S. Kiser, R. Fine, D.L. Bader, J. Shoemaker, R.H. and Boyd, M.R. 1989 "New soluble-formazan assay for HIV-1 cytopathic effects: application to high-flux screening of synthetic and natural products for AIDS-antiviral activity". *J Natl Cancer Inst* 81 577-586). Subject cells were infected with test virus at an moi of 0 025 to 0 819 or mock infected with medium only and added at 2 x $10^4$ cells per well into 96 well plates containing half-log dilutions of test compounds. Six days later, 50 µl of XTT (1mg/ml XTT tetrazolium, 0.02 nM phenazine methosulfate) was added to the wells and the plate was reincubated for four hours. Viability, as determined by the amount of XTT formazan produced, was quantified spectrophotometrically by absorbance at 450 nm. Data from CPE assays were expressed as the percent of formazan produced in compound-treated cells compared to formazan produced in wells of uninfected, compound-free cells. The fifty percent effective concentration ($EC_{50}$) was calculated as the concentration of compound that effected an increase in the percentage of formazan production in infected, compound-treated cells to 50% of that produced by uninfected, compound-free cells The 50% cytotoxicity concentration ($CC_{50}$) was calculated as the concentration of

compound that decreased the percentage of formazan produced in uninfected, compound-treated cells to 50% of that produced in uninfected, compound-free cells. The therapeutic index was calculated by dividing the cytotoxicity ($CC_{50}$) by the antiviral activity ($EC_{50}$).

Susceptibility assays

Compounds were tested in phenotypic susceptibility assays at Virologic, Inc., (See Petropoulos C.J., Parkin N.T., Limoli K.L., Lie Y.S., Wrin T., Huang W., Tian H., Smith D., Winslow G.A., Capon DJ, Whitcomb JM. 2000, "A novel phenotypic drug susceptibility assay for human immunodeficiency virus type 1," *Antimicrob Agents Chemother* 44(4):920-928) or using the assay described here. MT-2 cells were infected with either HIV-1 *NL4-3* or HIV-1 *NL4-3*(I84V/L90M) and incubated in the presence of serial 0.5 log dilutions of test compounds. Three days later, culture supernatants were collected and virus production, as determined by p24 ELISA, was assayed Percent inhibition was calculated as p24 concentration in compound-treated samples as compared to infected, compound-free controls. Inhibition of viral replication is determined by measuring reduction in HIV p24 present in the culture supernatant, using a Beckman-Coulter p24 HIV-1 Ag EIA kit and following the supplied protocol. Absorbance is read on a MRX microplate reader (Dynex Technologies) The $EC_{50}$ was calculated as the concentration of compound that effected a decrease in the p24 production by infected, compound-treated cells to 50% of that produced by infected, compound-free cells

HIV-1 Protease RET Assay

Ki's for the inhibitors of HIV-1 protease were determined using a resonance energy transfer (RET) assay. A mutant form of this enzyme (Q7S) is used for this assay because it is more stable against auto-proteolysis than the wild-type protein. This enzyme is first partially purified as inclusion bodies from cell lysate. It is then solubilized in 8M urea and passed through a Q-Sepharose column (Pharmacia) for further purification. To refold this protein, samples containing Q7S is dialyzed into 50mM sodium phosphate pH 7.0, 50mM NaCl, 10mM DTT, and 10% glycerol

The commercially available peptide substrate (Molecular Probes Cat. # H-2930) RE(EDANS)SQNYPIVQK(DABCYL)R is used to assess activity and Ki's. This peptide is cleaved quantitatively by HIV-1 Pr at the Tyr-Pro bond. The EDANS fluorophore absorbs at 340nm and emits at 490nm. The reaction is carried out in a 96 well plate in a total volume of 100µL and is run for 12 minutes at 37C under steady-state conditions with 5µM substrate and 2nM active dimer enzyme concentration. The literature value Km for this substrate and enzyme is 103 +/- 8µM (See Matayoshi, et al, "Novel Fluorogenic Substrates for Assaying Retroviral Proteases by Resonance Energy Transfer," *Science* 247, 954 (1990)) The buffer for this reaction is 0.1M sodium acetate pH 4.8, 1M NaCl, 1mM EDTA, 5mM dithiothreitol, 10% dimethyl sulfoxide and 1mg/ml bovine serum albumin. Inhibition curves are fit using the Morrison tight binding equation.

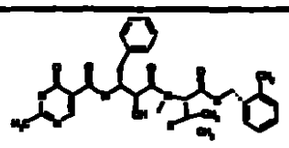
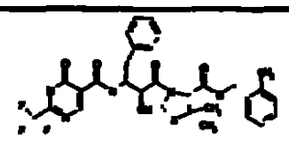
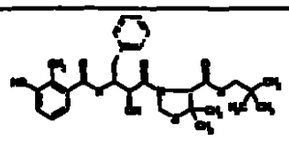
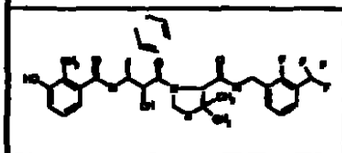
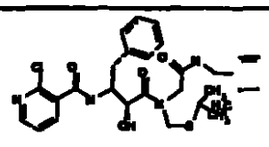
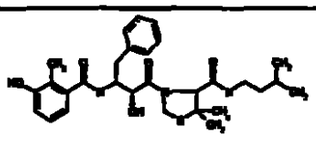
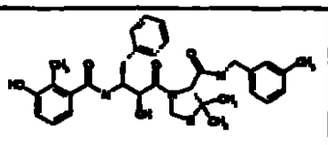
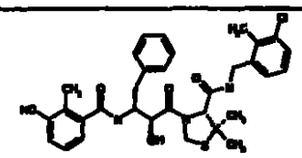
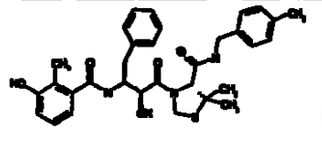
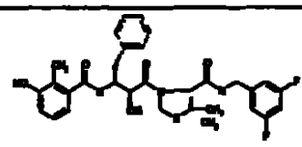
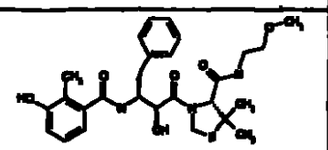
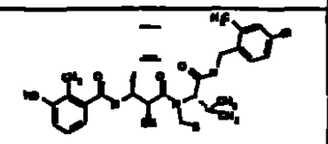
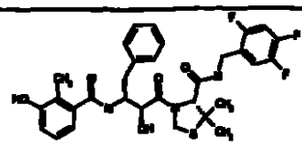
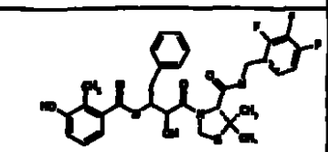
| Example No | Ave. $K_i$ (nM) | Ave CPE $EC_{50}$ (mM) | $EC_{50}$ or $IC_{50}$ (mM) |
|---|---|---|---|
| A3 | 1 7 | 0.37 | |
| A4 | 4.1 | 0.591 | |
| A5 | 2 | 0.433 | |
| A6 | 0.22 | 0 036 | |
| A7 | 0 49 | 0.104 | 0.832 |
| A8 | 0.23 | 0.036 | |
| A9 | 4 | 0.565 | |
| A10 | 51 | > 1 | |
| A11 | 19 | 0.93 | |
| A12 | 1.7 | 1.09 | |
| A13 | 44.1 | > 1 | |
| A14 | 0 44 | 0 052 | 0.071* |
| A15 | 10 9 | 0 13 | |
| A16 | 0.63 | 0.134 | |
| A17 | < 0 1 | 0.045 | 0.102* |
| A18 | 0 38 | 0.193 | |
| A19 | 10 | 0.442 | |
| A20 | 0.13 | 0.037 | 0.147* |
| A21 | 1 9 | 0.717 | |
| A22 | 0 32 | 0 061 | 0.226* |
| A23 | 0 65 | 0 072 | |
| A24 | 0 18 | 0.104 | 0.831 |
| A25 | 5 8 | 0.248 | |
| A26 | 0 38 | 0.119 | 0.321* |
| A27 | 0 62 | 0'072 | |

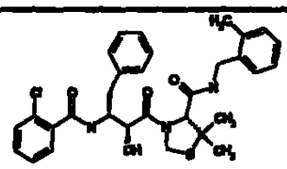
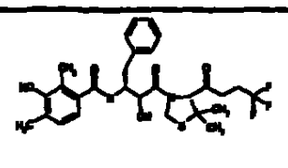
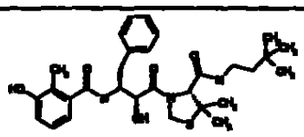
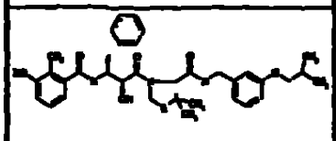
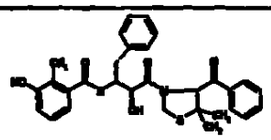
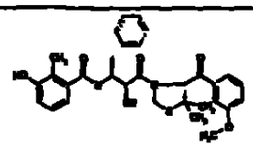
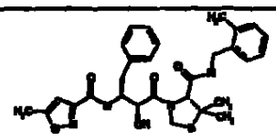
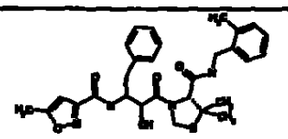
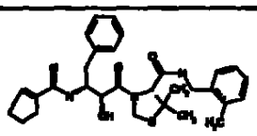
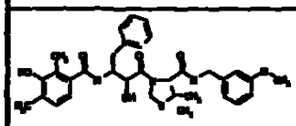
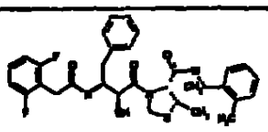
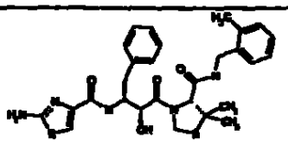
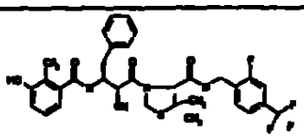
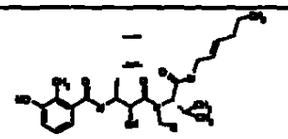
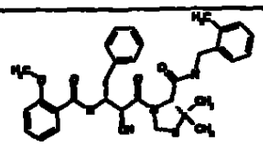
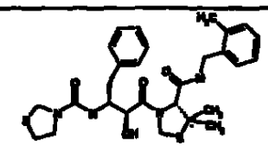
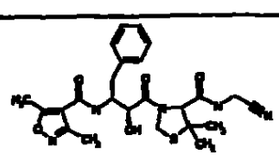
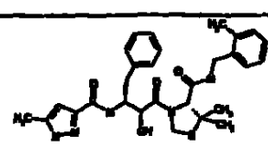
| Example No. | Ave. $K_i$ (nM) | Ave CPE $EC_{50}$ (mM) | $EC_{50}$ or $IC_{50}$ (mM) |
|---|---|---|---|
| A28 | < 0.1 | 0.041 | |
| A29 | < 0.1 | 0.117 | |
| A30 | 1.1 | 0.507 | 0.829* |
| A31 | < 0.1 | 0.041 | |
| A32 | < 0.1 | 0.045 | 0.486 |
| A33 | < 0.1 | 0.577 | |
| A34 | < 0.1 | 0.036 | |
| A35 | < 0.1 | 0 017 | 0.063 |
| A36 | 0.59 | 0 519 | |
| A37 | 0.13 | 0.161 | |
| A38 | 0.17 | 0.078 | 0.401 |
| A39 | 0.27 | 0.367 | |
| A40 | 1.2 | 0.275 | |
| A41 | 1.6 | 0.527 | |
| A42 | 0.23 | 0.126 | 0.307 |
| A43 | 0.35 | 0.561 | |
| A44 | 0 14 | 0.022 | 0.472 |
| A45 | 0.51 | 0.165 | |
| A46 | 0.31 | 0 091 | 0.79 |
| A47 | 2.3 | 1 813 | |
| A48 | 0.19 | 0.417 | |
| A49 | 1.2 | 0.13 | |
| A50 | 0.26 | 0.224 | |
| A51 | 1.3 | 0.667 | |
| A52 | 37 | | |
| B1 | 2 5 | 0.905 | |
| B2 | 0.78 | 0.369 | |
| B3 | 4 | 0 409 | |
| B8 | 0 31 | 0.095 | 0.405* |
| B4 | 1 7 | 0 551 | |
| B5 | 1.6 | 0.508 | |
| B6 | 1 6 | 0 589 | |
| B7 | 1.9 | 0 68 | |
| B8 | 1.5 | 0.552 | |
| B10 | < 0.1 | 1.1 | |
| B11 | 1 2 | 1.175 | 1.716* |
| B12 | 0 45 | 1.398 | |
| B13 | 19%@64nM | | |
| B14 | 3.7 | 3.054 | |
| B15 | 2 | 1.086 | |
| B16 | < 0.1 | 0.298 | 1.754 |
| B17 | 0.42 | 0.534 | 1.579 |
| B18 | 0 29 | 0.457 | |
| B19 | < 0.1 | 0.124 | 1.369 |
| B20 | 2.1 | 0 427 | |

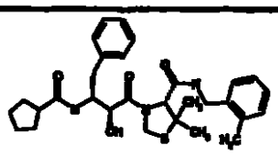
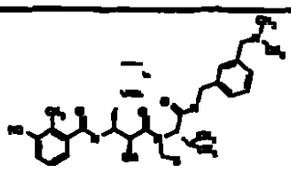
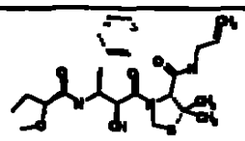
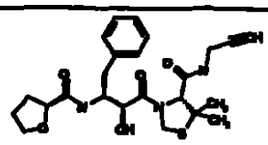
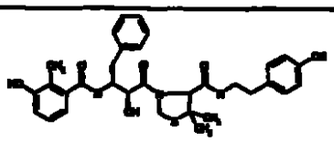
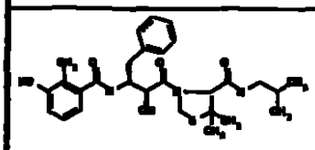
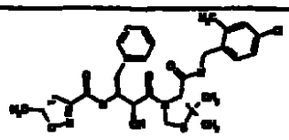
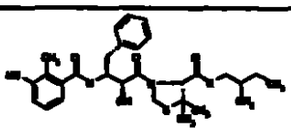
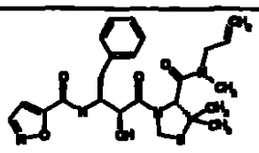
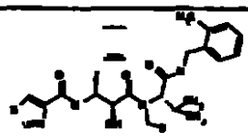
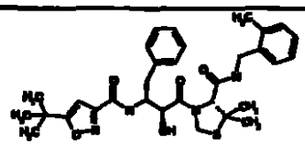
| Example No | Ave. $K_i$ (nM) | Ave CPE $EC_{50}$ (mM) | $EC_{90}$ or $IC_{90}$ (mM) |
|---|---|---|---|
| B21 | 4.6 | 0 598 | |
| B22 | 1.8 | 1 613 | |
| B23 | 0 42 | 1 42 | |
| B24 | 5 5 | 2.316 | |
| B25 | 2.7 | 1.794 | |
| B26 | 2.9 | 1.712 | |
| B27 | 3.5 | | |
| B28 | 153 | | |
| B29 | 0.12 | 1.256 | |
| B30 | 1.1 | 1.227 | |
| B31 | 1.5 | 1.316 | |
| B32 | 4 9 | | |
| B33 | 1.2 | 1.286 | |
| B34 | | | |
| B35 | | | |
| B36 | < 0 1 | 0 615 | |
| B37 | 0.11 | 0 736 | |
| B38 | | | |
| B39 | 0 16 | | |
| B40 | 2.8 | 1 396 | |
| B41 | 0.15 | | |
| B42 | 0.73 | | |
| B43 | 0.2 | | |
| B44 | 0 76 | 0 629 | |
| B45 | 19.7 | | |
| B46 | 12.5 | | |
| B47 | 6.9 | | |
| B48 | 12 | > 3.2 | |
| B49 | 17.2 | | |
| C1 | 0 38 | 0 627 | 0.427 |
| C3 | 1 3 | 0 5 | |
| C4 | 4.2 | | |
| C4 | 69 | | |
| C5 | 3 2 | | |
| C6 | < 0.1 | 0 164 | 1 475 |
| C7 | 7.9 | | |
| C8 | 0.26 | 0.447 | |
| C9 | 0.34 | 0.233 | |
| C10 | 36 | | |
| C11 | 1 1 | 1.562 | |
| D1 | <0.01 | 0.052 | 0.601 |
| D3 | 0 5 | 0.162 | 1.954 |
| D4 | 0.7 | 0.016 | 1.954 |

*$IC_{50}$ (mM) Data was determined at Virologic Inc against the 46I, 84V, 90M virus

The following compounds have been prepared according to the procedures described herein and have demonstrated the noted activity:

| MOLSTRUCTURE | $K_i$ | $EC_{50}$ | MOLSTRUCTURE | $K_i$ | $EC_{50}$ |
|---|---|---|---|---|---|
|  | 209 | 10 |  | 1700 | 10 |
|  | 0.1 | 0.053 |  | 62 | |
|  | 0 75 | | | | |
|  | 0.1 | 0.072 |  | 1 5 | 0.076 |
|  | 0.2 | 0 113 |  | 0.73 | 0 141 |
|  | 0.36 | 0 144 |  | 0.24 | 0 158 |
| | | |  | 0.28 | 0.207 |
|  | 0.17 | 0.289 |  | 0 11 | 0.334 |

| MOLSTRUCTURE | $K_i$ | $EC_{50}$ | MOLSTRUCTURE | $K_i$ | $EC_{50}$ |
|---|---|---|---|---|---|
|  | 0 2 | 0.585 |  | 9.6 | 0.723 |
|  | 4.7 | 1.064 |  | 1 1 | 1 114 |
|  | 2.5 | 1.221 |  | 7 4 | |
|  | 2 6 | 1.3095 |  | 2 6 | 1.3095 |
|  | 3 4 | |  | 3.7 | 1.332 |
|  | 72 | |  | 2.3 | 1.378 |
|  | 11 1 | 1 401 |  | 2 6 | 1 416 |
|  | 2.1 | 1.488 |  | 14 | 1 512 |
|  | 18.5 | |  | 19 5 | 3 |

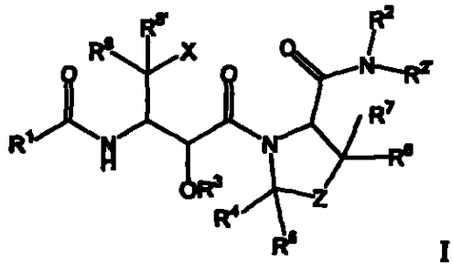
| MOLSTRUCTURE | $K_i$ | $EC_{50}$ | MOLSTRUCTURE | $K_i$ | $EC_{50}$ |
|---|---|---|---|---|---|
|  | 12.1 | |  | 10.5 | 3.2 |
|  | 17.3 | 3 303 |  | 16.8 | 3.745 |
|  | 13.1 | |  | 0.1 | |
|  | 28 | 4.132 |  | 0.1 | |
|  | 24.6 | 4.951 |  | 55.8 | 10 |
|  | 214 | 10 | | | |

The following compounds have been prepared according to the procedures described herein and have demonstrated the noted activity:

While the invention has been described in terms of preferred embodiments and specific examples, those skilled in the art will recognize that various changes and modifications can be made through routine experimentation without departing from the spirit and scope of the invention. Thus, the invention should be understood as not being limited by the foregoing detailed description, but as being defined by the appended claims and their equivalents

WE CLAIM:

1. A compound having the Formula I:



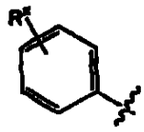
I

wherein

$R^1$ is a 5- or 6-membered mono-cyclic carbocyclic or heterocyclic group, wherein said carbocyclic or heterocyclic group is saturated, partially unsaturated or fully unsaturated and is unsubstituted or substituted by one or more suitable substituents,

$R^2$ is a substituted alkyl group, a substituted or unsubstituted alkenyl group, a substituted or unsubstituted alkynyl group, a substituted phenyl group, a substituted phenylalkyl group, a substituted or unsubstituted phenylalkenyl group or a substituted or unsubstituted phenylalkynyl group,

$R^Z$ is H or a substituted or unsubstituted $C_1$-$C_4$ alkyl group,

X is  , wherein $R^x$ is H or one or more suitable substituents;

Z is S, O, SO, $SO_2$, $CH_2$ or CFH;

$R^3$ is H or a substituted or unsubstituted $C_1$-$C_4$ alkyl group,

$R^4$, $R^5$, $R^6$ and $R^7$ are independently selected from H or a $C_1$-$C_6$ alkyl group, and

$R^8$ and $R^{8'}$ are independently selected from H, halo, a $C_1$-$C_4$ aliphatic group or a $C_1$-$C_4$ halo-substituted aliphatic group;

where any of said substituted alkyl, alkenyl or alkynyl groups are substituted by one or more suitable substituents,

provided that said 5- or 6-membered mono-cyclic heterocycloalkyl, heterocycloalkenyl or heteroaryl group contains at least two heteroatoms when $R^2$ is a

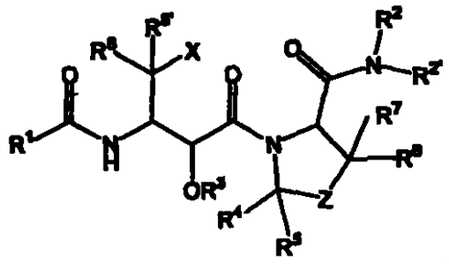
substituted phenyl group, a substituted phenylalkyl group, a substituted or unsubstituted phenylalkenyl group or a substituted or unsubstituted phenylalkynyl group; or

provided that said alkyl, alkenyl or alkynyl moiety of said substituted phenylalkyl, phenylalkenyl or phenylalkynyl group is substituted by one or more substituents selected from halo or keto; or

provided that said substituted phenyl group or phenyl moiety of said substituted phenylalkyl, phenylalkenyl or phenylalkynyl group is substituted by one or more suitable substituents other than halo or methyl;

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate thereof.

2. A compound having the Formula I:



I

wherein:

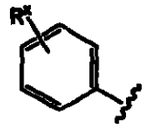
$R^1$ is a 5- or 6-membered monocyclic cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group, where said cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group is unsubstituted or substituted with one or more substituents independently selected from alkyl, haloalkyl, amino, cyano, halogen, hydroxyl, alkoxy, haloalkoxy, alkylenedioxy, di-haloalkylenedioxy, aryloxy, cycloalkoxy, cycloalkylalkoxy, cycloalkenoxy, cycloalkenylalkoxy, heterocycloalkoxy, heterocycloalkylalkoxy, heterocycloalkenyloxy, heterocycloalkenylalkoxy, heteroaryloxy, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylamino, dialkylamino, keto, alkylsulfonyl, arylsulfonyl, alkylcarbonylamino, alkylthio, haloalkylthio and arylthio, wherein any of the alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents are further substituted by one or more groups independently selected from

alkyl, haloalkyl, aryl, nitro, amino, alkylamino, dialkylamino, halogen, hydroxyl, alkoxy, haloalkoxy, aryloxy, mercapto, alkylthio, haloalkylthio and arylthio groups;

$R^2$ is a substituted alkyl group, a substituted or unsubstituted alkenyl group, or a substituted or unsubstituted alkynyl group, wherein said alkyl, alkenyl or alkynyl group is a straight or branched chained group, and

where said substituted alkyl, alkenyl or alkynyl group is substituted by one or more substituents independently selected from amino, cyano, halogen, hydroxyl, alkoxy, haloalkoxy, aryloxy, cycloalkoxy, cycloalkylalkoxy, cycloalkenyloxy, cycloalkenylalkoxy, heterocycloalkoxy, heterocycloalkylalkoxy, heterocycloalkenyloxy, heterocycloalkenylalkoxy, heteroaryloxy, alkylamino, dialkylamino, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylthio, haloalkylthio, arylthio and heteroarylthio groups, wherein any of the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, or heteroaryl moieties present in the above substituents are further substituted by one or more groups independently selected from alkyl, haloalkyl, halogen, hydroxyl, alkoxy, haloalkoxy, alkylthio and haloalkylthio groups,

$R^7$ is H, methyl, ethyl or propyl, where said methyl, ethyl or propyl is unsubstituted or substituted by halo or hydroxyl,

X is  , wherein $R^x$ is H or one or more substituents independently selected from halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl, alkylenedioxy, di-haloalkylenedioxy, alkylamino, dialkylamino, alkylthio and haloalkylthio;

Z is S, O, SO, $SO_2$, $CH_2$ or CFH;

$R^3$ is H;

$R^4$, $R^5$, $R^6$ and $R^7$ are independently selected from H or methyl; and

$R^8$ and $R^9$ are independently selected from H, halogen, methyl, monohalo-methyl, dihalo-methyl and tri-halomethyl;

or a prodrug, pharmaceutically active metabolite or pharmaceutically active salt or solvate thereof.

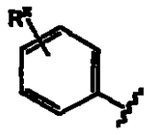
3. The compound according to claim 2, wherein

$R^1$ is phenyl, pyrrolyl, pyrrolidinyl, isoxazolyl, pyrazolyl, thiazolyl, tetrahydrofuranyl, furanyl, thienyl or tetrahydropyridazinyl, where said phenyl, pyrrolyl, pyrrolidinyl, isoxazolyl, pyrazolyl, thiazolyl, tetrahydrofuranyl, furanyl, thienyl or tetrahydropyridazinyl is unsubstituted or substituted with one or more substituents independently selected from alkyl, haloalkyl, halogen, and hydroxyl,

$R^2$ is a substituted alkyl group, a substituted or unsubstituted $C_1$-$C_6$ alkenyl group, or a substituted or unsubstituted $C_1$-$C_6$ alkynyl group, wherein said alkyl, alkenyl or alkynyl group is a straight or branched chained group, and

where said substituted alkyl, alkenyl or alkynyl group is substituted by one or more substituents independently selected from cyano, halogen and alkylamino;

$R^7$ is H, methyl or ethyl;

X is  , wherein $R^x$ is H, halogen, or alkoxy;

Z is S, O, $CH_2$ or CFH,

$R^3$, $R^4$, $R^5$, $R^8$ and $R^9$ are each H; and

$R^6$ and $R^7$ are independently selected from H or methyl;

or a prodrug, pharmaceutically active metabolite or pharmaceutically active salt or solvate thereof.

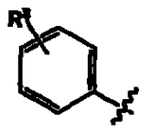
4 The compound according to claim 2, wherein:

$R^1$ is phenyl, where said phenyl is substituted with one or more substituents independently selected from alkyl, halogen or hydroxyl;

$R^2$ is a $C_1$-$C_6$ alkenyl group or a $C_1$-$C_6$ alkynyl group, wherein said alkenyl or alkynyl group is a straight or branched chained group, and

where said alkenyl or alkynyl group is unsubstituted or is substituted by one or more halogen substituents;

$R^7$ is H;

X is  , wherein $R^x$ is H;

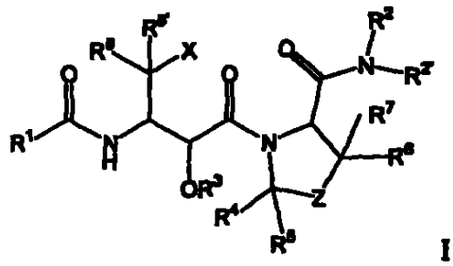
Z is S;

$R^3$, $R^4$, $R^5$, $R^8$ and $R^{8'}$ are each H, and

$R^6$ and $R^7$ are each methyl;

or a prodrug, pharmaceutically active metabolite or pharmaceutically active salt or solvate thereof.

A compound having the Formula I:



I

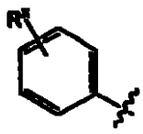
wherein:

$R^1$ is a 5- or 6-membered mono-cyclic cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group, where said cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group is unsubstituted or substituted with one or more substituents independently selected from alkyl, haloalkyl, amino, cyano, halogen, hydroxyl, alkoxy, haloalkoxy, alkylenedioxy, dihaloalkylenedioxy, aryloxy, cycloalkyloxy, cycloalkylalkoxy, cycloalkenyloxy, cycloalkenylalkoxy, heterocycloalkoxy, heterocycloalkylalkoxy, heterocycloalkenyloxy, heterocycloalkenylalkoxy, heteroaryloxy, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylamino, dialkylamino, keto, alkylsulfonyl, arylsulfonyl, alkylcarbonylamino, alkylthio, haloalkylthio and arylthio, wherein any of the alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents are substituted by one or more groups independently selected from alkyl, haloalkyl, aryl, nitro, amino, alkylamino, dialkylamino, halogen, hydroxyl, alkoxy, haloalkoxy, aryloxy, mercapto, alkylthio, haloalkylthio and arylthio groups,

$R^2$ is a substituted phenyl group, a substituted phenylalkyl group, a substituted or unsubstituted phenylalkenyl group or a substituted or unsubstituted phenylalkynyl group;

where said alkyl, alkenyl or alkynyl moiety of said phenylalkyl, phenylalkenyl or phenylalkynyl group is a straight or branched chain moiety;

$R^{2'}$ is H, methyl, ethyl or propyl, where said methyl, ethyl or propyl is unsubstituted or substituted with halo or hydroxyl;

X is  , wherein $R^x$ is H or one or more substituents independently selected from halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl, alkylenedioxy, di-haloalkylenedioxy, alkylamino, dialkylamino, alkylthio and haloalkylthio,

Z is S, O, SO, $SO_2$, $CH_2$ or CFH,

$R^3$ is H,

$R^4$, $R^5$, $R^6$ and $R^7$ are independently selected from H or methyl; and

$R^8$ and $R^{8'}$ are independently selected from H, halogen, methyl, monohalo-methyl, dihalo-methyl and tri-halomethyl;

provided that said 5- or 6-membered mono-cyclic heterocycloalkyl, heterocycloalkenyl or heteroaryl group contains at least two heteroatoms; or

provided that said alkyl, alkenyl or alkynyl moiety of said substituted phenylalkyl, phenylalkenyl or phenylalkynyl group is substituted by one or more substituents selected from halo or keto, or

provided that said substituted phenyl group or phenyl moiety of said substituted phenylalkyl, phenylalkenyl or phenylalkynyl group is substituted by one or more substituents other than halo or methyl, where said one or more substituents is independently selected from haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkoxyalkyl, alkylcarbonylalkyl, haloalkoxyalkyl, aryloxyalkyl, alkylthioalkyl, haloalkylthioalkyl, arylthioalkyl, cyanoalkyl, aminoalkyl, alkylaminoalkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, nitro, amino, cyano, hydroxyl, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, alkylenedioxy, aryloxy, cycloalkoxy, cycloalkylalkoxy, cycloalkenyloxy, cycloalkenylalkoxy, heterocycloalkoxy, heterocycloalkylalkoxy, heterocycloalkenyloxy, heterocycloalkenylalkoxy, heteroaryloxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy,

arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyoxycarbonyl, carboxyl, carbamoyl, formyl, keto, thioketo, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino, cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, haloalkylthio, arylthio and heteroarylthio groups, wherein any of the alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl moieties present in the above substituents are unsubstituted or substituted by one or more groups independently selected from alkyl, haloalkyl, halogen, hydroxyl, alkoxy, haloalkoxy, alkylthio and haloalkylthio groups,

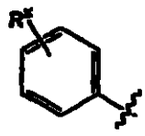
or a prodrug, pharmaceutically active metabolite or pharmaceutically active salt or solvate thereof.

6 The compound according to claim 5, wherein.

$R^1$ is phenyl, pyrrolyl, pyrrolidinyl, isoxazolyl, pyrazolyl, thiazolyl, tetrahydrofuranyl, furanyl, thienyl or tetrahydropyridazinyl, where said phenyl, pyrrolyl, pyrrolidinyl, isoxazolyl, pyrazolyl, thiazolyl, tetrahydrofuranyl, furanyl, thienyl or tetrahydropyridazinyl is unsubstituted or substituted with one or more substituents independently selected from alkyl, haloalkyl, halogen, and hydroxyl;

$R^2$ is a substituted phenylalkyl group, where said alkyl moiety of said substituted phenylalkyl group is a straight or branched chain alkyl moiety;

$R^{2'}$ is H, methyl, ethyl or propyl, where said methyl, ethyl or propyl is unsubstituted or substituted with hydroxyl;

X is  , wherein $R^x$ is H, halogen, or alkoxy;

Z is S, O, $CH_2$ or CFH;

$R^3$, $R^4$, $R^5$, $R^8$ and $R^{8'}$ are each H; and

$R^6$ and $R^7$ are independently selected from H or methyl;

provided that $R^1$ is selected from isoxazolyl, pyrazolyl, thiazolyl or tetrahydropyridazinyl, where said is isoxazolyl, pyrazolyl, thiazolyl or tetrahydropyridazinyl is unsubstituted or substituted with one or more substituents independently selected from alkyl, haloalkyl, halogen, and hydroxyl when $R^2$ is a substituted or unsubstituted phenylalkyl group or

provided that $R^1$ is selected from phenyl, pyrrolyl, pyrrolidinyl, isoxazolyl, pyrazolyl, thiazolyl, tetrahydrofuranyl, furanyl, thienyl or tetrahydropyridazinyl when $R^2$ is a substituted phenylalkyl group and said phenyl moiety of said substituted phenylalkyl group comprises one or more substituents other than halo or methyl, where said one or more substituents is independently selected from haloalkyl, amino, hydroxyl, alkoxy, haloalkoxy, alkylenedioxy, di-haloalkylenedioxy, cycloalkylalkyloxy, dialkylamino, alkylsulfonyl and alkylthio;

or a prodrug, pharmaceutically active metabolite or pharmaceutically active salt or solvate thereof.

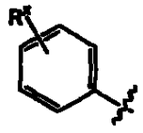
7 The compound according to claim 5, wherein

$R^1$ is phenyl, where said phenyl is substituted with one or more substituents independently selected from methyl, halogen or hydroxyl;

$R^2$ is a substituted phenylalkyl group, where said alkyl moiety of said substituted phenylalkyl group is a straight or branched chain alky moiety;

where said phenyl moiety of said substituted phenylalkyl group comprises one or more substituents other than halo or methyl, where said one or more substituents is independently selected from trifluoromethyl, amino, hydroxyl, $C_1$-$C_4$alkoxy, alkylenedioxy, di-fluoro-alkylenedioxy, cyclopropylmethoxy, di-methyl-amino, methanesulfonyl and methylthio;

$R^7$ is H, methyl or ethyl,

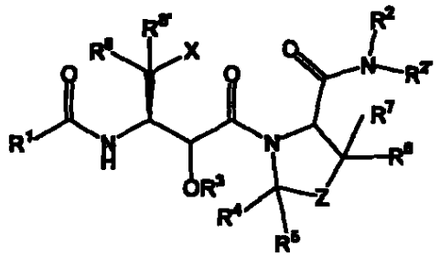
X is  , wherein $R^x$ is H,

Z is S or O, and

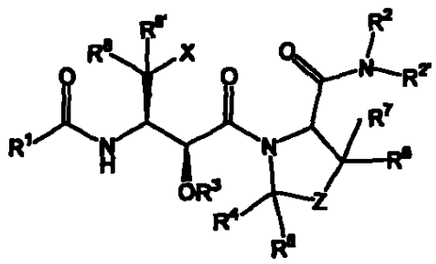
$R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$ and $R^{8'}$ are each H,

or a prodrug, pharmaceutically active metabolite or pharmaceutically active salt or solvate thereof.

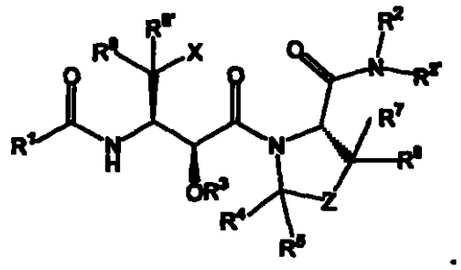
8 The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to any one of claims 1, 2 or 5, having the formula.



9 The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to any one of claims 1, 2 or 5, having the formula



10. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to any one of claims 1, 2 or 5, having the formula:



11. A pharmaceutical composition comprising:

a therapeutically effective amount of at least one HIV agent selected from compounds, prodrugs, pharmaceutically acceptable salts, pharmaceutically active metabolites, and pharmaceutically acceptable solvates defined in any one of claims 1, 2 or 5; and

a pharmaceutically acceptable carrier, diluent, vehicle, or excipient.

12. The pharmaceutical composition according to claim 11, wherein the composition further comprises a therapeutically effective amount of at least one HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents.

13. The pharmaceutical composition according to claim 12, wherein the composition further comprises a therapeutically effective amount of at least one antiviral agent selected from the group consisting of non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors

14. The pharmaceutical composition according to claim 13, further comprising a therapeutically effective amount of at least one HIV protease inhibitor

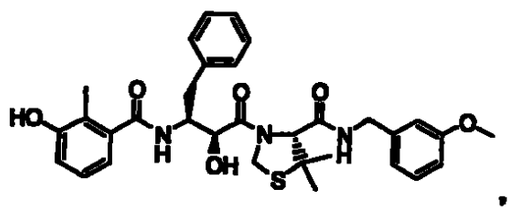
15. A method of treating a mammalian disease condition mediated by HIV protease activity, comprising administering to a mammal in need thereof a therapeutically effective amount of at least one compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate defined in any one of claims 1, 2 or 5.

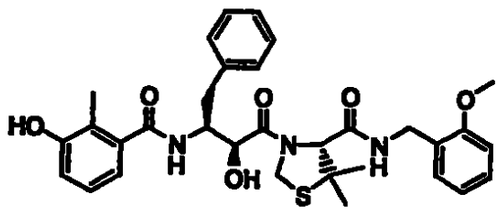
16. A method of inhibiting the activity of HIV protease in a subject in need thereof, comprising contacting the HIV protease with an effective amount of at least one compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate defined in any one of claims 1, 2 or 5.

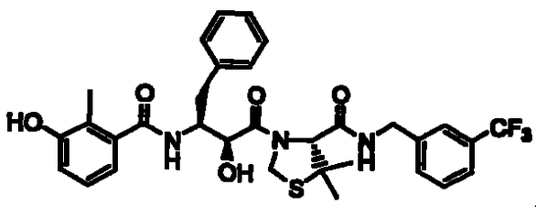
17. A method of preventing or treating infection by HIV in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1, 2 or 5.

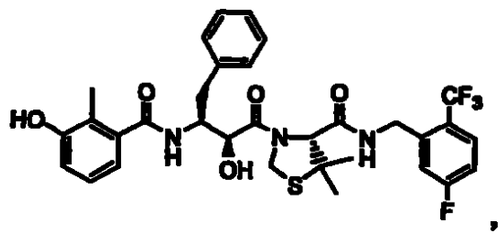
18 The method according to claim 17, wherein the compound is administered in combination with a therapeutically effective amount of at least one HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents.

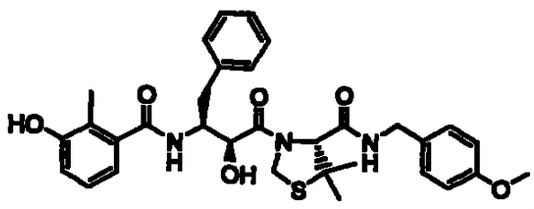
19. A compound selected from

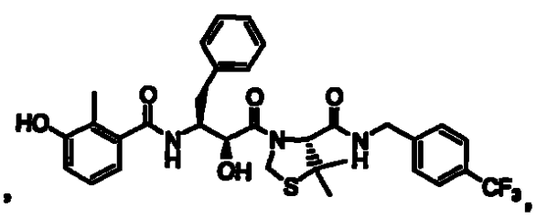

,

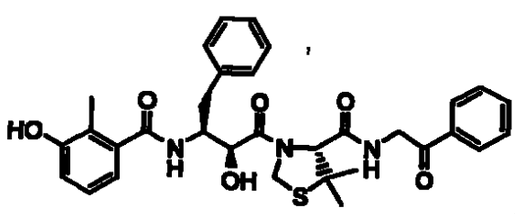

,

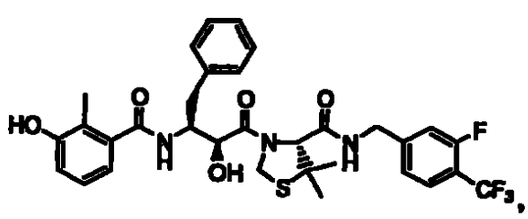

,

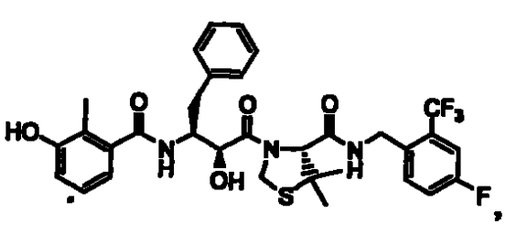

,

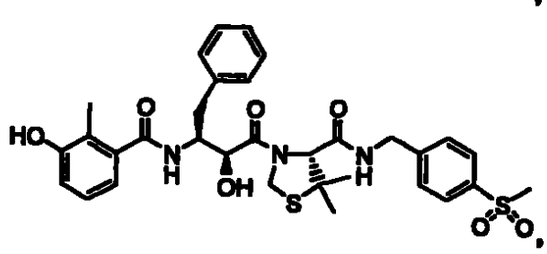

,

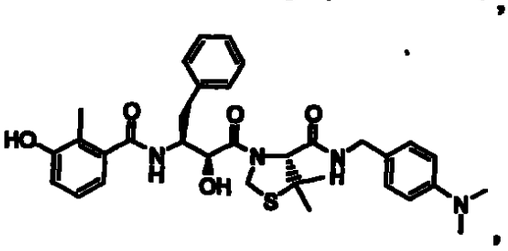

,

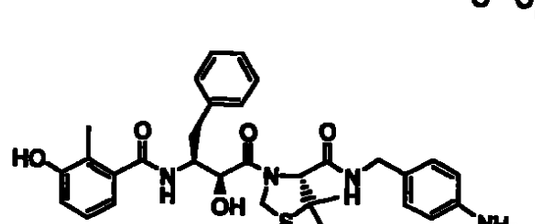

,


,


,

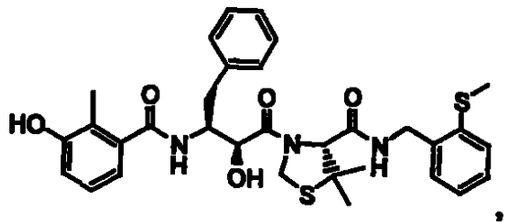

,

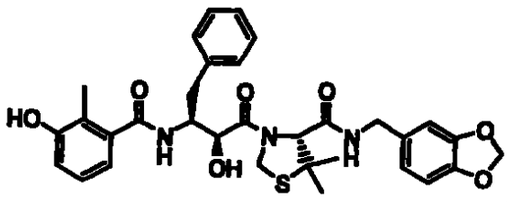

,

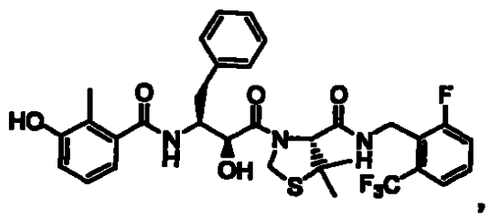

,

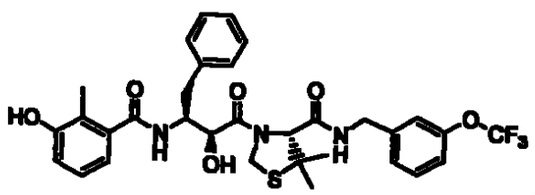

,

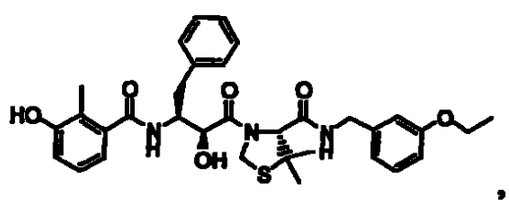

,

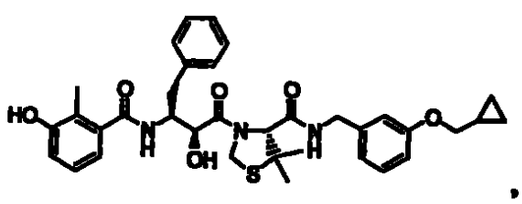


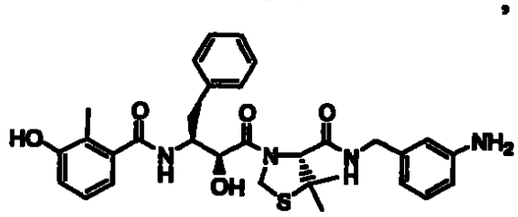


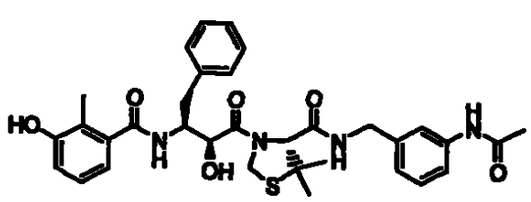


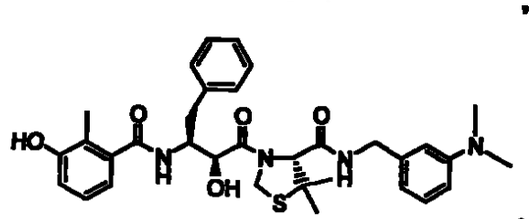


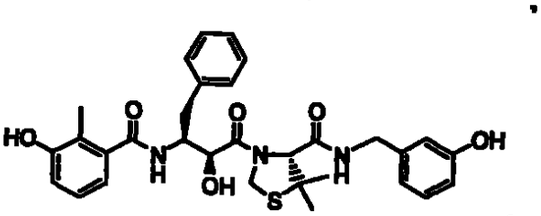


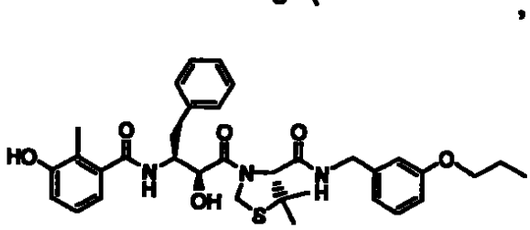


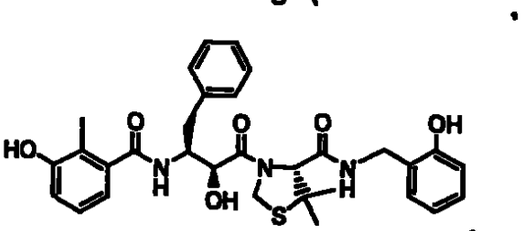


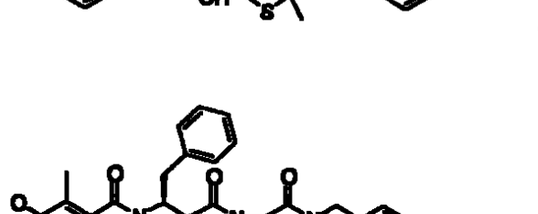


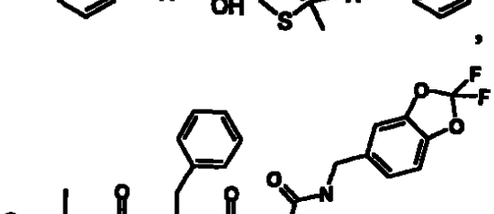


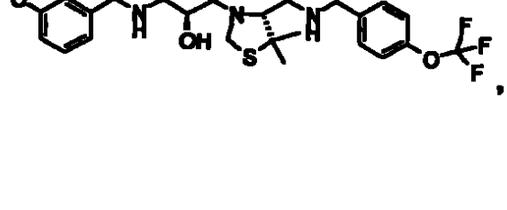


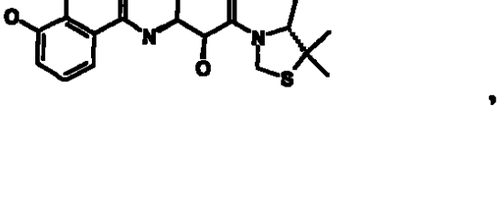


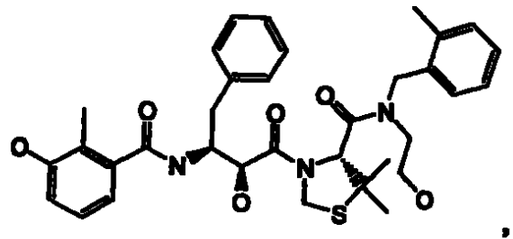




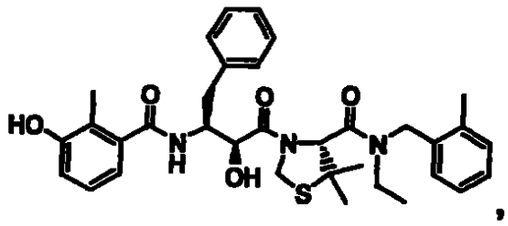




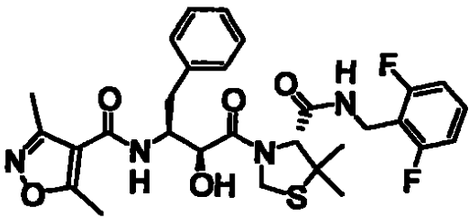




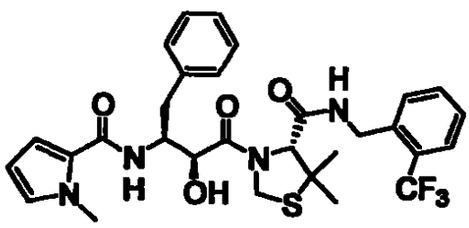
,



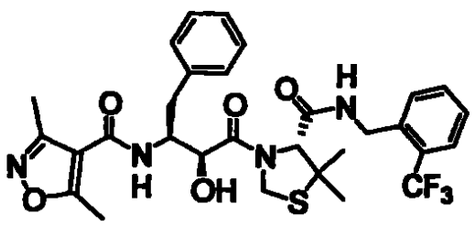
,



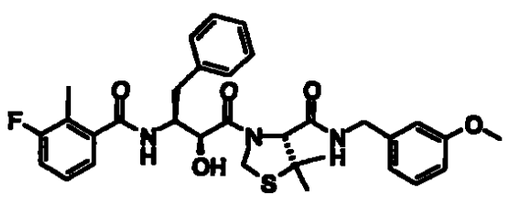
,



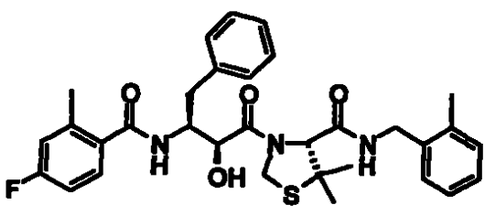
,



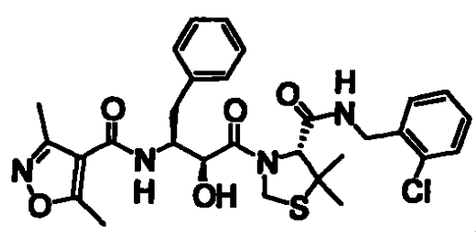
,



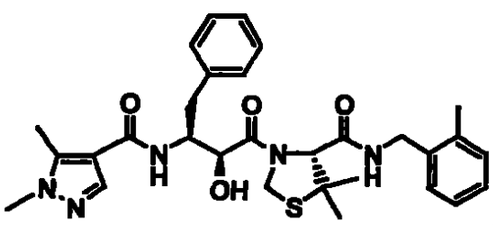
,



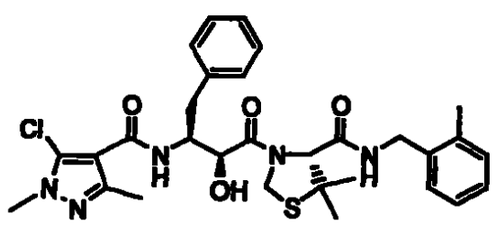
,



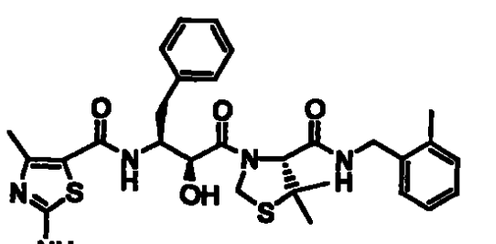
,



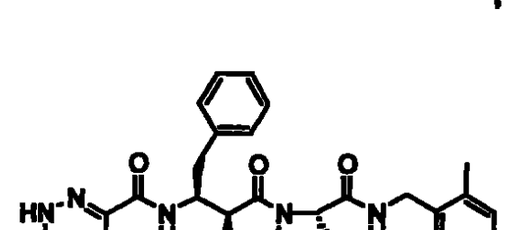
,



,



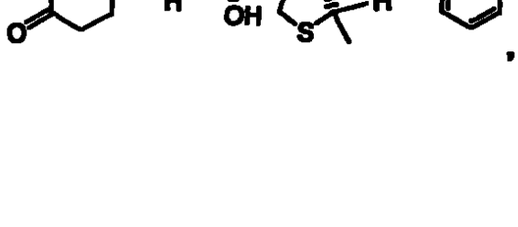
,



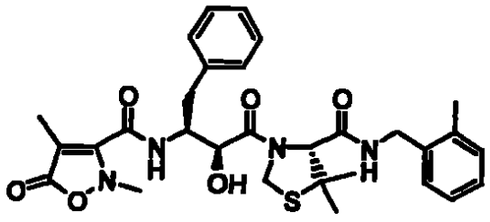
,

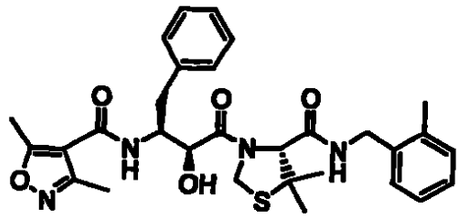


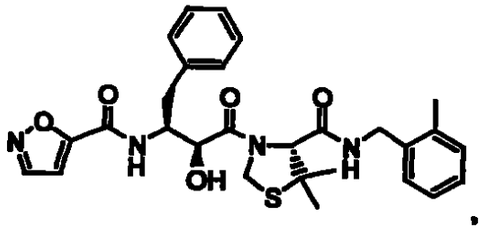
,

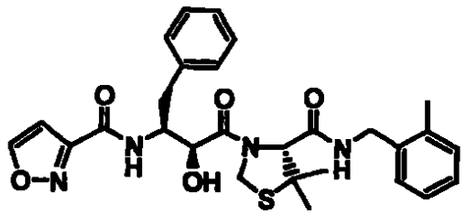


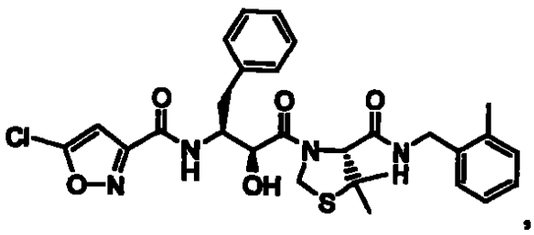
,

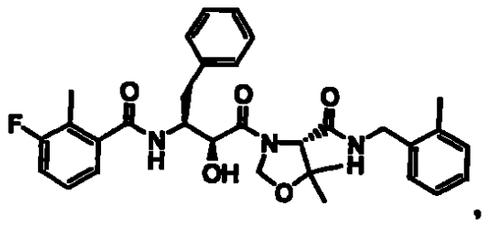

,

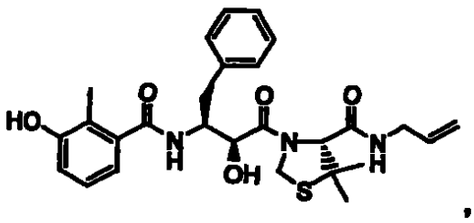

,

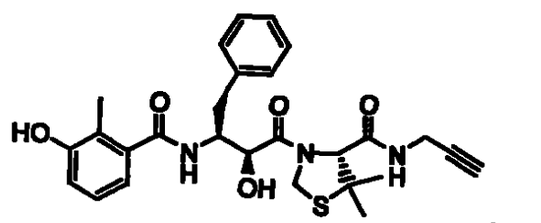

,

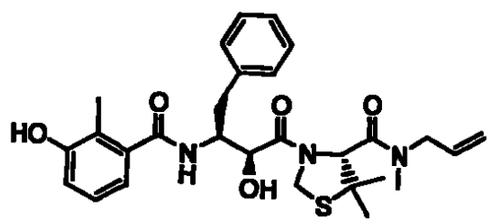

,

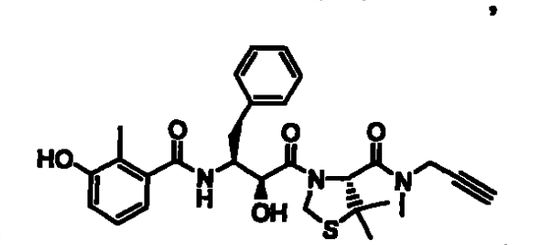

,

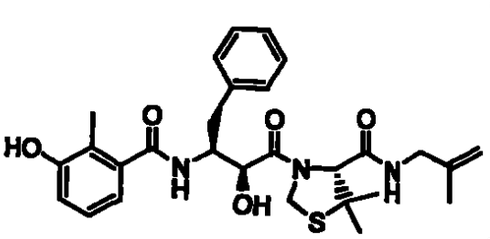

,

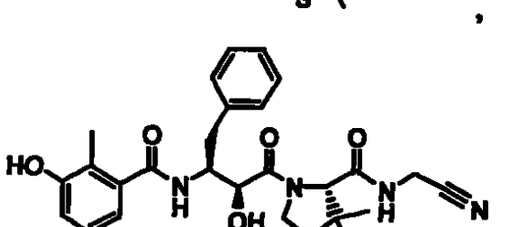

,

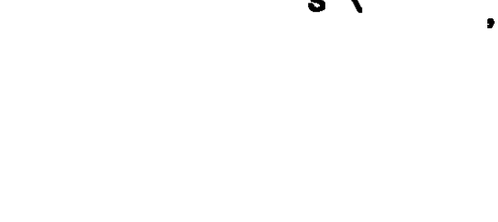

,

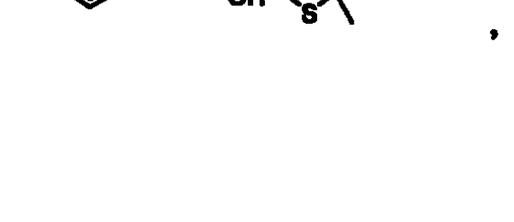

,

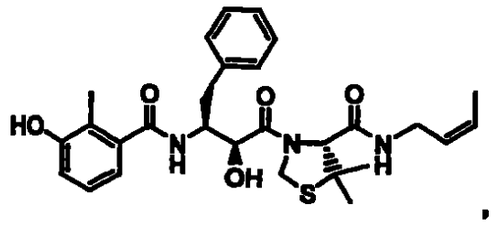

,

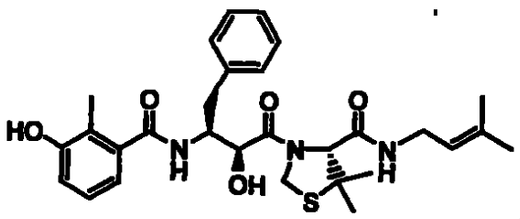

,

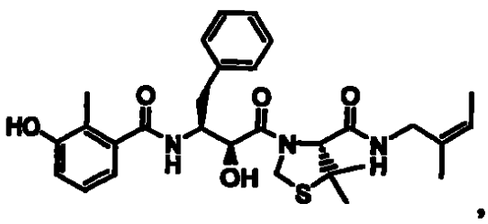

,

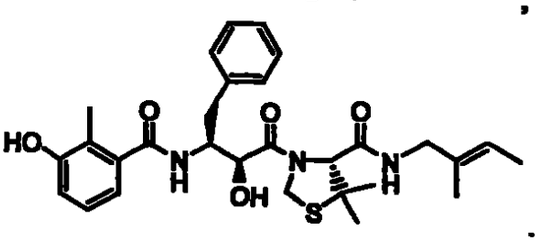

,

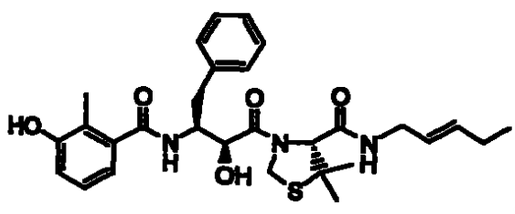

,

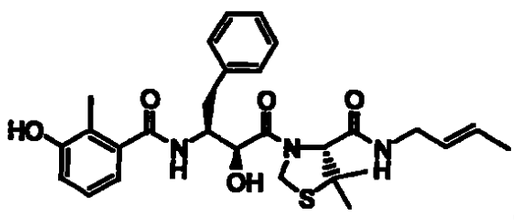

,

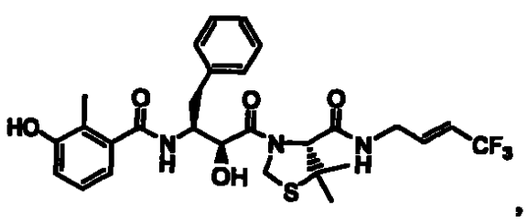

,

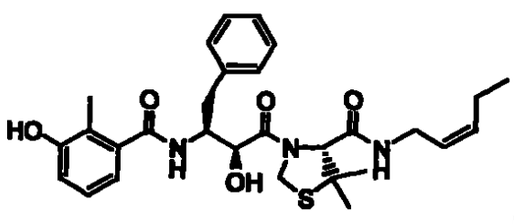

,

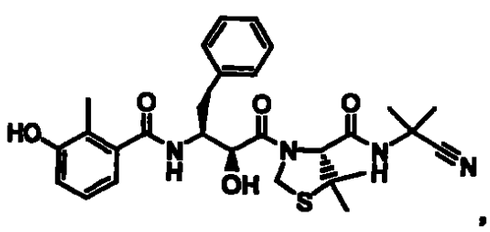

,

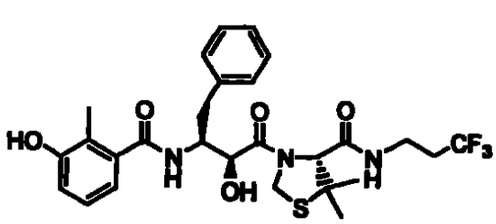

,

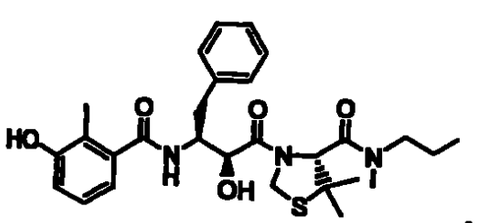

,

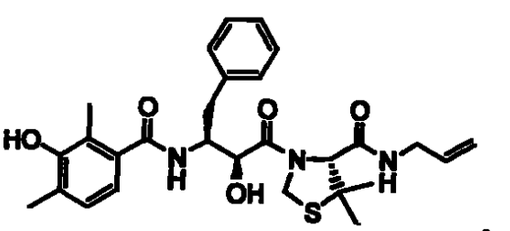

,

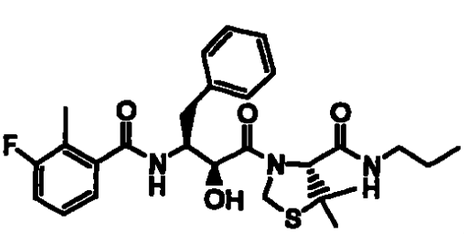

,

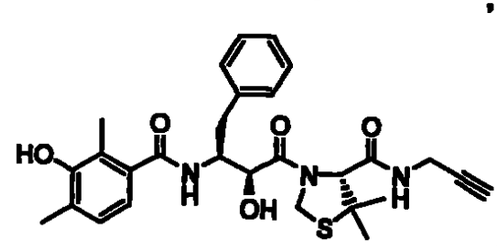

,


,


,

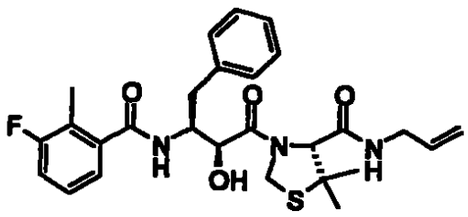

,

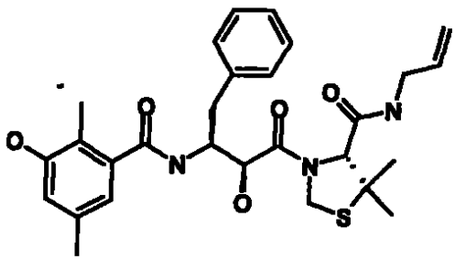

,

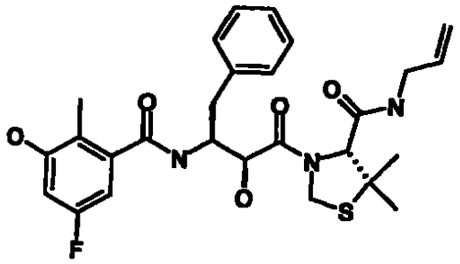

,

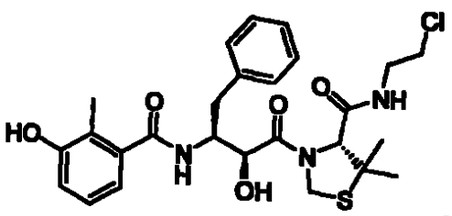

,

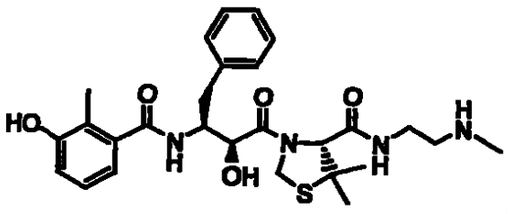

,

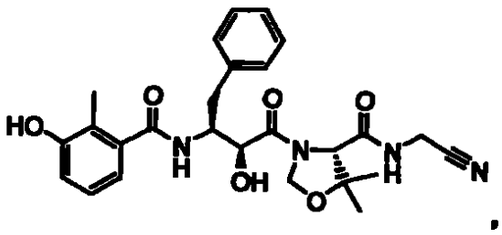


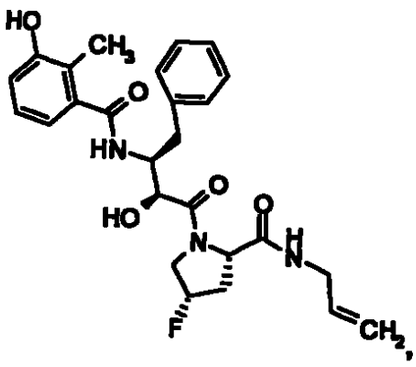


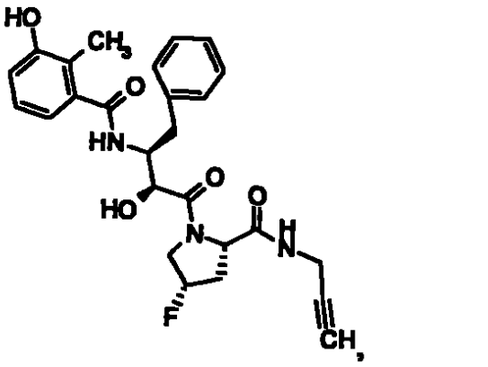


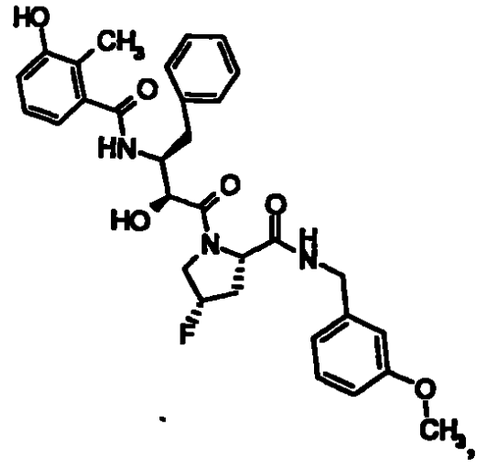


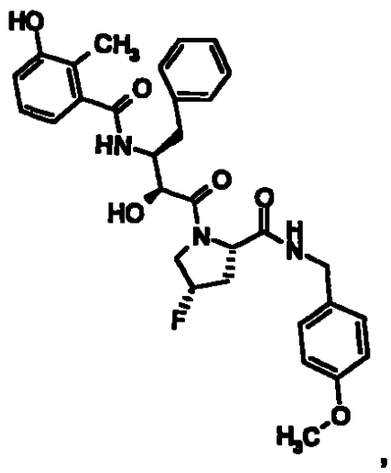


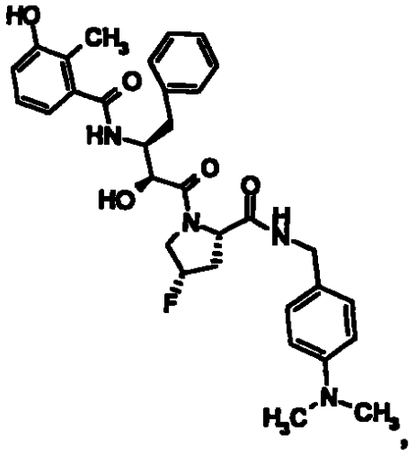


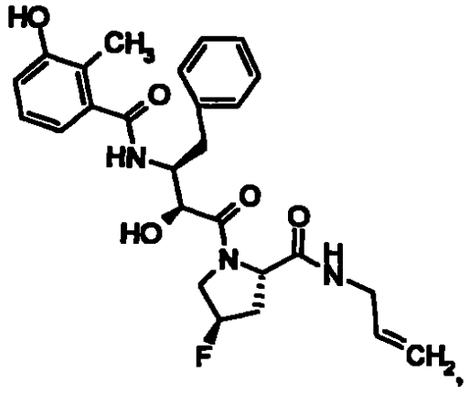


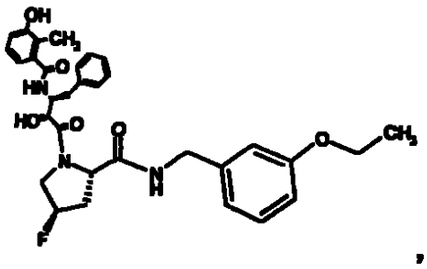


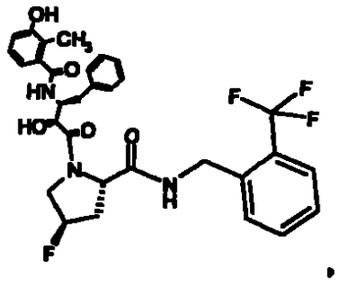


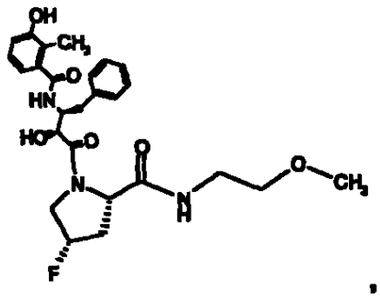


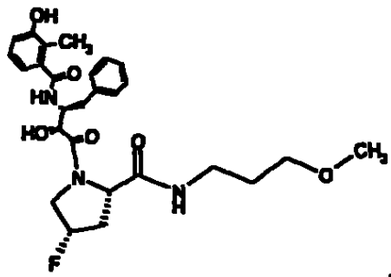


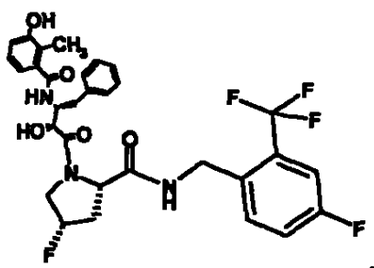


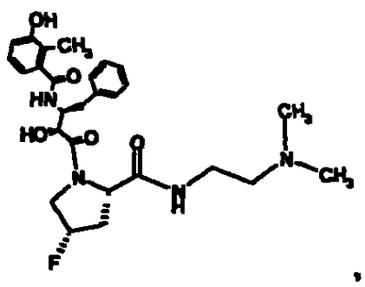


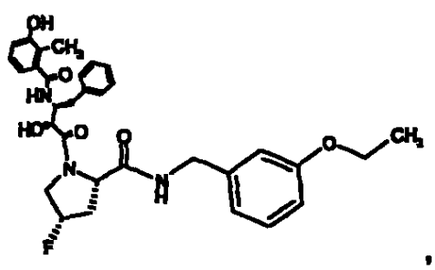


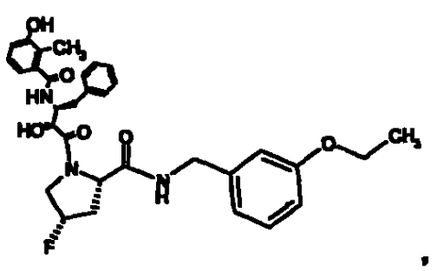

,

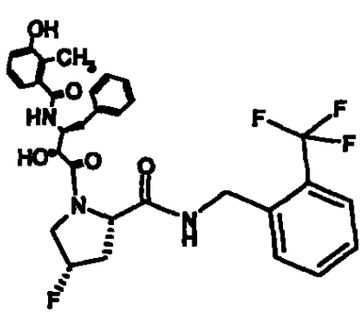

,


,


,


,


, and



and the prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts and solvates thereof.

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES (PCT)

**VERSIÓN CORREGIDA**

(19) rganización Mundial de Propiedad Intelectual
Oficina Internacional

(43) Fecha Internacional de Publicación
19 de diciembre de 2002 (19.12 2002)

(10) Número Internacional de Publicación

PTC WO 02/100845 A1

(51) Clasificación Internacional de Patentes[7] C07D 277/06 A61K 31/425, C07D 417/12, 403/12, 207/16, A61P 31/18

(21) No. Solicitud Internacional PCT/US02/18548

(22) Fecha de Presentación Internacional. 11 de junio de 2002 (11 06 2002)

(25) Idioma de Presentación Inglés

(26) Idioma de Publicación Inglés

(30) Datos relativos a la Prioridad
60/297,460 11 de junio de 2001 (11 06 2001) US
60/297,729 12 de junio de 2001 (12 06 2001) US

(71) Solicitante (*para todos los países destinatarios con excepción de US*) AGOURON PHARMACEUTICALS, INC [US/US], 10350 North Torrey Pines Road, La Jolla, CA 92037 (US)

(72) Inventores CANON-KOCH, Stacie, S , 5940 La Jolla Mesa Drive, La Jolla, CA 92137 (US) ALEXANDER, Therese, N , 6557 Thornwood Street, San Diego, CA 92111 (US) BARVIAN, Mark, 1225 Olivia Avenue, Ann Arbor, MI 48104 (US) BOLTON, Gary, 4800 Hillway Court, Ann Arbor, MI 48105 (US) BOYER, Fredrick, E , 482 Pleasant Ridge Drive, Canton Township, MI 48188 (US) BURKE, Benjamin, J , 5761 Campanile Way, San Diego, CA 92115 (US) HOLLER, Tod, 2381 Placid Way, Ann Arbor, MI 48105 (US) JEWELL, Tanya, M., 12604 Torrey Bluff Drive #400, San Diego, CA 92130 (US) PRASAD JOGYULA, Vara, 3129 Fawn Meadow Court, Ann Arbor, MI 48105 (US) KUCERA, David, J , 14099 Recuerdo Drive, Del Mar, CA 92014 (US) MACHAK, Jeff; 12980 Easton Court, Shelby Township, MI 48315 (US) MITCHELL, Lennert, J , 520 N Woodlawn Avenue, Chula Vista, CA 91910 (US) MURPHY, Sean, T , 7716 Dover Drive, Ypsilanti, MI 48197 (US) REICH, Siegfried, H , 311 Glenmont Drive, Solana Beach CA 92075 (US) SKALITZKY, Donald, J , 4269 Taos Drive, San Diego, CA 92117 (US) TAT-LOCK, John, H , 13153 Dressage Lane, San Diego, CA 92130 (US) VARNEY, Michael, D., 738 Barbara Avenue, Solana Beach, CA 92075 (US) VIRGIL, Scott, C , 3950 Mahalia Avenue, Apt S23, San Diego, CA 92122 (US) WORLAND, Stephen, T , 727 Hoaka Drive, Del Mar, CA 92014 (US) MELNICK, Michael, 3813 Weeburn Court, Ann Arbor, MI 48108 (US) LINTON Maria, A., 11320 Red Cedar Drive, San Diego, CA 92131 (US) WEBBER, Stephen, E , 3531 Milikan Avenue, San Diego, CA 92122 (US)

(74) Agentes MANDRA, Raymond, R et al , Fitzpatrick, Cella, Harper & Scinto, 30 Rockefeller Plaza, New York, NY 10112-3801 (US)

(81) Países destinatarios *(nacional)* AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW

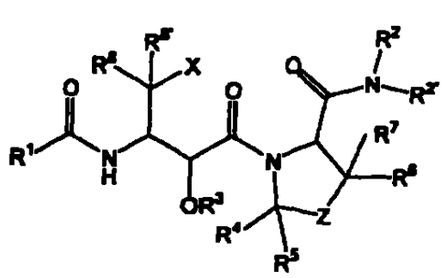
(84) Países destinatarios *(regional)* Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Publicado
- *Con informe internacional de búsqueda*

(48) Fecha de publicación de esta versión corregida
20 de marzo de 2003

*[Continúa en la siguiente página]*

(54) Título: INHIBIDORES DE PROTEASA VIH, COMPOSICIONES QUE CONTIENEN LOS MISMOS, SUS USOS FARMACÉUTICOS Y MATERIALES PARA SU SÍNTESIS



(57) Extracto Se divulgan compuestos de Fórmula (I), donde las variables de la fórmula son como se definen aquí, que inhiben o bloquean ventajosamente la actividad biológica de la proteasa VIH Estos compuestos, así como composiciones farmacéuticas que contienen estos compuestos, son útiles para tratar pacientes o anfitriones infectados con el virus VIH También se describen intermedios y métodos sintéticos para preparar tales compuestos

WO 02/100845 A1

(15) Información relacionada con la Corrección
Véase Gaceta PCT No 12/2003 del 20 de marzo de 2003, sección II

*Para códigos de dos letras y otras abreviaturas, remítase a la "Notas Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada edición regular del Boletín Oficial PCT*

# INHIBIDORES DE PROTEASA VIH, COMPOSICIONES QUE CONTIENEN LOS MISMOS, SUS USOS FARMACÉUTICOS Y MATERIALES PARA SU SÍNTESIS

## ANTECEDENTES DE LA INVENCIÓN

### Campo de la Invención

Esta invención se refiere a compuestos novedosos útiles como inhibidores de proteasa VIH y al uso de tales compuestos como agentes antivirales para tratamiento de individuos infectados con VIH Esta invención se relaciona igualmente con métodos de preparación de estos compuestos y a intermedios que son útiles en la preparación de los mismos.

### Arte Previo Relacionado

El Síndrome de la Inmunodeficiencia Adquirida (SIDA) causa una falla gradual del sistema inmunitario del cuerpo así como un deterioro progresivo de los sistemas nerviosos central y periférico. Puesto que su reconocimiento inicial a comienzos de la década de los 80, el SIDA se ha difundido rápidamente y ha alcanzado ahora proporciones epidémicas en un segmente relativamente limitado de la población. Una investigación intensiva ha llevado al descubrimiento del agente responsable, el retrovirus III T-linfotrópico humano (HTLV-III), ahora más comúnmente designado como el virus de la inmunodeficiencia humana o VIH.

El VIH es un miembro de la clase de virus conocida como retrovirus. El genoma retroviral se compone de ARN que se convierte a ADN por transcripción reversa. Este ADN retroviral se integra entonces en forma estable en el cromosoma de una célula anfitriona y, empleando el proceso replicativo de las células anfitrionas, produce partículas retrovirales nuevas y desarrolla la infección a otras células. El VIH parece poseer una afinidad particular para la célula de linfocito T-4 humano que juega un papel vital en el sistema inmunitario del cuerpo. La infección VIH de estos glóbulos blancos agota esta población de leucocitos. Eventualmente, el sistema inmunitario se hace inoperante e ineficaz contra varias enfermedades

oportunistas tales como, entre otras, neumonía por Pneumocystis carinii, sarcoma de Kaposi, y cáncer del sistema linfático

Aunque el mecanismo exacto de la formación y funcionamiento del virus VIH no ha sido entendido, la identificación del virus ha llevado a algún avance en controlar la enfermedad Por ejemplo, se ha descubierto que el fármaco azidotimidina (AZT) es efectivo para inhibir la transcripción reversa del genoma retroviral del virus VIH, proporcionando así una medida de control, si bien no una cura, para pacientes afligidos con SIDA La búsqueda continúa para encontrar fármacos que puedan curar o, por lo menos, facilitar una medida mejorada de control del mortal virus VIH.

La replicación retroviral caracteriza rutinariamente el procesamiento post-translacional de poliproteínas El procesamiento se lleva a cabo mediante la enzima proteasa VIH viralmente codificada. Esto proporciona polipéptidos maduros que subsiguientemente ayudarán en la formación y función de virus infecciosos. Si este proceso molecular se reprime, entonces se termina la producción normal de VIH Por lo tanto, los inhibidores de proteasa VIH pueden funcionar como agentes virales anti-VIH.

La proteasa VIH es uno de los productos transcritos del gen pol de la proteína estructural VIH Esta proteasa retroviral específicamente divide otros polipéptidos estructurales en sitios discretos para liberar estas proteínas y enzimas estructurales recién activadas, haciendo así el virión competente para replicación. Como tal, la inhibición de la proteasa VIH por compuestos potentes puede prevenir la integración proviral de linfocitos T infectados durante la fase temprana del ciclo de vida del VIH-1, así como inhibir el procesamiento proteolítico viral durante su fase tardía Adicionalmente, los inhibidores de proteasa pueden tener las ventajas de ser más fácilmente disponibles, subsistir más prolongadamente en el virus, y ser menos tóxicos que los fármacos actualmente a disposición, posiblemente debido a su especificidad para la proteasa retroviral

Inhibidores relacionados de proteasas VIH se han descrito, por ejemplo, en Patente de los Estados Unidos No 5.962.640 Patente de los

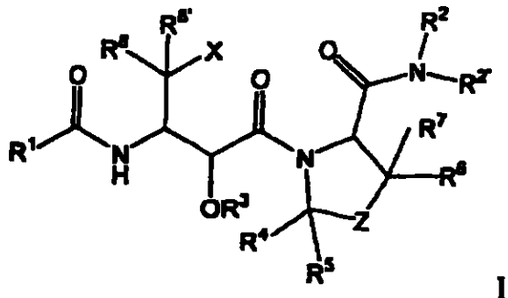
93

Estados Unidos No. 5,932 550 Patente Australiana No 705193, Solicitud de Patente Canadiense No. 2,179,935, Solicitud de Patente Europea No. 0 751 145, y Solicitud de Patente Japonesa No 100867489 Otros inhibidores relacionados de proteasa VIH se han descrito en K. Yoshimura, y colegas, *Proct Natl Acad Sci USA*, 96, 8675-8680 (1999) y T Mimoto, y colegas, *J Med Chem*, 42, 1789-1802 (1999).

El tratamiento continuo de individuos infectados con VIH con compuestos que inhiben la proteasa VIH ha llevado al desarrollo de virus mutantes que poseen proteasas resistentes al efecto inhibidor de estos compuestos Por lo tanto, para ser eficaces, los nuevos inhibidores de proteasa VIH tienen que ser efectivos no sólo contra cepas tipo-silvestre de VIH, sino que tienen además que demostrar eficacia contra las cepas mutantes recientemente emergentes que son resistentes a los inhibidores de proteasa disponibles en el comercio En consecuencia, subsiste la necesidad de nuevos inhibidores que tomen como blanco de acción la proteasa VIH tanto en cepas tipo-silvestre como mutantes de VIH.

## SUMARIO DE LA INVENCIÓN

Esta invención se relaciona con compuestos útiles para inhibir la actividad de proteasa VIH de Fórmula I.



I

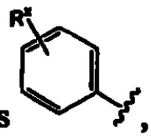
en donde:

$R^1$ es un grupo carbocíclico o heterocíclico mono-cíclico de 5 o 6 miembros, en donde dicho grupo carbocíclico o heterocíclico es saturado,

parcialmente insaturado o completamente insaturado y es no sustituido o sustituido por uno o más sustituyentes apropiados,

$R^2$ es un grupo alquilo sustituido, un grupo alquenilo sustituido o no sustituido, un grupo alquinilo sustituido o no sustituido, un grupo fenilo sustituido, un grupo fenilalquilo sustituido, un grupo fenilalquenilo sustituido o no sustituido o un grupo fenilalquinilo sustituido o no sustituido,

$R^{2'}$ es H o un grupo $C_1$-$C_4$ alquilo sustituido o no sustituido;

X es  , en donde $R^x$ es H o uno o más sustituyentes apropiados,

Z es S, O, SO, $SO_2$, $CH_2$ o CFH;

$R^3$ es H o un grupo $C_1$-$C_4$ alquilo sustituido o no sustituido,

$R^4$, $R^5$, $R^6$ y $R^7$ se seleccionan independientemente de H o un grupo $C_1$-$C_6$ alquilo, y

$R^8$ y $R^{8'}$ se seleccionan independientemente de H, halo, un grupo $C_1$-$C_4$ alifático o un grupo alifático $C_1$-$C_4$ halo-sustituido,

donde cualquiera de dichos grupos alquilo, alquenilo o alquinilo sustituido se sustituyen por uno o más sustituyentes apropiados

con la condición que dicho grupo heterocicloalquilo, heterocicloalquenilo o heteroarilo mono-cíclico de 5- ó 6-miembros contenga por lo menos dos heteroátomos cuando $R^2$ es un grupo fenilo sustituido, un grupo fenilalquilo sustituido, un grupo fenilalquenilo sustituido o no sustituido o un grupo fenilalquinilo sustituido o no sustituido, o

con la condición que dicha fracción alquilo, alquenilo o alquinilo de dicho grupo fenilalquilo, fenilalquenilo o fenilalquinilo sustituido se sustituya por uno o más sustituyentes seleccionados de halo o aceto; o

con la condición que dicho grupo fenilo sustituido o fracción fenilo de dicho grupo fenilalquilo, fenilalquenilo o fenilalquinilo sustituido se sustituya por uno o más sustituyentes apropiados distintos de halo o metilo

La presente invención se relaciona con compuestos de Fórmula I más adelante, y profármacos, metabolitos farmacéuticamente activos, y sales farmacéuticamente aceptables y solvatos de los mismos que inhiben la proteasa codificada por el virus de la inmunodeficiencia humana (VIH) tipo 1 (VIH-1) o tipo 2 (VIH-2), así como cepas mutantes del mismo. Estos compuestos son útiles en el tratamiento de infección por VIH y el tratamiento del síndrome de la inmunodeficiencia adquirida (SIDA) Los compuestos, sus sales farmacéuticamente aceptables, y las composiciones farmacéuticas de la presente invención pueden usarse solas o en combinación con otros antivirales, inmunomoduladores, antibióticos o vacunas. Los compuestos de la presente invención pueden convertirse igualmente en profármacos, por derivación, de acuerdo con técnicas convencionales. Se divulgan métodos de tratar SIDA, métodos de tratar la infección VIH y métodos de inhibir la proteasa VIH

## DESCRIPCIÓN DETALLADA DE LA INVENCIÓN E INCORPORACIONES PREFERIDAS

De acuerdo con una convención usada en el arte,  se emplea en fórmulas estructurales aquí para describir el enlace que es el punto de unión de la fracción o sustituyente al núcleo o estructura medular.

Tal como se emplea aquí, el término "alifático" representa un hidrocarburo de cadena recta o ramificada, saturado o insaturado, que contiene 1 a 10 átomos de carbono que pueden no sustituirse o sustituirse por uno o más de los sustituyentes descritos a continuación. El término "alifático" pretende abarcar grupos alquilo, alquenilo y alquinilo.

Tal como se emplea aquí, el término "alquilo" representa un hidrocarburo saturado o insaturado de cadena recta o ramificada, que contiene 1 a 10 átomos de carbono que pueden no sustituirse o sustituirse por uno o más de los sustituyentes descritos más adelante. Sustituyentes ejemplares alquilo incluyen, pero no se limitan a metilo (Me), etilo (Et),

propilo, isopropilo, butilo, isobutilo, t-butilo, y similares. El término " alquilo inferior" se refiere a un grupo alquilo que contiene de 1 a 6 átomos de carbono.

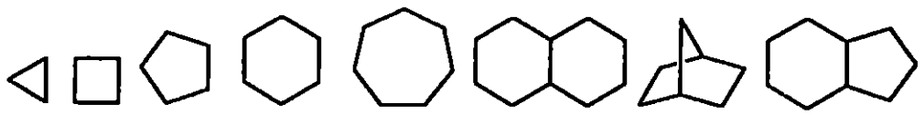
El término "alquenilo" representa un hidrocarburo de cadena recta o ramificada, que contiene uno o más enlaces dobles carbono-carbono y que tiene 2 a 10 átomos de carbono que pueden no sustituirse o sustituirse por uno o más de los sustituyentes Sustituyentes ejemplares alquenilo incluyen, pero no se limitan a etenilo, propenilo, butenilo, alilo, pentenilo y similares.

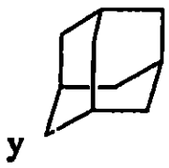
El término "alquinilo" representa un hidrocarburo de cadena recta o ramificada, que contiene uno o más enlaces triples carbono-carbono y que tiene 2 a 10 átomos de carbono que pueden no sustituirse o sustituirse por uno o más de los sustituyentes descritos más adelante. Una fracción alquinilo puede contener igualmente uno o más enlaces dobles carbono-carbono. Sustituyentes ejemplares alquinilo incluyen, pero no se limitan a etinilo, butinilo, propinilo (propargilo) isopropinilo, pentinilo, hexinilo y similares.

El término "carbocíclico" representa un grupo hidrocarburo cíclico saturado, parcialmente saturado, o completamente insaturado (aromático) que contiene de 3 a 14 átomos de carbono que pueden no sustituirse o sustituirse por uno o más de los sustituyentes descritos aquí más adelante. El término "carbocíclico" pretende abarcar grupos hidrocarburo mono-, bi- y tri-cíclicos saturados, parcialmente saturados, o completamente insaturados; por ejemplo, grupos cicloalquilo, cicloalquenilo y arilo. El término "carbocíclico" pretende abarcar además grupos hidrocarburo bi- y tri-cíclico que contienen cualquier combinación de fracciones de anillo que son saturadas, parcialmente saturadas, o completamente insaturadas (aromáticas) Carbociclos parcialmente saturados incluyen, por ejemplo, dihidroarenos (por ejemplo, indanilo) o tetra-hidro-arenos (por ejemplo, tetrahidronaftaleno), en donde pueden ocurrir uno cualquiera o más puntos de saturación en cualquier fracción del anillo del carbociclo Además, se entiende que el enlace entre cualquier grupo carbocíclico bi- o tri-cíclico y

cualquier otro sustituyente o grupo variable puede hacerse en cualquier posición apropiada del carbociclo. El término grupo "alifático-carbocíclico" pretende abarcar grupos alifáticos que tienen un sustituyente carbocíclico (por ejemplo, fenilmetil- (bencil), feniletil-, ciclopropilmetil-, etc ), en donde la fracción carbocíclica y la fracción alifática de los mismos puede sustituirse independientemente por uno o más sustituyentes adecuados.

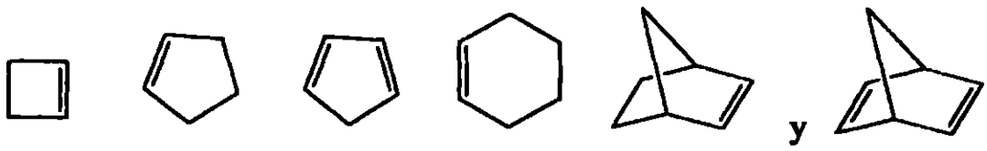
"Cicloalquilo" representa un grupo que comprende un hidrocarburo no-aromático monocíclico, bicíclico, o tricíclico que contiene de 3 a 14 átomos de carbono que pueden no sustituirse o sustituirse por uno o más de los sustituyentes descritos más adelante Cicloalquilos ejemplares incluyen anillos monocíclicos que tienen de 3-8 átomos de carbono, tales como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y similares Ejemplos ilustrativos de grupos cicloalquilo incluyen los siguientes



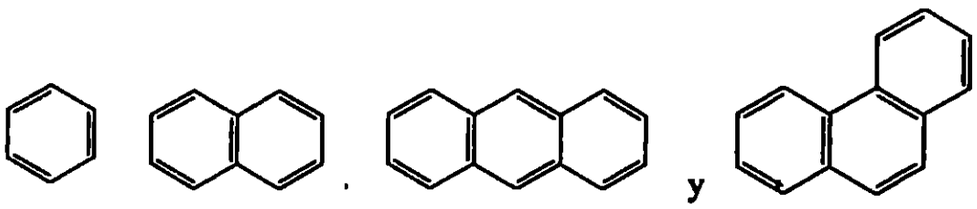


y

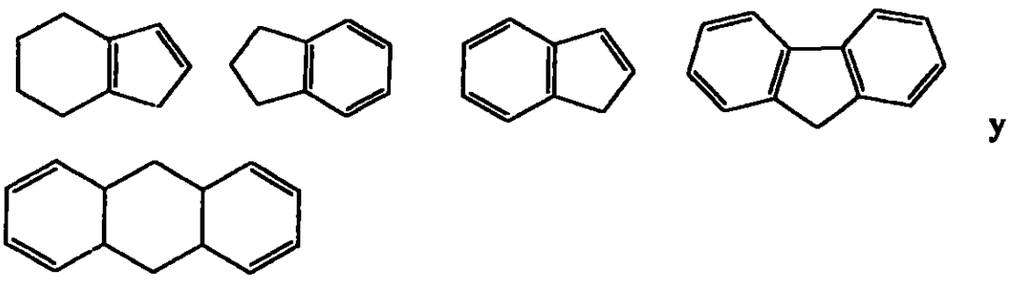
"Cicloalquenilo" representa un grupo que comprende un hidrocarburo no-aromático monocíclico, bicíclico, o tricíclico que contiene de 4 a 14 átomos de carbono los cuales pueden no sustituirse o sustituirse por uno o más de los sustituyentes descritos más adelante y contiene por lo menos un doble enlace carbono-carbono. Cicloalquenilos ejemplares monocíclicos incluyen grupos que tienen de 4-8, preferiblemente 5-6, átomos de carbono, tales como ciclopentenilo, ciclopentadienilo, ciclohexenilo, cicloheptenilo y similares Ejemplos ilustrativos de grupos cicloalquenilo incluyen los siguientes:



"Arilo" representa un grupo que comprende un radical aromático, monovalente monocíclico, bicíclico, o tricíclico que contiene de 6 a 18 átomos de anillo de carbono, que pueden no sustituirse o sustituirse por uno o más de los sustituyentes descritos más adelante. Ejemplos ilustrativos de grupos arilo incluyen los siguientes·

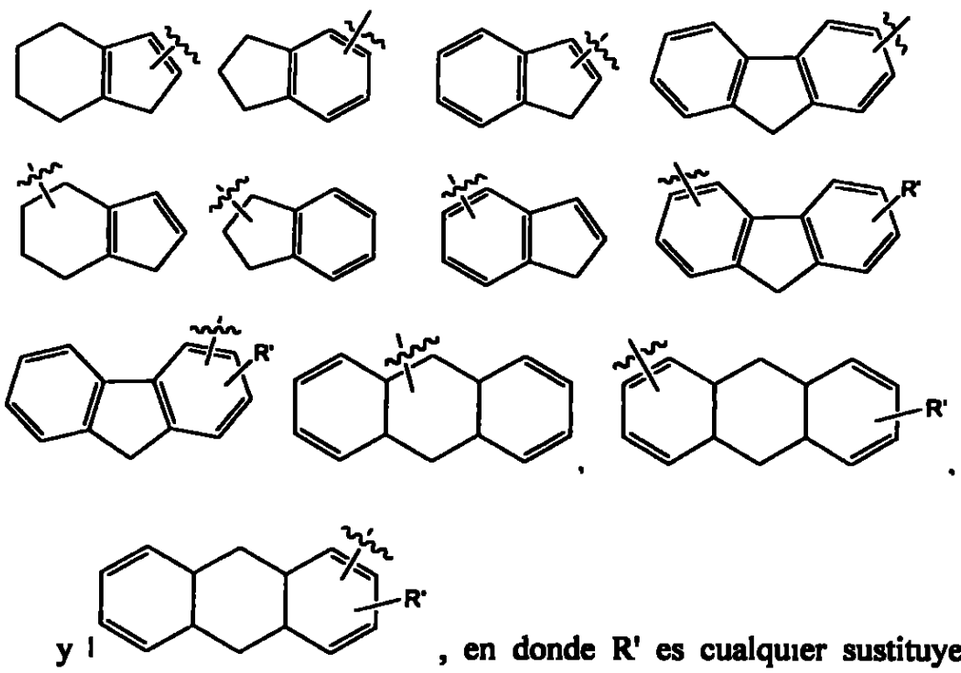


El término "carbocíclico" pretende igualmente abarcar grupos mixtos cicloalquilo/cicloalquenilo/arilo bi- y tri-cíclicos, que pueden no sustituirse o sustituirse por uno o más de los sustituyentes descritos más adelante Ejemplos ilustrativos de tales grupos mixtos bi- y tri-cíclicos incluyen los siguientes·



Se entiende que el enlace o sustitución de cualquier grupo carbocíclico o heterocíclico bi-cíclico o tri-cíclico descrito aquí puede estar en cualquier posición apropiada de cualquier anillo

Ejemplos ilustrativos de tal enlace en grupos carbocíclicos mixtos bi- y tri-cíclicos incluyen los siguientes:



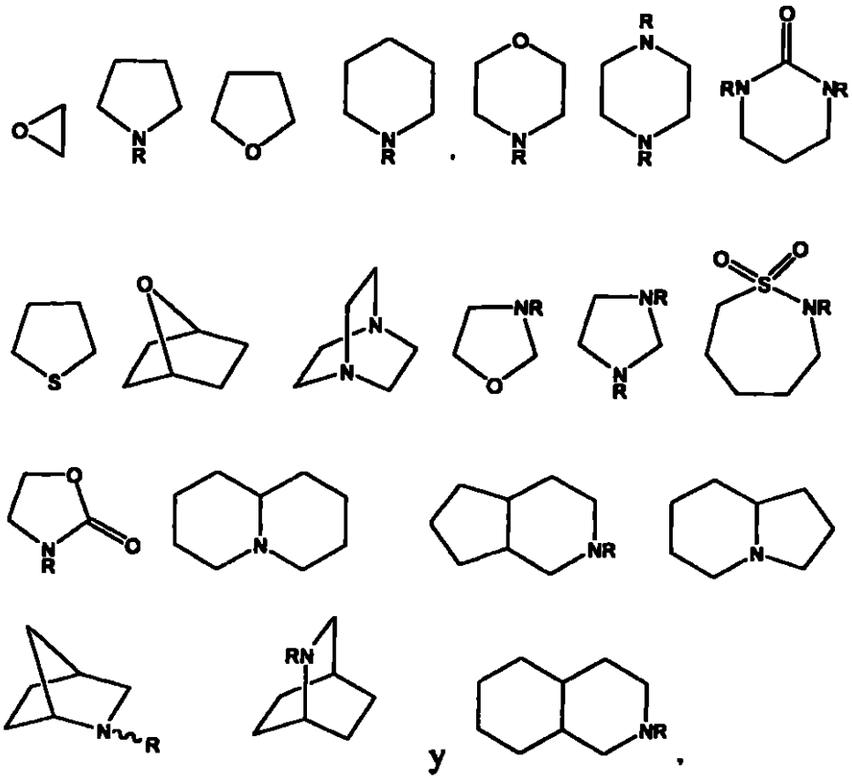

y 

, en donde R' es cualquier sustituyente adecuado.

El término "heterocíclico" representa un grupo cíclico saturado, parcialmente saturado, o completamente insaturado (aromático) que contiene de 3 a 18 átomos de anillo, el cual incluye 1 a 5 heteroátomos seleccionados de nitrógeno, oxígeno y azufre, y que puede no sustituirse o sustituirse por uno o más de los sustituyentes descritos aquí más adelante El término "heterocíclico" pretende abarcar grupos cíclicos con heteroátomos mono-, bi- y tri-cíclicos saturados, parcialmente saturados, o completamente insaturados; por ejemplo, grupos heterocicloalquilo, heterocicloalquenilo y heteroarilo. El término "heterocíclico" pretende igualmente abarcar grupos bi- y tri-cíclicos que contienen cualquier combinación de fracciones de anillo que son saturadas, parcialmente saturadas, o completamente insaturadas (aromáticas). Heterociclos parcialmente saturados incluyen, por ejemplo, dihidroheteroarenos (por ejemplo, dihidroindol) o tetrahidro-heteroarenos (por ejemplo, tetrahidroquinolina), en donde uno cualquiera o más puntos de saturación pueden ocurrir en cualquier fracción del anillo del heterociclo. Además, se entiende que el enlace entre cualquier grupo heterocíclico bi- o tri-cíclico y cualquier otro sustituyente o grupo variable puede hacerse en cualquier posición apropiada del heterociclo (es decir, no hay la restricción de que un

sustituyente o grupo variable tenga que enlazarse a la fracción que contiene el heteroátomo de un grupo heterocíclico bi- o tri-cíclico). El término grupo "alifático-heterocíclico" pretende abarcar grupos alifáticos que tienen un sustituyente heterocíclico (por ejemplo, piridilmetil-, tiazolilmetil-, tetrahidrofuranilmetil-, etc.) en donde la fracción heterocíclica y la fracción alifática del mismo puede sustituirse independientemente por uno o más sustituyentes apropiados.

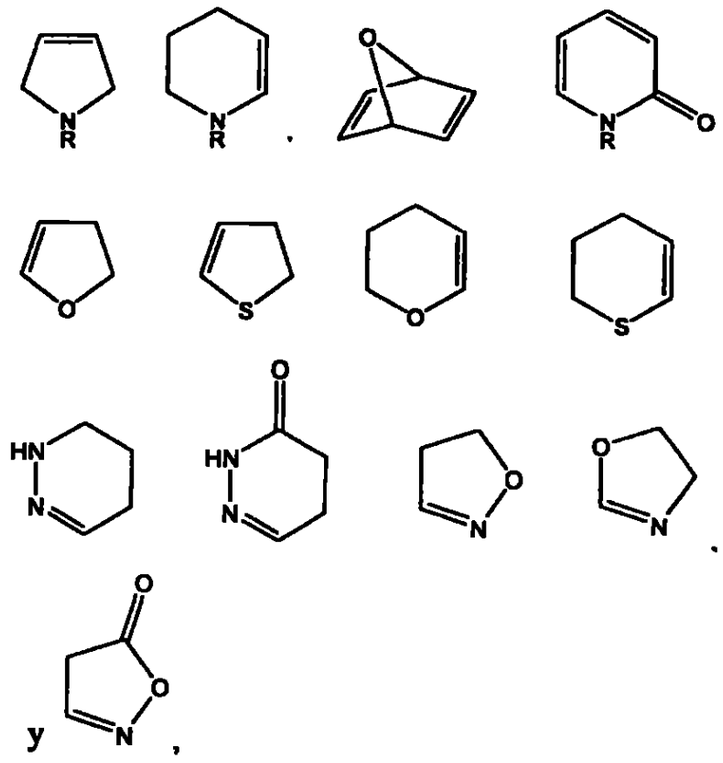
"Heterocicloalquilo" representa un grupo que comprende un radical monocíclico, bicíclico, o tricíclico monovalente saturado, que contiene 3 a 18 átomos de anillo, el cual incluye 1 a 5 heteroátomos seleccionados de nitrógeno, oxígeno y azufre, y que pueden no sustituirse o sustituirse por uno o más de los sustituyentes descritos más adelante. Ejemplos ilustrativos de grupos heterocicloalquilo incluyen, pero no se limitan a, azetidinilo, pirrolidilo, piperidilo, piperazinilo, morfolinilo, tetrahidro-2H-1,4-tiazinilo, tetrahidrofurilo, tetrahidropiranilo, 1,3-dioxolanilo, 1,3-dioxanilo, 1,4-dioxanilo, 1,3-oxatiolanilo, 1,3-oxatianilo, 1,3-ditianilo, azabicilo[3.2.1]octilo, azabicilo[3.3.1]nonilo, azabicilo[4.3.0]nonilo, oxabicilo [2.2.1] heptilo, 1,5,9-triazaciclododecilo, y similares. Ejemplos ilustrativos de grupos heterocicloalquilo incluyen los siguientes:



y

en donde R es H, alquilo, hidroxilo o representa un compuesto de acuerdo con Fórmula I, y el enlace descrito como " ", representa enlazamiento a cualquiera de las dos cara de la fracción bi-cíclica (es decir, endo o exo).

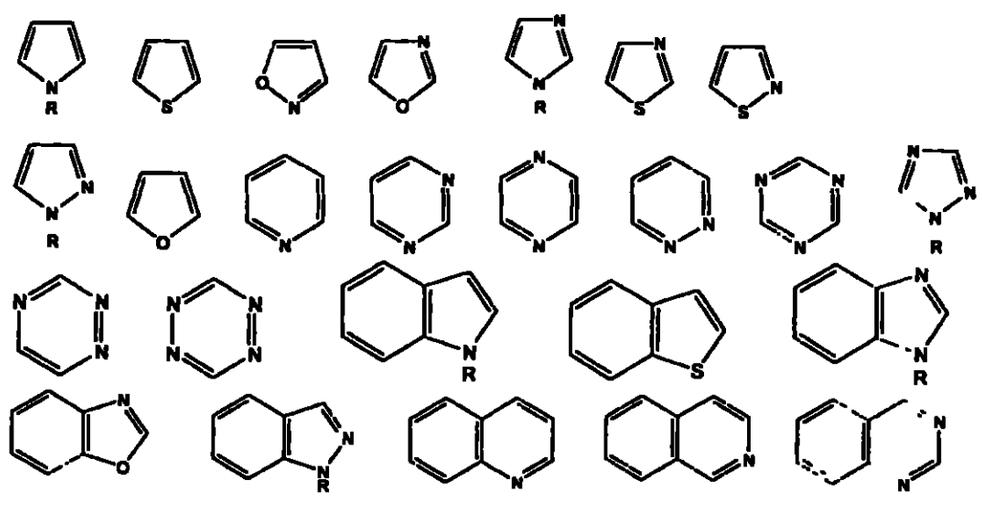
El término "heterocicloalquenilo" se utiliza aquí para representar un radical monocíclico, bicíclico, o tricíclico monovalente, no-aromático que contiene 4 a 18 átomos de anillo, el cual puede incluir de 1 a 5 heteroátomos seleccionados de nitrógeno, oxígeno y azufre, y que pueden no sustituirse o sustituirse por uno o más de los sustituyentes descritos más adelante y que contiene por lo menos un doble enlace de heteroátomo carbono-carbono o heteroátomo-carbono Heterocicloalquenilos ejemplares monocíclicos incluye grupos que tienen de 4-8, preferiblemente 5-6, átomos de anillo. Ejemplos ilustrativos de grupos heterocicloalquenilo incluyen, pero no se limitan a, dihidrofurilo, dihidropiranilo, isoxazolinilo, dihidropiridilo, tetrahidropirídilo, y similares. Ejemplos ilustrativos de grupos heterocicloalquenilo incluyen los siguientes

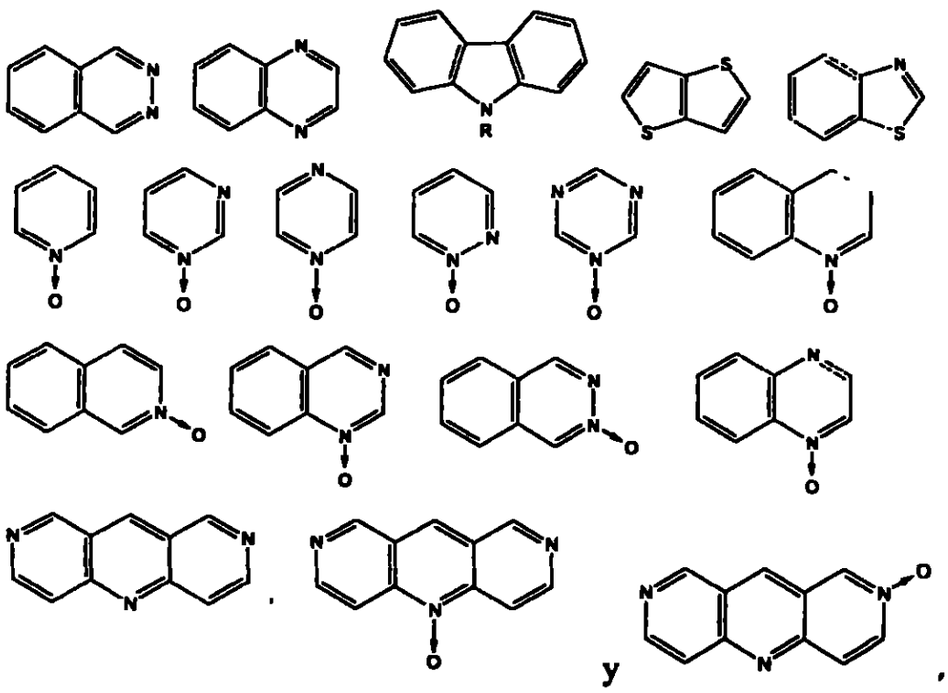



y ,

en donde R es H, alquilo, hidroxilo o representa un compuesto de acuerdo con Fórmula I.

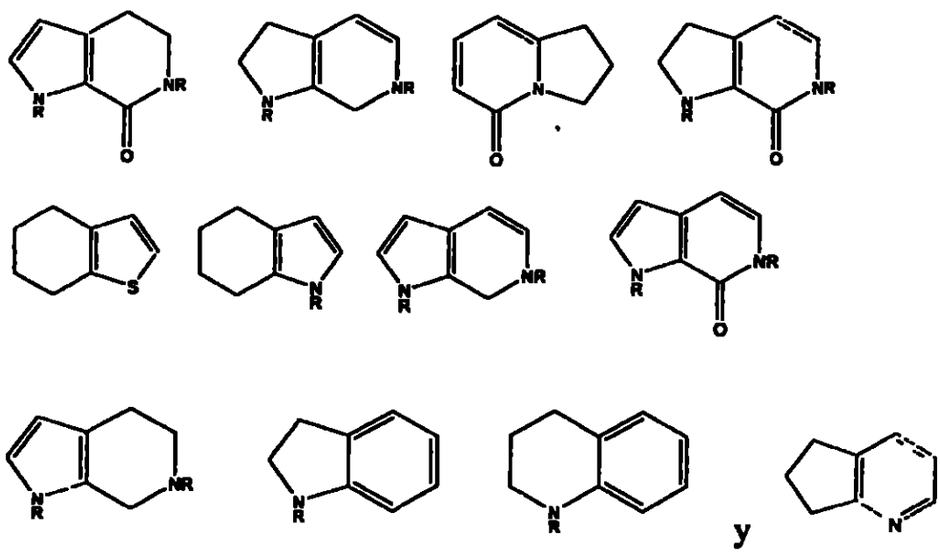
"Heteroarilo" representa un grupo que comprende un radical monocíclico, bicíclico, o tricíclico monovalente, aromático, que contiene 5 a 18 átomos de anillo, incluyendo 1 a 5 heteroátomos seleccionados de nitrógeno, oxígeno y azufre, que pueden no sustituirse o sustituirse por uno o más de los sustituyentes descritos más adelante. Tal como se emplea aquí, el término "heteroarilo" pretende abarcar además el derivado N-óxido (o derivados N-óxido, si el grupo heteroarilo contiene más de un nitrógeno de tal modo que pueda formarse más de un derivado N-óxido) de los grupos heteroarilo que contienen nitrógeno descritos aquí Ejemplos ilustrativos de grupos heteroarilo incluyen, pero no se limitan a, tienilo, pirrolilo, imidazolilo, pirazolilo, furilo, isotiazolilo, furazanilo, isoxazolilo, tiazolilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, triazinilo, benzo[b]tienilo, nafto[2,3-b]tiantrenilo, isobenzofuranilo, cromenilo, xantenilo, fenoxatienilo, indolizinilo, isoindolilo, indolilo, indazolilo, purinilo, isoquinolilo, quinolilo, ftalazinilo, naftiridinilo, quinoxalinilo, quinzolinilo, benzotiazolilo, benzimidazolilo, tetrahidroquinolinilo, cinnolinilo, pteridinilo, carbazolilo, beta-carbolinilo, fenantridinilo, acridinilo, perimidinilo, fenantrolinilo, fenazinilo, isotiazolilo, fenotiazinilo, y fenoxazinilo. Ejemplos ilustrativos de derivados N-óxido de grupos heteroarilo incluyen, pero no se limitan a, piridil N-óxido, pirazinil N-óxido, pirimidinil N-óxido, piridazinil N-óxido, triazinil N-óxido, isoquinolil N-óxido, y quinolil N-óxido Otros ejemplos de grupos heteroarilo incluyen las siguientes fracciones



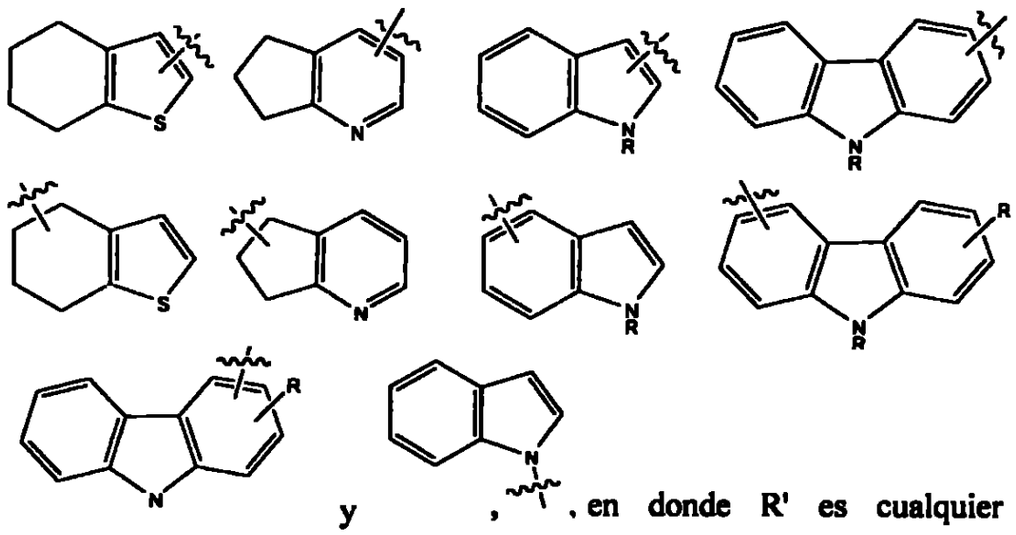


en donde R es H, alquilo, hidroxilo o representa un compuesto de acuerdo con Fórmula I.

El término "heterocíclico" pretende abarcar igualmente grupo heterocicloalquilo/heterocicloalquenilo/heteroarilo mixtos bi- y tri-cíclicos, que pueden no sustituirse o sustituirse por uno o más de los sustituyentes descritos más adelante. Ejemplos ilustrativos de tales grupos heterocíclico mixtos bi- y tri-cíclicos incluyen los siguientes.



Ejemplos ilustrativos de tal enlace en grupos heterocíclico mixtos bi- y tri-cíclico incluyen los siguientes



y , en donde R' es cualquier sustituyente adecuado.

En los compuestos de esta invención, los grupos alquilo, alquenilo y alquinilo pueden sustituirse opcionalmente por uno o más sustituyentes apropiados independientemente seleccionados de grupos fenilo, nitro, amino, ciano, halógeno, hidroxilo, alcoxi, haloalcoxi, ariloxi, cicloalquiloxi, cicloalquilalquiloxi, cicloalquenıloxı, cicloalquenılalquiloxı, heterocicloalcoxı, heterocicloalquilalquiloxi, heterocicloalquenıloxi, heterocicloalquenilalquiloxı, heteroarıloxi, alquilcarbonilo, alquenılcarbonılo, alquinilcarbonılo, alquiloxıcarbonilo, alquenıloxıcarbonilo, alquınıloxicarbonılo, alquılcarboniloxi, alquenılcarboniloxı, alquınilcarbonıloxı, arılcarbonilo, arılcarboniloxı, ariloxıcarbonılo, cıcloalquilcarbonılo, cicloalquilcarboniloxı, cıcloalquioxıcarbonilo, heteroarılcarbonilo, heteroarılcarboniloxi, heteroariloxicarbonılo, heterocicloalquilcarbonılo, heterocıcloalquilcarboniloxi, heterocicloalquıoxicarbonilo, carboxilo, carbamoilo, formılo, aceto (oxo), tıoaceto, sulfo, alquilamıno, alquenilamino, alquınılamino, cicloalquılamino, cicloalquenilamino, arilamıno, heterocıcloalquilamıno, heterocıcloalquenilamino, heteroarilamıno, dialquilamino, alquilamınocarbonilo, alquenilamınocarbonılo, alquinilaminocarbonilo, cıcloalquilaminocarbonilo, cıcloalquenilamıno, arilaminocarbonilo,

heterocicloalquilaminocarbonilo, heterocicloalquenilcarbonilo, heteroarilaminocarbonilo, dialquilaminocarbonilo, alquilaminotiocarbonilo, cicloalquilaminotiocarbonilo, arilaminotiocarbonilo, heterocicloalquilaminotiocarbonilo, heteroarilaminotiocarbonilo, dialquilaminotiocarbonilo, alquilsulfonilo, arilsulfonilo, alquilsulfenilo, arilsulfenilo, alquilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, heterocicloalquilcarbonilamino, heteroarilcarbonilamino, alquiltiocarbonilamino, cicloalquiltiocarbonilamino, ariltiocarbonilamino, heterocicloalquiltiocarbonilamino, heteroariltiocarbonilamino, alquilsulfoniloxi, arilsulfoniloxi, alquilsulfonilamino, arilsulfonilamino, mercapto, alquiltio, haloalquiltio, ariltio y heteroariltio, en donde cualquiera de las fracciones alquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, heteroarilo presentes en los anteriores sustituyentes pueden sustituirse adicionalmente. Las fracciones alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo, y heteroarilo de cualquiera de los anteriores sustituyentes puede sustituirse opcionalmente por uno o más grupos independientemente seleccionados de grupos alquilo (excepto para alquilo), haloalquilo, arilo, nitro, amino, alquilamino, dialquilamino, halógeno, hidroxilo, alcoxi, haloalcoxi, ariloxi, mercapto, alquiltio, haloalquiltio o ariltio.

En los compuestos de esta invención los grupos carboxílicos o heterocíclicos sustituidos pueden sustituirse opcionalmente por uno o más sustituyentes apropiados independientemente seleccionados de grupos alquilo, haloalquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, heteroarilo, nitro, amino, ciano, halógeno, hidroxilo, alcoxi, haloalcoxi, alqueniloxi, alquiniloxi, alquilenedioxi, ariloxi, cicloalquiloxi, cicloalquilalquiloxi, cicloalqueniloxi, cicloalquenilalquiloxi, heterocicloalcoxi, heterocicloalquilalquiloxi, heterocicloalqueniloxi, heterocicloalquenilalquiloxi, heteroariloxi, alquilcarbonilo, alquiloxicarbonilo, alquilcarboniloxi, arilcarbonilo, arilcarboniloxi, ariloxicarbonilo, cicloalquilcarbonilo,

cicloalquilcarboniloxi, cicloalquioxicarbonilo, heteroarilcarbonilo, heteroarilcarboniloxi, heteroariloxicarbonilo, heterocicloalquilcarbonilo, heterocicloalquilcarboniloxi, heterocicloalquioxicarbonilo, carboxilo, carbamoilo, formilo, aceto (oxo), tioaceto, sulfo, alquilamino, cicloalquilamino, arilamino, heterocicloalquilamino, heteroarilamino, dialquilamino, alquilaminocarbonilo, cicloalquilaminocarbonilo, arilaminocarbonilo, heterocicloalquilaminocarbonilo, heteroarilaminocarbonilo, dialquilaminocarbonilo, alquilaminotiocarbonilo, cicloalquilaminotiocarbonilo, arilaminotiocarbonilo, heterocicloalquilaminotiocarbonilo, heteroarilaminotiocarbonilo, dialquilaminotiocarbonilo, alquilsulfonilo, arilsulfonilo, alquilsulfenilo, arilsulfenilo, alquilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, heterocicloalquilcarbonilamino, heteroarilcarbonilamino, alquiltiocarbonilamino, cicloalquiltiocarbonilamino, ariltiocarbonilamino, heterocicloalquiltiocarbonilamino, heteroariltiocarbonilamino, alquilsulfoniloxi, arilsulfoniloxi, alquilsulfonilamino, arilsulfonilamino, mercapto, alquiltio, haloalquiltio, ariltio y heteroariltio, en donde cualquiera de las fracciones alquilo, alquileno, arilo, cicloalquilo, heterocicloalquilo, heteroarilo presentes en los anteriores sustituyentes pueden sustituirse aun más. "Sustituyentes apropiados" preferidos incluyen alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halógeno, hidroxilo, alcoxi, alquilenodioxi, ariloxi, cicloalcoxi, heteroariloxi, alquiltio, haloalquiltio y carboxilo. Las fracciones alquilo, alquileno, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo de cualquiera de los sustituyentes interiores puede sustituirse opcionalmente por uno o más grupos independientemente seleccionados de. grupos alquilo, haloalquilo, nitro, amino, alquilamino, dialquilamino, halógeno, hidroxilo, alcoxi, haloalcoxi, mercapto, alquiltio, haloalquiltio o ariltio

Por ejemplo, en los compuestos de esta invención, la fracción fenilo sustituida o fenilo de $R^2$ puede comprender por lo menos un sustituyente (distinto de halo o metilo) seleccionado de los grupos haloalquilo, hidroxialquilo, alcoxialquilo, cicloalcoxialquilo, alquilcarbonilalquilo,

haloalcoxialquilo, ariloxialquilo, alquiltioalquilo, haloalquiltioalquilo, ariltioalquilo, cianoalquilo, aminoalquilo, alquilaminoalquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, heteroarilo, nitro, amino, ciano, hidroxilo, alcoxi, haloalcoxi, alqueniloxi, alquiniloxi, alquilenodioxi, ariloxi, cicloalquiloxi, cicloalquilalquiloxi, cicloalqueniloxi, cicloalquenilalquiloxi, heterocicloalcoxi, heterocicloalquilalquiloxi, heterocicloalqueniloxi, heterocicloalquenilalquiloxi, heteroariloxi, alquilcarbonilo, alquiloxicarbonilo, alquilcarboniloxi, arilcarbonilo, arilcarboniloxi, ariloxicarbonilo, cicloalquilcarbonilo, cicloalquilcarboniloxi, cicloalquioxicarbonilo, heteroarilcarbonilo, heteroarilcarboniloxi, heteroariloxicarbonilo, heterocicloalquilcarbonilo, heterocicloalquilcarboniloxi, heterocicloalquioxicarbonilo, carboxilo, carbamoilo, formilo, aceto (oxo), tioaceto, sulfo, alquilamino, cicloalquilamino, arilamino, heterocicloalquilamino, heteroarilamino, dialquilamino, alquilaminocarbonilo, cicloalquilaminocarbonilo, arilaminocarbonilo, heterocicloalquilaminocarbonilo, heteroarilaminocarbonilo, dialquilaminocarbonilo, alquilaminotiocarbonilo, cicloalquilaminotiocarbonilo, arilaminotiocarbonilo, heterocicloalquilaminotiocarbonilo, heteroarilaminotiocarbonilo, dialquilaminotiocarbonilo, alquilsulfonilo, arilsulfonilo, alquilsulfenilo, arilsulfenilo, alquilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, heterocicloalquilcarbonilamino, heteroarilcarbonilamino, alquiltiocarbonilamino, cicloalquiltiocarbonilamino, ariltiocarbonilamino, heterocicloalquiltiocarbonilamino, heteroariltiocarbonilamino, alquilsulfoniloxi, arilsulfoniloxi, alquilsulfonilamino, arilsulfonilamino, mercapto, alquiltio, haloalquiltio, ariltio y heteroariltio, en donde cualquiera de las fracciones alquilo, alquileno, arilo, cicloalquilo, heterocicloalquilo, heteroarilo presentes en los sustituyentes anteriores puede sustituirse adicionalmente. "Sustituyentes apropiados" preferidos incluyen alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halógeno, hidroxilo, alcoxi, alquilenodioxi, ariloxi, cicloalcoxi,

heteroariloxi, alquiltio, haloalquiltio y carboxilo Las fracciones alquilo, alquileno, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo de cualquiera de los anteriores sustituyentes puede sustituirse opcionalmente por uno o más grupos independientemente seleccionados de grupos alquilo, haloalquilo, nitro, amino, alquilamino, dialquilamino, halógeno, hidroxilo, alcoxi, haloalcoxi, mercapto, alquiltio, haloalquiltio o ariltio.

Si los sustituyentes en sí mismos no son compatibles con los métodos sintéticos de esta invención, el sustituyente puede protegerse con un grupo protector adecuado que es estable a las condiciones de reacción usadas en estos métodos El grupo protector puede retirarse en un punto apropiado en la secuencia de reacción del método para proveer un intermedio deseado o compuesto objetivo. Grupos protectores adecuados y los métodos para proteger y desproteger diferentes sustituyentes usando tales grupos protectores adecuados son bien conocidos por los expertos en el arte; ejemplos de los cuales pueden hallarse en T Greene y P. Wuts, *Protecting Groups in Chemical Synthesis* (3ª ed ), John Wiley & Sons, NY (1999), que se incorpora aquí por referencia en su integridad. En algunos casos, un sustituyente puede seleccionarse específicamente para que sea reactivo bajo las condiciones de reacción usadas en los métodos de esta invención. Bajo estas circunstancias, las condiciones de reacción convierten el sustituyente seleccionado en otro sustituyente que es útil en un compuesto intermedio en los métodos de esta invención o es un sustituyente deseado en un compuesto objetivo.

En los *compuestos* de esta invención, $R^2$ y $R^{2'}$, independientemente o tomados juntos, pueden ser un grupo protector nitrógeno apropiado Como se indicó anteriormente, grupos protectores nitrógeno son bien conocidos en el arte y puede emplearse cualquier grupo protector nitrógeno que sea útil en los métodos de preparar los compuestos de esta invención o pueda ser útil en los compuestos inhibidores de proteasa VIH de esta invención Grupos protectores nitrógeno ejemplares incluyen grupos alquilo, alquilo sustituido, carbamato, urea, amida, imida, enamina, sulfenilo, sulfonilo, nitro, nitroso, óxido, fosfinilo, fosforilo, sililo, organometálico, ácido

109

borínico y ácido bórico. Ejemplos de cada uno de estos grupos, métodos para proteger fracciones nitrógeno usando estos grupos y métodos para remover estos grupos de fracciones nitrógeno se divulgan en T. Greene y P. Wuts, *supra* Preferiblemente, cuando $R^2$ y/o $R^{2'}$ son independientemente grupos protectores nitrógeno apropiados, sustituyentes $R^2$ y $R^{2'}$ adecuados incluyen, pero no se limitan a, grupos protectores carbamato tales como alquiloxicarbonilo (por ejemplo, Boc t-butiloxicarbonilo) y ariloxicarbonilo (por ejemplo, Cbz:benciloxicarbonilo, o FMOC· fluoreno-9-metiloxicarbonilo), alquiloxicarbonilos (por ejemplo, metiloxicarbonilo), alquilo o arilcarbonilo, alquilo sustituido, especialmente arilalquilo (por ejemplo, tritilo (trifenilmetilo), bencilo y bencilo sustituido), y similares Cuando $R^2$ y $R^{2'}$ tomados juntos son un grupo protector nitrógeno adecuado, sustituyentes $R^2$ / $R^{2'}$ apropiados incluyen ftalimido y un stabase (1,2-bis (dialquilsilil))etileno).

Los términos "halógeno" y "halo" representan sustituyentes cloro, fluoro, bromo o yodo. "Heterociclo" tiene por objeto significar un grupo heteroarilo o heterocicloalquilo "Acilo" tiene por objeto significar un radical -C(O)-R, en donde R es un grupo alquilo, cicloalquilo, arilo, heterocicloalquilo o heteroarilo sustituido o no sustituido "Aciloxi" tiene por objeto significar un radical -OC(O)-R, en donde R es un grupo alquilo, cicloalquilo, arilo, heterocicloalquilo o heteroarilo sustituido o no sustituido "Tioacilo" tiene por objeto significar un radical -C(S)-R, en donde R es un grupo alquilo alquilo, cicloalquilo, arilo, heterocicloalquilo o heteroarilo sustituido o no sustituido "Sulfonilo" tiene por objeto significar un bi-radical $-SO_2-$. "Sulfenilo" tiene por objeto significar un bi-radical -SO-. "Sulfo" tiene por objeto significar un radical $-SO_2H$. "Hidroxi" tiene por objeto significar el radical -OH "Amina" o "amino" tiene por objeto significar el radical $-NH_2$. "Alquilamino" tiene por objeto significar el radical $-NHR_a$, donde $R_a$ is un grupo alquilo. "Dialquilamino" tiene por objeto significar el radical $-NR_aR_b$, donde $R_a$ y $R_b$ son cada uno independientemente un grupo alquilo, y pretende incluir grupos heterocicloalquilos, en donde $R_a$ y $R_b$, tomados juntos, forman un anillo

heterocíclico que incluye la amina nitrogenada "Alcoxi" tiene por objeto significar el radical -$OR_a$, en donde $R_a$ es un grupo alquilo Grupos ejemplares alcoxi incluyen metoxi, etoxi, propoxi, y similares. Grupos "alcoxi inferior" poseen fracciones alquilo que tienen de 1 a 4 carbonos. "Alcoxicarbonilo" tiene por objeto significar el radical -$C(O)OR_a$, donde $R_a$ es un grupo alquilo. "Alquilsulfonilo" tiene por objeto significar el radical -$SO_2R_a$, donde $R_a$ es un grupo alquilo "Alquilenodioxi" tiene por objeto significar el radical divalente -$OR_aO$- el cual se enlaza a átomos adyacentes (por ejemplo, átomos adyacentes en un anillo fenilo o naftilo), en donde $R_a$ es un grupo alquilo inferior "Alquilaminocarbonilo" tiene por objeto significar el radical -$C(O)NHR_a$, donde $R_a$ es un grupo alquilo. "Dialquilaminocarbonilo" tiene por objeto significar el radical -$C(O)NR_aR_b$, donde $R_a$ y $R_b$ son cada uno independientemente un grupo alquilo "Mercapto" tiene por objeto significar el radical -SH. "Alquiltio" tiene por objeto significar el radical -$SR_a$, donde $R_a$ es un grupo alquilo. "Carboxi" tiene por objeto significar el radical -C(O)OH "Aceto" u "oxo" tiene por objeto significar el di-radical =O. "Tioaceto" tiene por objeto significar el di-radical =S. "Carbamoilo" tiene por objeto significar el radical -$C(O)NH_2$. "Cicloalquilalquilo" tiene por objeto significar el radical -alquil-cicloalquilo, en donde alquilo y cicloalquilo se define como más arriba, y se representa por el arreglo de enlace presente en los grupos -$CH_2$-ciclohexano o -$CH_2$-ciclohexeno. "Arilalquilo" tiene por objeto significar el radical -alquilarilo, en donde alquilo y arilo se define como más arriba, y se representa por el arreglo de enlace presente en un grupo bencilo "Aminocarbonilalquilo" tiene por objeto significar el radical -alquilC(O)$NH_2$ y se representa por el arreglo de enlace presente en el grupo -$CH_2CH_2C(O)NH_2$. "Alquilaminocarbonilalquilo" tiene por objeto significar el radical -alquilC(O)$NHR_a$, donde $R_a$ es un grupo alquilo y se representa por el arreglo de enlace presente en el grupo -$CH_2CH_2C(O)NHCH_3$ "Alquilcarbonilaminoalquilo" tiene por objeto significar el radical -alquilNHC(O)-alquilo y se representa por el arreglo de enlace presente en el grupo -$CH_2NHC(O)CH_3$ "Dialquilaminocarboriylalquilo" tiene por objeto

significar el radical-alquilC(O)$NR_aR_b$, donde $R_a$ y $R_b$ son cada uno independientemente un grupo alquilo. "Ariloxi" tiene por objeto significar el radical -$OR_c$, donde $R_c$ es un grupo arilo. "Heteroariloxi" tiene por objeto significar el radical –$OR_d$, donde $R_d$ es un grupo heteroarilo "Ariltio" tiene por objeto significar el radical -$SR_c$, donde $R_c$ es un grupo arilo. "Heteroariltio" tiene por objeto significar el radical -$SR_d$, donde $R_d$ es un grupo heteroarilo.

Si un compuesto inventivo es una base, una sal deseada puede prepararse por cualquier método apropiado en el arte, incluyendo el tratamiento de la base libre con un ácido inorgánico, tal como ácido clorhídrico ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico, y similares, o con un ácido orgánico, tal como ácido acético, ácido maleico, ácido succínico, ácido mandélico, ácido fumárico, ácido malónico, ácido pirúvico, ácido oxálico, ácido glicólico, ácido salicílico, ácido piranosidílico, tal como ácido glucurónico o ácido galacturónico, alfa-hidroxi ácido, tal como ácido cítrico o ácido tartárico, aminoácido, tal como ácido aspártico y ácido glutámico, ácido aromático, tal como ácido benzoico o ácido cinnámico, ácido sulfónico, tal como ácido p-toluenosulfónico o ácido etanesulfónico, o similares

Si un compuesto inventivo es un ácido, una sal deseada puede prepararse por culaquier método apropiado conocido en el arte, incluyendo tratamiento del ácido libre con una base orgánica o inorgánica, tal como una amina (primaria, secundaria, o terciaria); un hidróxido de metal alcalino o metal alcalinotérreo; o similares. Ejemplos ilustrativos de sales apropiadas incluyen sales orgánicas derivadas de aminoácidos tales como glicina y arginina; amoníaco, aminas primarias, secundarias, y terciarias; y aminas cíclicas, tales como piperidina, morfolina, y piperazina; así como sales inorgánicas derivadas de sodio, calcio, potasio, magnesio, manganeso, hierro, cobre, zinc, aluminio, y litio.

Igualmente pueden describirse incorporaciones específicas de los compuestos de esta invención que comprenden los compuestos representados por Fórmula I Por ejemplo, esta invención se relaciona con

112

compuestos útiles para inhibir la actividad de proteasa VIH de Fórmula I, más arriba, en donde

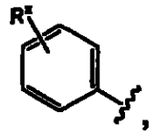
$R^1$ es un grupo cicloalquilo monocíclico de 5 ó 6 miembros, cicloalquenilo, arilo, heterocicloalquilo, heterocicloalquenilo o heteroarilo, donde dicho grupo cicloalquilo, cicloalquenilo, arilo, heterocicloalquilo, heterocicloalquenilo o heteroarilo no se sustituye o se sustituye con uno o más sustituyentes independientemente seleccionados de alquilo, haloalquilo, amino, ciano, halógeno, hidroxilo, alcoxi, haloalcoxi, alquilenedioxi, di-haloalquilenodioxi, ariloxi, cicloalcoxi, cicloalquilalcoxi, cicloalqueniloxi, cicloalquenilalcoxi, heterocicloalcoxi, heterocicloalquilalcoxi, heterocicloalqueniloxi, heterocicloalquenilalcoxi, heteroariloxi, alquilcarboniloxi, arilcarboniloxi, heteroarilcarboniloxi, alquilamino, dialquilamino, aceto, alquilsulfonilo, arilsulfonilo, alquilcarbonilamino, alquiltio, haloalquiltio y ariltio, en donde cualquiera de las fracciones alquilo, alquileno, arilo, cicloalquilo, heterocicloalquilo, heteroarilo presentes en los anteriores sustituyentes pueden sustituirse adicionalmente por uno o más grupos independientemente seleccionados de grupos alquilo, haloalquilo, arilo, nitro, amino, alquilamino, dialquilamino, halógeno, hidroxilo, alcoxi, haloalcoxi, ariloxi, mercapto, alquiltio, haloalquiltio y ariltio;

$R^2$ es un grupo alquilo sustituido, un grupo alquenilo sustituido o no sustituido, o un grupo alquinilo sustituido o no sustituido, en donde dicho grupo alquilo, alquenilo o alquinilo es un grupo de cadena recta o ramificada, y

donde dicho grupo alquilo, alquenilo o alquinilo sustituido se sustituye por uno o más sustituyentes independientemente seleccionados de grupos amino, ciano, halógeno, hidroxilo, alcoxi, haloalcoxi, ariloxi, cicloalcoxi, cicloalquilalcoxi, cicloalqueniloxi, cicloalquenilalcoxi, heterocicloalcoxi, heterocicloalquilalcoxi, heterocicloalqueniloxi, heterocicloalkenlalcoxi, heteroariloxi, alquilamino, dialquilamino, alquilsulfonilo, arilsulfonilo, alquilsulfenilo, arilsulfenilo, alquiltio, haloalquiltio, ariltio y heteroariltio, en donde cualquiera de las fracciones

alquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, heteroarilo presentes en los sustituyentes anteriores puede sustituirse adicionalmente por uno o más grupos independientemente seleccionados de grupos alquilo, haloalquilo, halógeno, hidroxilo, alcoxi, haloalcoxi, alquiltio y haloalquiltio;

$R^{2'}$ es H, metilo, etilo o propilo, donde dicho metilo, etilo o propilo no se sustituye o se sustituye por halo o hidroxilo;

X es  , en donde $R^x$ es H o uno o más sustituyentes independientemente seleccionados de halógeno, alquilo, haloalquilo, alcoxi, haloalcoxi, hidroxilo, alquilenodioxi, di-haloalquilenodioxi, alquilamino, dialquilamino, alquiltio y haloalquiltio;

Z es S, O, SO, $SO_2$, $CH_2$ ó CFH,

$R^3$ es H,

$R^4$, $R^5$, $R^6$ y $R^7$ se seleccionan independientemente de H o metilo; y

$R^8$ y $R^{8'}$ se seleccionan independientemente de H, halógeno, metilo, monohalo-metilo, dihalo-metilo y tri-halometilo,

o un profármaco, metabolito farmacéuticamente activo o sal farmacéuticamente activa o solvato de los mismos

En incorporaciones más específicas, esta invención se relaciona con compuestos de Fórmula I, más arriba, en donde

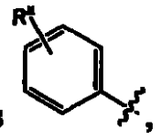
$R^1$ es fenilo, pirrolilo, pirrolidinilo, isoxazolilo, pirazolilo, tiazolilo, tetrahidrofuranilo, furanilo, tienilo o tetrahidropiridazinilo, donde dicho fenilo, pirrolilo, pirrolidinilo, isoxazolilo, pirazolilo, tiazolilo, tetrahidrofuranilo, furanilo, tienilo o tetrahidropiridazinilo no se sustituye o sustituye con uno o más sustituyentes independientemente seleccionados de alquilo, haloalquilo, halógeno, e hidroxilo,

$R^2$ es un grupo alquilo sustituido, un grupo $C_1$-$C_6$ alquenilo sustituido o no sustituido, un grupo $C_1$-$C_6$ alquinilo sustituido o no sustituido, en donde dicho grupo alquilo, alquenilo o alquinilo es un grupo de cadena recta o ramificada, y

114

donde dicho grupo alquilo, alquenilo o alquinilo sustituido se sustituye por uno o más sustituyentes independientemente seleccionados de ciano, halógeno y alquilamino;

$R^{2'}$ es H, metilo o etilo,

X es  , en donde $R^x$ es H, halógeno, o alcoxi,

Z es S, O, $CH_2$ ó CFH;

$R^3$, $R^4$, $R^5$, $R^8$ y $R^{8'}$ son cada uno H; y

$R^6$ y $R^7$ se seleccionan independientemente de H o metilo;

o un profármaco, metabolito farmacéuticamente activo o sal farmacéuticamente activa o solvato de los mismos

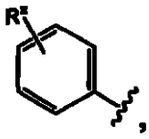
En incorporaciones específicas preferidas, esta invención se relaciona con compuestos de Fórmula I, más arriba, en donde:

$R^1$ es fenilo, donde dicho fenilo se sustituye con uno o más sustituyentes independientemente seleccionados de alquilo, halógeno o hidroxilo;

$R^2$ es un grupo $C_1$-$C_6$ alquenilo o un grupo $C_1$-$C_6$ alquinilo, en donde dicho grupo alquenilo o alquinilo es un grupo de cadena recta o ramificada, y

donde dicho grupo alquenilo o alquinilo no se sustituye o se sustituye por uno o más sustituyentes halógeno;

$R^{2'}$ es H;

X es  , en donde $R^x$ es H;

Z es S;

$R^3$, $R^4$, $R^5$, $R^8$ y $R^{8'}$ son cada uno H; y

$R^6$ y $R^7$ son cada uno metilo;

o un profármaco, metabolito farmacéuticamente activo o sal farmacéuticamente activa o solvato de los mismos

Más específicamente, esta invención se relaciona con compuestos útiles para inhibir la actividad de proteasa VIH de Fórmula I, más arriba, en

115

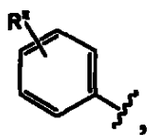
donde:

$R^1$ es un grupo cicloalquilo, cicloalquenilo, arilo, heterocicloalquilo, heterocicloalquenilo o heteroarilo mono-cíclico de 5 ó 6 miembros, donde dicho grupo cicloalquilo, cicloalquenilo, arilo, heterocicloalquilo, heterocicloalquenilo o heteroarilo no se sustituye o se sustituye con uno o más sustituyentes independientemente seleccionados de alquilo, haloalquilo, amino, ciano, halógeno, hidroxilo, alcoxi, haloalcoxi, alquilenodioxi, dihaloalquilenodioxi, ariloxi, cicloalcoxi, cicloalquilalcoxi, cicloalqueniloxi, cicloalquenilalcoxi, heterocicloalcoxi, heterocicloalquilalcoxi, heterocicloalqueniloxi, heterocicloalquenilalcoxi, heteroariloxi, alquilcarboniloxi, arilcarboniloxi, heteroarilcarboniloxi, alquilamino, dialquilamino, alquilsulfonilo, arilsulfonilo, alquilcarbonilamino, alquiltio, haloalquiltio y ariltio, en donde cualquiera de las fracciones alquilo, alquileno, arilo, cicloalquilo, heterocicloalquilo, heteroarilo presentes en los anteriores sustituyentes se sustituyen por uno o más grupos independientemente seleccionados de grupos alquilo, haloalquilo, arilo, nitro, amino, alquilamino, dialquilamino, halógeno, hidroxilo, alcoxi, haloalcoxi, ariloxi, mercapto, alquiltio, haloalquiltio y ariltio;

$R^2$ es un grupo fenilo sustituido, un grupo fenilalquilo sustituido, un grupo fenilalquenilo sustituido o no sustituido o un grupo fenilalquinilo sustituido o no sustituido;

donde dicha fracción alquilo, alquenilo o alquinilo de dicho grupo fenilalquilo, fenilalquenilo o fenilalquinilo es una fracción de cadena recta o ramificada,

$R^{2'}$ es H, metilo, etilo o propilo, donde dicho metilo, etilo o propilo no se sustituye o sustituye con halo o hidroxilo;

X es  , en donde $R^x$ es H o uno o más sustituyentes independientemente seleccionados de halógeno, alquilo, haloalquilo, alcoxi, haloalcoxi, hidroxilo, alquilenodioxi, di-haloalquilenodioxi, alquilamino,

dialquilamino, alquiltio y haloalquiltio;

Z es S, O, SO, $SO_2$, $CH_2$ ó CFH;

$R^3$ es H;

$R^4$, $R^5$, $R^6$ y $R^7$ se seleccionan independientemente de H o metilo, y

$R^8$ y $R^{8'}$ se seleccionan independientemente de H, halógeno, metilo, monohalo-metilo, dihalo-metilo y tri-halometilo;

con la condición que dicho grupo heterocicloalquilo, heterocicloalquenilo o heteroarilo mono-cíclico de 5 ó 6 miembros contiene por lo menos dos heteroátomos; o

con la condición que dicha fracción alquilo, alquenilo o alquinilo de dicho grupo fenilalquilo sustituido, fenilalquenilo o fenilalquinilo se sustituye por uno o más sustituyentes seleccionados de halo o aceto, o

con la condición que dicho grupo fenilo sustituido o fracción fenilo de dicho grupo fenilalquilo sustituido, fenilalquenilo o fenilalquinilo se sustituye por uno o más sustituyentes distintos de halo o metilo, donde dichos uno o más sustituyentes se seleccionan independientemente de grupos haloalquilo, hidroxialquilo, alcoxialquilo, cicloalcoxialquilo, alquilcarbonilalquilo, haloalcoxialquilo, ariloxialquilo, alquiltioalquilo, haloalquiltioalquilo, ariltioalquilo, cianoalquilo, aminoalquilo, alquilaminoalquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, heteroarilo, nitro, amino, ciano, hidroxilo, alcoxi, haloalcoxi, alqueniloxi, alquiniloxi, alquilenodioxi, ariloxi, cicloalcoxi, cicloalquilalcoxi, cicloalqueniloxi, cicloalquenilalcoxi, heterocicloalcoxi, heterocicloalquilalcoxi, heterocicloalkenoxi, heterocicloalquenilalcoxi, heteroariloxi, alquilcarbonilo, alquiloxicarbonilo, alquilcarboniloxi, arilcarbonilo, arilcarboniloxi, ariloxicarbonilo, cicloalquilcarbonilo, cicloalquilcarboniloxi, cicloalquioxicarbonilo, heteroarilcarbonilo, heteroarilcarboniloxi, heteroariloxicarbonilo, heterocicloalquilcarbonilo, heterocicloalquilcarboniloxi, heterocicloalquioxicarbonilo, carboxil. carbamoilo, formilo, aceto, tioaceto, sulfo, alquilamino, cicloalquilamino, arilamino, heterocicloalquilamino, heteroarilamino, dialquilamino, alquilaminocarbonilo,

cicloalquilaminocarbonilo, arilaminocarbonilo, heterocicloalquilaminocarbonilo, heteroarilaminocarbonilo, dialquilaminocarbonilo, alquilaminotiocarbonilo, cicloalquilaminotiocarbonilo, arilaminotiocarbonilo, heterocicloalquilaminotiocarbonilo, heteroarilaminotiocarbonilo, dialquilaminotiocarbonilo, alquilsulfonilo, arilsulfonilo, alquilsulfenilo, arilsulfenilo, alquilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, heterocicloalquilcarbonilamino, heteroarilcarbonilamino, alquiltiocarbonilamino. cicloalquiltiocarbonilamino, ariltiocarbonilamino, heterocicloalquiltiocarbonilamino, heteroariltiocarbonilamino, alquilsulfoniloxi, arilsulfoniloxi, alquilsulfonilamino, arilsulfonilamino, mercapto, alquiltio, haloalquiltio, ariltio y heteroariltio, en donde cualquiera de las fracciones alquilo, alquileno, arilo, cicloalquilo, heterocicloalquilo, o heteroarilo presentes en los anteriores sustituyentes no se sustituyen o se sustituyen por uno o más grupos independientemente seleccionados de alquilo, haloalquilo, halógeno, hidroxilo, alcoxi, haloalcoxi, alquiltio y haloalquiltio,

o un profármaco, metabolito farmacéuticamente activo o sal farmacéuticamente activa o solvato de los mismos. Si el grupo fenilo o fracción fenilo de $R^2$ contiene más de un sustituyente, los sustituyentes pueden ser los mismos o diferentes, y pueden seleccionarse independientemente de los sustituyentes ya descritos

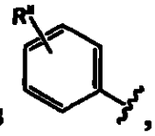
Más específicamente, esta invención se relaciona con compuestos útiles para inhibir la actividad de proteasa VIH de Fórmula I, más arriba, en donde

$R^1$ es fenilo, pirrolilo, pirrolidinilo, isoxazolilo, pirazolilo, tiazolilo, tetrahidrofuranilo, furanilo, tienilo o tetrahidropiridazinilo, donde dicho fenilo, pirrolilo, pirrolidinilo, isoxazolilo, pirazolilo, tiazolilo, tetrahidrofuranilo, furanilo, tienilo o tetrahidropiridazinilo no se sustituye o se sustituye con uno o más sustituyentes independientemente seleccionados de alquilo, haloalquilo, halógeno, e hidroxilo;

$R^2$ es un grupo fenilalquilo sustituido, donde dicha fracción alquilo

de dicho grupo fenilalquilo sustituido es una fracción alquilo de cadena recta o ramificada;

$R^{2'}$ es H, metilo, etilo o propilo, donde dicho metilo, etilo o propilo no se sustituye o se sustituye con hidroxilo,

X es  , en donde $R^x$ es H, halógeno, o alcoxi,

Z es S, O, $CH_2$ ó CFH;

$R^3$, $R^4$, $R^5$, $R^8$ y $R^{8'}$ son cada uno H, y

$R^6$ y $R^7$ se seleccionan independientemente de H o metilo;

con la condición que $R^1$ se selecciona de isoxazolilo, pirazolilo, tiazolilo o tetrahidropiridazinilo, donde dicho grupo es isoxazolilo, pirazolilo, tiazolilo o tetrahidropiridazinilo no se sustituye o se sustituye con uno o más sustituyentes independientemente seleccionados de alquilo, haloalquilo, halógeno, e hidroxilo cuando $R^2$ es un grupo fenilalquilo sustituido o no sustituido o

con la condición que $R^1$ se seleccione de fenilo, pirrolilo, pirrolidinilo, isoxazolilo, pirazolilo, tiazolilo, tetrahidrofuranilo, furanilo, tienilo o tetrahidropiridazinilo cuando $R^2$ es un grupo fenilalquilo sustituido y dicha fracción fenilo de dicho grupo fenilalquilo sustituido comprende uno o más sustituyentes distintos de halo o metilo, donde dichos uno o más sustituyentes se seleccionan independientemente de haloalquilo, amino, hidroxilo, alcoxi, haloalcoxi, alquilenodioxi, di-haloalquilenodioxi, cicloalquilalquiloxi, dialquilamino, alquilsulfonil y alquiltio;

o un profármaco, metabolito farmacéuticamente activo o sal farmacéuticamente activa o solvato de los mismos

En incorporaciones preferidas, esta invención se relaciona con compuestos de Fórmula I, más arriba, en donde.

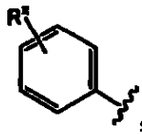
$R^1$ es fenilo, donde dicho fenilo se sustituye con uno o más sustituyentes independientemente seleccionados de metilo, halógeno o hidroxilo;

$R^2$ es un grupo fenilalquilo sustituido, donde dicha fracción alquilo

de dicho grupo fenilalquilo sustituido es una fracción alquilo de cadena recta o ramificada;

donde dicha fracción fenilo de dicho grupo fenilalquilo sustituido comprende uno o más sustituyentes distintos de halo o metilo, donde dichos uno o más sustituyentes se seleccionan independientemente de trifluorometilo, amino, hidroxil, $C_1$-$C_4$ alcoxi, alquilenodioxi, di-fluoro-alquilenodioxi, ciclopropilmetoxi, di-metil-amino, metanosulfonilo y metiltio;

$R^2$ es H, metilo o etil

X es  , en donde $R^x$ es H;

Z es S ó O; y

$R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$ y $R^{8'}$ son cada uno H;

O un profármaco, metabolito farmacéuticamente activo o sal farmacéuticamente activa o solvato de los mismos

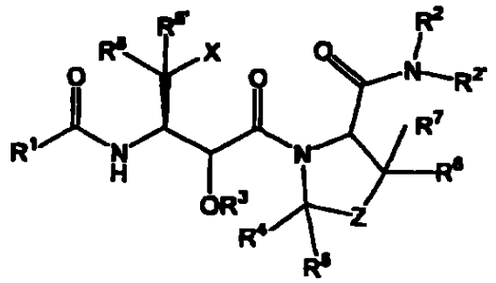
Todos los compuestos de esta invención contienen por lo menos un centro quiral y pueden existir como estereoisómeros simples (por ejemplo, enantiómeros simples o diastereómeros simples), cualquier mezcla de estereosisómeros (por ejemplo, cualquier mezcla de enantiómeros o diastereómeros) o mezclas racémicas de los mismos Todos los estereoisómeros simples, mezclas y racematos pretenden incluirse en la amplia órbita de la presente invención. Los compuestos identificados aquí como estereoisómeros simples tienen por objeto describir compuestos que están presentes en una forma que contiene por lo menos 90% de un estereoisómero simple de cada centro quiral presente en los compuestos. Donde no se especifique la estereoquímica de los carbonos quirales presentes en las estructuras químicas ilustradas aquí, la estructura química pretende abarcar compuestos que contienen estereoisómero de cada centro quiral presente en el compuesto. Preferiblemente, sin embargo, los compuestos inventivos se usan en forma ópticamente pura, es decir, estereoisoméricamente pura, o forma sustancialmente ópticamente pura

(sustancialmente estereoisoméricamente pura). Tal como se emplea aquí, el término pureza "estereoisomérica" (o pureza "óptica") se refiere a la pureza "enantiomérica" y/o pureza "diastereomérica" de un compuesto. Compuestos que son sustancialmente enantioméricamente puros contienen por lo menos 90% de un isómero simple y preferiblemente contienen por lo menos 95% de un isómero simple de cada centro quiral presente en el enantiómero. Compuestos que son sustancialmente diastereoméricamente puros contienen por lo menos 90% de un isómero simple de cada centro quiral presente en el diastereómero, y preferiblemente contienen por lo menos 95% de un isómero simple de cada centro quiral. Más preferiblemente, los compuestos sustancialmente enantioméricamente y diastereoméricamente puros en esta invención contienen por lo menos 97.5% de un isómero simple y muy preferiblemente contienen por lo menos 99% de un isómero simple de cada centro quiral en el compuesto. El término "racemico" o "mezcla racémica" se refiere a una mezcla de cantidades iguales de compuestos enantioméricos, que abarca mezclas de enantiómeros y mezclas de diastereómeros enantioméricos. Los compuestos de esta invención pueden obtenerse en forma estereoisoméricamente pura (es decir, enantioméricamente y/o diastereoméricamente pura) o sustancialmente estereoisoméricamente pura (es decir, sustancialmente enantioméricamente y/o diastereoméricamente pura) Tales compuestos pueden obtenerse sintéticamente, de acuerdo con los procedimientos descritos aquí usando materiales ópticamente o sustancialmente ópticamente puros. Alternativamente, estos compuestos pueden obtenerse por resolución/separación de una mezcla de estereoisómeros, incluyendo mezclas racémicas, usando procedimientos convencionales. Métodos ejemplares que pueden ser útiles para la resolución/separación de mezclas estereoisoméricas incluyen cromatografía y cristalización/re-cristalización. Otros métodos útiles pueden encontrarse en *"Enantiomers, Racemates, and Resolutions,"* J Jacques y colegas, 1981, John Wiley and Sons, New York, NY, cuya divulgación se incorpora aquí por referencia. Estereoisómeros preferidos de los compuestos de esta

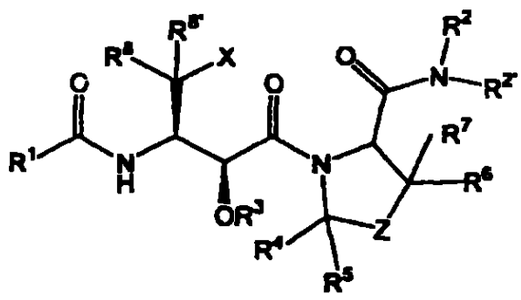
121

invención se describen aquí.

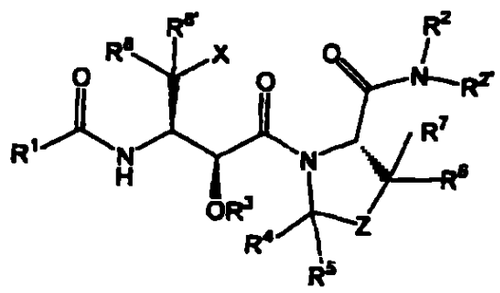
Incorporaciones especialmente preferidas de esta invención comprenden compuestos, en donde los centros estereogénicos (carbonos quirales) tienen la estereoquímica designada a continuación:



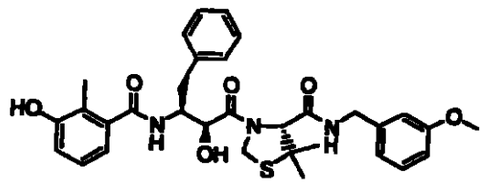
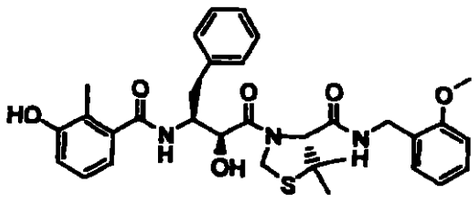
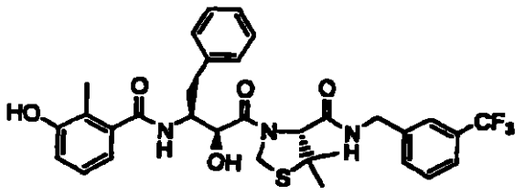
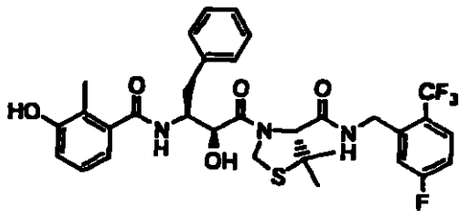
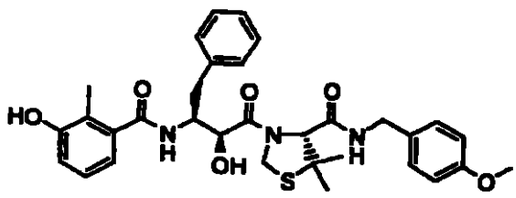
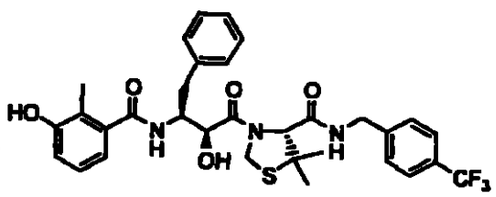
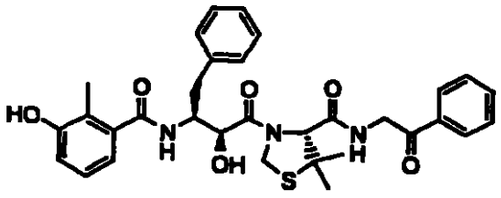
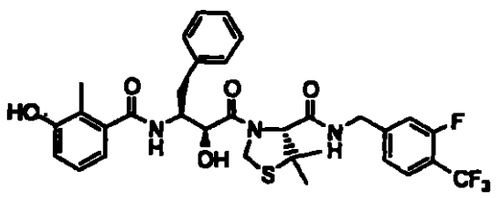
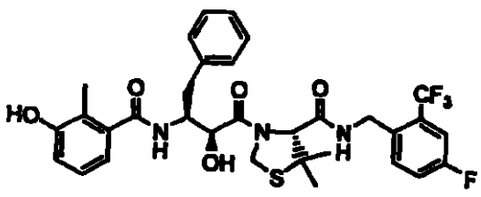
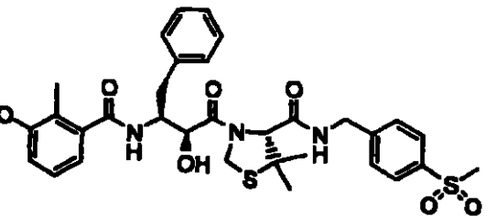
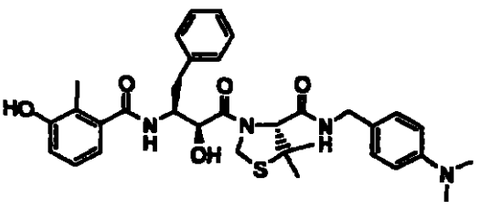
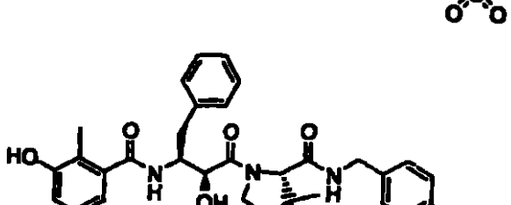
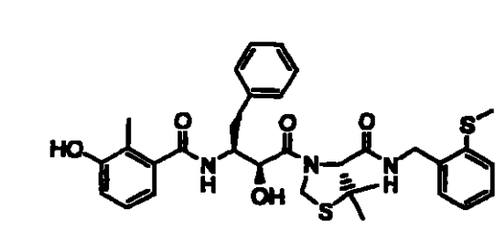
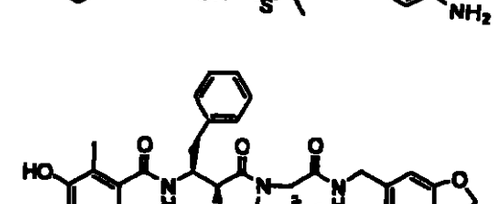
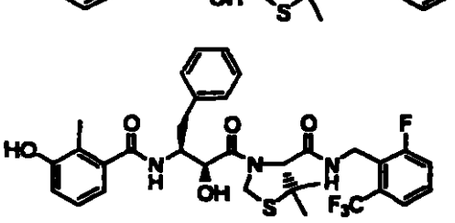
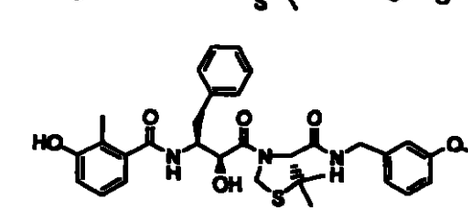
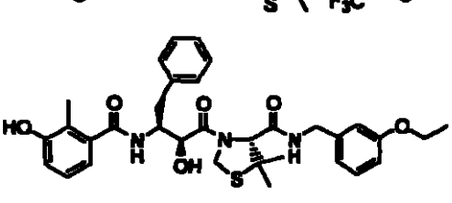
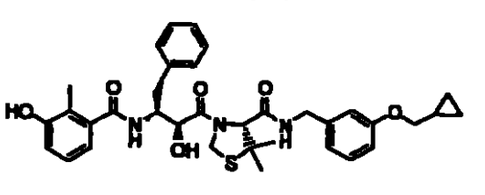
Más preferiblemente, por lo menos dos de los centros estereogénicos tienen la estereoquímica designada a continuación.

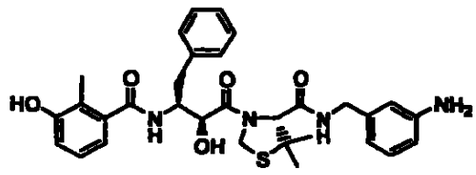


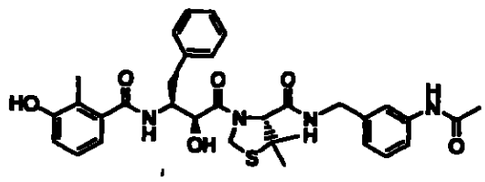
Aun más preferiblemente, por lo menos tres de los centros estereogénicos tienen la estereoquímica designada a continuación:

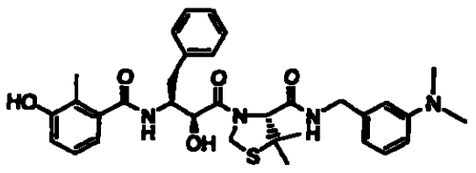


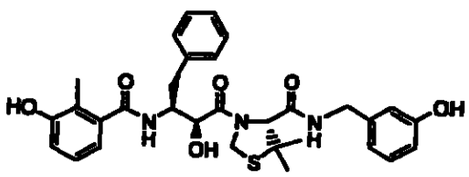
Compuestos ejemplares de esta invención incluyen.

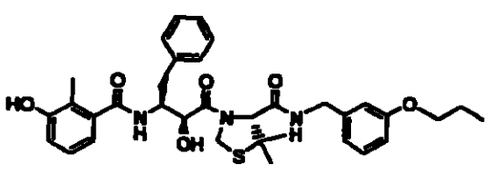



















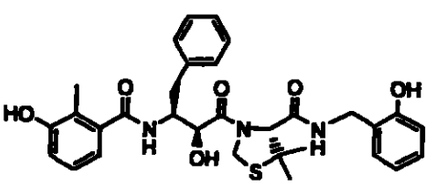


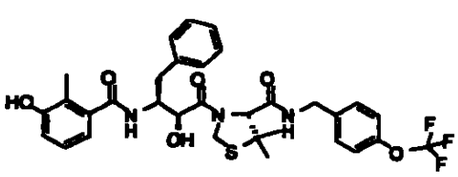


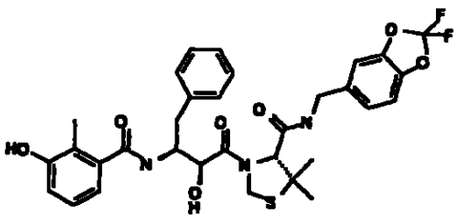


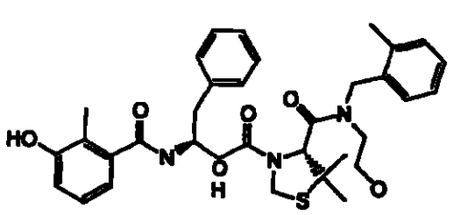


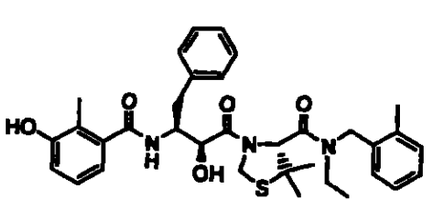


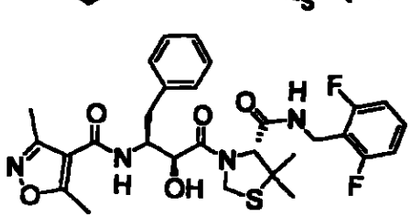


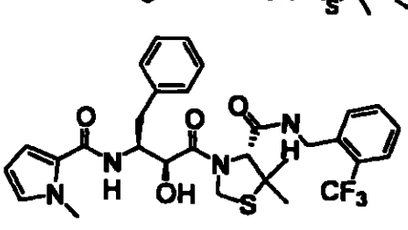


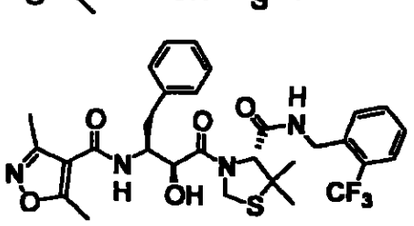


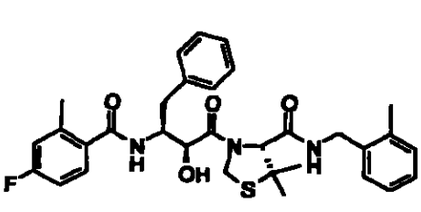


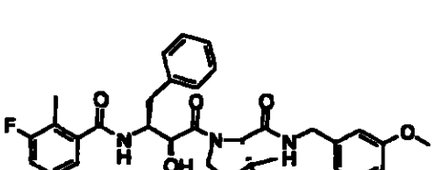


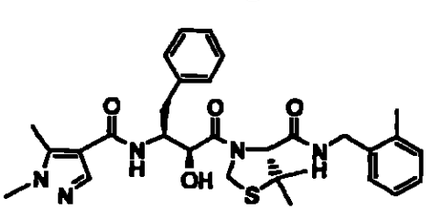


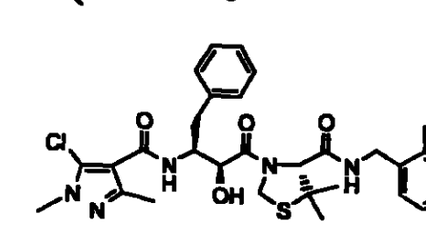


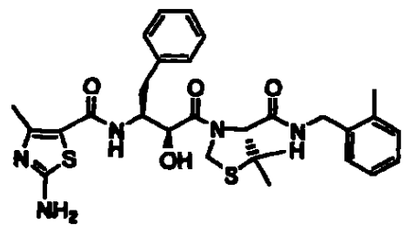
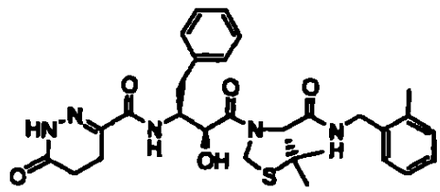
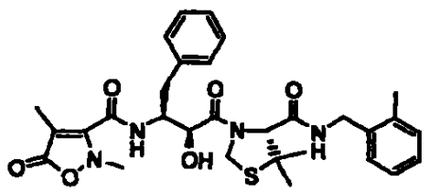
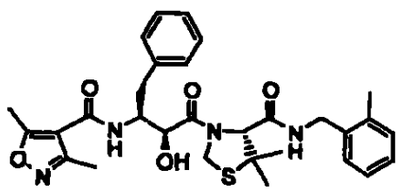
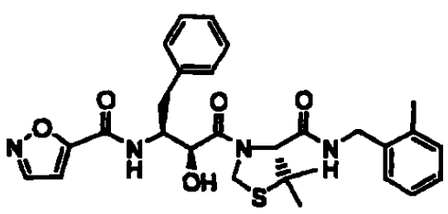
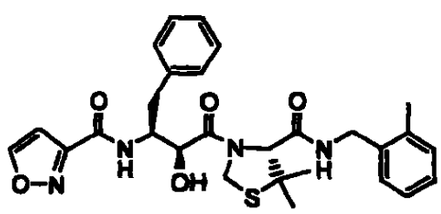
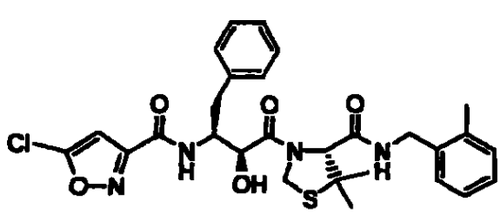
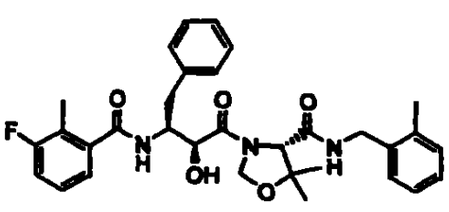
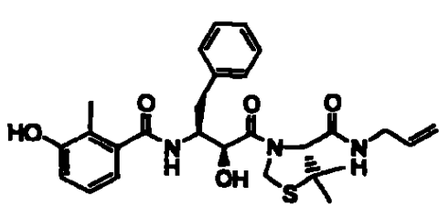
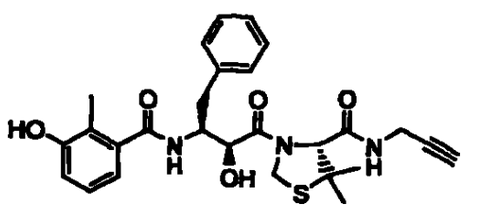
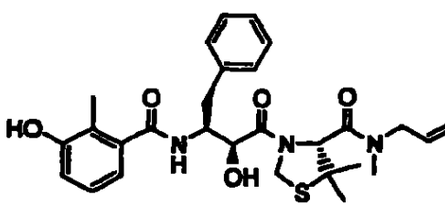
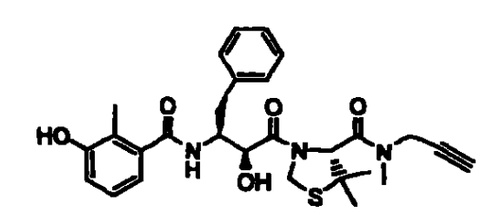
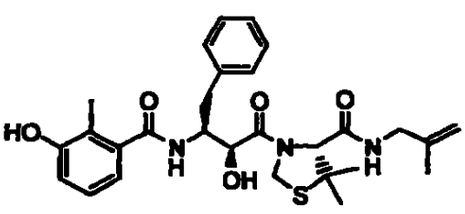
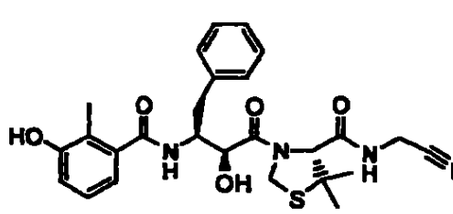
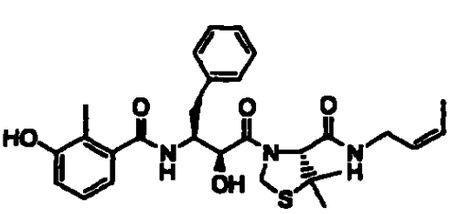
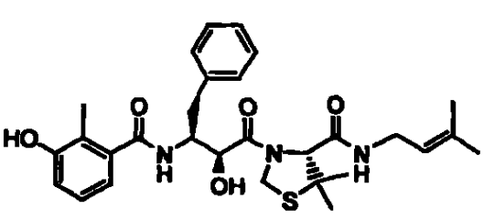


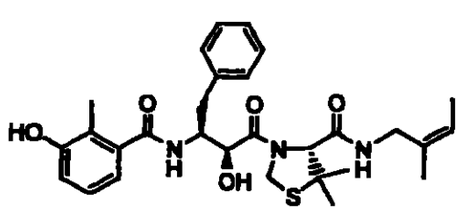


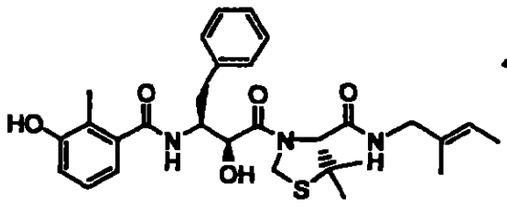


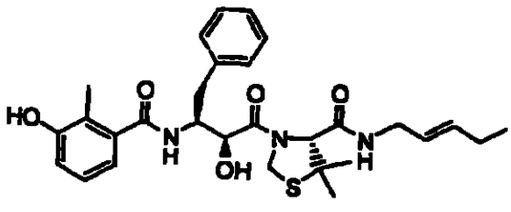


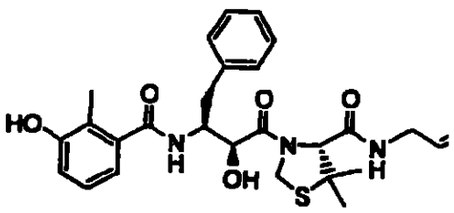


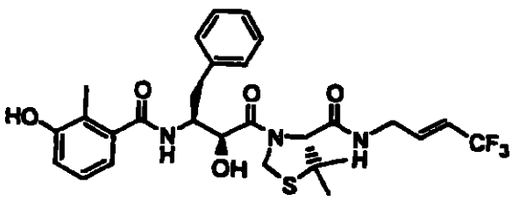

















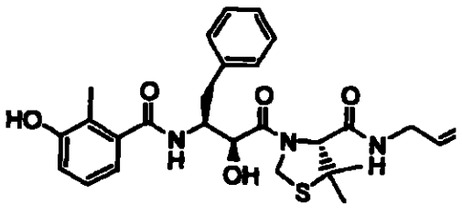


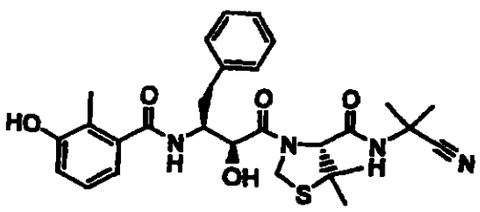


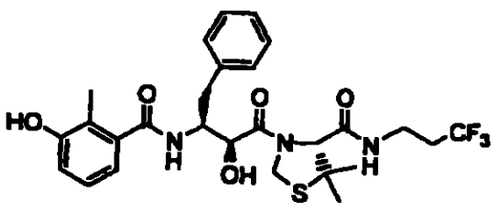


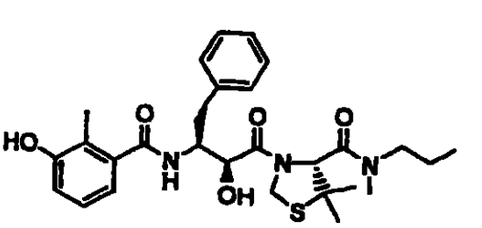


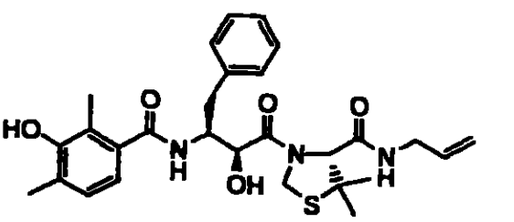


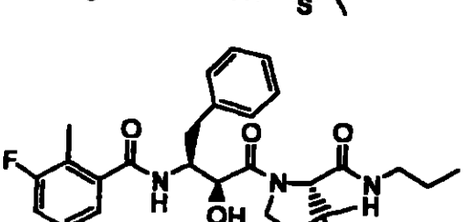


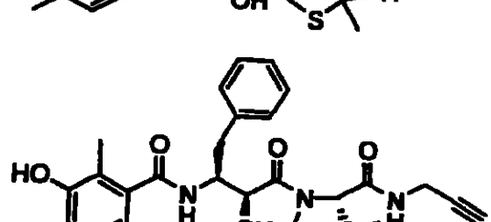


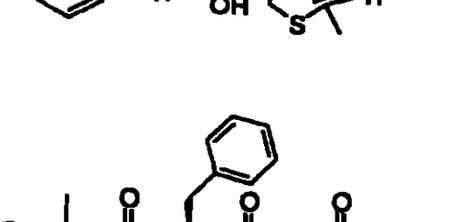


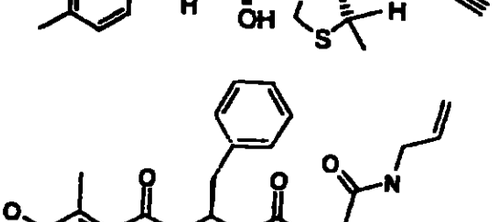


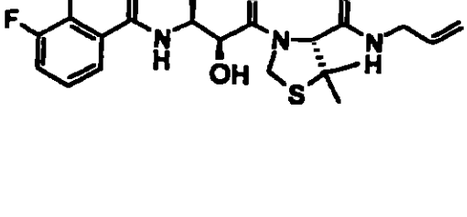


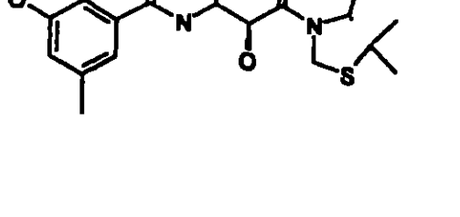


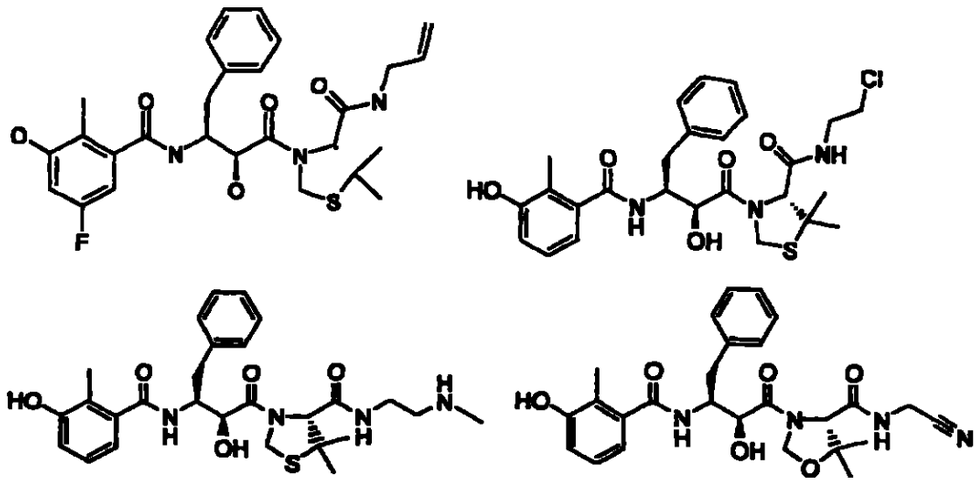






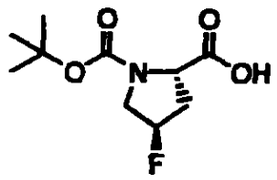




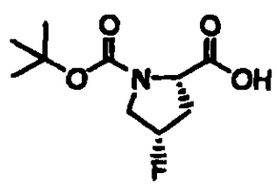


y los profármacos, metabolitos farmacéuticamente activos, y sales y solvatos farmacéuticamente aceptables de los mismos.

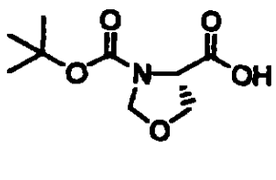
La invención se dirige igualmente a los intermedios de Fórmula II, que son útiles en la síntesis de ciertos compuestos de Fórmula I:



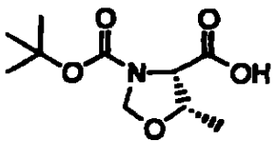
**20a**



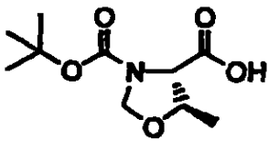
**20b**



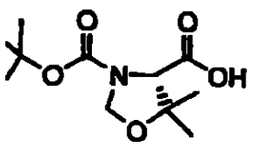
**20c**



**20d**



**20e**

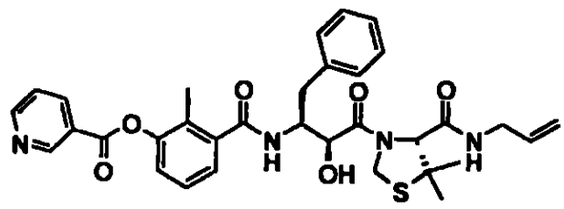


**20f**

Los compuestos inhibidores de proteasa VIH de esta invención incluyen profármacos, los metabolitos farmacéuticamente activos, y las sales y solvatos farmacéuticamente aceptables de los mismos. En incorporaciones preferidas, los compuestos de Fórmula I, profármacos, sales farmacéuticamente aceptables, y metabolitos farmacéuticamente activos y solvatos de los mismos demuestran una actividad inhibidora de la proteasa VIH, correspondiente a $K_i$ de por lo menos 100 nM, una $EC_{50}$ de

por lo menos 10 mM o una $IC_{50}$ de por lo menos 10 mM. Preferiblemente, los compuestos de esta invención demuestran una actividad inhibidora de proteasa VIH, correspondiente a un $K_i$ de por lo menos 10 nM, un $EC_{50}$ de por lo menos 1 mM o una $IC_{50}$ de por lo menos 1 mM. Más preferiblemente, los compuestos de esta invención demuestran una actividad inhibidora de proteasa VIH contra cepas mutantes deVIH, correspondiente a un $K_i$ de por lo menos 100 nM, una $EC_{50}$ de por lo menos 10 mM o una $IC_{50}$ de por lo menos 10 mM. Aun más preferiblemente, los compuestos de esta invención demuestran actividad inhibidora de proteasa contra cepas mutantes correspondiente a un $K_i$ de por lo menos 10 nM, una $EC_{50}$ de por lo menos 1 mM o una $IC_{50}$ de por lo menos 1 mM.

Un "profármaco" tiene por objeto significar un compuesto que se convierte bajo condiciones fisiológicas o por solvólisis o metabólicamente en un compuesto especificado que es farmacéuticamente activo. Un profármaco derivado de uno de los compuestos de esta invención que contiene una fracción, tales como por ejemplo $-CO_2R$, $-PO(OR)_2$ ó $-C=NR$, que puede dividirse bajo condiciones fisiológicas o por solvólisis Puede emplearse cualquier sustituyente R apropiado que provea un producto de solvólisis o escisión farmacéuticamente aceptable Un profármaco que contiene tal fracción puede prepararse de acuerdo con procedimientos convencionales por tratamiento de un compuesto de esta invención que contiene, por ejemplo, una fracción amido, ácido carboxílico, o hidroxilo con un reactivo adecuado. Un "metabolito farmacéuticamente activo" tiene por objeto significar un compuesto farmacológicamente activo producido mediante metabolismo en el cuerpo de un compuesto especificado Profármacos y metabolite activos de compuestos de esta invención de las Fórmulas ya descritas pueden determinarse usando técnicas conocidas en el arte, por ejemplo, mediante estudios metabólicos Véase, por ejemplo, "Design of Profármacos," (Bundgaard, ed ), 1985, Elsevier Publishers B.V., Amsterdam, Holanda. Los siguientes son ejemplos de profármacos que pueden convertirse en los compuestos de esta invención bajo condiciones fisiológicas, por solvólisis o metabólicamente



Una "sal farmacéuticamente aceptable" tiene por objeto significar una sal que conserva la eficacia biológica de los ácidos y bases libres de un compuesto especificado y que no es indeseable biológicamente ni bajo ninguna otra modalidad Ejemplos de sales farmacéuticamente aceptables incluyen sulfates, pirosulfatos, bisulfatos, sulfitos, bisulfitos, fosfatos, fosfatos monohidrogenados, fosfatos dihidrogenados, metafosfatos, pirofosfatos, cloruros, bromuros, yoduros, acetatos, propionatos, decanoatos, caprilatos, acrilatos, formatos, isobutiratos, caproatos, heptanoatos, propiolatos, oxalatos, malonatos, succinatos, suberatos, sebacatos, fumaratos, maleatos, butin-1,4-dioatos, hexin-1,6-dioatos, benzoatos, clorobenzoatos, metilbenzoatos, dinitrobenzoatos, hidroxibenzoatos, methoxibenzoatos, ftalatos, sulfonatos, xilenosulfonatos, fenilacetatos, fenilpropionatos, fenilbutiratos, citratos, lactatos, e hidroxibutiratos, glicolatos, tartratos, metano-sulfonatos (mesilatos), propanesulfonatos, naftaleno-1-sulfonatos, naftaleno-2-sulfonatos, y mandelatos. Un "solvato" tiene por objeto significar una forma de solvato farmacéuticamente aceptable de un compuesto especificado que conserva la eficacia biológica de tal compuesto Ejemplos de solvatos incluyen compuestos de la invención en combinación con agua, isopropanol, etanol, metanol, DMSO, acetato de etilo, ácido acético, o etanolamina. En el caso de compuestos, sales, o solvatos que son sólidos, se entiende por las personas expertas en el arte que los compuestos, sales, y solvatos inventivos pueden existir en diferentes formas de cristal, todas las cuales se pretende incluir en la órbita de la presente invención y fórmulas especificadas

La presente invención se dirige asimismo a un método de inhibir la actividad de la proteasa VIH, que comprende poner la proteasa en contacto con una cantidad efectiva de un compuesto de Fórmula I, o una sal

farmacéuticamente aceptable, profármaco, metabolito farmacéuticamente activo, o solvato del mismo Por ejemplo, la actividad de proteasa VIH puede inhibirse en tejido mamífero administrando un compuesto de Fórmula I o una sal farmacéuticamente aceptable, profármaco, metabolito farmacéuticamente activo, o solvato del mismo Más preferiblemente, el presente método se dirige a inhibir la actividad de proteasa VIH. "Tratar" o "tratamiento" tienen por objeto significar por lo menos la mitigación de una condición patológica en un mamífero, tal como un humano, que se alivia por la inhibición de la actividad de proteasas VIH. Los métodos de tratamiento para mitigación de una condición patológica incluyen el uso de los compuestos en esta invención en cualquier forma convencionalmente aceptable, por ejemplo, como una profiláctica. La actividad de los compuestos inventivos como inhibidores de la actividad de proteasa VIH puede medirse por cualquiera de los métodos apropiados conocidos por los expertos en el arte, incluyendo análisis *in vivo* e *in vitro*. Ejemplos de análisis adecuados para mediciones de actividad se describen aquí La administración de los compuestos de la Fórmula I y sus profármacos, sales, metabolitos activos, y solvatos farmacéuticamente aceptables puede llevarse a cabo de acuerdo con cualquiera de los modos generalmente aceptados de administración disponibles a los expertos en el arte. Ejemplos ilustrativos de modos apropiados de administración incluyen oral, nasal, parenteral, tópico, transcutáneo, y rectal

Un compuesto inventivo de Fórmula I o una sal farmacéuticamente aceptable, profármaco, metabolito activo, o solvate del mismo puede administrarse como una composición farmacéutica en cualquier forma farmacéutica reconocible como apropiada por el profesional experto Formas farmacéuticas apropiadas incluyen formulaciones sólidas, semisólidas, líquidas, o liofilizadas, tales como tabletas, polvos, cápsulas, supositorios, suspensiones, liposomas, y aerosoles. Composiciones farmacéuticas de la invención pueden incluir igualmente excipientes adecuados, diluyentes, vehículos, y portadores, así como otros agentes farmacéuticamente activos, dependiendo del uso previsto o modo de

130

administración. Métodos aceptables de preparar formas farmacéuticas apropiadas de las composiciones farmacéuticas pueden determinarse rutinariamente por los expertos en el arte Por ejemplo, preparaciones farmacéuticas pueden prepararse siguiendo técnicas convencionales del químico farmacéutico que incluyan pasos tales como mezclar, granular, y comprimir cuando sea necesario para formas de tabletas, o mezclar, envasar, y disolver los ingredientes según se estime apropiado, para obtener los productos deseados para administración oral, parenteral, tópica, intravaginal, intranasal, intrabronquial, intraocular, intra-auricural, y/o rectal.

La presente invención incluye composiciones farmacéuticas útiles para inhibir proteasa VIH, comprendiendo una cantidad efectiva de un compuesto de esta invención, y un portador farmacéuticamente aceptable. Composiciones farmacéuticas útiles para tratar la infección por VIH, o para tratar SIDA o ARC (complejo relacionado con SIDA,) se encuentran abarcadas también por la presente invención, así como un método de inhibiir proteasa VIH, y un método de tratar infección por VIH, o de tratar SIDA o ARC. Adicionalmente, la presente invención se dirige a una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto de la presente invención en combinación con una cantidad terapéuticamente efectiva de un agente de tratamiento de infección por VIH /SIDA seleccionado de.

1) un agente antiviral VIH/SIDA,
2) Un agente anti-infeccioso, y
3) un inmunomodulador.

La presente invención incluye asimismo el uso de un compuesto de la presente invención como ya se describió en la preparación de un medicamento para (a) inhibir proteasa VIH, (b) prevenir o tratar infección por VIH, o (c) tratar SIDA o ARC.

La presente invención incluye además el uso de cualquiera de los compuestos inhibidores de protease VIH de la presente invención como se describe anteriormente en combinación con uno o más agentes de

131

tratamiento de infección por VIH /SIDA seleccionados de un agente antiviral VIH/SIDA, un agente anti-infeccioso, y un inmunomodulador para la manufactura de un medicamento para (a) inhibir proteasa VIH, (b) prevenir o tratar infección por VIH, o (c) tratar SIDA o ARC, comprendiendo dicho medicamento una cantidad efectiva del compuesto inhibidor de proteasa VIH y una cantidad efectiva de uno o más agentes de tratamiento

En las composiciones farmacéuticas pueden emplearse portadores sólidos o líquidos farmacéuticamente aceptables, diluyentes, vehículos, o excipientes. Portadores sólidos ilustrativos incluyen almidón, lactosa, sulfato de calcio dihidrato, terra alba, sucrosa, talco, gelatina, pectina, acacia, estearato de magnesio, y ácido esteárico Portadores líquidos ilustrativos incluyen jarabe, aceite de maní, aceite de oliva, solución salina, y agua El portador o diluyente puede incluir un material apropiado de liberación prolongada, tales como gliceril monostearato o gliceril distearato, solo o con una cera Cuando se usa un portador líquido, la preparación puede emplearse en la forma de un jarabe, elíxir, emulsión, cápsula de gelatina blanda, líquido estéril inyectable (por ejemplo, solución), o una suspensión líquida no acuosa o acuosa. Una dosis de la composición farmacéutica contiene por lo menos una cantidad terapéuticamente efectiva del compuesto activo (es decir, un compuesto de Fórmula I o una sal farmacéuticamente aceptable, profármaco, metabolito activo, o solvato del mismo), y preferiblemente se compone de una o más unidades de posología farmacéutica. La dosis seleccionada puede administrarse a un mamífero, por ejemplo, un paciente humano, necesitado de tratamiento mediado por inhibición de actividad de proteasa VIH, por cualquier método conocido o apropiado de administrar la dosis, incluyendo. tópicamente, por ejemplo, como un ungüento o crema, oralmente; rectalmente, por ejemplo, como un supositorio; parenteralmente por inyección; o continuamente por infusión intravaginal, intranasal, intrabronquial, intra-auricular, o intraocular Una "cantidad terapéuticamente efectiva" tiene por objeto significar la cantidad de un agente inventivo que, cuando se administra a un mamífero necesitado

132

del mismo, es suficiente para realizar el tratamiento de condiciones patológicas aliviadas por la inhibición de la actividad de una o más variantes de la proteasa VIH. La cantidad de un compuesto dado de la invención que será terapéuticamente efectiva variará dependiendo de factores tales como el compuesto particular, la condición patológica y la gravedad de la misma, la identidad del mamífero necesitado de ella, cantidad que puede determinarse rutinariamente por profesionales.

Los compuestos de esta invención son también útiles en la preparación y ejecución de estudios análisis sistemático para la detección de compuestos antivirales Por ejemplo, los compuestos de esta invención son útiles para aislar mutantes enzimáticos que son excelentes herramientas de análisis sistemático para compuestos antivirales más potentes. Más aun, los compuestos de esta invención son útiles en comprobar o determinar el sitio de unión de otros antivirales a la proteasa VIH, por ejemplo, por inhibición competitiva. Por consiguiente, los compuestos de esta invención son productos comerciales a venderse para estos propósitos.

## MÉTODOS SINTÉTICOS GENERALES

Preferiblemente, los compuestos inventivos se preparar por los métodos de la presente invención, incluyendo los Métodos Generales indicados a continuación. Cuando no se especifica la estereoquímica en las estructuras químicas, puede utilizarse cualquiera de los dos estereocentros. Igualmente se aplican las siguientes abreviaturas: Boc (*tert*-butoxicarbonilo), Ac (acetilo), Cbz (benciloxicarbonilo), DMB (2,4-dimetoxibencilo), TBS (*tert*-butildimetilsililo), TBDPS (*tert*-butildifenilsililo), Ms (metanosulfonato), Ts (toluenosulfonato), Bn (bencilo), y Tr (trifenilmetilo)

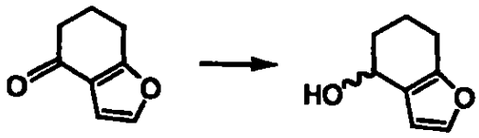
Todas las reacciones se llevaron a cabo en matraces sellados con tabique bajo una suave presión positiva de argón a menos que se indique otra cosa. Todos los reactivos comerciales y solventes se usaron como se recibieron de sus respectivos proveedores con las siguientes excepciones

133

Tetrahidrofurano (THF) se destiló de acetilo de benzofenona de sodio antes del uso Se destiló diclorometano ($CH_2Cl_2$) de hidruro de calcio antes del uso Se realizó cromatografía de destello usando gel de sílice 60 (Merck art. 9385). Se registraron espectros $^1H$ NMR a 300 MHz utilizando un espectrómetro Varian UNITY*plus* 300 Cambios químicos se reportan en ppm (δ) campo abajo en relativos al tetrametilsilano interno, y constantes de acoplamiento se dan en hertzios Se registraron espectros de absorción infrarroja usando un espectrómetro Perkin-Elmer 1600 serie FTIR. Se realizaron análisis elementales por Atlantic Microlab, Inc., Norcross, GA. Los puntos de fusión no se corrigieron

Todas las variantes amina P2' mencionadas en los Métodos Generales A-E descritos a continuación se adquirieron y usaron directamente o se sintetizaron en la siguiente forma.

**MÉTODO A: PROCEDIMIENTO REPRESENTATIVO PARA REDUCCIÓN DE CETONAS A ALCOHOLES.**



1 2

6,7-Dihidro-4-(5H)-benzofuranona (1) (1.00 g 7 34 mmol) se disolvió en metanol (55 mL). La mezcla se enfrió a 0 °C y se agregó en porciones $NaBH_4$ (0.31 g, 8.08 mmol) La reacción se agitó durante 2 h a 0 °C tiempo en el cual el metanol se evaporó. El residuo se disolvió en EtOAc y se vertió en $NaHCO_3$ (acuoso saturado) y se extrajo con EtOAc (3x10 mL). Los extractos orgánicos combinados se lavaron con salmuera (10 mL), se pasaron sobre un tapón corto de $Na_2SO_4$, y se concentraron *in vacuo* para producir 2 (1.01 g, 99%, como una mezcla de isómeros) como un aceite espeso, amarillo pálido, que era de calidad suficiente para llevarse al paso siguiente sin purificación adicional Rf (50% EtOAc/hexanos): 0.53

134

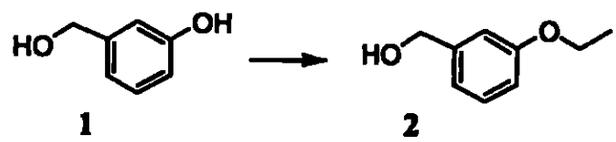
**MÉTODO B: PROCEDIMIENTO REPRESENTATIVO PARA REDUCCIÓN DE ÁCIDOS A ALCOHOLES.**



1 2

Ácido tíglico (1) (20.0 g, 0.200 mol) se disolvió en éter (80ml) y se agregó gota a gota durante 30 min a una suspensión de $LiAlH_4$ (15.0 g, 0 417 mol) en éter (80 ml) a 0 °C y la mezcla de la reacción se puso a calentar a temperatura ambiente. Después de 3 h la mezcla se enfrió nuevamente a 0 °C y se extinguió lentamente por la adición de $H_2O$ (15 ml), 15% NaOH (15 ml) y $H_2O$ (15 ml). La mezcla de la reacción se filtró para retirar el precipitado granular y se lavó concienzudamente con éter El filtrado se lavó sucesivamente con 1N HCl, $NaHCO_3$ (acuoso saturado), y salmuera Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron *in vacuo* para producir (*E*)-2-metil-but-2-en-1-ol (2) como un aceite transparente (12 8g, 74%)

**MÉTODO C: PROCEDIMIENTO REPRESENTATIVO PARA ALQUILACIÓN DE ALCOHOLES FENOLES.**



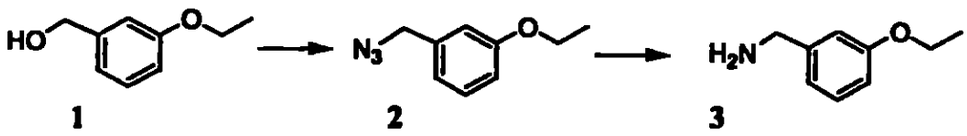
1 2

3-Hidroxibencilalcohol (1) (0 500 g 4.03 mmol) se disolvió en DMF (2 mL) a temperatura ambiente. Se agregaron bromuro de etilo (0 900 mL, 12.1 mmol) y $K_2CO_3$ finamente triturado (2 78 g, 20.1 mmol) y la mezcla de la reacción se agitó durante 5 h. Seguidamente se retiró el DMF *in vacuo* y el residuo se dividió en partes entre EtOAc y $H_2O$, y se extrajo con EtOAc (3x10 mL) Las capas orgánicas se lavaron con salmuera (10 mL) y

135

se pasaron sobre un tapón corto de $Na_2SCO_4$ Los solventes se retiraron *in vacuo* para producir alcohol 2 (0.55 g, 90%) como un aceite espeso, amarillo pálido, el cual era de calidad suficiente para llevarlo al paso siguiente sin purificación adicional. Rf (40% EtOAC/hexanos): 0.69

**MÉTODO D: PROCEDIMIENTO REPRESENTATIVO PARA CONVERSIÓN DE ALCOHOLES EN AMINAS.**




1 2 3

3-Etoxi-fenil-metanol (1) (1.23 g 8.08 mmol) se disolvió en $CH_2Cl_2$ (10 mL) a temperatura ambiente y se agregaron difenilfosforil azida (2.67 g, 9.70 mmol) y 1,8-diazabiciclo [5.4 0] undec-7-eno (1.45 mL, 9 70 mmol) La mezcla se agitó durante 5 h tiempo en el cual se retiró $CH_2Cl_2$ *in vacuo* y el residuo crudo se dividió en partes entre EtOAc y $H_2O$ y se extrajo con EtOAc (3x10 mL) Las capas orgánicas combinadas se lavaron con salmuera (10 mL), se pasaron sobre un tapón corto de $Na_2SO_4$, y se concentraron *in vacuo* para producir un aceite amarillo que se cargó directamente en una columna destello de gel de sílice y se eluyó rápidamente con 10% EtOAc/hexanos. Los solventes se retiraron *in vacuo* para producir azida 2 (1 43 g, 84%) como un aceite incoloro Rf (30% EtOAc/hexanos): 0.79

1-Azidometil-3-etoxi-benceno (2) (1.19 g 6.71 mmol) se disolvió en MeOH (15 mL) y se agregó paladio 10% sobre carbón activado, húmedo (20% en peso). La reacción se hidrogenó durante 30 min a 40 PSI en un Hidrogenador Parr La suspensión negra se filtró entonces a través de celita compactada y el metanol se retiró *in vacuo* para producir amina 3 (0.88 g, 88%) como un aceite espeso, amarillo pálido, el cual era de calidad suficiente para llevarlo a las reacciones de acoplamiento sin purificación adicional.

136

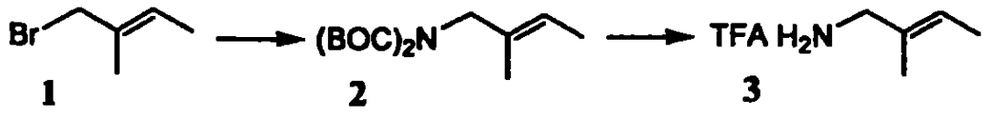
**MÉTODO E: PROCEDIMIENTO REPRESENTATIVO PARA CONVERSIÓN DE ALCOHOLES EN BROMUROS.**




1 2

Cis-2-penten-1-ol (1) (1 00 g, 11 6 mmol) y tetrabromuro de carbón (3 85 g, 13.9 mmol) se disolvieron en $CH_2Cl_2$ (75 mL). La mezcla se enfrió a 0 °C y se agregó gota a gota trifenilfosfina (3 65 mL, 13.9 mmol) disuelto en $CH_2Cl_2$ (50 mL) La mezcla se dejó calentar a temperatura ambiente y se agitó durante la noche. El $CH_2Cl_2$ se retiró *in vacuo* y el residuo crudo se cargó directamente en una columna de destello de gel de sílice y se eluyó rápidamente con 20% EtOAc/hexanos Los solventes se retiraron *in vacuo* para producir bromuro 2 (1-53 g, 88%) como un aceite volátil incoloro Rf (30% EtOAC/hexanos)· 0 89.

**MÉTODO F: PROCEDIMIENTO REPRESENTATIVO PARA CONVERSIÓN DE BROMUROS EN AMINAS.**

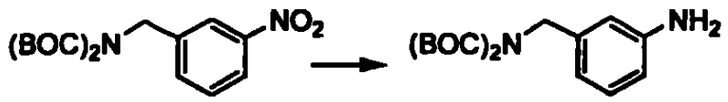



1 2 3

Una mezcla de bromuro 1 (3 00 g, 20.1 mmol), di-tert-butil-iminodicarboxilato (4.8 g, 22 mmol), y $K_2CO_3$ (3 10 g, 80 4 mmol) en DMF (30ml) se agitó a temperatura ambiente durante la noche. La mezcla dividió en partes entre 1N HCl y EtOAc. La capa orgánica se lavó con $H_2O$ y salmuera, luego se secó sobre $NaSO_4$ La concentración *in vacuo* proporcionó un aceite amarillo el cual, a la purificación por cromatografía de columna de destello (hexanos a gradiente 5% EtOAc/hexano), produjo amina 2 protegida como un aceite transparente (2.0g, 35%)

Una mezcla de la amina diBOC 2 (2 0 g, 7.0 mmol), ácido trifluoroacético (2 7 ml, 35 mmol) y $CH_2Cl_2$ (40 ml) se agitó a temperatura ambiente durante la noche. La mezcla de la reacción se concentró *in vacuo* para producir la sal TFA de (*E*)-2-metil-but-2-enilamina (3)

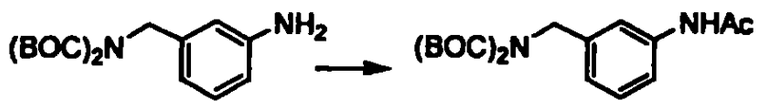
**MÉTODO G: PROCEDIMIENTO REPRESENTATIVO PARA REDUCCIÓN DE GRUPOS NITRO AROMÁTICOS POR HIDROGENACIÓN.**




1 2

Compuesto 1 (2.04, 5.79 mmol) se disolvió en EtOAc (20 mL) y se agregó paladio 10% sobre carbón activado, húmedo (20% en peso). La reacción se hidrogenó durante 4h a 45 PSI en un Hidrogenador Parr. La suspensión negra se filtró entonces a través de una celita compactada y el metanol se retiró *in vacuo* para producir anilina 2 (1.65 g, 88%) como un aceite espeso, amarillo pálido, el cual era de calidad suficiente para llevarse a la reacción de acetilación sin purificación adicional.

**MÉTODO H: PROCEDIMIENTO REPRESENTATIVO PARA ACETILACIÓN DE ANILINAS.**

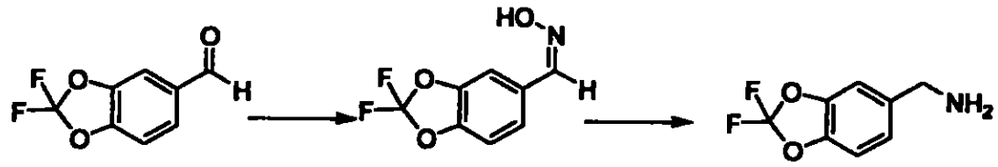



1 2

Anilina 1 (1.65 g, 5.12 mmol) se disolvió en $CH_2Cl_2$ (25 mL) a temperatura ambiente. Se agregaron cloruro de acetilo (0 48 g, 6 14 mmol) y *N,N*-diisopropiletilamina (0 79 g, 6.14 mmol), y la reacción se agitó durante la noche. El $CH_2Cl_2$ se retiró *in vacuo* y el residuo crudo se dividió

en partes entre EtOAc t 5% $KHSO_4$ y se extrajo con EtOAc (3x10 mL) Los extractos orgánicos combinados se lavaron con $NaHCO_3$ (acuoso saturado, 10 mL), salmuera (10 mL), y se secaron sobre $Na_2SO_4$ Los solventes se retiraron *in vacuo* para producir un aceite anaranjado el cual era de calidad suficiente para llevarlo al paso siguiente sin purificación adicional. Rf (50% EtOAC/hexanos): 0 42

**MÉTODO I: PROCEDIMIENTO REPRESENTATIVO PARA REDUCCIÓN DE ALDEHÍDOS A AMINAS.**

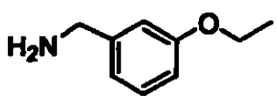



1 2 3

Hidroxil amina clorhidrato (758 mg, 10.7 mmol) y piridina (2.16 mL) se agregaron a una solución de 2,2-difluoro-5-formil beozodioxol (1) (2.00 g, 10.7 mmol) en MeOH (10 mL) Después de 18 horas el MeOH se retiró *in vacuo* La mezcla de la reacción se diluyó con EtOAc y se lavó secuencialmente con $H_2O$, 10% p/v $CuSO_4$, y salmuera y luego se secó sobre $MgSO_4$. La solución se concentró *in vacuo* La hidroxi imina se purificó por cromatografía de columna usando 20% EtOAc/hexanos para producir 1.37 g (64% rendimiento) de un sólido blanco La imina se sometió entonces a reducción LAH como se describe anteriormente para proporcionar amina **3**

Las siguientes aminas se sintetizaron para los números de ejemplos correspondientes:

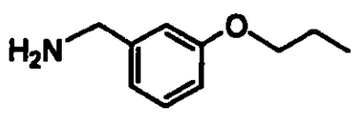
**Ejemplo A26**



139

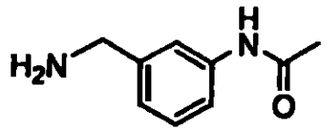
La amina se generó por alquilación de alcohol 3-hidroxibencílico con bromuro de etilo como se describe en método C más arriba seguido por conversión del alcohol a la amina como se describe en método D más arriba, [el cual] proporcionó la amina deseada

**Ejemplo A43**



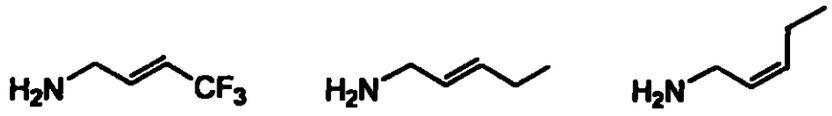
La amina se generó como se describe anteriormente para Ejemplo A43 usando propilbromuro como el agente alquilante.

**Ejemplo A33**



La amina se generó del desplazamiento de bromuro en 3-nitrobencilbromuro con amina di-BOC como se describe en método F más arriba La reducción de la fracción nitro a la anilina (método G más arriba) seguida por acetilación (método H más arriba) y el retiro de BOC (método F más arriba) proporcionó la amina deseada.

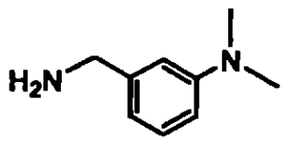
**Ejemplo A36, Ejemplo A37 y Ejemplo A40**



Las aminas se generaron de la conversión de los alcoholes primarios correspondientes como se describe en método E más arriba El desplazamiento del bromuro con la amina di-BOC y la desprotección con TFA (método F más arriba) proporcionó las aminas deseadas

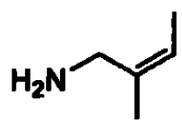
140

**Ejemplo A39**



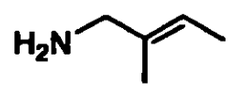
La amina se generó de alcohol 3-dimetilaminobencílico como se describe en método D más arriba

**Ejemplo A34**



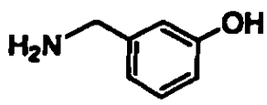
La amina se generó por reducción del éster de metilo correspondiente al alcohol primario (Wipf, *J Org Chem* **1994**, *59*, 4875-86.). La conversión al bromuro (método E más arriba) seguida por desplazamiento con amina diBOC y la desprotección (método F más arriba) proporcionaron la amina deseada.

**Ejemplo A35**



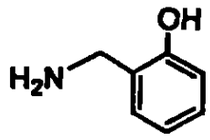
La amina se generó del ácido carboxílico correspondiente. La reducción del ácido como se describe en método B más arriba seguida por desplazamiento del bromuro como se describe en método E más arriba produjo el bromuro primario. La conversión del bromuro a la amina primaria seguida por el procedimiento descrito en método F más arriba

**Ejemplo A42**



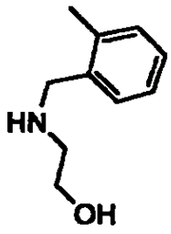
La amina se generó de alcohol 3-benciloxibencílico. La conversión a la azida y la reducción de la azida y el grupo protector bencilo se llevaron a cabo usando el método D como se describe más arriba con un tiempo de hidrogenación más prolongado

**Ejemplo A44**



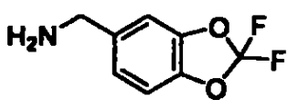
La mina se generó por reducción $LiAlH_4$ de 2-cianofenol (Ludeman, S.M , y colegas, *J Med Chem* **1975,** *18,* 1252-3 )

**Ejemplo A50**



La amina se generó de la condensación de o-tolualdehído con 2-aminoetanol seguida por reducción con borohidruro de sodio (*Tetrahedron Assym* **1997,** *8,* 2367-74.)

**Ejemplo A48**

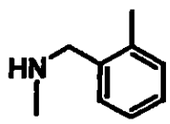


La amina se generó del aldehído correspondiente por el

142

procedimiento de aminación reductora descrito en método I más arriba

**Ejemplo A7**



La amina se generó por una aminación reductora con el aldehído correspondiente *(Arch Pharm* **1987**, 320, 647-54.)

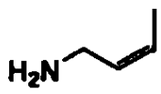
**Ejemplo A49**



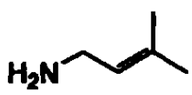
La amina se generó en el núcleo de tiazolidina en la siguiente forma·

Difenilclorofosfato (1 0 ml, 4 2 mmol) seguido por trietilamina (0.59 ml, 4.2 mmol) se agregaron a una solución enfriada a 0 °C de BOC-DMTA **1** (1.0 g, 3.8 mmol) en EtOAc (10 ml). La mezcla se agitó durante 1 h y en ese tiempo se agregaron trietilamina (0 59 ml, 4 2 mmol) y etanolamina (0.25 ml, 4.2 mmol). La reacción se dejó agitar durante la noche a temperatura ambiente y luego se dividió en partes entre 1N HC1 y EtOAc. La capa orgánica se lavó con $NaHCO_3$ (acuoso saturado) y salmuera. La capa orgánica se secó sobre $Na_2SO_4$ y se concentró *in vacuo* a un aceite amarillo pálido **2**. El aceite se agitó con cloruro de tionilo (2 ml) durante 45 min a temperatura ambiente. La mezcla se concentró *in vacuo* y el aceite residual se dividió en partes entre 1N NaOH y EtOAc La capa orgánica se extrajo con 1N HCl (2 x 20 ml). Las capas acuosas combinadas se basificaron con 1N NaOH y luego se extrajeron con EtOAc (3 x 60 ml). Las capas orgánicas se lavaron con salmuera, se secaron sobre $Na_2SO_4$ y se concentraron *in vacuo* para producir ácido (R)-5,5-dimetil-tiazolidino-4-carboxílico (2-cloro-etil)-amida **3** como un aceite transparente (0.39 g, 55%)

Las siguientes aminas se prepararon como se describe:



**Ejemplo A31**

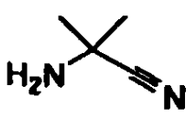


**Ejemplo A32**



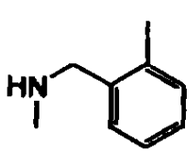
**Ejemplo A38**

Las aminas anteriores se prepararon de acuerdo con Carlsen, H. J, *J Heterocycle Chem* **1997**, *34*, 797-806



**Ejemplo A41**

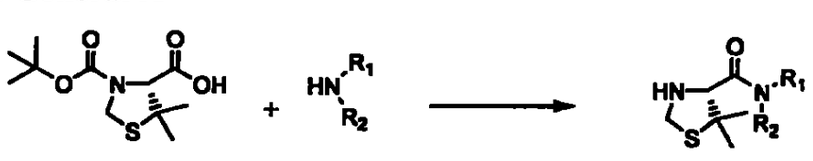
La amina anterior se preparó de acuerdo con O'Brien, P. M , *J Med Chem* **1994**, *37*, 1810-1822



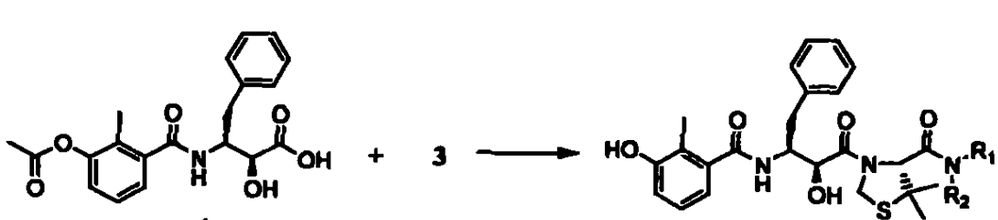
**Ejemplo A7**

La amina anterior se preparó de acuerdo con Weinheim, G. *Arch Pharm* **1987**, *320*, 647-654.

**Método General A**



1 2 3

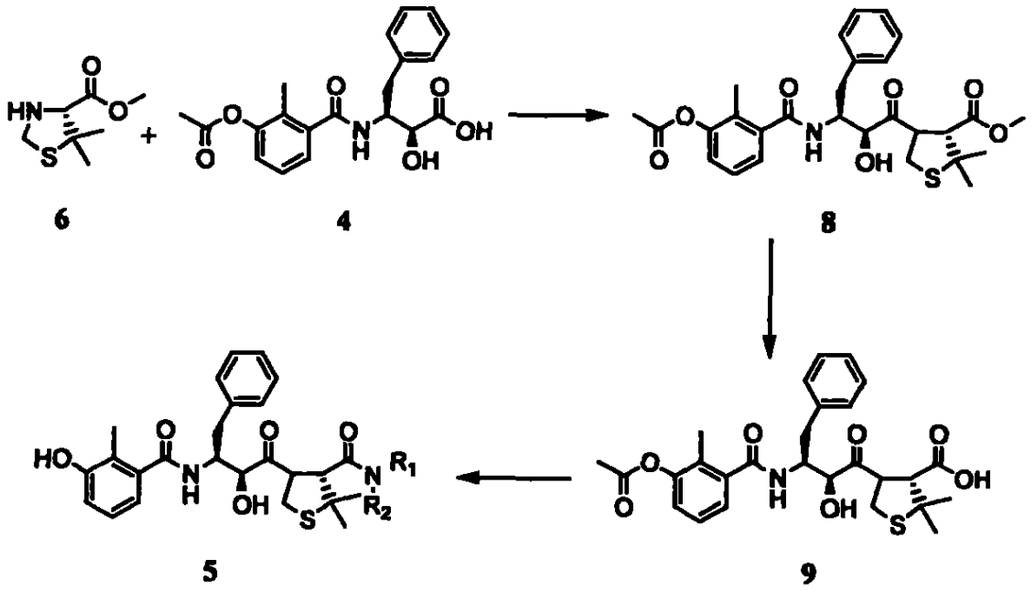


4 5

La síntesis de compuestos con la estructura general 5 es como sigue. El ácido carboxílico tiazolidina boc-protegida 1 se acopla a las aminas requeridas 2 para producir amino amidas 3 usando un proceso de dos pasos

144

El proceso incluye el tratamiento de **1** con **2** en la presencia de difenilclorofosfato o HATU, seguido por exposición a ácido metano sulfónico. Los compuestos finales **5** se obtienen por un acoplamiento mediado por DCC de **3** y **4** seguido por desprotección del fenol P2. Los compuestos finales se purificaron por cromatografía de destello o HPLC preparativa

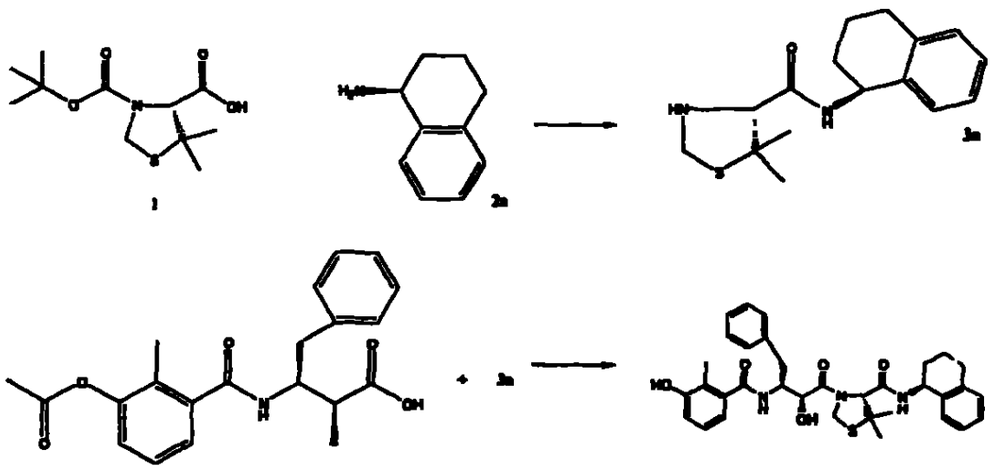


**6** **4** **8**

**5** **9**

Una aproximación alternativa a la estructura general **5** es como sigue. El éster de tiazolidina **6** se acopla al ácido **7** bajo condiciones de reacción de carbodiimida, resultante en producto **8** que se convierte a ácido **9** por hidrólisis de base suave. El ácido **9** se combina con varias aminas, usando difenilfosforil azida, seguida por escisión del acetato P2 para producir los compuestos finales **5** Los productos se purificaron por cromatografía de destello o HPLC preparativa

**Método Específico A.**



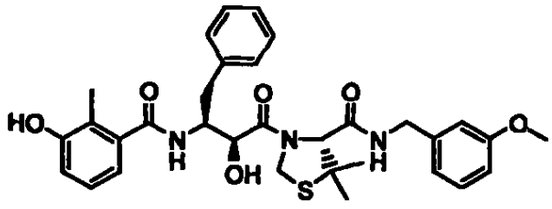
**Ejemplo A1: ácido 3-[2-hidroxi-3-(3-hidroxi-2-metil-benzoilamino)-4-fenil-butiril]-5,5-dimetil-tiazolidino-4-carboxílico (1, 2, 3, 4-tetrahidro-naftalen-1-il)-amida**

El compuesto del título se preparó como sigue. Ácido (R)-5,5-dimetil-tiazolidino-3,4-dicarboxílico *3-tert*-butil éster **1** (0.3 g, 1 15 mmol) se disolvió en EtOAc (3 mL) y se enfrió a 0 °C. Se agregó difenil clorofosfato (0.26 mL, 1.26 mmol) seguido por TEA (0.18 mL, 1.26 mmol). La reacción se agitó a 0 °C durante 1h, y se trató con (S)- 1 , 2, 3, 4-tetrahidro-1-naftilamina (0 19 g, 1 26 mmol). La mezcla de la reacción se agitó a temperatura ambiente durante la noche, luego se dividió en partes entre 1N HCl (5 mL) y EtOAc (10 mL). La capa orgánica se lavó con $NaHCO_3$ saturado, salmuera, se secó sobre $Na_2SO_4$ y se concentró a un aceite amarillo claro El aceite crudo resultante se disolvió en EtOAc (5 mL) y luego se enfrió a 0 °C. Se agregó ácido metanosulfónico (0.36 mL, 5.32 mmol) y la solución se agitó a 0 °C durante 15 minutos, luego a temperatura ambiente durante 1h. La mezcla se enfrió nuevamente a 0 °C y se extinguió con 5% $Na_2CO_3$ (5 mL) luego se extrajo con EtOAc (10 mL) La capa orgánica se lavó con salmuera, se secó sobre $Na_2SO_4$ y se concentró en vacuo para producir **3a** como un aceite amarillo. El aceite amarillo **3a** (0.34 g, 1 15 mmol) se disolvió en EtOAc (12 mL). Se agregó AMB-AHPBA **4** (0.40 g, 1 09 mmol) seguido por HOBt (0.15 g, 1 09 mmol) La mezcla se

146

agitó a temperatura ambiente 1h, luego se enfrió a 0 °C Se agregó lentamente DCC (0.24 g, 1.15 mmol) como solución en EtOAc (6 mL) La mezcla se calentó a temperatura ambiente y se agitó durante la noche La mezcla se filtró y el filtrado se lavó con 1N HCl (10 mL), $NaHCO_3$ saturado (10 mL), salmuera (10 mL), se secó sobre $Na_2SO_4$ y se concentró para producir un sólido blanco crudo (contaminado con DCU). El DCU se retiró por cromatografía de destello (30% a 50% EtOAc en hexanos) para proporcionar un sólido blanco, el cual se disolvió en MeOH (2 mL) y se trató con 4N HCl en 1,4-dioxano (0 26 mL, 1.1 mmol). La reacción se agitó a temperatura ambiente durante la noche, luego se dividió en partes entre 1N HCl (10 mL) y EtOAc (10 mL) La capa orgánica se lavó con $NaHCO_3$ saturado, se secó sobre $Na_2SO_4$ y se concentró a un residuo el cual se purificó por cromatografía de destello (60% EtOAc en hexanos) para proporcionar el compuesto del título como un sólido blanco: mp=125-126 °C, IR (cm-) 3320, 2932, 1704, 1644, 1530, 1454, 1361, 1284; $^1$HNMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8 28 (d, *J*= 8.6, 1H), 8.21 (d, *J*= 8 8, 1H), 7 35-6.91 (m, 10H), 6.76 (d, J= 8 0, 1H), 6.54 (d, J= 7 5, 1H), 5.34 (d, J= 6 0, 1H), 5.13 (d, *J*= 9.0, 1H), 5.02 (d, *J*= 9.0,1H), 4.60-4.30 (m, 4H), 2.81-2.68 (m, 4H), 1.81 (s, 3H), 1.78-1.60 (m, 4H), 1.48 (s, 3H), 1 45 (s, 3 H), análisis calculado para $C_{34}H_{39}N_3O_5S_1$1.5 $H_2O$: C, 64.95; H, 6 73; N, 6 68 Hallado: C, 64.88, H, 6 31, N, 6.18.

**Ejemplo A2: ácido (R)-3-((2S, 3R)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 3-metoxi-bencilamida**

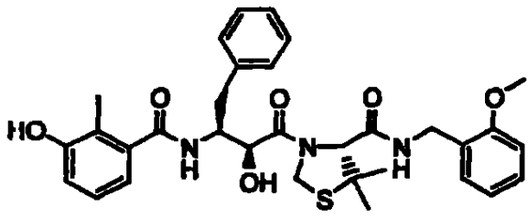


Sólido blanco. mp 108-110 °C, IR (puro, $cm^{-1}$) 3310, 2965, 1644, 1586,

1531, 1455, 1359, 1284; $^1$H NMR (DMSO-$d_6$) δ 9 37 (s, 1H), 8 40 (t, *J*= 6.0,1H), 8.09 (d, *J*= 8.1, 1H), 7.31-6.52 (m, 12H), 5.49 (d, *J*=6.0, 1H), 5.12 (d, *J*= 9.3, 1H), 5 00 (d, *J*= 9.3, 1H), 4 44-4.35 (m, 3H), 4.42 (s, 1H), 4.09 (dd, *J*= 15 0, 6.0, 1H), 3.69 (s, 3H), 2.87-2.67 (m, 2H), 1 82 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3 H); análisis calculado para $C_{32}H_{37}N_3O_6S$-0.75 $H_2O$: C, 63.50; H, 6.41, N, 6.94. Hallado. C, 63.60, H, 6.23; N, 6 80.

Los siguientes ejemplos se prepararon por el método específico descrito a grandes rasgos más arriba usando la amina 2 requerida

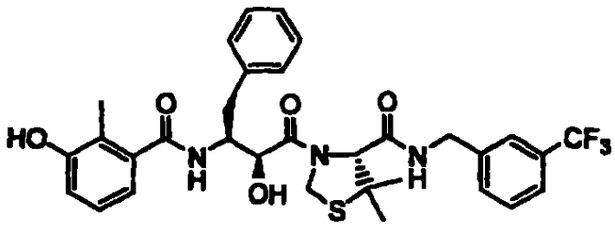
**Ejemplo A3: ácido (R)-3-(2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 2-metoxi-bencilamida**



Sólido blanco· mp = 123-125 °C; IR (cm-$^1$) 3318, 2965, 1644, 1525, 1495, 1464, 1286, 1246, 1120, 1030, $^1$HNMR (DMSO-$d_6$) δ 9 36 (s, 1H), 8 26 (t, *J*= 5.9, 1H), 8.14 (d,*J*= 8.0, 1H), 7.39-7.13 (m, 6H), 6.95-6.76 (m, 5H), 6 53 (d, *J*= 7.5, 1H), 5 49 (d, J= 6.0, 1H), 5.13 (d, J= 9.0, 1H), 5 01 (d, *J*= 9.0, 1H), 4.47 (s, 1H), 4.41-4 16 (m, 4H), 3.78 (s, 3H), 2.90-2 62 (m, 2H), 1.81 (s, 3H), 1 49 (s, 3H). 1.32 (s, 3H); análisis calculado para $C_{32}H_{37}N_3O_6S$-0 75 $H_2O$. C, 63.50; H, 6 41, N, 6.94. Hallado. C, 63.68, H, 6.20, N, 6 54.

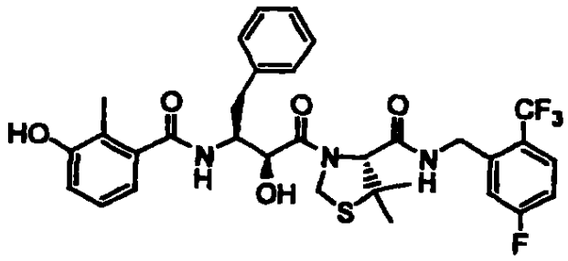
**Ejemplo A4: ácido 3-(2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 3-trifluorometil-bencilamida**

148



Sólido blanco mp = 108-110 °C, IR ($cm^{-1}$) 3308, 3065, 1646, 1540, 1456, 1362, 1329, 1284, 1165, 1125, 1074, $^1$HNMR (DMSO-$d_6$) δ 9 38 (s, 1H), 8 56 (t, *J*= 6.0, 1H), 8 12 (d, *J*= 8.2, 1H), 7 65 (s, 1H), 7 60-7 47 (m, 3H), 7 28-7.13 (m, 5H), 6.96-6.92 (m, 1H). 6.77 (d, *J*= 8.0, 1H), 6.53 (d, *J*= 7.5, 1H), 5 45 (d, *J*= 6 0, 1H), 5 14 (d, *J*= 9 2, 1H), 5.00 (d, *J*= 9.2, 1H), 4.53-4.41 (m, 4H), 4 22 (dd, *J*= 16.0, 6 0, 1H), 2.86-2.66 (m, 2H), 1 81 (s, 3H), 1 49 (s, 3H), 1 31 (s, 3 H); análisis calculado para $C_{32}H_{34}F_3N_3O_5$, S. C, 61.04; H, 5.44; N, 6 67. Hallado: C, 61:03; H, 5 56; N, 6.51

**Ejemplo A5: ácido 3-(2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metianoil}amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico fluoro trifluorometil-bencilamida**

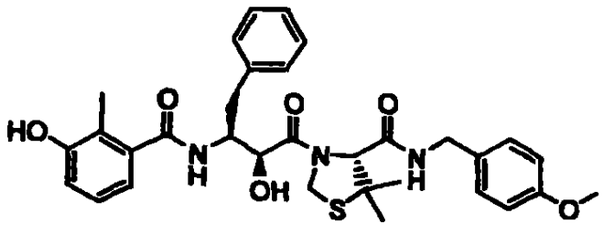


$^1$H NMR (DMSO-$d_6$) δ 9.33 (s, 1H), 8.69 (t, *J*= *5 6,* 1H), 8.12-6.56 (m, 11H), 5.50 (d, *J*= *6 0,* 1H), 5.22 (d, *J*= 9 3,1H), 5.06 (d, *J*= 9.3, 1H), 4.60-4.36 (m, 5H), 4 50 (s, 1H), 2 89-2.67 (m, 2H), 1.83 (s, 3H), 1 55 (s, 3H), 1 39 (s, 3H); análisis calculado para $C_{32}H_{33}N_3O_5SF_4$· C, 59.34, H, 5.14; N, 6.49, S, 4 95. Hallado: C, 59.06, H, 5.31; N, 6.22, S, 4 66.

**Ejemplo A6: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-**

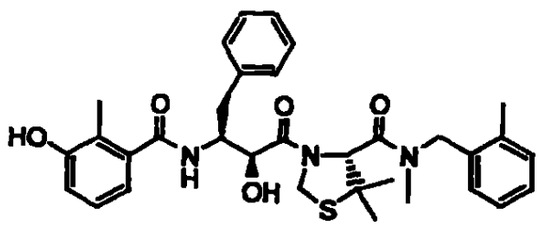
149

**fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 4-metoxi-bencilamida**



IR (puro $cm^{-1}$) 3335, 2920, 1641, 1516, 1463, 1374, 1285, 1249. 1172, 1118, $^1$HNMR (DMSO-$d_6$) δ 9.38 (s, 1H), 8.37 (t, *J*= 5.5, 1H), 8.12 (d, *J*= 8 2, 1H), 7.33-7.13 (m, 7H), 6.94 (t, J= 7.7, 1H), 6 84-6 79 (m, 3H), 6.54 (d, *J*= 7.0, 1H), 5.48 (d, *J*= 6 6, 1H), 5.12 (d, *J*= *9 2,* 1H), 5.00 (d, *J*= 9.2, 1H), 4.49-4.42 (m, 3H), 4 32 (dd, *J*= 6.2, 14.8, 6 , 1H), 4 09 (dd, *J* = 14.8, 5.3, 1H), 3.67 (s, 3H), 2.87-2.68 (m, 2H), 1.82 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3H); HRMS (ESI) m / z calculado para $C_{32}H_{37}N_3O_6SNa$ $(M + Na)^+$ 614 2301, hallado 614.2305; análisis calculado para $C_{32}H_{37}N_3O_6S$-0.75 $H_2O$· C, 63.50, H, 6.41, N, 6 94. Hallado: C, 63 65, H, 6 43; N, 6 74

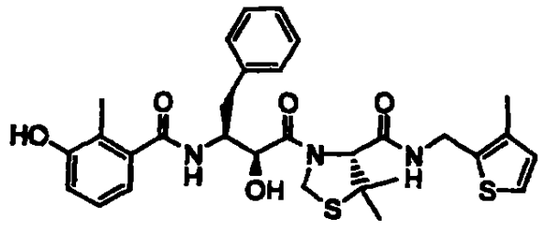
**Ejemplo A7: ácido 3-[2-hidroxi-3-(3-hidroxi-2-metil-benzoilamino)-4-fenil-butiril]-5,5-dimetil-tiazolidino-4-carboxílico metil-(2-metil-bencil)-amida**



$^1$H NMR (DMSO-$d_6$) δ 9 36 (s, 1H), 8.44 (t, *J*= 7 98, 1 H), 8.13-8 07 (m, 2H), 7 34-7.13 (m, 9H), 6.93 (t, *J*= 7 9, 1H), 6.78 (d, *J*= 7.7,1H), 6.53 (d, *J*= 7.1, 1H), 5.58 (d, *J*= 6.8, 1H), 5.45 (d, *J*= 7 0,1H), 5 12 (dd *J*= 7.8 8 2 1H), 4.51-4.31(m, 6H), 2 86-2 67 (m, 2H), 2 19 (s, 3H), 1.81 (s, 3H), 1 51 (s, 3H), 1.34 (s, 3H); análisis calculado para $C_{33}H_{39}N_3O_5$, S-0.37 $H_2O$: C,

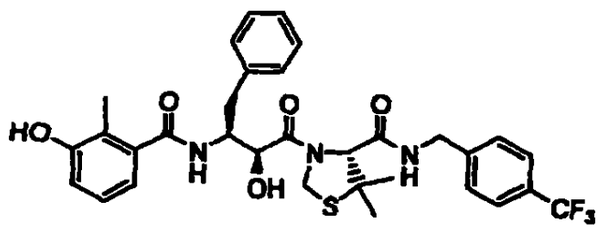
66.45, H, 6.72, N, 7.15. Hallado: C. 66.34; H, 7.28; N, 7.45.

**Ejemplo A8: ácido 3-[2-hidroxi-3-(3-hidroxi-2-metil-benzoilamino)-4-fenil-butiril]-5,5-dimetil-tiazolidino-4-carboxílico metil-(3-metil-tiofen-2-ilmetil)-amida**



IR (puro o KBr $cm^{-1}$) 3150, 3000, 2942, 2187, 1712, 1600, 1567, 1505; $^1H$ NMR (DMSO-$d_6$) δ 9 36 (s, 1H), 8.44 (t, *J*= 7.98, 1H), 8.13-8.07 (m, 2H), 7.34-7.13 (m, 5H), 6.93 (t, *J*= 7 9, 1H), 6 78 (d, *J*= 7.7, 1H), 6.53 (d, *J*= 7.1, 1H), 5 45 (d, *J*= 7.0, 1H), 5.12 (dd, *J*= 7 8, 8.2 1H), 4.51-4 31(m, 4H), 2.86-2 67 (m, 2H), 2 19 (s, 3H), 1.81 (s, 3H), 1.51 (s, 3H), 1.34 (s, 3H); análisis calculado para $C_{30}H_{35}N_3O_5S_2$ calculado C, 61 94 H, 6.06 N, 7 22. Hallado C, 62.38 H, 6.23, N, 7 17

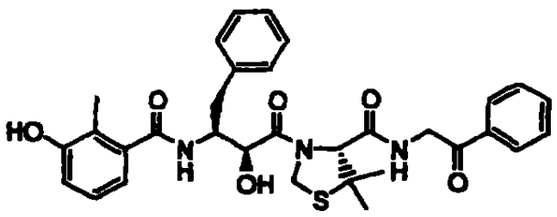
**Ejemplo A9: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 4-trifluorometil-bencilamida**



IR (puro $cm^{-1}$) 3343, 2931, 1543, 1530, 1454, 1326, 1122; $^1H$ NMR (DMSO-$d_6$) δ 9 38 (s, 1H), 8.57 (t, *J*= 5.0, 1H), 8.15 (d, *J*= 8.4, 1H), 7.59 (d, *J*= 8.2, 2H), 7 50 (d, *J*= 8.2, 2H), 7.28-7 13 (m, 5H), 6 93 (t, *J*= 7.5,

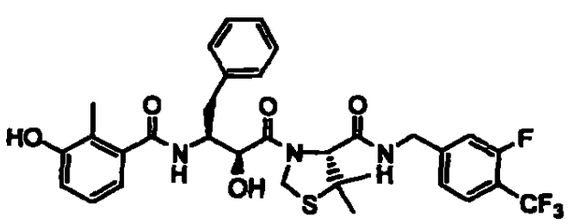
1H), 6.77 (d, *J*= 7 7, 1H), 6 54 (d, *J*= 7.3, 1H), 5.50 (s br, 1H), 5.15.(d, *J*= 9.2, 1H), 5 02 (d, *J*= 9.2, 1H), 4.47-4.21 (m, 5H), 2.85-2.67 (m, 2H), 1 81 (s, 3H), 1.51 (s, 3H), 1.34 (s, 3H),), HRMS (ESI) ***m / z*** calculado para $C_{32}H_{34}F_3$ $N_3O_5SNa$ $(M + Na)^+$ 652 2063, hallado 652.2044; análisis calculado para $C_{32}H_{34}F_3$ $N_3O_5S$-0.25 $H_2O$: C, 60 60; H, 5 48; N, 6 63. Hallado C, 60 50; H, 5 29; N, 6 48.

**Ejemplo A10: ácido (R)-3-((2S,3S)-2-Hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico (2-oxo-2-fenil-etil)-amida**



$^1H$ NMR (DMSO-$d_6$) δ 9.39 (s, 1H), 8.36 (t, *J*= 4.8, 1H), 8.15 (d, *J*= 8 1, 1H), 7.98 (d, *J*= 7.4, 1H), 7.65 (m, 1H), 7 52 (m, 2H), 7.32-7.11 (m, 6H), 6.93 (t, *J*= 7.9, 1H), 6 76 (d, *J*= 7 9, 1H), 6 54 (d, *J*= 7 5, 1H), 5.42 (d, *J*= 6 4, 1H), 5 08 (d, *J*= 9.3, 1H), 5.02 (d, *J*= 9.0, 1H), 4.78-4.30 (m, 5H), 2.84-2.66 (m, 2H), 1.81 (s, 3H), 1.57 (s, 3H), 1.45 (s, 3H); HRMS (ESI) ***m / z*** calculado para $C_{32}H_{35}N_3O_6SNa$ $(M + Na)^+$ 612 2139, hallado 612 2141

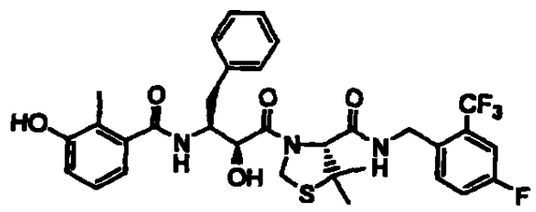
**Ejemplo A11: ácido 3-(2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil-amino}-4-fenil-butanoil-5,5-dimetil-tiazolidino-4-carboxílico 3-fluoro-4-trifluoro metil-bencilamida**



152

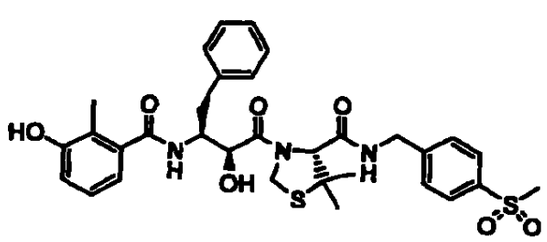
$^1$H NMR (DMSO-$d_6$) δ 9.34 (s, 1H), 8 62 (t, *J*= 5 9, 1H), 8.09-6 54 (m, 11H), 5.45 (s br, 1H). 5 18 (d, *J*= 9.2, 1H), 5 03 (d, *J*= 9 2, 1H), 4 55-4.00 (m, 5H), 4 45 (s, 1H), 2.86-2 49 (m, 2H), 1.82 (s, 3H), 1 53 (s, 3H), 1 36 (s, 3H); análisis calculado para $C_{32}H_{33}N_3O_5SF_4$: C, 59 34, H, 5 14; N, 6.49; S, 4 95 Hallado. C, 59.14, H, 5.29; N, 6.21; S, 4.67

**Ejemplo A12: ácido 3-(2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metianoil-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico-2-trifluorometil-4-fluoro-bencilamida**



$^1$H NMR (DMSO-$d_6$) δ 9.33 (s, 1H), 8 65 (t, *J*= 5 9, 1H), 8.12-6 54 (m, 11H), 5 45 (d, *J*= 6.9, 1H), 5 18 (d, *J*= 9 2, 1H), 5 05 (d, *J*= 9 2, 1H), 4.59-4 34 (m, 5H), 4 50 (s, 1H), 2.85-2.67 (m, 2H), 1.82 (s, 3H), 1 53 (s, 3H), 1 37 (s, 3H); análisis calculado para $C_{32}H_{33}N_3O_5SF_4$: C, 59 34; H, 5.14, N, 6.49; S, 4.95. Hallado· C, 59.26; H, 5 35; N, 6.23; S, 4.69

**Ejemplo A13: ácido 3-[2-hidroxi-3-(3-hidroxi-2-metil-benzoilamino)-4-fenil-butiril]-5,5-dimetil-tiazolidino-4-carboxílico 4-metanosulfonil-benzamida**

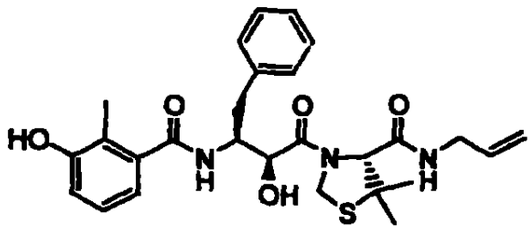


$^1$H NMR (DMSO-$d_6$) δ 9.38 (s, 1H), 8.37 (t, *J*= 5.5, 1H, ), 8.12 (d, 1H, *J*= 8 2, 1H), 7 33-7.13 (m, 7H), 6.94 (t, 1H, *J*= 7.7, 1H, ), 6 84-6 79 (m, 3H), 6.54 (d, 1H, *J*= 7 3, 1H), 5.48 (d, *J*=6.6, 1H), 5.12 (d, *J*= 9.2, 1H), 5.00 (d,

153

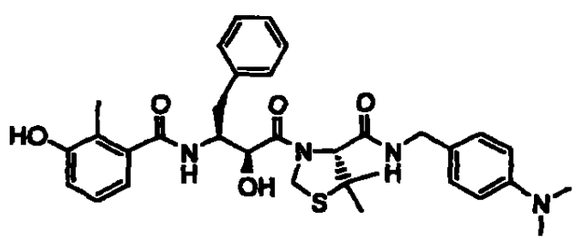
1H, *J*=9.2, 1H), 4.49-4.42 (m, 3H), 4 32 (dd, *J*= 14.8, 6.2, 1H, ), 4.09 (dd, 1H, *J*= 14 8, 5.3, 1H), 3.47 (s, 3H), 2.87-2.68 (m, 2H), 1.82 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3H), análisis calculado para $C_{32}H_{37}N_3O_7S_2$ C, 60 07; H, 5.83; N, 6.57 Hallado C, 60 25; H, 6.13; N, 6.74.

**Ejemplo A14: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico alilamida**



IR (puro $cm^{-1}$) 3342, 2966, 1637, 1531, 1460, 1366, 1284, 1108; $^1H$ NMR (DMSO-$d_6$, ) δ 9.36 (s, 1H), 8 13-8 07 (m, 2H), 7.34-7.13 (m, 5H), 6.93 (t, *J*= 7.9, 1H), 6.78 (d, *J*= 7.7, 1H), 6.53 (d, *J*= 7.0, 1H), 5.82-5.70 (m, 1H), 5.46 (d, *J*= 6.6, 1H), 5.23-4.97 (m, 4H), 4.40 (m, 3H), 3.81-3 59 (m, 2H), 2.86-2.67 (m, 2H), 1 81 (s, 3H), 1.50 (s, 3H), 1.35 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{27}H_{33}N_3O_5S$ Na $(M + Na)^+$ 534.2039, hallado 534.2062, análisis calculado para $C_{27}H_{33}N_3O_5S$ C, 63 38; H, 6 50, N, 8.21. Hallado; C, 63.68; H, 6.57; N, 8.29

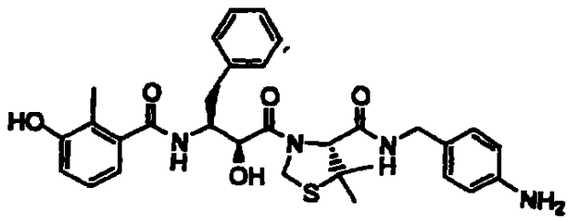
**Ejemplo A15: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 4-dimetilamino-bencilamida**



154

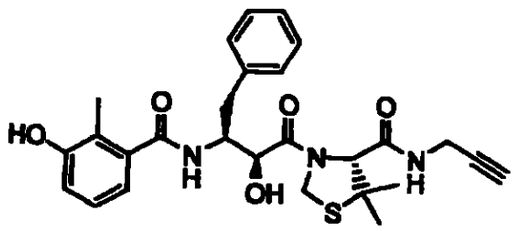
IR (puro $cm^{-1}$) 3331, 2931. 1643, 1519, 1455, 1349, 1284; $^1H$ NMR (DMSO-$d_6$) δ 9 37 (s, 1H), 8.26 (m, 1H), 8.12 (d, *J*= 7.1, 1H) 7 38-6.92 (m, 8H), 6.78 (t, *J*= 7.9, 1H), 6.60 (d, *J*= 8.6, 1H), 6.55 (d, *J*= 7 3. 1H), 6.42 (d, *J*= 8.2, 1H), 5 46 (d, *J*= 6.0, 1H), 5 11 (d, *J*= 9 3, 1H), 5 00 (d, *J*= 9.3, 1H), 4.45 (m, 3H). 4.25 (m, 1H), 4.03 (m, 1H). 2 80 (s, 3H), 2 87-2.73 (m, 2H), 1.82 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{33}H_{40}N_4O_5SNa$ $(M + Na)^+$ 627.2612, hallado 627.2607.

**Ejemplo A16: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 4-amino-bencilamida**



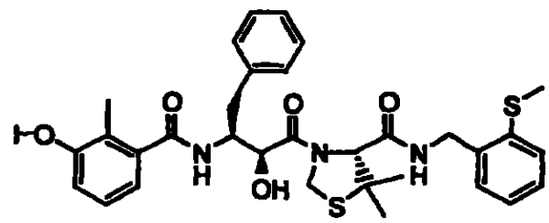
Sólido amarillo pálido. mp= 107-109 °C, IR ($cm^{-1}$) 3378, 2919, 1631, 1518, 1453, 1382, 1281, 1121; $^1H$ NMR(DMSO-$d_6$) δ 9.36 (s, 1H), 8.21 (t, *J*=6 0, 1H), 7 40-7.10 (m, 6H), 8 12 (d, *J* = 8.1, 1H), 6.92 (d, *J*= 8.4, 2H), 6.77 (d, *J*= 7.2, 1H), 6.54 (d, *J*= 7.2, 1H), 6 44 (d, *J*= 8.4, 2H), 5.44 (d, *J*= 6.0, 1H), 5.10 (d, *J*= 9.2, 1H), 4.99 (d, *J*= 9.2, 1H), 4.90 (s, 2H), 4 50-4 32 (m, 3H), 4.22-3.93 (m, 2H), 2.90-2.60 (m, 2H), 1 81 (s, 3H), 1.47 (s, 3H), 1.31 (s, 3 H); análisis calculado para $C_{31}H_{36}N_4O_5S$ 0.25 $H_2O$: C, 64.06; H, 6.33; N, 9.64. Hallado: C, 64.17; H, 6.38; N, 9.60.

**Ejemplo A17: ácido 3-(2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico prop-2-inilamida**



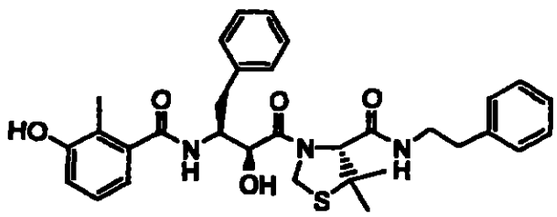
$^1$H NMR (DMSO-$d_6$) δ 9 33 (s, 1H), 8.38 (t, *J*= 5.5, 1H), 8 08 (d, *J*= 8 3, 1H), 7.35-6.53 (m, 8H), 5.46 (d, *J*= 6 6, 1H), 5.10 (d, *J*= 9 2, 1H), 5.02 (d, *J*= 9.2, 1H), 4.44-4.40 (m, 1H), 4 40 (s, 1H), 3.85 (m, 3H), 3 08 (t, *J*= 2.5, 1H), 2.88-2 68 (m, 2H), 1 82 (s, 3H), 1.51 (s, 3H), 1.37 (s, 3H); análisis calculado para $C_{27}H_{31}N_3O_5S$: C, 63.63; H, 6 13; N, 8.24; S, 6 29. Hallado C, 63.50; H, 6.33, N, 7.81, S, 5.68.

**Ejemplo A18: ácido 3-(2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoilamino}-4-fenil-butanoil)]-5,5-dimetil-tiazolidino-4-carboxílico (2-metilsulfanil-fenil)-amida**



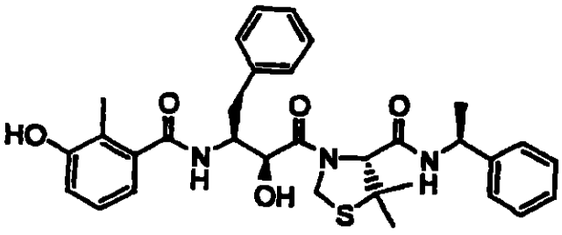
$^1$H NMR (DMSO-$d_6$) δ 9.33 (s, 1H), 8.41 (t, *J*= 5 7, 1H), 8 10 (d, *J*= 8 3, 1H) δ .09-6.54 (m, 12H), 5 46 (d, *J*= 6 6, 1H), 5 14 (d, *J*= 9.2, 1H), 5.04 (d, *J*=9.2, 1H), 4.50-4 02 (m, 4H), 4.50 (s, 1H), 2.89-2.69 (m, 2H), 2 51 (s, 3H), 1.84 (s, 3H), 1 53 (s, 3H), 1.39 (s, 3H); análisis calculado para $C_{32}H_{37}N_3O_5S_2$ C, 63.24; H, 6.14, N, 6.91. Hallado. C, 63.01; H, 6 30, N, 6 53

**Ejemplo A19: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico fenetil-amida**



$^1$H NMR (DMSO-$d_6$) δ 9 41 (s, 1H), 8 38 (t, *J*=4 8, 1H), 8 16 (d, *J*= 8.1, 1H), 8.01 (d, *J*= 7.4, 1H), 7.64 (m, 1H), 7.52 (m, 2H), 7 32-7 11 (m, 6H), 6.93 (t, *J*= 7.9, 1H), 6 76 (d, *J*= 7.9, 1H), 6.54 (d, *J*= 7.5, 1H), 5 42 (d, *J*= 6.4, 1H), 5.10 (d, *J*= 9.3, 1H), 5 05 (d, *J*= 9.0, 1H), 4 80-4.32 (m, 5H), 2.84-2.66 (m, 4H), 1.80 (s, 3H), 1.56 (s, 3H), 1.45 (s, 3H), análisis calculado para $C_{32}H_{37}N_3O_5S$· C, 66 76, H, 6 48; N, 7-30 Hallado C, 66.50, H, 6.56, N, 7.23.

**Ejemplo A20: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico ((S)-1-fenil-etil)-amida**

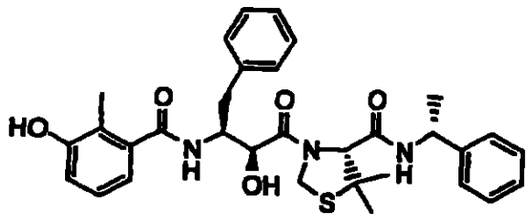


Sólido blanco· mp 114-115 °C; IR(puro, $cm^{-1}$) 3306, 2971, 1643, 1531, 1451, 1372, 1284, 1211, 1107; $^1$H NMR (DMSO-$d_6$) δ 9 36 (s, 1H), 8.45 (d, *J*= 8 2, 1H), 8 19 (d, *J*= 8.2, 1H), 7.32-7 18 (m, 10H), 6.96-6.91 (m, 1H), 6 76 (d, *J*= 8.1, 1H), 6 54 (d, *J*= 7.5, 1H), 5.36 (d, *J* = 7 2, 1H), 5.08 (d, *J*= 9.7, 1H), 5.01 (d, *J*= 9 7, 1H), 4.95-4.85 (m, 2H), 4 48 (s, 1H), 4 45-4 30 (m, 1H), 2.80-2 60 (m, 2H), 1 79 (s, 3H), 1.47 (s, 3H), 1.36 (d, *J*= 7 2, 3H), 1 30 (d, *J*= 7 0, 3H); análisis calculado para $C_{32}H_{37}N_3O_5S$•025 $H_2O$: C, 66.24; H, 6 51, N, 7.24 Hallado C, 66.30, H, 6 56; N, 6.89

**Ejemplo A21: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-**

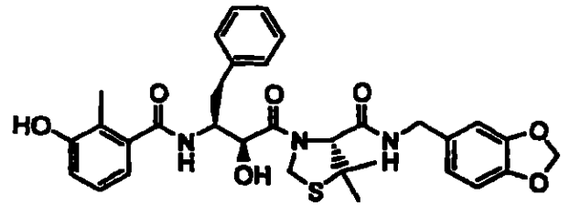
157

**fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico ((R)-1-fenil-etil)-amida**



Sólido blanco· mp 114-115 °C; IR(puro, $cm^{-1}$) 3299, 1643, 1583, 1520, 1454, 1377, 1284, 1104; $^1H$ NMR (DMSO-$d_6$, ) δ 9.35 (s, 1H), 8 36 (d, *J*= 8.2, 1H), 8 15 (d, *J*= 8 2, 1H), 7.44-7 13 (m, 10H), 6.96-6.91 (m, 1H), 6 75 (d, *J*= 8.1, 1H), 6.52 (d, *J*= 6.7.1H), 5.38 (d, *J*= 6.9, 1H), 5.15 (d, *J*= 9.7, 1H), 4.99 (d, *J*= 9.7, 1H). 5.28-4.74 (m, 1H), 4 52(s, 1H), 4.49-4 35 (m, 2H), 2 80-2.60 (m, 2H), 1.79 (s, 3H), 1.50 (s, 3H), 1.38 (s, 3H), 1 34 (d, *J*= 7.0, 3H), análisis calculado para $C_{32}H_{37}N_3O_5S$•0 25 $H_2O$: C, 66.24, H, 6 51; N, 7.24 Hallado· C, 66 38, H, 6.52; N, 7.30.

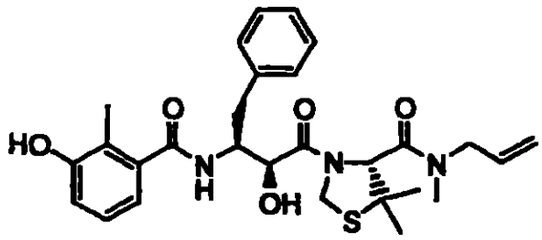
**Ejemplo A22: ácido 3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico (benzo[1,3]dioxol-5-ilmetil)-amida**



IR (puro o KBr $cm^{-1}$) 3302, 2922, 2351, 2333, 1768, 1750, 1646 1537; $^1H$ NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8 44 (s, 1H), 8.13 (d, *J*= 7 9 1H), 7.34-7.13 (m, 5H), 6.99-6.77 (m, 4H), 6.78 (d, *J*= 7.7, 1H), 5 93 (d, *J*= 7.1, 2H), 5.15 (d, *J*= 7.0, 1H), 5.08 (d, *J*= 7 8, 1H), 4.43 (d, *J* =9 32, 2H), 4.34 (m, 2H), 4.12 (d, *J*= 6 18, 1H), 4.08 (d, *J*= 6.08, 1H), 2 86-2.67 (m, 2H), 2.55 (s, 1H), 1.81 (s, 3H). 1.51 (s, 3H), 1.39 (s, 3H); análisis calculado $C_{32}H_{35}N_3O_7S$•0.65 TFA•1.0 $H_2O$· C, 57.31 H, 5 44 N, 6 02. Hallado: C,

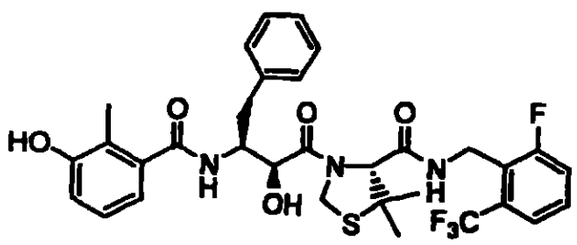
57.58 H, 5 47 N, 5.85.

**Ejemplo A23: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico alil-metil-amida**



IR (puro, $cm^{-1}$) 3380, 2943, 1637, 1460, 1284, $^1H$ NMR (DMSO-$d_6$) δ 9 37 (s, 1H), 8.24 (d, *J* =8.4, 1H), 734-7.15 (m, 5H), 6.94 (t, *J*= 7.5, 1H), 6.77 (d, *J*= 7 7, 1H), 6 53 (d, *J*=7.5, 1H), 5.99 (m, 1H), 5.70-5 65 (m, 1H), 5.49-5.00 (m, 5H), 4 30-3.85 (m, 4H), 3.08 (s, 3H), 2 78-2.65 (m, 2H), 1 80 (s, 3H), 1 58 (s, 3H), 1.38 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{28}H_{35}N_3O_5SNa$ $(M+Na)^+$ 548.2190, hallado 548.2178.

**Ejemplo A24: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico fluoro-trifluorometil-bencilamida**

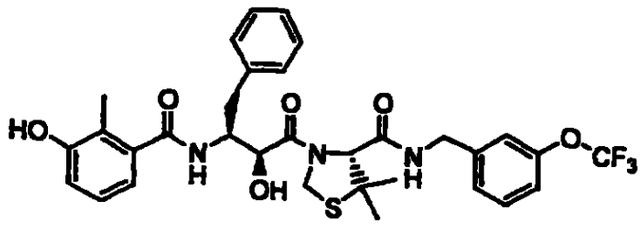


$^1H$ NMR (DMSO-$d_6$) δ 9 34 (s, 1H), 8 32 (t, *J*= 6 0, 1H), 8.20 (d, *J*= 8 4, 1H), 7.70-7.56 (m, 3H), 7 37 (d, *J*= 6.9, 2H), 7.27 (t, *J*= 7 5, 2H), 7 18 (t, *J*= 7.4, 1H), 6.97 (t, *J*= 7 0, 1H), 6.79 (d, *J*= 7 0, 1H), 6 58 (d, *J*= 6.6, 1H), 5.15 (d, *J*= 9 0, 1H), 5.02 (d, *J*= 9.0, 1H), 4.60-4.48 (m, 3H), 4.48-4 32 (m, 2H), 2.88-2.65 (m, 2H), 1.83 (s, 3H), 1 48 (s, 3H), 1.34 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{32}H_{33}N_3O_5SF_4Na$ $(M+Na)^+$ 670.1969, hallado

159

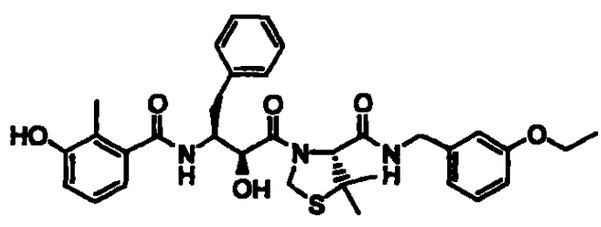
670 1999; análisis calculado para $C_{32}H_{33}N_3O_5S\ F_4 \cdot 1\ H_2O$, 0 3 TFA· C, 55.94, H, 5 08, N, 6.00 Hallado C, 55.74, H, 4.98; N, 5 94

**Ejemplo A25: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 3-trifluorometoxi-bencilamida**



Sólido blanco. mp= 102-105 °C; IR ($cm^{-1}$) 3306, 2966, 1644, 1586, 1520, 1216, 1166; $^1H$ NMR (DMSO-$d_6$) δ 9.38 (s, 1H), 8.53 (t, *J*= 6.0, 1H), 8 12 (d, *J*= 8.1, 1H), 7.40-7.13 (m, 9H), 6.96-6.91 (m, 1H), 6 77 (d, *J*= 8 2, 1H), 6 54 (d, *J*= 7 7, 1H), 5 48 (d, *J*= 6.4, 1H), 5.13 (d, *J*=9 2, 1H), 5 00 (d, *J*=9.2, 1H), 4.46-3.97 (m, 5H), 2 87-2 67 (m, 2H), 1 81 (s, 3H), 1 50 (s, 3H), 1 30 (s, 3H); análisis calculado para $C_{32}H_{34}F_3\ N_3O_6S \cdot 0.25\ H_2O$ C, 59.11, H, 5 35, N, 6.46 Hallado· C, 58.91, H, 5.40; N, 6.30.

**Ejemplo A26: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 3-etoxi-bencilamida**

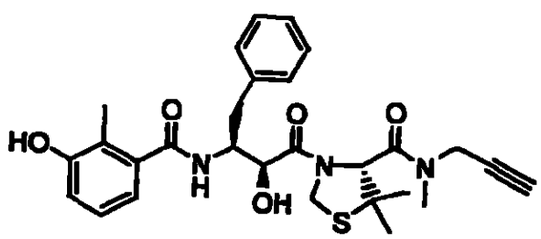


Sólido blanco mp = 105-107 °C, IR ($cm^{-1}$) 3322, 3063, 2978, 1643, 1585, 1538, 1454, 1354, 1265, 1159, 1050, $^1H$ NMR (DMSO-$d_6$) δ 9 38 (s, 1H), 8.40 (t, *J*= 5.6, 1H), 8.11 (d, *J*= 8 2, 1H), 7 30-6.70 (m, 11H), 6 53 (d, *J*= 7 5, 1H), 5.48 (d, *J*= 5.9, 1H), 5.11 (d, *J*= 8 9, 1H), 5.00 (d, *J*= 8-9, 1H),

160

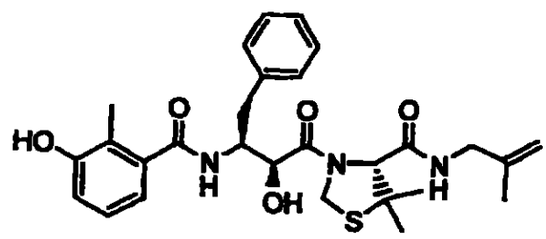
4 50-4.20 (m, 4H), 4.07 (dd, *J*= 15 0, 5.3, 1H), 3 94 (dd, *J*= 14 0, 6 9, 2H), 2-90-2 62 (m, 2H), 1.81 (s, 3H), 1 49 (s, 3H), 1.34 (s, 3H), 1.25 (t, *J*= 6.9, 3H); análisis calculado para $C_{33}H_{39}N_3O_6S \cdot 0.75\ H_2O$: C, 64.01, H, 6.59; N, 6.79 Hallado. C, 63.89, H, 6.27; N, 6.44.

**Ejemplo A27: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico metil-prop-2-inil-amida**



IR (puro, $cm^{-1}$) 3378, 1643, 1461, 1279, 1108, $^1H$ NMR (DMSO-$d_6$) δ 9 37 (s, 1H), 8.21 (d, *J* = 9 2, 1H), 7 33-7 13 (m, 5H), 6 94 (t, *J*= 7.7, 1H), 6 78 (d, *J*= 8.1, 1H), 6.52 (d, *J*= 7 0, 1H), 5.45 (d, *J*= 6.8, 1H), 5.16 (d, *J*= 9 2, 1H), 5 02 (d, *J*= 9.2, 1H), 4.98 (s, 1H), 4.47-4.13 (s, 3H), 4-03-3.92 (m, 1H), 3 17 (s, 3H), 2.88 (s, 1H), 2 79-2 50 (m, 2H), 1 80 (s, 3H), 1.57 (s, 3H), 1.36 (s, 3H); análisis calculado para $C_{28}H_{33}N_3O_5S \cdot 0\ 6H_2O \cdot$ C, 62 95; H, 6 45, N, 7.86. Hallado: C, 62.95; H, 6.39; N, 7 69.

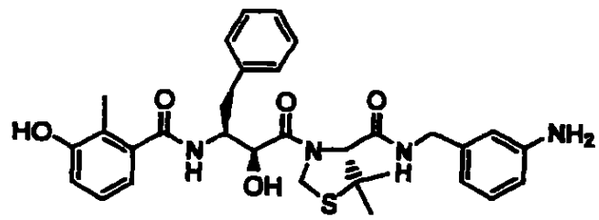
**Ejemplo A28: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico (2-metil-alil)-amida**



$^1H$ NMR (DMSO-$d_6$) δ 9 33, (s, 1H), 8 18-7 79 (m, 2H), 7.39-7.12 (m, 5H), 6 92 (t, *J*= 8 1, 1H), 6 75 (d, *J*= 8.1, 1H), 6 53 (d, *J*= 7.0, 1H), 5.09 (d, *J*=

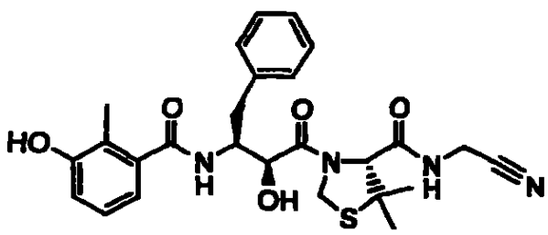
9.2, 1H), 4 96 (d, *J*= 9.2, 1H), 4.70 (s, 1H), 4.43 (s, 1H), 4.40 (br s, 2H) 3.81-3.49 (m, 4H), 2.85-2.65 (m, 2H), 1.82 (s, 3H), 1 63 (s, 3H), 1.49 (s, 3H), 1.35 (s, 3H); análisis calculado para $C_{28}H_{35}N_3O_5S$: C, 63.97; H, 6 71; N, 7.99 Hallado· C, 63 85, H, 6.92; N, 7 65.

**Ejemplo A29: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 3-amino-bencilamida**



IR (puro, $cm^{-1}$) 3401, 2943, 1643, 1525, 1461, 1373, $^1H$ NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.28 (t, *J*= 8 0, 1H), 8.12 (d, *J*= 8 9, 1H), 7.33-6.37 (m, 12H), 5 45 (d, *J*= 7.0, 1H), 5.10 (d, *J*= 8.9, 1H), 4.99 (d, *J*= 8.9, 1H), 4.50-4 35 (m, 3H), 4.30-3 90 (m 2H), 2.90-2.70 (m, 2H), 2.06 (s, 2H), 1.81 (s, 3H), 1 48 (s, 3H), 1.33 (s, 3H), análisis calculado para $C_{31}H_{36}N_4O_5S \cdot 0.5\ H_2O$· C, 63 57; H, 6.37; N, 9.57. Hallado C, 63 59, H, 6.38; N, 9 58

**Ejemplo A30: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico cianometilamida**

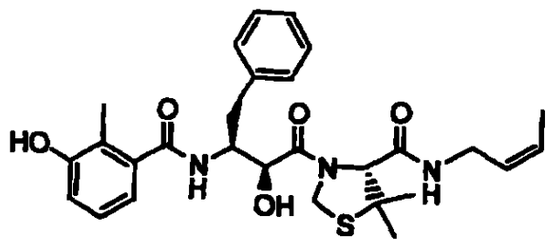


$^1H$ NMR (DMSO-$d_6$) δ 9 34 (s, 1H), 8 65 (s, 1H), 8 15 (m, 1H), 7 42-7 19 (m, 5H), 6 94 (t, *J* = 7.9, 1H), 6 81 (d, *J*= 7.9, 1H), 6.62 (d, *J*= 7.9, 1H), 5 22 (d, *J*= 9.7, 1H), 5.05 (d, *J*= 9.7, 1H), 4 61-4.36 (m, 4H), 3.01-2.71 (m,

162

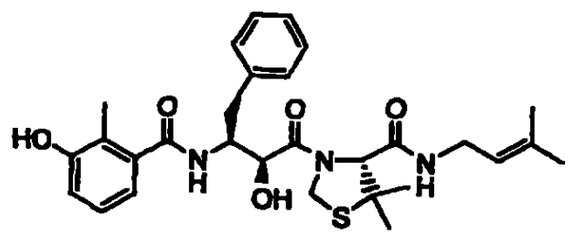
4H), 1.84 (s, 3H), 1 47 (s, 3H), 1.34 (s, 3H); análisis calculado para $C_{26}H_{30}N_4O_5S$: C, 61 16, H, 5 92, N, 10.97. Hallado· C, 61 24, H, 6.14, N, 10 62.

**Ejemplo A31: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico (Z)-but-2-enilamida**



$^1$H NMR (DMSO-$d_6$) δ 9 37 (s, 1H), 8 35 (m, 1H), 8.12 (m, 1H), 7.15-6.98 (m, 6H), 6.77 (d, *J* = 7.7, 1H), 6.68 (d, *J*= 7.5, 1H), 5.60-5 33 (m, 3H), 5.18 (d, *J*= 9.2, 1H), 5 02 (d, *J*= 9.2, 1H), 4 52-4.39 (m, 3H), 3.79-3.68 (m, 2H), 2 92-2 62 (m, 2H), 1.80 (s, 3H), 1.61 (d, *J*= 6 9, 3H), 1.51 (s, 3H), 1 38 (s, 3H); análisis calculado para $C_{28}H_{35}N_3O_5S$ C, 63.97; H, 6.71; N, 7.99 Hallado C, 63.73; H, 6.75; N, 7.83.

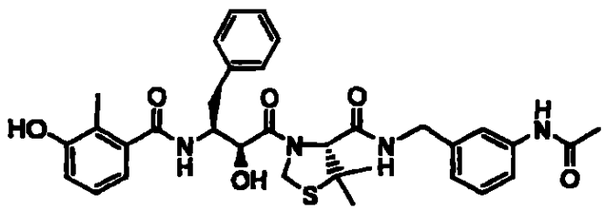
**Ejemplo A32: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico (3-metil-but-2-enil)-amida**



$^1$H NMR (DMSO-$d_6$) δ 9 33 (s, 1H), 8.19 (d, *J*= 8 6, 1H), 7.96 (s br, 1H), 7.39-7.18 (m, 5H). 6 91 (t, *J*= 7.6, 1H), 6 79 (d, *J*= 7.9, 1H), 6.55 (d, *J*= 7.1, 1H), 5.41 (m br, 1H), 5 21 (m, 2H), 5.02 (d, *J*= 9 1, 1H), 4.57-4.37 (m, 3H), 3.79-3 61 (m, 2H), 2.90-2.71 (m, 2H), 1.81 (s, 3H), 1.63 (s, 6H), 1.52

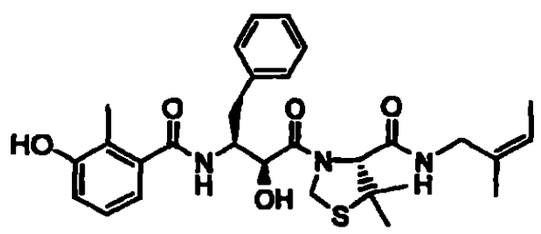
(s, 3H), 1 40 (s, 3H); análisis calculado para $C_{29}H_{37}N_3O_5S$ C, 64.54, H, 6.91; N, 7.79. Hallado: C, 64.75; H, 6.82; N, 7.43

**Ejemplo A33: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5-5-dimetil-tiazolidino-4-carboxílico 3-acetilamino-bencilamida**



Sólido blanco: mp = 145-147 °C; IR (puro, $cm^{-1}$) 3378, 2919, 1637, 1514, 1461, 1361; $^1H$ NMR (DMSO-$d_6$) δ 9.87 (s, 1H), 9.36 (s, 1H), 8.45-8 40 (m, 1H), 8.12 (d, *J*= 7.9, 1H), 7 49-6.91 (m, 10H), 6.77 (d, *J*=7 9, 1H), 6-55 (d, *J*=7.9, 1H), 5.49 (d, *J*= 7 0, 1H), 5 10 (d, *J*= 9.3, 1H), 5 00 (d, *J*= 9.3, 1H), 4.44-3.95 (m, 5H), 2.90-2.62 (m, 2H), 2 00 (s, 3H), 1 80 (s, 3H), 1.48 (s, 3H), 1 32 (s, 3H); análisis calculado para $C_{32}H_{38}N_4O_6S \cdot 1.5\ H_2O$: C, 61 38, H, 6 40; N, 8 68. Hallado. C, 61 49; H, 6.14; N, 8 35.

**Ejemplo A34: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico ((Z)-2-metil-but-2-enil)-amida**

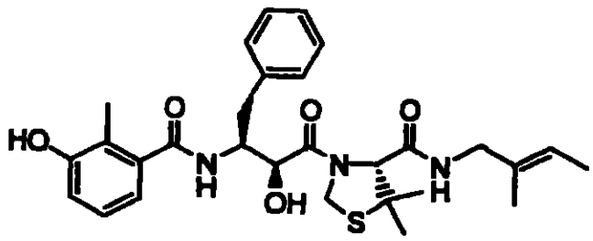


$^1H$ NMR(DMSO-$d_6$, ) δ 9.36 (s, 1H), 8 16 (d, *J*= 8.4, 1H), 8 00 (t, *J*= 5 3, 1H), 7.36-7.13 (m, 5H), 6 94 (t, *J*=7 7, 1H), 6.77 (d, *J*= 8.1, 1H), 6 53 (d, *J*= 7 3, 1H), 5.37 (d, *J*=5.7, 1H), 5.24 (m, 1H), 5 12 (d, *J*= 9.0, 1H), 5 00 (d, *J*= 9 0, 1H), 4.48-4.39 (m, 3H), 3 71 (d, *J*= 3.7, 2H), 2.82-2.65 (m, 2H),

164

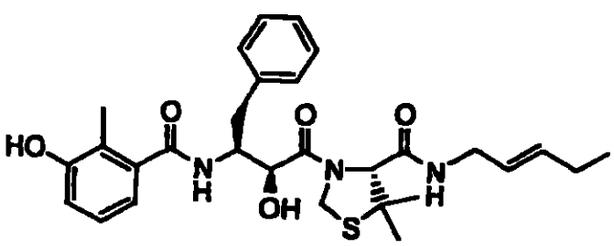
1.80 (s, 3H), 1 61 (m, 6H), 1.49 (s, 3H), 1 35 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{29}H_{37}N_3O_5SNa$ $(M + Na)^+$ 562.2346, hallado 562 2360, análisis calculado para $C_{29}H_{37}N_3O_5S$: C, 64 54; H, 6.91, N, 7.79 Hallado, C, 64.33, H, 6.92, N, 7.60.

**Ejemplo A35: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico ((E)-2-metil-but-2-enil)-amida**



$^1$H NMR(DMSO-$d_6$) δ 9.37(s, 1H), 8 11 (d, *J*= 8 2, 1H), 7 96 (t, *J*= 5 5, 1H), 7.34-7 13 (m, 5H), 6 94 (t, *J*= 7 7, 1H), 6 77 (d, *J*= 8.1, 1H), 6 53 (d, *J*= 7 3, 1H), 5.44 (d, *J*= 6.6, 1H), 5.34 (d, *J*= 6 6, 1H), 5 10 (d, *J*= 9.0, 1H), 4.98 (d, *J*= 9 1, 1H), 4.47-4.36 (m, 3H), 3.71 (dd, *J*= 14 7, 6.6, 1H), 3 46 (dd, *J*= 14.5, 4 8, 1H), 2 85-2 67 (m, 2H), 1 81 (s, 3H), 1.50 (m, 9H), 1 35 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{29}H_{37}N_3O_5SNa$ $(M + Na)^+$ 562 2346, hallado 562 2220

**Ejemplo A36: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico (E)-pent-2-enilamida**

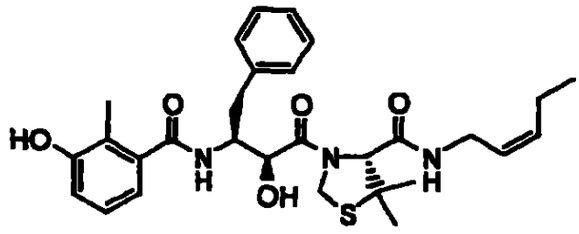


Sólido blanco: mp =113-115 °C; IR(puro, $cm^{-1}$) 3315, 2964, 1643, 1584,

165

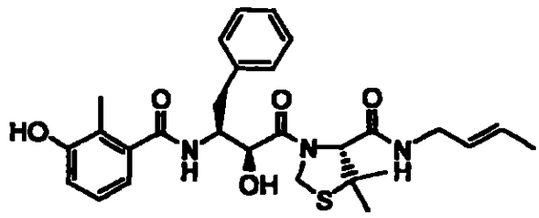
1530, 1454, 1371, 1283, 1104, 969; $^1$H NMR (DMSO-$d_6$, ) δ 9.35 (s, 1H), 8.11 (d, *J*= 8 2, 1H), 8.02 (t, *J*= 5.6, 1H), 7 33-7.13 (m, 5H), 6 96-6.90 (m, 1H), 6 76 (d, *J*= 8.2, 1H), 6 52 (d, *J*= 7.5, 1H), 5 66-5.56 (m, 1H), 5.43 (d, *J*= 6.8, 1H), 5.38-5 31 (m, 1H), 5 10 (d, *J*= 8.9, 1H), 4.99 (d, *J*= 8.9, 1H), 4 47-4 39 (m, 2H), 4.38 (s, 1H), 3 72-3 53 (m, 2H), 2 84-2.66 (m, 2H), 1.98-1 83 (m, 2H), 1.80 (s, 3H), 1 48 (s, 3H), 1.34 (s, 3H), 0 87 (t, *J*= 7 3, 3H); análisis calculado para $C_{29}H_{37}N_3O_5S$•0 5 $H_2O$· C, 63 48; H, 6 98; N, 7.66. Hallado: C, 63.30; H, 7.00; N, 7 28

**Ejemplo A37: ácido (R)-3-((2S,3S)-2-hidroxi-3-{{1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico (Z)-pent-2-enilamida**



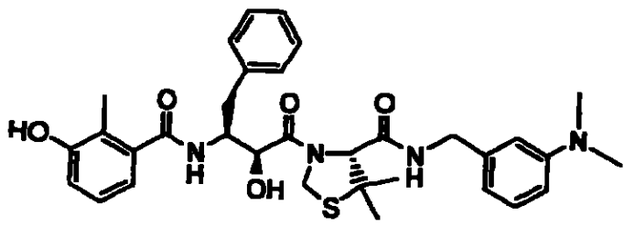

Sólido blanco. mp = 112-113 °C; IR (puro, $cm^{-1}$) 3320, 2965, 1659, 1643, 1538, 1455, 1372, 1285, 1210, 1105, 1048; $^1$H NMR (DMSO-$d_6$) δ 9.35 (s, 1H), 8.11 (d, *J*= 7.9, 1H), 8 03 (t, *J* = 5.3, 1H), 7.35-7.13 (m, 5H), 6.96-6 90 (m, 1H), 6.76 (d, *J*= 8.1, 1H), 6.53 (d, *J*= 7 3, 1H), 5.42 (d, *J*= 6.7, 1H), 5 37-5 35 (m, 1H), 5.29-5.23 (m, 1H), 5 09 (d, *J*= 9.2, 1H), 4.99 (d, *J*= 9 2, 1H), 4.45-4.38 (m, 2H), 4.36 (s, 1H), 3.80-3 62 (m, 2H), 2.84-2.70 (m, 2H), 2.07-1 97 (m, 2H), 1.80 (s, 3H), 1.48 (s, 3H), 1.34 (s, 3H), 0 90 (t, *J*= 7 5, 3H); análisis calculado para $C_{29}H_{37}N_3O_5S$•0 5 $H_2O$ C, 63.48; H, 6 98; N, 7.66 Hallado C, 63.60, H, 6.92; N, 7 48.

**Ejemplo A38: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico (E)-but-2-enilamida**



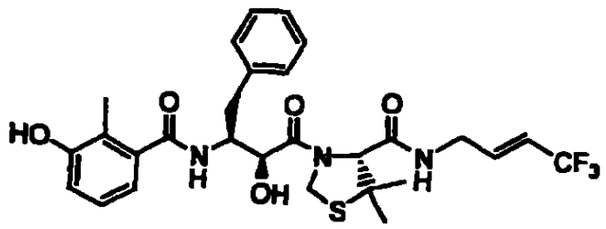
$^1$H NMR (DMSO-$d_6$) δ 9 39 (s, 1H), 8 19 (m br, 1H), 8.03 (m br, 1H), 7.40-7.16 (m, 5H), 6 94 (t, *J*= 7 1, 1H), 6 79 (d, *J*= 7.7, 1H), 6 55 (d, *J*= 7.5, 1H), 5.64-5.31 (m, 3H), 5.19 (d, *J* = 9.2, 1H), 5.02 (d, *J*= 9.2, 1H), 4.55-4 38 (m, 3H), 3 80-3 69 (m, 2H), 2.84-2 70 (m, 2H), 1 80 (s, 3H), 1.61 (s br, 3H), 1.51 (s, 3H), 1.39 (s, 3H), análisis calculado para $C_{28}H_{35}N_3O_5S$ C, 63.73, H, 7.07; N, 7.96 Hallado: C, 63.41; H, 7 23; N, 7.71

**Ejemplo A39: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 3-dimetilamino-bencilamida**



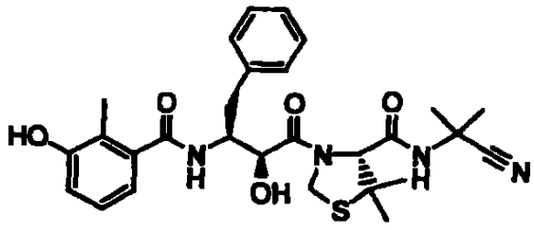
Sólido blanco: mp = 105-106 °C; IR (puro, $cm^{-1}$) 2219, 2966, 1732, 1644, 1585, 1531, 1494, 1454, 1373, 1264, 1047; $^1$H NMR (DMSO-$d_6$) δ 9.37 (s, 1H), 8 33 (t, *J*= 6.1, 1H), 8 08 (d, *J* = 8.1, 1H), 7.32-6.52 (m, 12H), 5 54 (d, *J*= 6 0, 1H), 5 10 (d, *J*= 9 2, 1H), 4.99 (d, *J*= 9.2 1H), 4.43-4 31 (m, 4H), 4.03 (dd, *J*= 15.3, 5.3, 1H), 2 84 (s, 6H), 2 84-2 67 (m, 2H), 1 81 (s, 3H), 1 49 (s, 3H), 1 35 (s, 3H). Análisis calculado para $C_{33}H_{40}N_4O_5S \cdot 0.1\ H_2O$: C, 65 35; H, 6.68; N, 9.24. Hallado; C, 65.49, H, 6 67; N, 9.30.

**Ejemplo A40: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico ((E)-4,4,4-trifluoro-but-2-enil)-amida**



Espuma blanca, IR (puro, $cm^{-1}$) 3332, 1661, 1641, 1584, 1531, 1443 1280, 1119; $^1H$ NMR (DMSO-ds) δ 9.36 (s, 1H). 8.32 (t, *J*= 5.6, 1H), 8 15 (d, *J*= 8.4, 1H), 7 35-7.12 (m, 5H), 7 00-6.90 (m 1H), 6.77 (d, *J*= 7.3, 1H), 6.52 (d, *J*= 7 3, 1H), 6 49-6 40 (m, 1H), 6.08-6.00 (m, 1H), 5.49 (d, *J*= 6 4, 1H), 5.15 (d, *J*= 9.2, 1H), 5 01 (d, *J*= 9 2, 1H), 4 50-4 40 (m, 2H), 4.38 (s, 1H), 4.10-3.90 (m, 1H), 3.80-3.70 (m, 1H), 2.90-2.60 (m, 2H), 1.80 (s, 3H), 1.51 (s, 3H), 1 34 (s, 3H); análisis calculado para $C_{28}H_{32}F_3N_3O_5S$: C, 58.02, H, 5 56, N, 7.25 Hallado C, 58.37, H, 5.70; N, 6.91

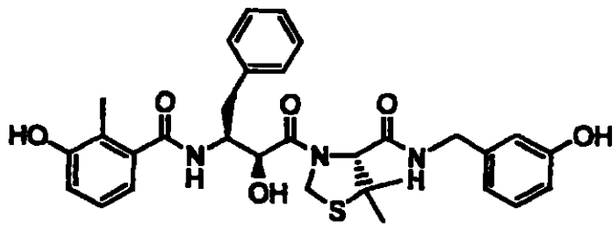
**Ejemplo A41: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico (1-ciano-1, 1-dimetil-metil)-amida**



$^1H$ NMR (DMSO-$d_6$) δ 9-39 (s, 1H), 8 31-8.12 (m, 2H), 7 38-7.17 (m, 5H), 6 97 (t, *J*= 7.3, 1H), 6.79 (d, *J*= 7.7, 1H), 6.59 (d, *J*= 7 4, 1H), 5.41 (m br, 1H), 5.21 (d, *J*= 9.2, 1H), 5.00 (d, *J*= 9.2, 1H), 4 58-4 35 (m, 3H), 2 85-2.62 (m, 2H), 1.81 (s, 3H), 1.62 (s, 6H), 1 47 (s, 3H), 1 39 (s, 3H); análisis calculado para $C_{28}H_{34}N_4O_5S$: C, 62 43, H, 6 36, N, 10.40. Hallado· C, 62.12; H, 6.55, N, 10.13.

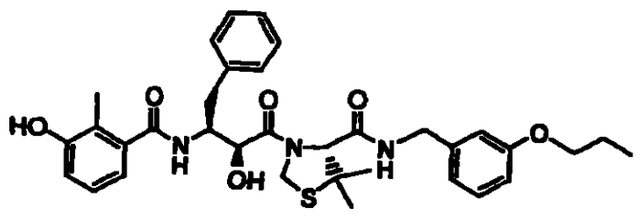
**Ejemplo A42: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-**

**carboxílico 3-hidroxi-bencilamida**



$^1$H NMR (DMSO-$d_6$) δ 9 37 (s, 1H), 9.30 (s, 1H), 8.35 (t, *J*= 5.9, 1H), 8.11 (d, *J*= 8 1, 1H), 733-7 15 (m, 5H), 7 04 (t, *J*=7.7, 1H), 6.94 (t, *J*= 7.9, 1H), 6.77 (d, *J*= 8.1, 1H), 6.70-6.54 (m, 4H), 5.49 (s br, 1H), 5.11 (d, *J*= 9 2, 1H), 5.00 (d, *J*= 9 3, 1H), 4.43 (m, 3H), 4.27 (dd, *J* = 15 2, 6 0, 1H), 4.07 (dd, *J*= 15.0, 5 5, 1H), 2.88-2.67 (m, 2H), 1 82 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H); análisis calculado para $C_{31}H_{35}N_3O_6S\cdot H_2O$: C, 62.50, H, 6.26; N, 7 05. Hallado: C, 62 66, H, 6 19, N, 6 83

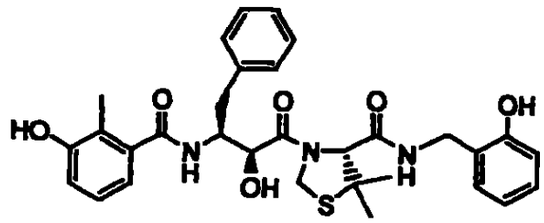
**Ejemplo A43: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 3-propoxi-bencilamida**



Espuma blanca, IR (cm$^{-1}$) 3319, 2966, 1644, 1585, 1531, 1454, 1373, 1264, 1047; $^1$H NMR (DMSO-$d_6$) δ 9 37 (s, 1H), 8.40 (t, *J*= 5.8, 1H), 8.10 (d, *J*= 8.4, 1H), 7 31-6.71 (m, 11H), 6 53 (d, *J*= 7.3, 1H), 5.46 (d, *J*= 6 4, 1H), 5.12 (d, *J*= 9.2, 1H), 5.00 (d, *J*= 9.2, 1H), 4.50-4-20 (m, 4H), 4 11 -3.83 (m, 3H), 2.90-2.62 (m, 2H), 1 81 (s, 3H), 1 72-1.60 (m, 2H), 1.49 (s, 3H), 1.34 (s, 3H), 0 92 (t, *J*= 7 3, 3H). Análisis calculado para $C_{34}H_{41}N_3O_6S\cdot 0.25$ $H_2O$: C, 65.42, H, 6 70; N, 6.73. Hallado. C, 65.49; H, 6.67; N, 6 70.

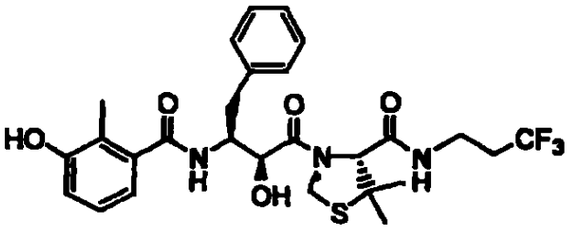
**Ejemplo A44: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-**

**fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 2-hidroxi-bencilamida**



$^1$H NMR (DMSO-$d_6$) δ 9 50 (s, 1H), 9 36 (s, 1H), 8 33 (t, *J*= 5.5, 1H), 8.14 (d, *J*= 8.2, 1H), 7.32-7 12 (m, 6H), 7.04-6 91 (m, 2H), 6.76 (m, 2H), 6 68 (t, *J*= 7 5, 1H), 6 54 (d, *J*= 7.5, 1H), 5.46 (d, *J*= 6.6, 1H), 5 13 (d, *J*= 9.2, 1H), 5.01 (d, *J*= 9.3, 1H), 4.47 (m, 3H), 4 28-4.19 (m, 2H), 2.86-2 67 (m, 2H), 1.82 (s, 3H), 1.49 (s, 3H), 1.32 (s, 3H), HRMS (ESI) *m / z* calculado para $C_{31}H_{36}N_3O_6S$ $(M + H)^+$ 578.2325, hallado 578.2325.

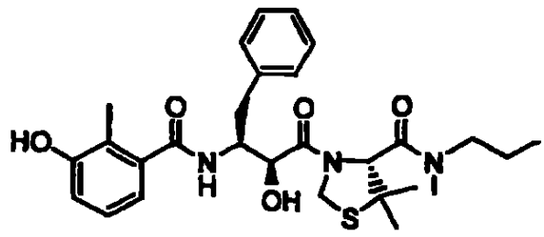
**Ejemplo A45: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil)-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico (3,3,3-trifluoro-propil)-amida**



$^1$H NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.20 (t, *J*= 5.5, 1H), 8.13 (d, *J*= 8.2, 1H), 7.34-7.13 (m, 5H), 6 93 (t, *J*= 7.7, 1H), 6.76 (d, *J*= 8 1, 1H), 6 08 (d, *J*= 7.5, 1H), 5.44 (d, *J*= 6 8, 1H), 5.10 (d, *J*= 9 2, 1H), 5.05 (d, *J*= 9.2, 1H), 4 48-4 38 (m, 2H), 4.35 (s, 1H), 3 32-3.25 (m, 2H), 2 75-2.70 (m, 2H), 2.44-2 35 (m, 2H), 1 80 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{27}H_{33}N_3O_5SF_3$ $(M + H)^+$ 568.2093, hallado 568 2118.

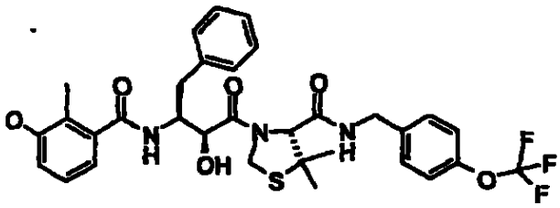
**Ejemplo A46: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-**

**fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico metil-propil-amida**



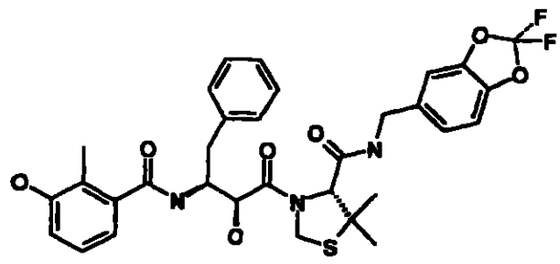
Sólido blanco: mp = 108-110 °C; IR ($cm^{-1}$) 3325, 2964, 1637, 1522, 1456, 1372, 1284; $^1H$ NMR (DMSO-$d_6$) δ 9 35 (s, 1H), 8.22 (d, *J*= 8 6, 1H), 7.34-7 12 (m, 5H), 6.96-6 90 (m, 1H), 6.77-6.75 (m, 1H), 6.53-6.50 (m, 1H), 5.46 (d, *J*= 6 4, 1H), 5 18-4 70 (m, 3H), 4 48-4.20 (m, 2H), 3 31 (s, 3H), 2.90-2.50 (m, 2H). 1.80 (s, 3H), 1.80-1.77 (m, 2H), 1.56 (s, 3H), 1-56-1.36 (m, 2H), 1 37 (s, 3H), 0 79 (t, *J*= 7.5, 3H). Análisis calculado para $C_{28}H_{37}N_3O_5S$•1 0 $H_2O$ C, 63.63, H, 7 20; N, 7 60 Hallado C, 62.03; H, 6.93, N, 7.33.

**Ejemplo A47: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino)-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 4-trifluorometoxi-bencilamida**



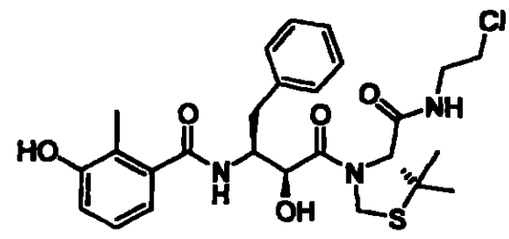
Sólido blanco· $^1H$ NMR (DMSO) δ 9.37 (s, 1H), 8 51 (t, *J*= 5.9, 1H), 8 13 (d, *J*= 7 3, 1H), 7.39 (d, *J*= 8.6, 1H), 7.32-7.10 (m, 8H), 7.00-6.90 (m, 1H), 6 76 (d, *J*= 8 2, 1H), 6 53 (d, *J*= 7 3, 1H), 5 49 (d, *J*= 6.6, 1H), 5.14 (d, *J*= 9 3, 1H), 5.00 (d, *J*= 9.3, 1H), 4.49-4.37 (m, 4H), 4 17 (dd, *J*= 15.0, 5 7, 1H), 2.90-2.64 (m, 2H), 1.81 (s, 3H), 1.49 (s, 3H), 1 32 (s, 3H), HRMS (ESI) *m / z* calculado para $C_{32}H_{35}N_3O_6F_3S$ $(M + H)^+$ 646.2199, hallado 646 2184

**Ejemplo A48: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico (2,2-difluoro-benzo[1,3]dioxol-5-ilmetil)-amida**



$^1$H NMR (DMSO-$d_6$) δ 9 36 (s, 1H), 8.55 (t, *J*= 5.8, 1H), 8.14 (d, *J*= 8.4, 1H), 7.29-7.11 (m, 8H), 6 94 (t, *J*= 7 8, 1H), 6 77 (d, *J*= 7 9, 1H), 6.54 (d, *J*= 7 4, 1H), 5 58 (d, *J*= 8.2, 1H), 5 17 (d, *J*= 9.2, 1H), 5 02 (d, *J*= 9 2, 1H), 4.49-4.39 (m, 3H), 4.43 (s, 1H), 4.21 (dd, *J*= 5.4, 15.3, 1H), 2.83 (m, 1H), 2.71 (dd, *J*= 13 5, 10.7, 1H), 2.20 (s, 3H), 1 51 (s, 3H), 1.34 (s, 3H);
HRMS (ESI) *m / z* calculado para $C_{32}H_{34}F_2N_3O_7S$ $(M + H)^+$ 642 2086, hallado 642.2099; análisis calculado para $C_{32}H_{33}F_2N_3O_7S$ C, 59.90, H, 5 18; N, 6.55 Hallado. C, 60.01; H, 5.27, N, 6 29.

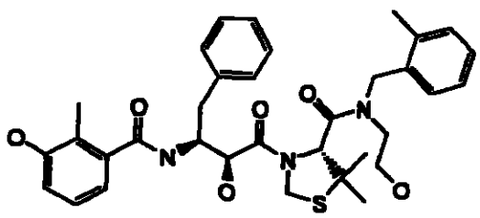
**Ejemplo A49: ácido (R)-3-[(2S,3S)-2-hidroxi-3-(3-hidroxi-2-metil-benzoilamino)-4-fenil-butiril]-5,5-dimetil-tiazolidino-4-carboxílico (2-cloro-etil)-amida**



$^1$H NMR (DMSO-$d_6$) δ 9 40 (s, 1H), 8.31 (t, 1H, *J*= 5 5), 8 17 (d, 1H, *J*= 8.4), 7.37-7.16 (m, 5H), 6.96 (t, 1H, *J*= 7 9), 6.79(d, 1H, *J*= 8 1), 6.55 (d, 1H, *J*= 7.5), 5.47 (d, 1H, *J*=6.8), 5 11 (d, 1H, *J*= 9.3), 5 03 (d, 1H, *J*= 9.3), 4 50 - 4 45 (m, 2H), 4.41 (s, 1H), 3.64-3.58 (m, 2H), 3.46-3 34 (m, 2H), 2.86-2.69 (m, 2H), 1 82 (s, 3H), 1.53 (s, 3H), 1.40 (s, 3H). Masa exacta

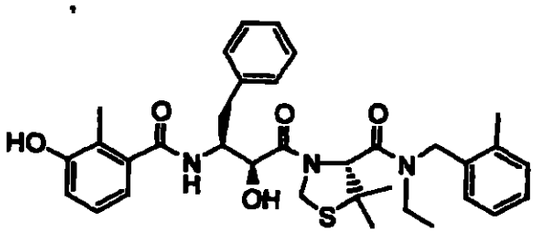
calculada para $C_{26}H_{33}N_3O_5SCl$ $(M + H)^+$ 534.1829, hallado 534.1841.

**Ejemplo A50: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico (2-hidroxi-etil)-(2-metil-bencil)-amida**



$^1$HNMR (DMSO-$d_6$) δ 9.38 (s, 1H), 8.29 (d, *J*= 8.4, 1H), 7 42-6.87 (m, 10H), 6 78 (d, *J*= 7 1, 1H), 6.55 (d, *J*= 6.8, 1H), 5.44 (d, *J*= 6.8, 1H), 5.26(d, *J*=10 0, 1H), 5.08 (s, 1H), 5.04 (d, *J*= 9.2, 1H), 4 82-4.67 (m, 2H), 4.55-4 24 (m, 3H), 3 67 (m, 2H), 3.47 (m, 2H), 2.78 (m, 2H), 2 24 (s, 3H), 1 82 (s, 3H), 1.61 (s, 3H), 1 45 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{34}H_{42}N_3O_6S$ $(M + H)^+$ 620.2794, hallado 620.2798; análisis calculado para $C_{34}H_{41}N_3O_6S \cdot 1\ H_2O$. C, 64 03, H, 6 80, N, 6 59. Hallado: C, 63 66, H, 6 40; N, 6.59.

**Ejemplo A51: ácido 3-[2-hidroxi-3-(3-hidroxi-2-metil-benzoilamino)-4-fenil-butiril]-5,5-dimetil-tiazolidino-4-carboxílico metil-(2-etil-bencil)-amida**

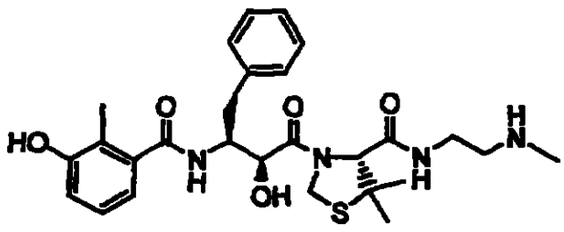


Sólido blanco: $^1$H NMR (DMSO-$d_6$) δ 9 40 (s, 1H), 8.45 (t, *J*= 7.99, 1H), 8 10 (d, *J*= 8 1, 1H), 7.41-6 91 (m, 12H), 6 62 (d, *J*= 7 8, 1H), 5 41 (d, *J*=6.8, 1H), 5.12 (dd, *J*= 8 1, 7.8, 1H), 4.44-4 35 (m, 3H), 4.42 (s, 1H), 2 91-2 67 (m, 2H), 2.54-2.21 (q, *J*= 6.89, 2H), 2.1 (s, 3H), 1.88 (s, 3H),

173

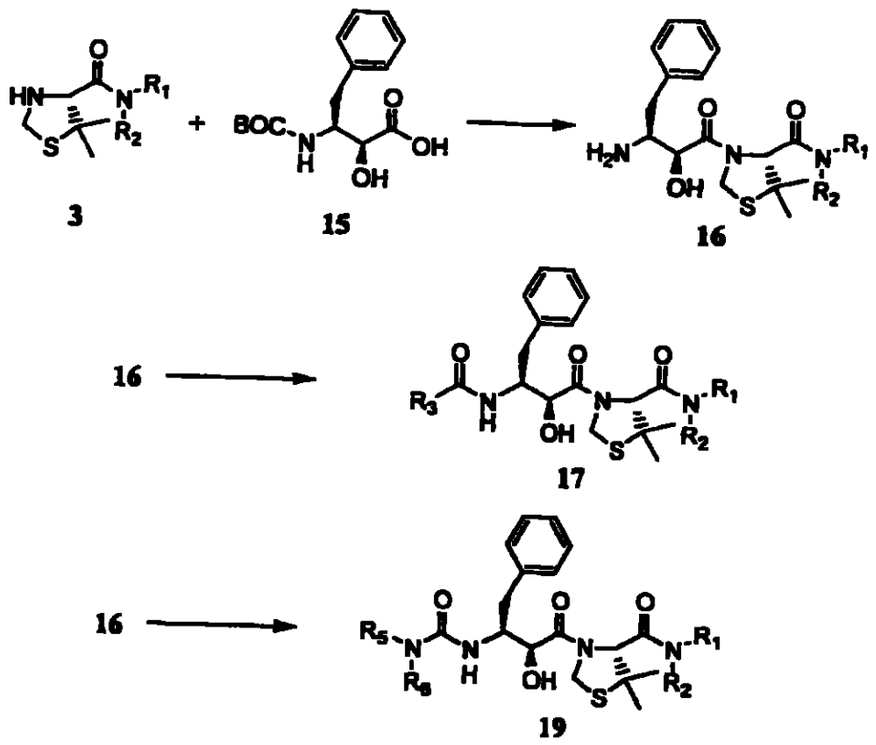
1 56 (t, *J*= 6.90, 3H), 1 49 (s, 3H), 1.34 (s, 3H); análisis ($C_{34}H_{41}N_3O_5S$•0 75 $H_2O$) calculado C (62.34), H (6.43), N (6.23), hallado C (62.72), H (6.52), N (5 97). HRMS (ESI) *m/z* calculado para 604.2845. Hallado 604.2845

**Ejemplo A52: ácido 3-((2S,3S)-2-hidroxi-3-{{1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico (2-metilamino-etil)-amida**



Sólido blanco: $^1$H NMR (DMSO-$d_6$) δ 9.40 (s, 1H). 8.45-8 01 (m, 1H), 7 41-7 13 (m, 12H), 6.98 (t, *J*= 7.8, 1H), 6.78 (d, *J*= 6.85, 1H), 6 55 (d, *J*= 6.99, 1H), 5.41 (m, 1H), 5.12-4.98 (m, 2H), 4.44-4.35 (m, 2H), 3 15 (m, 2H), 2.91-2.67 (m, 2H), 1 84 (s, 3H), 1 66 (q, *J*= 8.2, 4H), 1.34 (s, 3H), análisis ($C_{27}H_{36}N_4O_5S$•0.50 $H_2O$) calculado C (60 31), H (6 94), N (10.42), hallado C (60.59), H (6 50), N (8.08). HRMS (ESI) *m/z* calculado para 556 2771, hallado 556 2770.

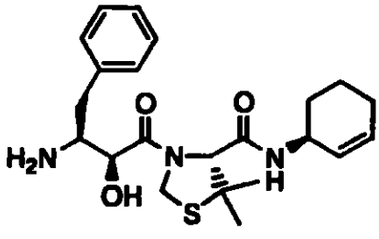
**Método General B**



Amidas de la estructura general **3** (sintetizadas en la misma forma que en la sección Métodos A) se acoplan a ácido boc-protegido **15,** y se exponen a ácido metanosulfónico para producir aminas **16.** Sometiendo las aminas **16** a las condiciones de reacción descritas produjo una serie de amidas **17** y ureas **19.**

Síntesis de aminas del tipo general **16.**

**16a**



El compuesto del título se preparó en la siguiente forma Ácido (R)-5,5-dimetil-tiazolidino-3,4-dicarboxílico 3-*tert*-butil éster **1** (1 95 g, 7.47 mmol) se disolvió en EtOAc (25 mL) y se enfrió a 0°C. Se agregó difenil clorofosfato (1.71 mL, 8.23 mmol) seguido por TEA (1.14 mL, 8.23 mmol) La reacción se agitó a 0°C durante 1h, y se trató con (S)-ciclohex-2-

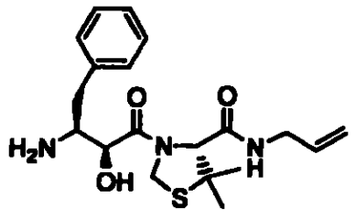
enilamina (0.8 g, 8 23 mmol) La mezcla de reacción se agitó a temperatura ambiente durante la noche, luego se dividió en partes entre 1N HCl (25 mL) y EtOAc (30 mL). La capa orgánica se lavó con $NaHCO_3$ saturado, salmuera, se secó sobre $Na_2SO_4$ y se concentró a un aceite amarillo. El aceite resultante (2 54 g, 7.47 mmol) se disolvió en EtOAc (30 mL) y luego se enfrió a 0°C Se agregó ácido metanosulfónico (2.27 mL, 33 62 mmol) y la solución se agitó a 0°C durante 15 minutos, luego a temperatura ambiente durante 4h. La mezcla se enfrió nuevamente a 0°C y se extinguió con 10% $Na_2CO_3$ (30 mL) luego se extrajo con EtOAc (30 mL) La capa orgánica se lavó con salmuera, se secó sobre $Na_2SO_4$ y se concentró *in vacuo* para producir un aceite amarillo 3. El aceite amarillo resultante (1 86 g, 7 74 mmol) se disolvió en EtOAc (77 mL). Se agregó BOC-AHPBA 4 (2.29 g, 7.74 mmol) seguido por HOBt (1 05g, 7 74 mmol). La mezcla se agitó a temperatura ambiente 1h, luego se enfrió a 0°C. DCC (1.60 g, 7 74 mmol) se agregó lentamente como solución en EtOAc (30 mL). Se dejó calentar gradualmente la mezcla a una temperatura ambiente y se agitó durante la noche La mezcla se filtró y el filtrado se lavó con 1N HCl (40 mL), $NaHCO_3$ saturado (40 mL), salmuera (40 mL), se secó sobre $Na_2SO_4$ y se concentró para producir un sólido blanco crudo (contaminado con DCU) El DCU se retiró por cromatografía de destello (30% a 50% EtOAc en hexanos) para proporcionar un sólido blanco (4 g, 7.73 mmol), el cual se disolvió en EtOAc (30 mL) y luego se enfrió a 0 °C. Se agregó ácido metanosulfónico (2 35 mL, 34 76 mmol) y la solución se agitó a 0°C durante 15 minutos, luego a temperatura ambiente durante 3h. La mezcla se enfrió nuevamente a 0°C y se extinguió con 10% $Na_2CO_3$ (35 mL), luego se extrajo con EtOAc (30 mL) La capa orgánica se lavó con salmuera, se secó sobre $Na_2SO_4$ y se concentró *in vacuo* para producir un material que se recristalizó de 60% EtOAc en hexanos para proporcionar el compuesto del título (2.41g, 80%) como un sólido blanco $^1H$ NMR (DMSO-$d_6$) δ 8 21 (d, $J$ = 8 1, 1 H), 7 31 -7.17 (m, 5H), 5.80 (d, J = 5.6, 1H), 5 52-5 48 (m, 2H), 5 30-5.25 (m, 2H), 4.89 (s, 2H), 4.26 (s, 1H), 4.21-4 00 (m, 3H), 3.15-2 70 (m, 2H), 2.50-2.00 (m, 2H), 2.00-1.00 (m, 4H), 1 49 (s, 3H), 1.31 (s, 3H),

176

análisis calculado para $C_{22}H_{31}N_3O_3S$ C, 63 28, H, 7.48, N, 10 06 Hallado: C, 63.40; H, 7.20; N, 9.98

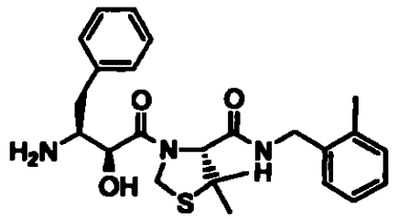
**Las siguientes aminas a-h se prepararon por el método específico bosquejado más arriba usando la amina requerida.**

**16a**

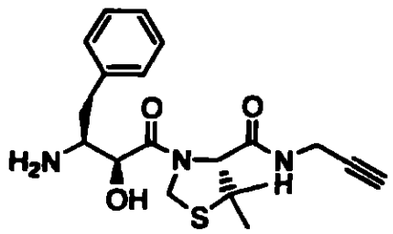


$^1$HNMR (DMSO-$d_6$) δ 8.36 (t, *J*= 6.0, 1H), 7.36-7.14 (m, 5H), 5-70 (m, 1H), 5.34 (s br, 1H), 5.12 (d, *J*= 17 0, 1H), 4.96-4.88 (m, 3H), 4 34 (s, 1H), 4.10 (d, *J*= 7 0, 1H), 3.80-3.55 (m, 2H), 3.06 (d, *J*= 13.0, 1H), 2.87 (t, *J*= 9 0, 1H), 2.38 (dd, *J*= 13.0, 10.0, 1H), 1 52 (s, 3H), 1.33 (s, 3H).

**16b**



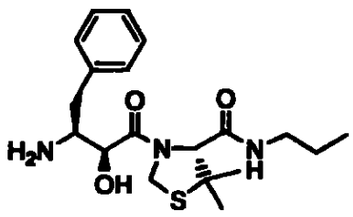
**16c**



$^1$H NMR (DMSO-$d_6$) δ 8.69 (t, *J*= 5.3, 1H), 7 34-7 14 (m, 5H), 5 34 (s br, 1H), 4 90 (s, 2H), 4 29 (s, 1H), 4 08 (d, *J*= 7.0, 1H), 3.90-3.70 (m, 2H), 3.07 (dd, *J*= 13.4, 2 5, 1H), 2 96 (t, *J*= 2 6, 1H), 2.88, (ddd, *J*= 9 8, 8 0, 2.8.

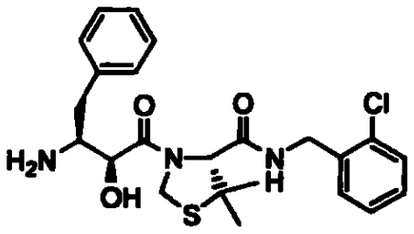
1H), 2 37 (dd, *J*= 13.2, 9.9, 1H), 1.50 (s, 3H), 1 32 (s, 3H).

**16d**



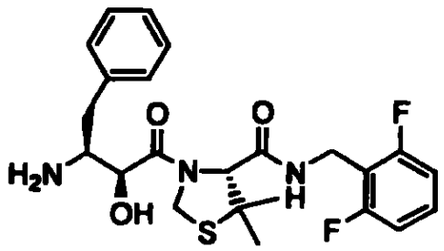
$^1$H NMR (DMSO-$d_6$) δ 8 13 (t, *J*= 5 4, 1H), 7 35-7.15 (m, 5H), 5 28 (d, *J*= 8.1, 1H), 4 79 (m, 2H), 4.27 (s, 1H), 4.07 (t, *J*= 7.1, 1H), 3 10-2 71 (m, 4H), 2 37 (dd, *J*= 13.2, 9 9, 1H), 1 49 (s, 3H), 1 34 (m, 2H), 1.33 (s, 3H), 0 77 (t, *J*= 7 4, 3H).

**16e**



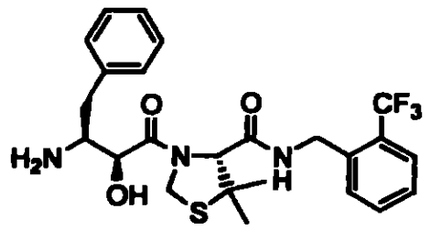
Rendimiento aislado 84%, MS (APCI, m/z) 461, 463 (M+H)

**16f**



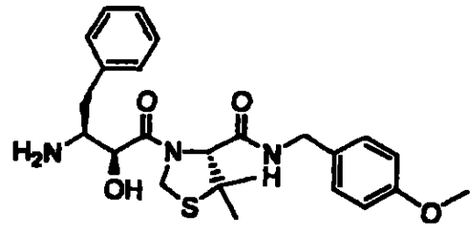
Rendimiento aislado: 93%; MS (APCI, *m/z)* 464 (M+H)

**16g**



Rendimiento aislado· 86%; MS (APCI, m/z): 496 (M+H).

**16h**



Rendimiento aislado. 87 % MS-APCI (*m/z*+)· 458

**Síntesis de productos finales del tipo general 17 de 16a-h, Métodos Generales:**

Formación de amida – A una solución de ácido, amina 16 y HOBT en $CH_2Cl_2$ se agregó EDC y la solución se agitó durante la noche a temperatura ambiente La solución se concentró *in vacuo* y el residuo se disolvió en acetato de etilo y una pequeña porción de agua La solución se lavó con $NH_4Cl$ saturado o 0.5N HCl (2x), $NaHCO_3$ saturado (2x), salmuera (1x), se secó con $MgSO_4$ y se concentró *in vacuo* El residuo resultante se sometió a cromatografía de destello de gel de sílice o HPLC preparativa para proporcionar el producto deseado

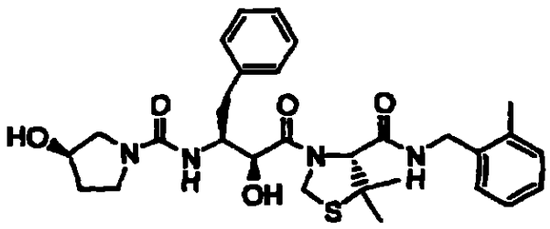
Formación de urea #1 – La amina correspondiente e isocianato (1 1-1.2 eq.) se tomaron en diclorometano y se agitó a temperatura ambiente bajo nitrógeno. (1.5 hr a durante la noche) El solvente se retiró entonces *in vacuo* y el residuo resultante se sometió a cromatografía de destello de gel

de sílice o HPLC preparativa para proporcionar el producto deseado.

Formación de urea #2 - La amina correspondiente se disolvió en $CH_2Cl_2$ y se trató con diisopropiletilamin (1 5 eq ) y fosgeno (1 eq., 20% solución, en tolueno) a -78°C La solución resultante se calentó a temperatura ambiente y se trató con la amina de estructura general 16 El residuo resultante se sometió a cromatografía de destello de gel de sílice o HPLC preparativa para proporcionar el producto deseado.

Síntesis Específica de Urea

**Ejemplo B1: ácido 3-(2-hidroxi-3-{[1-(3-hidroxi-pirrolidino-il)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico-2-metil-bencilamida**



(R)-Pirrolidino-3-ol (0 21 g, 2.40 mmol) se disolvió en $CH_2Cl_2$ seco (15 mL) y se enfrió a -78°C bajo argón con agitación magnética. A esta solución se agregó diisopropiletilamina (0 63 mL, 3.63 mmol) seguido por fosgeno como una 20% solución en tolueno (1.2 mL, 2 40 mmol). La solución amarilla resultante se agitó durante 20 min a -78°C luego se calentó a temperatura ambiente. La solución se concentró y re-disolvió en $CH_2Cl_2$ seco (5 mL) y THF (5 mL). A esto se agregó diisopropiletilamina (0 31 mL, 1 81 mmol) seguido por **16c.** El resultado se agitó durante 16h a 23°C luego se diluyó con EtOAc (50 mL). La mezcla se lavó secuencialmente con 10% ácido cítrico (1 x 50 mL), $NaHCO_3$ saturado (1 x 50 mL), $H_2O$ (1 x 50 mL). Los orgánicos se secaron sobre $Na_2SO_4$, se filtraron, y se concentraron. El residuo se purificó cromatografía de

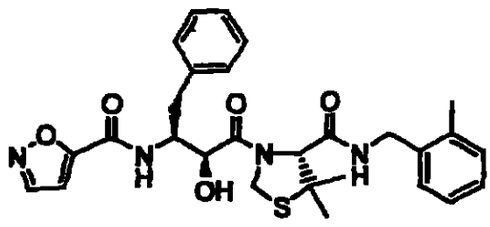
180

columna de destello (5% MeOH in EtOAc) para producir el compuesto del título (0.12 g, 18%) como una espuma blanca.

$^1$H NMR (DMSO-$d_6$) δ 8.38 (t, *J*= 5 7, 1H), 7.34-7.09 (m, 10H), 5.99 (d, *J*= 8.3, 1H), 5.04 (d, *J*= 9.5, 1H), 4.96 (d, *J*= 9.5, 1H), 4 49 (s, 1H), 4 48-4.38 (m, 3H), 4.22-3.83 (m, 4H), 3 29-3.04 (m, 3H), 2 77-2.70 (m, 2H), 2.28 (s, 3H), 1 52 (s, 3H), 1 32 (s, 3H), 1.82-1.69 (m, 2H), HRMS (ESI) *m/z* calculado para $C_{29}H_{38}N_4O_5SNa$ $(M + Na)^+$ 577.2455, hallado 577.2440; análisis calculado para $C_{29}H_{38}N_4O_5S \cdot 2H_2O$ C, 58.96; H, 7.17; N, 9 48; S, 5.43. Hallado: C, 58.90; H, 6.40, N, 9.23, S, 5.24.

Los siguientes ejemplos se prepararon por el método específico correspondiente bosquejado más arriba usando el fragmento P2 requerido.

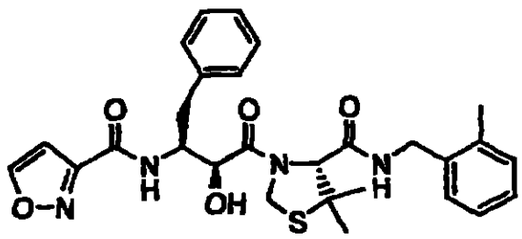
**Ejemplo B2: ácido isoxazol-5-carboxílico {(1S,2S)-1-bencil-3-[(R)-5,5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-amida**



Sólido blanco mp = 82-84 °C; IR (puro, $cm^{-1}$) 3313, 2967, 3656, 1538, 1454, 1372, 1283, 1211, 1108, 916, $^1$H NMR (DMSO-$d_6$) δ 8.91 (d, *J*= 8.6, 1H), 8.67 (d, *J*=2.0, 1H), 8.35 (t, *J*= 5.0, 1H), 7.31-7 08 (m, 9H), 7.03 (d, *J*=2.0, 1H), 5 63 (d, *J*= 6.9, 1H), 5.02 (d, *J*= 8.6, 1H), 4 97 (d, *J*= 8 6, 1H), 4.60-4.30 (m, 4H), 4.14-4.00 (m, 1H), 2.90-2.75 (m, 2H), 2.23 (s, 3H), 1 49 (s, 3H), 1.28 (s, 3H), HRMS (ESI) *m / z* calculado para $C_{28}H_{32}N_4O_5SNa$ $(M+Na)^+$ 559.1986, hallado 559.1994; análisis calculado para $C_{28}H_{32}N_4O_5S \cdot 0.5H_2O$: C, 61-63, H, 6.10, N, 10 27. Hallado. C, 61 40; H, 5.91; N, 9 97

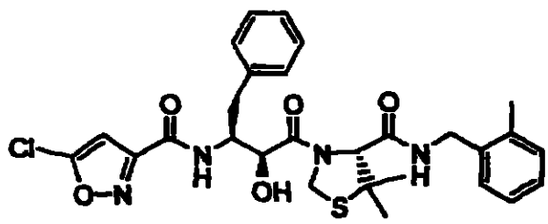
181

**Ejemplo B3: ácido isoxazol-3-carboxílico {(1S,2S)-1-bencil-3-[(R)-5,5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-amida**



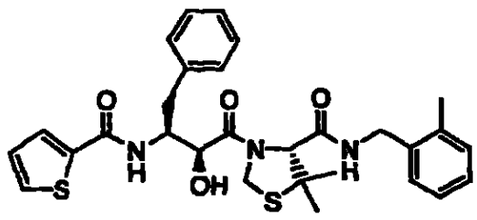
Sólido blanco; IR (puro, $cm^{-1}$) 3436, 1643, 1537, 1425, 1378; $^1H$ NMR (DMSO-$d_6$) δ 9.03 (s, 1H), 8.66 (d, *J*= 8.7, 1H), 8 32 (t, *J*= 5 3, 1H), 7.30-7 11 (m, 9H), 679 (s, 1H), 5 67 (d, *J*= 6 8, 1H), 4 97 (s, 2H), 4 47-4 32 (m, 4H), 4 09 (dd, *J*= 15.0, 5 0, 1H), 2 84 (m, 2H), 2.24 (s, 3H), 1.49 (s, 3H), 1.34 (m, 3H), HRMS (ESI) *m / z* calculado para $C_{28}H_{32}N_4O_5SNa$ $(M + Na)^+$ 559 1986, hallado 559 1980.

**Ejemplo B4: ácido 5-cloro-isoxazol-3-carboxílico {(1S,2S)-1-bencil-3-[(R)-5,5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-amida**



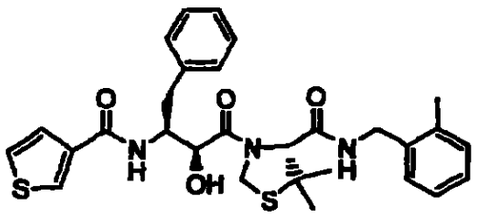
Sólido blanco; IR (puro, $cm^{-1}$) 3320, 2969, 1657, 1547, 1434, 1372, 1266; $^1H$ NMR (DMSO-$d_6$) δ 8 74 (d, *J*= 8.2, 1H), 8.29 (t, *J*= 5.5, 1H), 7 28-7 08 (m, 9H), 6.90 (s, 1H), 5 72 (d, *J*= 7 1, 1H), 4 96 (s, 2H), 4.44 (m, 3H), 4.32 (dd, *J*= 15 2, 6 0, 1H), 4.09 (dd, *J*= 15.2, 4 6, 1H), 2.85 (m, 2H), 2.83 (s, 3H), 1 49 (s, 3H), 1 33 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{28}H_{31}N_4O_5SClNa$ $(M + Na)^+$ 593 1596, hallado 593 1569

**Ejemplo B5: ácido (R)-3-{(2S,3S)-2-hidroxi-4-fenil-3-((1-tiofen-2-il-metanoil)-amino]-butanoil}-5,5-dimetil-tiazolidino-4-carboxílico 2-metil-bencilamida**



Sólido blanco mp = 98-101 °C, IR (puro, $cm^{-1}$) 3416, 1644, 1538, 1455, 1372, 1291, 1107; $^1H$ NMR (DMSO-$d_6$) δ 8 56 (d, *J*= 8.0, 1H), 8 38 (t, *J*= 4 8, 1H), 7 85 (d, *J*= 3.5, 1H), 7 69 (d, *J*= 4-8, 1H), 7 36-7 08 (m, 10H), 5.38 (d, *J*= 7 2, 1H), 5 10 (d, *J*= 8.8, 1H), 4.98 (d, *J*= 8.8, 1H), 4.54-4 20 (m, 5H), 2 90-2 70 (m, 2H), 2 25 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{29}H_{33}N_3O_4S_2Na$ $(M + Na)^+$ 574.1805, hallado 574.1818, análisis calculado para $C_{29}H_{33}N_3O_4S_2 \cdot 0.75\ H_2O$: C, 61 62; H, 6 15; N, 7.43. Hallado: C, 61.31; H, 5 97; N, 7.28.

**Ejemplo B6: ácido (R)-3-{(2S,3S)-2-hidroxi-4-fenil-3-[(1-tiofen-3-il-metanoil)-amino]-butanoil}-5,5-dimetil-tiazolidino-4-carboxílico 2-metil-bencilamida**

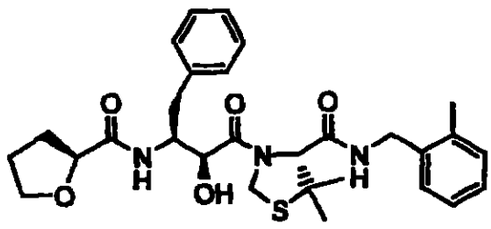


Sólido blanco mp = 98-100 °C, IR (puro, $cm^{-1}$) 3312, 3086, 2966, 1644, 1538, 1455, 1372, 1286, 1109; $^1H$ NMR (DMSO-$d_6$) δ 8 42-8 34 (m, 2H), 8 14 (m, 1H), 7 54-7.06 (m, 11H), 5.74 (d, *J*= 9.3, 1H), 5.35 (d, *J*= 6 8, 1H), 4 99 (d, *J*= 9.3, 1H), 4.53 (d, *J*= 3.0, 1H), 4.50 (s, 1H), 4 42 (dd, *J*= 15.0, 7.0, 1H), 4-40-4.30 (m, 1H), 4.15 (dd, *J*= 15 0, 5 0, 1H), 2.90-2.70

183

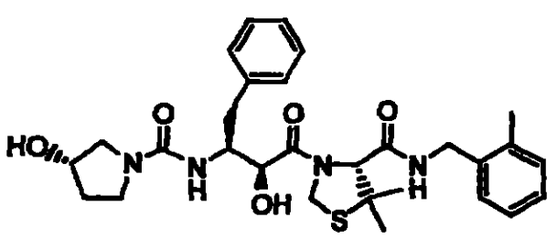
(m, 2H), 2.26 (s, 3H), 1.50 (s, 3H), 1.35 (s, 3H), HRMS (ESI) *m / z* calculado para $C_{29}H_{33}N_3O_4S_2Na$ $(M + Na)^+$ 574.1805, hallado 574 1789; análisis calculado para $C_{29}H_{33}N_3O_4S_2 \cdot 1H_2O$· C, 61.14, H, 6.19; N, 7 38 Hallado: C, 60.74, H, 5 90; N, 7 15

**Ejemplo B7: ácido (R)-3-{(2S,3S)-2-hidroxi-4-fenil-3-[((S)-1-tetrahidro-furan-2-il-metanoil)-amino]-butanoil}-5,5-dimetil-tiazolidino-4-carboxílico 2-metil-bencilamida**



Sólido blanco: mp = 82-84 °C; IR (puro, $cm^{-1}$) 3314, 2969, 1651, 1531, 1456, 1372, 1109, 1071; $^1H$ NMR (DMSO-$d_6$) δ 8.35 (t, *J*=6.0, 1H), 7 60 (d, *J*= 9.2, 1H), 7.31-7.09 (m, 9H), 5.45 (d, *J*= 6.8, 1H), 4 97 (d, *J*= 9.5, 1H), 4.93 (d, *J*= 9 5, 1H), 4 46 (s, 1H), 4.41-4.07 (m, 4H), 3 77-3 65 (m, 3H), 2.78-2.64 (m, 2H), 2.26 (s, 3H), 2 00-1 80 (m, 1H), 1.60 (m, 1H), 1.49 (s, 3H), 1 44-1.38 (m, 2H), 1 34 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{29}H_{37}N_3O_5S$ Na $(M + Na)^+$ 562 2346, hallado 562 2345, análisis calculado para $C_{29}H_{37}N_3O_5S \cdot 0.5\ H_2O$ C, 63.48; H, 6.98; N, 7.66 Hallado C, 63.61, H, 6 85; N, 7.58.

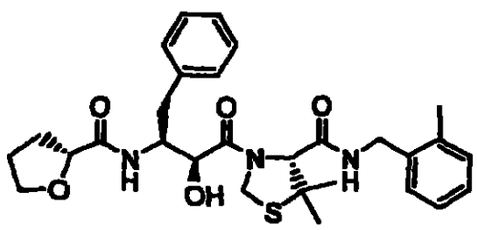
**Ejemplo B8: ácido 3-(2-hidroxi-3-{[1-(3-hidroxi-pirrolidino-il)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico-2-metil-bencilamida**



184

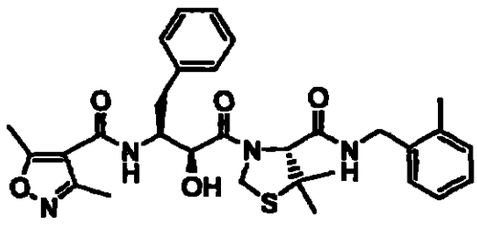
$^1$H NMR (DMSO-$d_6$) δ 8 38 (t, *J*= 5.5, 1H), 7 34-7.09 (m, 10H), 5.99 (d, *J*= 8 2, 1H), 5 04 (d, *J*= 9.5, 1H), 4 96 (d, *J*= 9 5, 1H), 4.49 (s, 1H), 4.48-4 38 (m, 3H), 4 35-4.16 (m, 3H), 4 00 (m, 1H), 3.29-3 04 (m, 3H), 2 78-2.70 (m, 2H), 2 28 (s, 3H), 1.83-1.65 (m, 2H), 1.52 (s, 3H), 1 36 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{29}H_{38}N_4O_5SNa$ (M + Na)$^+$ 577.2455, hallado 577.2473; análisis calculado para $C_{29}H_{38}N_4O_5S•2H_2O$: C, 58.96; N, 9.48. Hallado. C, 58.68; N, 9.11.

**Ejemplo B9: ácido (R)-3-{(2S,3S)-2-hidroxi-4-fenil-3-[((R)-1-tetrahidro-furan-2-il-metanoil)-amino]-butanoil}-5,5-dimetil-tiazolidino-4-carboxílico 2-metil-bencilamida**



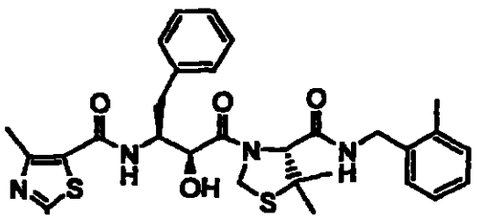
Sólido blanco; IR (puro, cm$^{-1}$) 3324, 2959, 2873, 1724, 1651, 1526, 1455, 1372, 1289, 1073, $^1$H NMR (DMSO-$d_6$) δ 8 35 (t, *J*= 4.9, 1H), 7.77 (d, *J*= 8.9, 1H), 7.52-7.09 (m, 9H), 5 51 (d, *J*= 6.6, 1H), 4 97-4.89 (m, 2H), 4 52-3.66 (m, 8H), 2.90-2 60 (m, 2H), 2 25 (s, 3H), 1.99-1.63 (m, 4H), 1 48 (s, 3H), 1.33 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{29}H_{37}N_3O_5SNa$ (M + Na)$^+$ 562 2346, hallado 562.2366. Análisis calculado para $C_{29}H_{37}N_3O_5S•0.25\ H_2O$: C, 64 01; H, 6.95; N, 7.72. Hallado C, 64 20; H, 6.90, N, 7.82.

**Ejemplo B10: ácido 3,5-dimetil-isoxazol-4-carboxílico {(1S,2S)-1-bencil-3-[(R)-5,5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-amida**



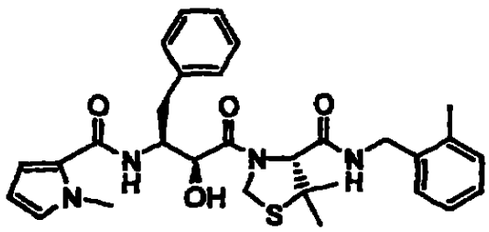
Rendimiento aislado 92%; $^1$H-NMR (400 MHz, dmso-$d_6$): δ 8 38 (t, 1H), 8.13 (d, 1H), 7.04 -7 35 (m, 10H), 5.52 (d, 1H), 5.09 (d, 1H), 5.0 (d, 1H), 4.53 (m, 1H), 4 5 (s, 1H), 4.48 (m, 2H), 4.17 (dd, 1H), 2.87 (dd, 1H), 2 7 (q, 1H), 2.26 (s, 6H), 2.09 (s, 3H), 1 52 (s, 3H), 3.35 (s, 3H), IR (KBr en cm$^{-1}$)· 3313, 1643, 1521, 743; MS (APCI, m/z) 565 (M+H), 519, 265; $C_{30}H_{36}N_4O_5S$•1.0.69 $H_2O$ calculado: C 62 43, H 6 53, N 9.71, observado: C 63.81, H 6.43, N 9.92, HPLC . Rf (mın.) 20.167; pureza: 98%.

**Ejemplo B11: ácido 2,4-dimetil-tiazol-5-carboxílico {1-bencil-3-[5, 5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-amida**



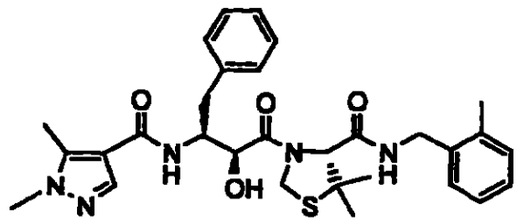
Rendimiento aislado. 80%, $^1$H-NMR (400 MHz, dmso-$d_6$)· δ 8.35 (t, 1H), 8.14 (d, 1H), 7.0 -7.35 (m, 10H), 5.48 (d, 1H), 5 04 (d, 1H), 5 0 (d, 1H), 4.52 (m, 1H), 4.4 (s, 1H), 4.35 (m, 2H), 4.14 (dd, 1H), 2.78 (d, 2H), 2.57 (s, 3H), 2.30 (s, 3H), 2 26 (s, 3H), 1 48 (s, 3H), 1.35 (s, 3H) , IR (KBr en cm$^{-1}$) 3310, 1641, 1534, 743; MS (APCI, m/z): 581 (M+H), 317, 265, 259; $C_{30}H_{36}N_4O_4S2$ 0.39 $H_2O$ calculado: C 61.30, H 6.31, N 9 53, observado. C 62.04, H 6.25, N 9.65, HPLC . Rf (min ) 19.613, pureza 98%.

**Ejemplo B12: ácido (R)-3-{(2S,3S)-2-hidroxi-3-[(1-metil-1H-pirrol-2-carbonil)-amino]-4-fenil-butiril}-5,5-dimetil-tiazolidino-4-carboxílico 2-metil-bencilamida**



Rendimiento aislado 82%, $^1$H-NMR (400 MHz, dmso-$d_6$) δ 8 35 (t, 1H), 7.91 (d, 1H), 7.35 -7 04 (m, 10H), 6.78 (s, 2H), 5 96 (s, 1H), 5 35 (d, 1H), 5 13 (s, 1H), 5.0 (d, 1H), 4 48 (s, 2H), 4 38 (dd, 1H), 4.30 (m, 1H), 4.13 (dd, 1H), 3.7 (s, 3H), 2.8 (m, 2H), 2.26 (s, 3H), 1 52 (s, 3H), 1 35 (s, 3H) ; IR (KBr en cm$^{-1}$): 3324, 1639, 1538, 735, MS (APCI, m/z) 549 (M+H), 503, 382, 285; $C_{30}H_{36}N_4O_4S1.2$ 44 $H_2O$ calculado: C 60 80, H 6 95, N 9 45, observado. C 65 67, H 6 61, N 10.21, HPLC : Rf (min.) 20 745, pureza. 100%.

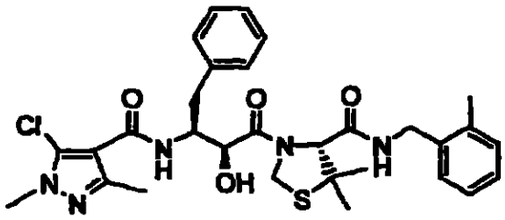
**Ejemplo B13: ácido (R)-3-{(2S,3S)-3-[(1,5-dimetil-1H-pirazol-4-carbonil)-amino]-2-hidroxi-4-fenil-butiril}-5,5-dimetil-tiazolidino-4-carboxílico 2-metil-bencilamida**



Rendimiento aislado 68%, $^1$H-NMR (400 MHz, dmso-$d_6$): δ 8 30 (t, 1H), 7.83 (d, 1H), 7 31 -7.04 (m, 10H), 6.30 (s, 1H), 5 48 (d, 1H), 4.92 (s, 2H), 4.30 - 4.48 (m, 4H), 4.17 (dd, 1H), 3 7 (s, 3H), 2 74 (m, 2H), 2.26 (s, 3H), 2 8 (s, 3H), 3.48 (s, 3H), 1 30 (s, 3H), IR (KBr en cm$^{-1}$)· 3313, 1645, 1532, 744; MS (APCI, m/z) 564 (M+H), 300, 272, $C_{30}H_{37}N_5O_4S1.0.5$ $H_2O$ calculado: C 62.86, H 6.69, N 12.22, observado· C 63.92, H 6 62, N 12 42; HPLC · Rf (min.) 19 724; pureza 100%.

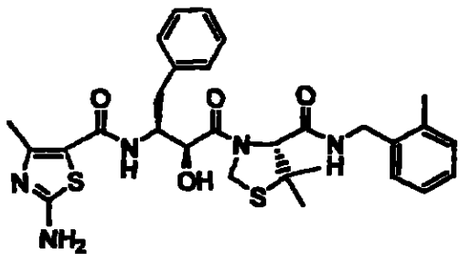
187

**Ejemplo B14: ácido 3-{(S)-3-[(5-cloro-1,3-dimetil-1H-pirazol-4-carbonil)-amino}-2-hidroxi-4-fenil-butiril}-5,5-dimetil-tiazolidino-4-carboxílico 2-metil-bencilamida**



Rendimiento aislado: 92%; $^1$H-NMR (400 MHz, dmso-$d_6$): δ 8 35 (t, 1H), 7 74 (d, 1H), 7 30 -7 0 (m, 10H), 5-44 (d, 1H), 4.96 (q, 2H) 4.48 (m, 1H), 4 35 (m, 2H), 4 13 (dd, 1H), 2 74 (m, 2H), 2.22 (s, 3H), 2 09 (s, 3H), 1.48 (s, 3H), 1.26 (s, 3H); IR (KBr en cm$^{-1}$) 3438, 3313, 1693, 1649, 1513, 1372, 754; MS (APCI, m/z) 598 (M+H), 334, 276, 174, $C_{30}H_{36}N_5O_4S1$ C 11.0.17 $H_2O$ calculado C 59.93, H 6.09, N 11 65, observado: C 60.24, H 6.07, N 11 71, HPLC . Rf (mın.) 19 829; pureza 100%.

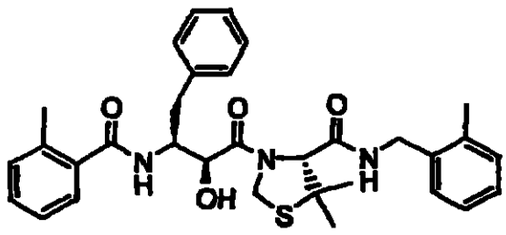
**Ejemplo B15: ácido 2-amino-4-metil-tiazol-5-carboxílico {(S)-1-bencil-3-(5,5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-amida**



Rendimiento aislado. 42%, $^1$H-NMR (400 MHz, dmso-$d_6$). δ 8.48 (brs, 1H), 8.35 (brs, 1H), 7.44 (d, 1H), 7 35 - 7 04 (m, 9H), 6 91 (s, 1H), 5.37 (d, 1H), 4.96 (q, 2H), 4 48-4 0 (m, 5H), 2, 96 (m, 2H), 2.22 (2, 3H), 2 13 (s, 3H), 1.48 (s, 3H), 1 30 (s, 3H), IR (KBr en cm$^{-1}$)· 3307, 1625, 1495; MS (APCI, m/z)· 582 (M+H), 442, 318; $C_{29}H_{35}N_5O_4S_2C11$ calculado· C 60 13,

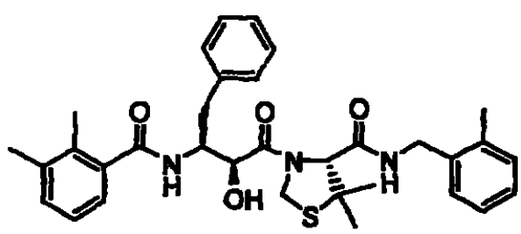
H 6.5, N 10 82, observado. C 59.87, H 6.06, N 12 04; HPLC Rf (mın ) 17.981; pureza: 98%.

**Ejemplo B16: ácido 3-[2-hidroxi-3-(2-metil-benzoilamino)-4-fenil-butiril]-5,5-dimetil-tiazolidino-4-carboxílico 2-metil-bencilamida**



Rendimiento aislado. 76%, $^1$H-NMR (400 MHz, dmso-$d_6$)· δ 8 31 (t, 1H), 8.22 (d, 1H), 7 32 -7.04 (m, 13H), 5.48 (d, 1H), 5.13 (d, 1H), 5.0 (d, 1H), 4.48 (s, 2H), 4.38 (dd, 2H), 4 09 (dd, 1H), 2.83 (d, 1H), 2.70 (t, 1H), 2 26 (s, 3H), 2.01 (s, 3H), 1.48 (s, 3H), 1 33 (s, 3H); IR (KBr en cm$^{-1}$)· 3309, 1641, 1520, 742; MS (APCI, m/z) 560 (M+H), 514, 296, 265; $C_{32}H_{37}N_3O_4S1$ 0.64 $H_2O$ calculado C 67-40, H 6.59, N 7 37, observado: C 68.79, H 6.49, N 7.52; HPLC : Rf(min ) 21 024; pureza. 98%

**Ejemplo B17: ácido 3-[3-(2,3-dimetil-benzoilamino)-2-hidroxi-4-fenil-butiril]-5,5-dimetil-tiazolidino-4-carboxílico 2-metil-bencilamida**

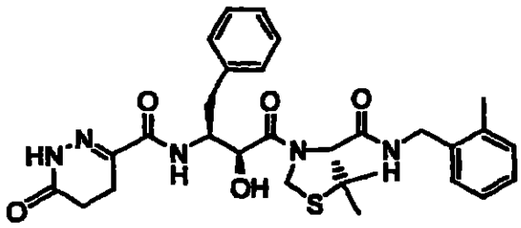


Rendimiento aislado: 72%, $^1$H-NMR (400 MHz, dmso-$d_6$). δ 8 33 (t, 1H), 8 22 (d, 1H), 7.35 -6.83 (m, 12H), 5 48 (d, 1H), 5 13 (d, 1H), 5 04 (d, 1H), 4 48-4 30 (m, 4H), 4.09 (dd, 1H), 2.84 (d, 1H), 2.70 (t, 1H), 2 26 (s, 3H), 2 17 (s, 3H), 1.87 (s, 3H), 1 48 (s, 3H), 1 30 (s, 3H), IR (KBr en cm$^{-1}$). 3307, 1640, 1515, 743 ; MS (APCI, m/z). 574 (M+H), 528, 310, 265,

189

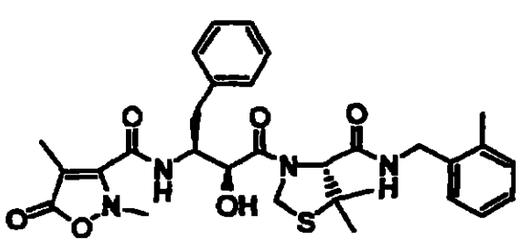
$C_{33}H_{39}N_3O_4S1$ 0.54 $H_2O$ calculado C 68 05, H 6 76, N 7 21, observado: C 69.20, H 6.76, N 7 34, HPLC Rf(mın ) 21 449; pureza: 99%.

**Ejemplo B18: ácido 6-oxo-1,4,5,6-tetrahidro-piridazina-3-carboxílico {1-bencil-3-[5,5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-amida**



Rendımiento aislado· 67%, $^1$H-NMR (400 MHz, dmso-$d_6$)· δ 8.35 (t, 1H), 8.09 (d, 1H), 7.30 -7.0 (m, 10H), 5.6 (d, 1H), 4.91 (d, 1H), 4.83 (d, 1H), 4 44 (s, 1H), 4 30 (m, 3H), 4.17 (dd, 1H), 2.78 (d, 2H), 2.61 (t, 2H), 2.30 (t, 2H), 2.22 (s, 3H), 1 48 (s, 3H), 1 30 (s, 3H); IR (KBr en $cm^{-1}$) 3306, 1650, 1521, 742 ; MS (APCI, m/z)· 566 (M+H), 520, 265; $C_{29}H_{35}N_5O_5S1$. 0 7 $H_2O$ calculado. C 60.23, H 6.34, N 12.11, observado: C 61.57, H 6.24, N 12.38, HPLC : Rf (mın.) 18.455; pureza 97%

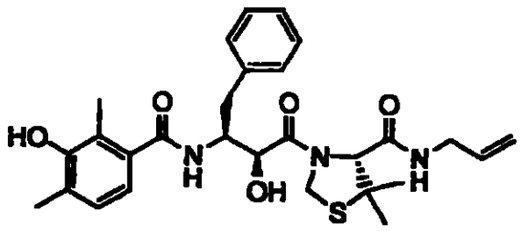
**Ejemplo B19: ácido 2,4-dimetil-5-oxo-23-dihidro-isoxazol-3-carboxílico {1-bencil-3-[5,5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-amida**



Rendimiento aislado: 73%; $^1$H-NMR (400 MHz, dmso-$d_6$): δ 8 91 (d, 1H), 8 35 (t, 1H), 7.30 -7 04 (m, 9H), 5.70 (d, 1H), 5 0 (d, 2H), 4.44 (s + m, 3H), 4 31 (dd. 1H), 4.13 (dd, 1H), 2.91 (s + m, 4H), 2.65 (t, 1H), 2.22 (s, 3H),

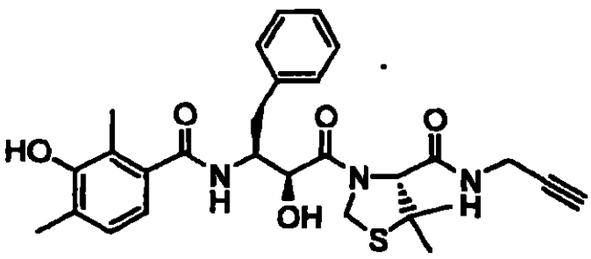
1.52 (s, 3H), 1.48 (s, 3H), 1.30 (s, 3H) ; IR (KBr en $cm^{-1}$). 3325, 2932, 1729, 1649, 1527, 742, MS (APCI, m/z) 581 (M+H), 539, 493, 225; $C_{30}H_{36}N_4O_6S1$ calculado: C 62.29. H 5.61, N 9 19, observado: C 62.05, H 6.25, N 9 65; HPLC · Rf (mın.) 19.638, pureza 100%.

**Ejemplo B20: ácido (R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2,4-dimetil-fenil)-metanoil]-amino)-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico alilamida**



$^1$H NMR (DMSO-$d_6$) δ 8.23 (s, 1H), 8.10-8.03 (m, 2H), 7.33-7 12 (m, 5H), 6.85 (d, *J*= 7.7, 1H), 6.51 (d, *J*= 7 7, 1H), 5 82-5.70 (m, 1H), 5 44 (d, *J*= 6 8, 1H), 5 22-4.97 (m, 4H), 4 50-4.30 (m, 3H), 3.84-3.60 (m, 2H), 2.84-2 66 (m, 2H), 2.13 (s, 3H), 1.85 (s, 3H), 1 49 (s, 3H), 1.35 (s, 3H); HRMS (ESI) *m/z* calculado para $C_{28}H_{36}N_3O_5S$ (M + H)$^+$ 526 2376, hallado 526 2380, análisis calculado para $C_{28}H_{35}N_3O_5S$•0 2 TFA: C, 62.19; H, 6.47, N, 7.66 Hallado. C, 62.27; H, 6.78; N, 7 26.

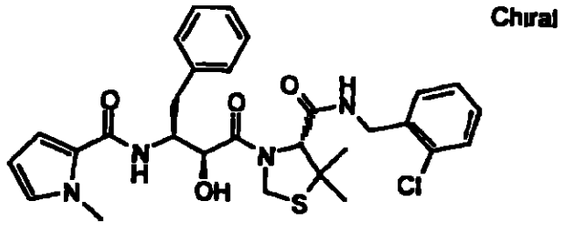
**Ejemplo B21: ácido 3-(2-hidroxi-3-{[1-(3-hidroxi-2,4-dimetil-fenil)-metianoil]-amino}-4-fenil-butinoil)-5,5-dimetil-tiazolidino-4-carboxílico prop-2-inilamida**



$^1$H NMR (DMSO-$d_6$) δ 8 40 (t, *J*= 5 4, 1H), 8.22 (s, 1H), 8 02 (d, *J*= 8 2,

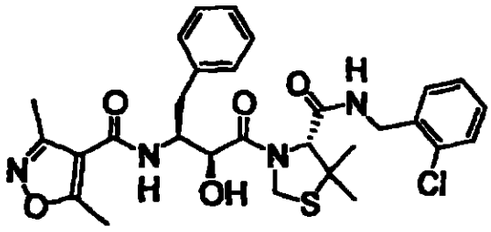
1H), 7.35-6.52 (m, 7H), 5 44 (d, *J*= 6 8, 1H), 5.10 (d, *J*= 9.1, 1H), 5.02 (d, *J*= 9.1, 1H), 4.46-4.40 (m, 2H), 4.40 (s, 1H), 3 86 (s br, 2H), 3 08 (t, *J*= 1.8, 1H), 2.82-2.72 (m, 2H), 2.15 (s, 3H), 1.88 (s, 3H), 1 51 (s, 3H), 1.37 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{28}H_{34}N_3O_5S$ $(M + H)^+$ 524.2219, hallado 524.2219; análisis calculado para $C_{28}H_{33}N_3O_5S \cdot 0\ 5H_2O$: C, 63.13; H, 6 43; N, 7.89; S, 6 02 Hallado· C, 62 80, H, 6.64, N, 7 71 ,S, 5 69.

**Ejemplo B22: ácido 3-{2-hidroxi-3-[(1-metil-1H-pirrol-2-carbonil)-amino]-4-fenil-butiril}-5,5-dimetil-tiazolidino-4-carboxílico 2-cloro-bencilamida**




Rendimiento aislado: 50%; $^1$H-NMR (400 MHz, dmso-$d_6$): 6 40-7 40 (m, 11H), 6 00 (m, 1H), 4.20-5.20 (m, 7H), 3 71, 3 54 (s, 3H), 2 70-2 90 (m, 2H), 1.52 (d, *J*= 2.0 Hz, 3H), 1 32 (d, *J*= 2 1 Hz, 3H); MS (APCI, m/z)· 570 (M+H)

**Ejemplo B23: ácido 3,5-dimetil-isoxazol-4-carboxílico {1-bencil-3-[4-(2-cloro-bencilcarbamoil)-5,5-dimetil-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-amida**

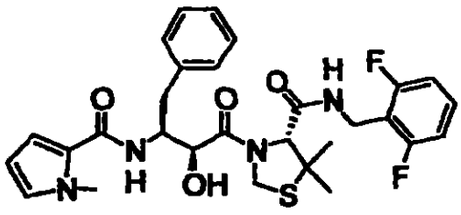



Rendimiento aislado· 55%; $^1$H-NMR (400 MHz, dmso-$d_6$)· 7.00-7.40 (m,

192

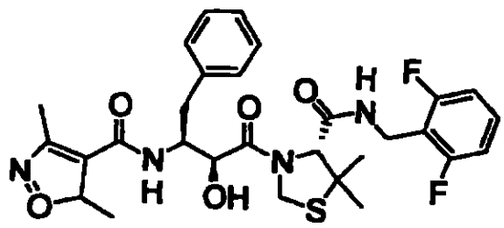
9H), 4 36-5-08 (m, 7H), 2.70-2 90 (m, 2H), 2 34, 2.25 (s, 3H), 2.18, 2.12 (s, 3H), 1 56 (d, *J*= 8.5 Hz, 3H), 1.35 (d, *J*= 6.2 Hz, 3H); MS (APCI, m/z) 586 (M+H), $C_{29}H_{33}ClN_4O_5S$ $0.42H_2O$ calculado: C 58 77, H 5 75, N 9 45, observado: C 58 37, H 5 73, N 9.19.

**Ejemplo B24: ácido 3-{2-hidroxi-3-[(1-metil-1H-pirrol-2-carbonil)-amino]-4-fenil-butiril}-5,5-dimetil-tiazolidino-4-carboxílico 2,6-difluoro-bencilamida**



Rendimiento aislado. 75%; $^1$H-NMR (400 MHz, dmso-$d_6$). 6.40-7 40 (m, 10H), 6 00 (m, 1H), 4 20-5 20 (m, 7H), 3.64, 3 61 (s, 3H), 2 70-2-90 (m, 2H), 1.52, 1 49 (s, 3H), 1.33, 1.29 (s, 3H); MS (APCI, m/z) 571 (M+H), $C_{29}H_{32}F_2N_4O_4S$ calculado. C 61.04, H 5.65, N 9.82, observado C 60.86, H 5.94, N 9.71.

**Ejemplo B25: ácido 3,5-dimetil-isoxazol-4-carboxílico {1-bencil-3-{4-(2,6-difluoro-bencilcarbamoil)-5,5-dimetil-tiazolidino-3-il)-2-hidroxi-3-oxo-propil}-amida**

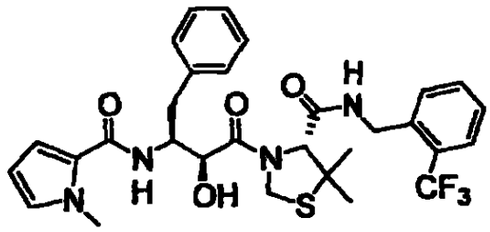


Rendimiento aislado: 75%; $^1$H-NMR (400 MHz, dmso-$d_6$)· 6.60-7 40 (m, 8H), 4.26-5 08 (m, 7H), 2.70-2.90 (m, 2H), 2 32, 2 28 (s, 3H), 2.16, 2.13 (s, 3H), 1 56, 1.53 (s, 3H), 1 37, 1.34 (s, 3H), MS (APCI, m/z): 587 (M+H);

193

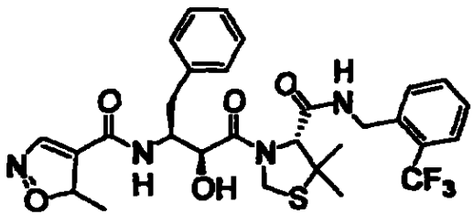
$C_{29}H_{32}F_2N_4O_5S$ calculado: C 59 37, H 5.50, N 9 55, observado C 59 12, H 5.88, N 9.50.

**Ejemplo B26: ácido 3-{2-hidroxi-3-[(1-metil-1H-pirrol-2-carbonil)-amino]-4-fenil-butiril}-5,5-dimetil-tiazolidino-4-carboxílico 2-trifluorometil-bencilamida**



Rendimiento aislado 83%; $^1$H-NMR (400 MHz, dmso-$d_6$) 6.40-7.60 (m, 11H), 6.00 (m, 1H), 4.20-5.20 (m, 7H), 3.70, 3.54 (s, 3H), 2.70-2 90 (m, 2H), 1.52 (s, 3H), 1 36, 1.29 (s, 3H); MS (APCI, m/z). 619 (M+H); $C_{30}H_{33}F_3N_4O_4S$ calculado: C59 79, H5.52, N9.30, observado: C59 42, H5.55, N9.06.

**Ejemplo B27: ácido 3,5-dimetil-isoxazol-4-carboxílico {1-bencil-3-[5, 5-dimetil-4-(2-trifluorometil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-amida**

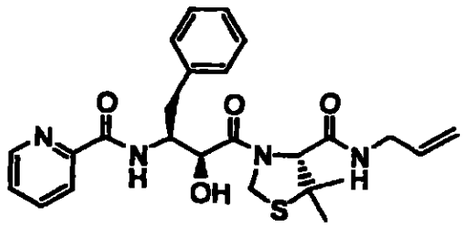


Rendimiento aislado: 93%, $^1$H-NMR (400 MHz, dmso-$d_6$). 7.05-7.60 (m, 9H), 4 36-5.08 (m, 7H), 2 70-2.90 (m, 2H), 2.30, 2 21 (s, 3H), 2-15, 2 05 (s, 3H), 1.54, 1 52 (s, 3H), 1.39, 1 32 (s, 3H), MS (APCI, m/z). 619 (M+H); $C_{30}H_{33}F_3N_4O_5S$ calculado· C58.24, H5 38, N9 06, observado. C57.87, H5 68, N9.02

**Ejemplo B28: N-[(1S,2S)-3-(4-alquilcarbamoil-5,5-dimetil-tiazolidino-3-**

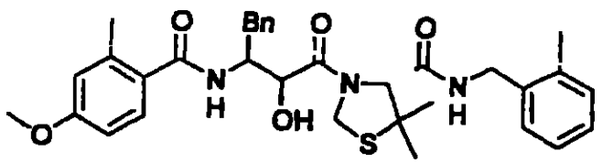
194

**il)-1-bencil-2-hidroxi-3-oxo-propil]-nicotinamida**



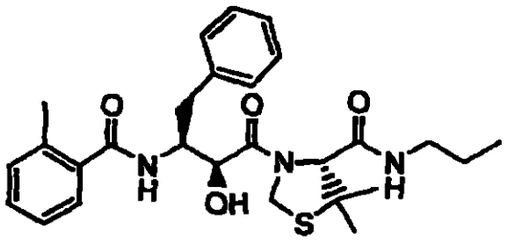
Sólido blanco· $^1$H NMR (DMSO-$d_6$) δ 8 81 (d, *J*= 8 6, 1), 8 77 (d, *J*= 6 2, 1H), 8.12 (m, 1H), 7 99 (m, 1H), 7.63 (m, 1H), 7.32-7.12 (m, 7H), 5 78 (m, 1H), 5 18 (m , 2H), 4.56 (m , 3H), 4.40 (m, 4H), 2.87-2.67 (m, 2H), 1 49 (s, 3H), 1 34 (s, 3H), análisis ($C_{26}H_{32}N_4O_4S$•0.5 $H_2O$•0 5 TFA) calculado C (57.65), H (6.36) N (10.19), hallado C (57.73), H (5.91), N (10 15). HRMS (ESI) *m/z* calculado para 483 2075, hallado 497.2066.

**Ejemplo B29: ácido 3-(2-hidroxi-3-(4-metoxi-2-metil-benzoilamino)-4-fenil-butiril]-5,5-dimetil-tiazolidino-4-carboxílico 2-metil-bencilamida**



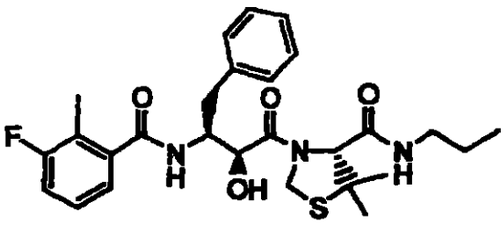
Rendimiento aislado 56%. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8 32 (t, 1H), 8 09 (d, 1H), 7 33-7.27 (m, 3H), 7.23-7.19 (m, 2H), 7.15-7 08 (m, 5H), 6 69 (d, 2H), 5.46 (d, 1H), 5 13 (d, 1H), 4.99 (d, 1H), 4.49 (s, 2H), 4 41-4.36 (m, 2H), 4.10 (dd, 1H), 3.71 (s, 3H), 2 84-2 81 (m, 1H), 2.72 (t, 1H), 2 24 (s, 3H), 2.07 (s, 3H), 1 48 (s, 3H), 1 33 (s, 3H); MS-APCI (m/z+)· 326, 590 (M+H). HPLC: Rf (min.) 21 26, pureza 100%, $C_{33}H_{39}N_3O_5S_1$•0.4 $H_2O$ calculado: C66.40, H6.72, N7 04, hallado C66.38, H6 71, N6.94.

**Ejemplo B30: ácido (R)-3-{(2S,3S)-2-hidroxi-4-fenil-3-[(1-o-tolil-metanoil)-amino]-butanoil}-5,5-dimetil-tiazolidino-4-carboxílico propilamida**



IR (puro, $cm^{-1}$) 3318, 2964, 1642, 1530, 1445, 1372, $^1H$ NMR (DMSO) δ 8 21 (d, *J*= 8 4, 1H), 7 90 (t, *J*= 5.6, 1H), 7.35-7 07 (m, 9H), 5 45 (d, *J*= 6 8, 1H), 5.09 (d, *J*= 9 2, 1H), 5.00 (d, *J*= 9.2, 1H), 4.50-4 38 (m, 2H), 4.37 (s, 1H), 3.01 (q, *J*= 6.9, 2H), 2.90-2.60 (m, 2H), 2.02 (s, 3H), 1.49 (s, 3H), 1 44-1.35 (m, 2H), 1.34 (s, 3H), 0 82 (t, *J*= 7.5, 3H), HRMS (ESI) ***m / z*** calculado para $C_{27}H_{36}N_3O_4S$ $(M + H)^+$ 498.2424, hallado 498.2427.

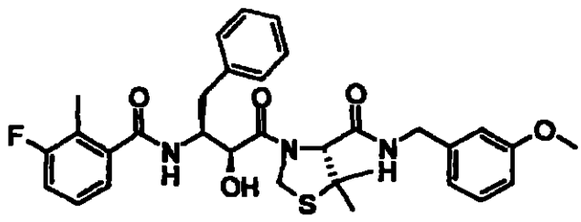
**Ejemplo B31: ácido (R)-3-((2S,3S)-3-{[1-(3-fluoro-2-metil-fenil)-metanoil]-amino}-2-hidroxi-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico propilamida**



Sólido blanco $^1H$ NMR (DMSO) δ 8 34 (d, *J*= 8 1, 1H), 7 91 (t, *J*= 5.9, 1H), 7.40-7.10 (m, 7H), 6-93 (d, *J*= 6 9, 1H), 5.51 (d, *J*= 6.2, 1H), 5.08 (d, *J*= 8.8, 1H), 5.00 (d, *J*= 8 8, 1H), 4.50-4 39 (m, 2H), 4 38 (s, 1H), 3 00 (dd, *J*= 12.3, 5.9, 2H), 2.90-2.60 (m, 2H), 1 89 (s, 3H), 1.49 (s, 3H), 1.40-1 34 (m, 2H), 1.34 (s, 3H), 0.82 (t, *J*= 7.7, 3H); HRMS (ESI) ***m / z*** calculado para $C_{27}H_{35}N_3O_4FS$ $(M + H)^+$ 516.2332, hallado 516.2339

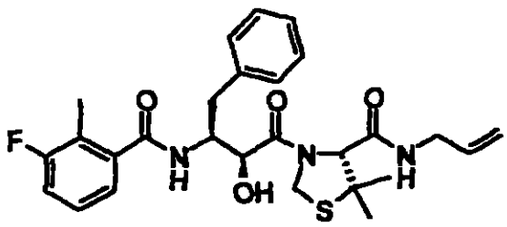
**Ejemplo B32: ácido (R)-3-((2S,3S)-3-{[1-(3-fluoro-2-metil-fenil)-metanoil]-amino}-2-hidroxi-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 3-metoxi-bencilamida**

196



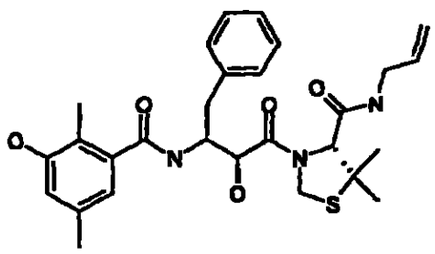
Sólido blanco: $^1$H NMR (DMSO) δ 8.43 (t, *J*= 5.9, 1H), 8.34 (d, *J*= 8 1, 1H), 7 31-6.72 (m, 12H), 5.57 (d, *J*= 6.8, 1H), 5-12 (d, *J*= 9 3, 1H), 5.01 (d, *J*= 9 3, 1H), 4.50-4.30 (m, 4H), 4.12 (dd, *J*= 15.7, 5.9, 1H), 3.69 (s, 3H), 2.95-2.62 (m, 2H), 1.90 (s, 3H), 1 49 (s, 3H), 1.34 (s, 3H), HRMS (ESI) *m / z* calculado para $C_{32}H_{37}N_3O_5SF$ $(M + H)^+$ 594 2434, hallado 594 2438.

**Ejemplo B33: ácido (R)-3-((2S,3S)-3-{[1-(3-fluoro-2-metil-fenil)-metanoil]-amino}-2-hidroxi-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico alilamida**



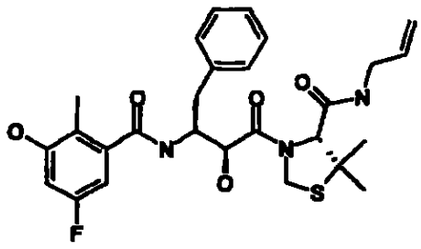
Sólido blanco $^1$H NMR (DMSO) δ 8.34 (d, *J*= 8 3, 1H), 8.10 (t, *J*= 5 7, 1H), 7.40-6.90 (m, 8H), 5 81-5.69 (m, 1H), 5 54 (d, *J*= 6.6, 1H), 5.30-4.90 (m, 4H), 4.50-4.35 (m, 3H), 3 80-3.65 (m, 2H), 2.90-2.60 (m, 2H), 1.89 (s, 3H), 1.49 (s, 3H), 1.35 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{27}H_{33}N_3O_4SF$ $(M + H)^+$ 514 2182, hallado 514.2176.

**Ejemplo B34: ácido 3-[(2S,3S)-2-hidroxi-3-(3-hidroxi-2,5-dimetil-benzoilamino)-4-fenil-butiril]-5,5-dimetil-tiazolidino-4-carboxílico alilamida**



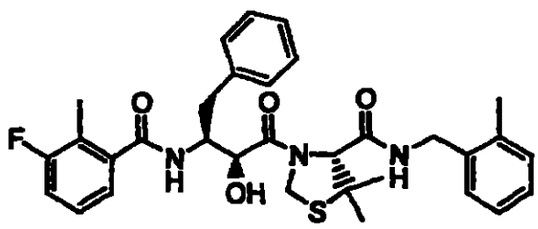
$^1$H NMR (DMSO-$d_6$) δ 9.23 (s, 1H), 8.09 (m, 2H), 7.35-7.17 (m, 5H), 6 60 (s, 1H), 6.37 (s, 1H), 5 74(m, 1H), 5.41 (brs, 1H), 5.20 (dd, *J*= 17.2, 1.6, 1H), 5 11 (d, *J*= 9.2, 1H), 5.02 (dd, *J*= 10 2, 1.5, 1H), 5.00 (d, *J*= 9.1, 1H), 4 46-4 37 (m, 3H), 3.79 (ddd, *J*= 15.9, 5 5, 5.3, 1H), 3 63 (ddd, *J*= 15.9, 5 4, 5.3, 1H), 2.82 (dd, *J*= 13.9, 0 3, 1H), 2.71 (dd, *J*= 13.6, 10 7, 1H), 2 16 (s, 3H), 1.76 (s, 3H), 1.53 (s, 3H), 1.36 (s, 3H); análisis calculado para $C_{28}H_{35}N_4O_5S$•0.3$H_2O$ C, 63 32; H, 6.76; N, 7 91. Hallado C, 63 35; H, 6.70; N, 7 71

**Ejemplo B35: ácido 3-[(2S,3S)-3-(5-fluoro-3-hidroxi-2-metil-benzoilamino)-2-hidroxi-4-fenil-butiril]-5,5-dimetil-tiazolidino-4-carboxílico alilamida**



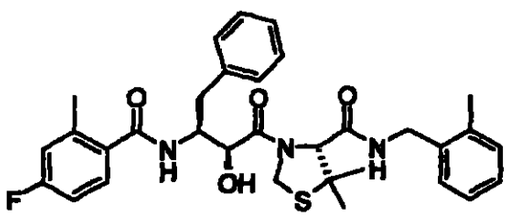
$^1$H NMR (DMSO-$d_6$) δ 9.94 (s, 1H), 8.23 (d, *J*= 8 2, 1H), 8.10 (t, *J*= 5.6, 1H), 7.33-7.17 (m, 5H), 6.58 (dd, *J*= 10.6, 2.5, 1H), 6 32 (dd, *J*= 8 8, 2 5, 1H), 5.78 (m, 1H), 5.54 (brs, 1H), 5.21 (dd, *J*= 17.2, 1.7, 1H), 5 10 (d, *J*= 9 1, 1H), 5.03 (dd, *J*= 10.2, 1.5, 1H), 5 01 (d, *J*= 9 1, 1H), 4.50-4.42 (m, 3H), 3.78 (ddd, *J*= 15.9, 5.4, 5.4, 1H), 3.63 (ddd, *J*= 15.9, 5 4, 5 3, 1H), 2.84 (dd, *J*= 14.5, 3.3, 1H), 2 70 (dd, *J*= 13 5, 10 3, 1H), 1 75 (s, 3H), 1.50 (s, 3H), 1 36 (s, 3H); análisis calculado para $C_{27}H_{32}FN_3O_5S$•0 3$H_2O$ C, 60.61, H, 6 14, N, 7.85 Hallado C, 60.63, H, 6.08; N, 8 07.

**Ejemplo B36: ácido (R)-3-((2S,3S)-3-{[1-(3-fluoro-2-metil-fenil)-metanoil]-amino}-2-hidroxi-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 2-metil-bencilamida**



$^1$H NMR (DMSO) δ 8 85-8.35 (m, 2H), 7.38-6.90 (m, 12H), 5 55 (d, *J*= 5.9, 1H), 5.12 (d, *J*=9.2, 1H), 5.01 (d, *J*=9.2, 1H), 4.58-4-32 (m, 4H), 4 10 (dd, *J*= 15.0, 4.6, 1H), 2.92-2.62 (m, 2H), 2.24 (s, 3H), 1 90 (s, 3H), 1 49 (s, 3H), 1.34 (s, 3H); HRMS (ESI) *m/z* calculado para $C_{32}H_{37}N_3O_4FS$ $(M + H)^+$ 578 2489, hallado 578 2486; análisis calculado para $C_{32}H_{36}N_3O_4FS$•0 2 EtOAc. C, 66.17; H, 6 37; N, 7.06. Hallado C, 66 30; H, 6.54; N, 6 74

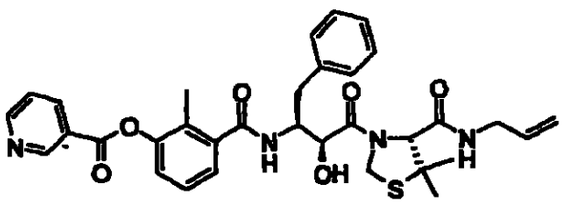
**Ejemplo B37: ácido (R)-3-((2S,3S)-3-{[1-(4-fluoro-2-metil-fenil)-metanoil]-amino}-2-hidroxi-4-fenil-butanoil)-5,5-dimetil-tiazolidino-4-carboxílico 2-metil-bencilamida**



Sólido blanco: $^1$H NMR (DMSO) δ 8 40-8.30 (m, 2H), 7.35-6 90 (m, 12H), 5.53 (d, *J*= 6 8, 1H), 5.13 (d, *J*= 9.0, 1H), 5.00 (d, *J*= 9.0, 1H), 4.48 (s, 1H), 4 47-4.45 (m, 2H), 4.38 (dd, *J*= 15.0, 5.9, 1H), 4 10 (dd, *J*= 15 0, 4.8, 1H), 2 90-2.62 (m, 2H), 2.24 (s, 3H), 2.04 (s, 3H), 1.48 (s, 3H), 1.33 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{32}H_{37}N_3O_4SF$ $(M + H)^+$ 578 2463, hallado 578 2489

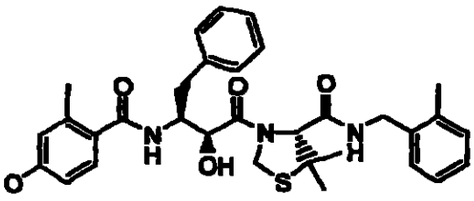
**Ejemplo B38: ácido nicotínico 3-[(1S,2S)-3-((R)-4-alilcarbamoil-5,5-**

**dimetil-tiazolidino-3-il)-1-bencil-2-hidroxi-3-oxo-propilcarbamoil]-2-metil-fenil éster**



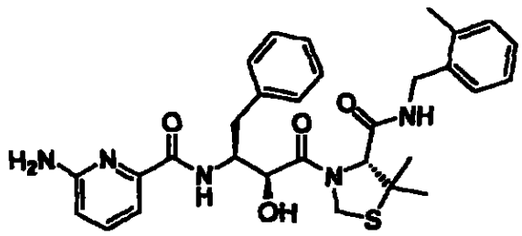
Sólido blanco: $^1$H NMR (DMSO) δ 9.26 (dd, *J*= 2.0, 0.9, 1H), 8 90 (dd, *J*= 5 6, 2.0, 1H), 8 47 (dt, *J*= 7.9, 2.0, 1H), 8.40 (d, *J*= 8.2, 1H), 8 1 (t, *J*=5 7, 1H), 7.65 (ddd, *J*=7 9, 5 6, 0.9, 1H), 7.40-7.10 (m, 8H), 5 82-5 68 (m, 1H), 5.6 (d, *J*= 6 2, 1H), 5 30-4 90 (m, 4H), 4 50-4.40 (m, 2H), 4 40 (s, 1H), 3.80-3.70 (m, 2H), 3.00-2 60 (m, 2H), 1.85 (s, 3H), 1.49(s, 3H), 1 34(s, 3H).

**Ejemplo B39: ácido (R)-3-[(2S,3S)-2-hidroxi-3-(4-hidroxi-2-metil-benzoilamino)-4-fenil-butiril]-5,5-dimetil-tiazolidino-4-carboxílico 2-metil-bencilamida**



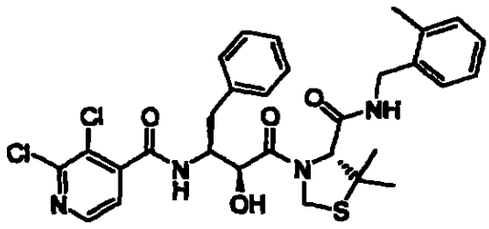
Sólido blanco: $^1$H NMR (DMSO) δ 9.55 (s, 1H), 8 32 (t, *J*= 4 9, 1H), 8.00 (d, *J*= 8 4, 1H), 7.36-7.00 (m, 10H), 6 54-6 48 (m, 2H), 5.44 (d, *J*= 6.6. 1H), 5 13 (d, *J*= 9.2, 1H), 4.99 (d, *J*= 9 2, 1H), 4 50-4.32 (m, 4H), 4 11 (dd, *J*= 15 0, 4.8, 1H), 3.50-2.80 (m, 2H), 2.25 (s, 3H), 2.04 (s, 3H), 1.49 (s, 3H), 1 33 (s, 3H); análisis calculado para $C_{32}H_{37}N_3O_5S$•0.25 $H_2O$: C, 66.24, H, 6.51; N, 7.24. Hallado· C, 66 25; H, 6 55; N, 7 35.

**Ejemplo B40: ácido 6-amino-piridina-2-carboxílico {(1S,2S)-1-bencil-3-[(R)-5,5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-amida**



$^1$H NMR (DMSO-$d_6$) δ 8 44 (d, 1H, *J*= 5 6), 8 36 (d, 1H, *J*= 9.3), 7.69-7.49 (t, 1H, *J*= 7.7), 7.34-7 06 (m, 10H), 6.61 (d, 1H, *J*= 8.4) 6 27 (br s, 2H) 5 47 (d, 1H, *J*= 7 1), 5.00 (m, 2H), 4.54-4.43 (m, 2H), 4.50 (s, 1H), 4 38 (dd 1H, *J*= 6 4, 15.2), 4 19 (dd, 1H, *J*= 4 6, 14.7), 2.87-2.65 (m, 2H), 2.28 (s, 3H), 1.53 (s, 3H), 1 38 (s, 3H) Masa exacta calculada para $C_{30}H_{36}N_5O_4S$ (M + H)$^+$ 562 2488, hallado 562.2493.

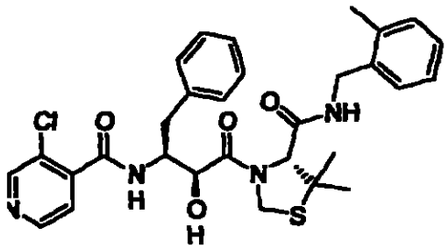
**Ejemplo B41: {(1S,2S)-1-Bencil-3-[(R)-5,5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-2,3-dicloro-isonicotinamida**



$^1$H NMR (DMSO-$d_6$ ) δ 8.89 (d, 1H, *J*=8.42), 8.40 (t, 1H, *J*= 5.5), 8 38 (d, 1H, *J*= 4.8), 7 30-7 08 (m, 10H), 5.58 (d, 1H, *J*= 7 3), 5.07 (d, 1H, *J*= 8.8), 5.00 (d, 1H, *J*= 8 8), 4 54-4.50 (m, 1H), 4.51 (s, 1H), 4 43-4.36 (m, 2H), 4.16 (dd, 1H, *J*= 5.1, 15.0), 2 89-2.85 (m, 1H), 2 71-2 63 (m, 1H), 2.26 (s, 3H), 1.50 (s, 3H), 1.35s (s, 3H). Masa exacta calculada para $C_{30}H_{33}N_4O_4SCl_2$ (M + H)$^+$ 615.1600, hallado 615 1581 Análisis calculado para $C_{30}H_{32}N_4O_4SCl_2$ C, 58.54; H, 5.24, N, 9.10. Hallado: C, 58.48; H, 5 10; N, 8.80.

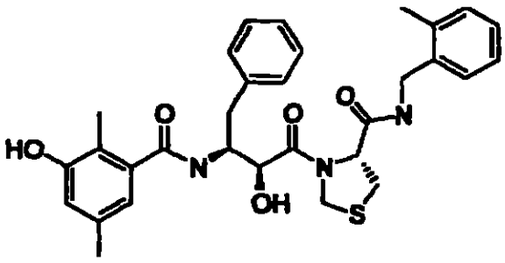
**Ejemplo B42: {(1S,2S)-1-Bencil-3-[(R)-5,5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-3-cloro-**

**isonicotinamida**



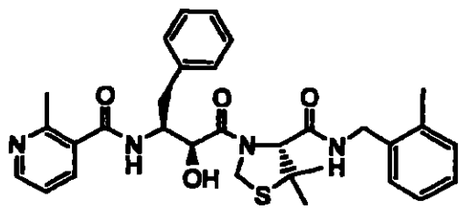
$^1$H NMR (DMSO-$d_6$) δ 8.82 (d, 1H, *J*= 8 6), 8.62 (s, 1H), 8 52 (d, 1H, *J*= 4.9), 8.39 (d, 1H, *J*= 5 1), 7 29-7 09 (m, 10H), 5.54 (d, 1H, *J*= 7 1), 5.09 (d, 1H, *J*= 9.0), 4.99 (d, 1H, *J*= 9 0), 4.56-4 49 (m, 1H), 4 51 (s, 1H), 4.44-4.37 (m, 2H), 4 15 (dd; 1H, *J*= 5 1, 15 0), 2.88-2.83 (m, 1H), 2.74-2 65 (m, 1H), 2 26 (s, 3H), 1.50 (s, 3H), 1.35s (s, 3H) Masa exacta calculada para $C_{30}H_{33}N_4O_4SCl$ $(M)^+$ 581.1989, hallado 581 1983

**Ejemplo B43: ácido (R)-3-[(2S,3S)-2-hidroxi-3-(3-hidroxi-2,5-dimetil-benzoilamino)-4-fenil-butiril]-5,5-dimetil-tiazolidino-4-carboxílico 2-metil-bencilamida**



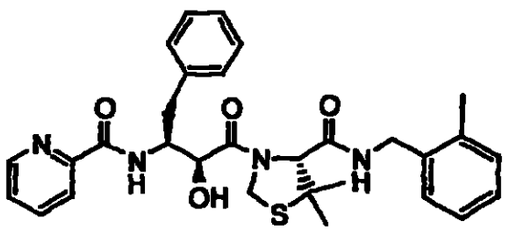
$^1$H NMR (DMSO-$d_6$) δ 9.24 (s, 1H), 8 31 (t, *J*= 5.6, 1H), 8.10 (d, *J*= 8.2, 1H), 7 34-7.09 (m, 9H), 6 60 (s, 1H), 6.38 (s, 1H), 5 42 (brs, 1H), 5.14 (d, *J*= 9.1, 1H), 5 01 (d, *J* = 9.1, 1H), 4 50 (s, 1H), 4 50-4 37 (m, 3H), 4.11 (dd, *J*= 15.1, 4 7, 1H), 2.76 (m, 2H), 2.26 (s, 3H), 2.16 (s, 3H), 1.77 (s, 3H), 1.50 (s, 3H), 1 35 (s, 3H), HRMS (ESI) *m / z* calculado para $C_{33}H_{40}N_3O_5S$ $(M + H)^+$ 590.2689, hallado 590 2676; análisis calculado para $C_{33}H_{39}N_3O_5S$•0.3 $H_2O$: C, 66 60, H, 6.71, N, 7.06 Hallado. C, 66.65, H, 6.69; N, 7.05.

**Ejemplo B44: N-{(1S,2S)-1-Bencil-3-[5, 5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-2-metil-nicotinamida**



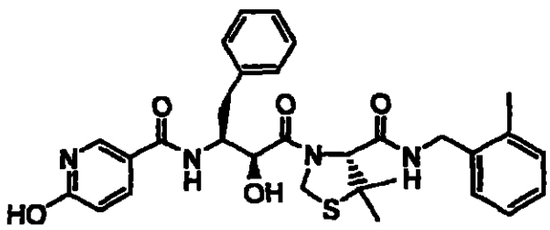
Sólido blanco· $^1$H NMR (DMSO-$d_6$) δ 8 53-8 33 (m, 2H), 7.47 (d, *J*= 7 82, 1H), 7.38-7.10 (m, 12H), 5.62 (d, *J*= 7 94, 1H), 5.18 (dd, *J*= 9.6, 7.6, 2H), 4.43-4.37 (m, 3H), 4.17 (dd, *J*= 7.81, 6 99, 1H), 2.87-2.67 (m, 2H), 2 28 (s, 3H), 2.21(s, 3H), 1 49 (s, 3H), 1.34 (s, 3H); análisis ($C_{31}H_{36}N_4O_4S$•1.0 $H_2O$ •1.0 MeCN) calculado C (63 95) H (6.67), N (11.30), hallado C (63.94), H (6 75), N (11.26) HRMS (ESI) *m/z* calculado para 561.2544, hallado 561.2556

**Ejemplo B45: ácido piridin-2-carboxílico {(1S,2S)-1-bencil-3-{5,5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-amida**



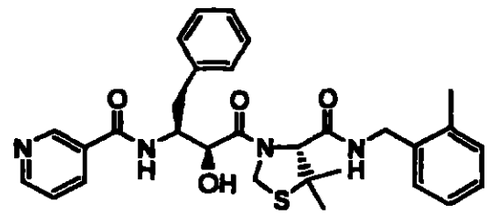
Sólido blanco: $^1$H NMR (DMSO-$d_6$) δ 8.89 (d, *J*= 7.86, ), 8.66 (d, *J*= 4.2, 1H), 8 39 (t, *J*= 6.54, 1H), 7 89 (m 2H), 7.32-7 12 (m, 9H), 5.68 (d, *J*= 7.28, 1H), 5.03 (dd, *J*= 9.7, 8 3, 2H), 4.56 (m, 3H), 4.40 (d, *J*= 7.5, 1H), 4.35 (d, *J*= 7.5, 1H), 4.21 (d, *J*= 6.7, 1H), 2.87-2.67 (m, 2H), 2 25 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H), análisis ($C_{30}H_{34}N_4O_4S$•0 1 $H_2O$•0 1 EtOAc) calculado C (65.52), H (6.33), N (10 05), hallado C (65.78), H (6.69), N (9.66) HRMS (ESI) *m/z* calculado para 547-2380, hallado 547 2373

**Ejemplo B46: ácido piridin-2-5-hidroxi-carboxílico {(1S,2S)-1-bencil-3-[5,5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il}-2-hidroxi-3-oxo-propil}-amida**



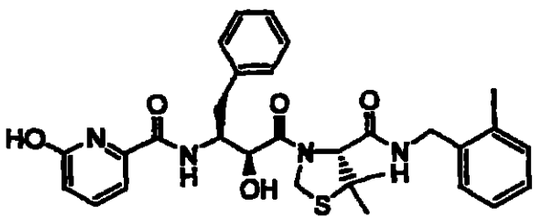
Sólido blanco. $^1$H NMR (DMSO-$d_6$) δ 8 89 (d, *J*= 7.9, 1), 8.66 (d, *J*= 42, 1H), 8 39 (t, *J* = 6.54, 1H), 7.89 (m, 2H), 7 32-7 12 (m, 9H), 5 68 (d, *J*= 7.2, 1H), 5 03 (dd, *J*= 9.7, 8.3, 2H), 4 56 (m, 3H), 4 40 (d, *J*= 7.5, 1H), 4.35 (d, *J*= 7.5, 1H), 4.21 (d, *J*= 6 7, 1H), 2.87-2 67 (m, 2H), 2.25 (s 3H), 1-49 (s, 3H), 1 34 (s, 3H), análisis ($C_{30}H_{34}N_4O_5S$•0.5 $H_2O$•0.5 EtOAc) calculado C (62.29), H (6 42), N (9.91), hallado C (62.53), H (6.84), N (10 10). HRMS (ESI) *m/z* calculado para563 2325, hallado 563.2328

**Ejemplo B47: N-{(1S,2S)-1-bencil-3-[5-5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-nicotinamida**



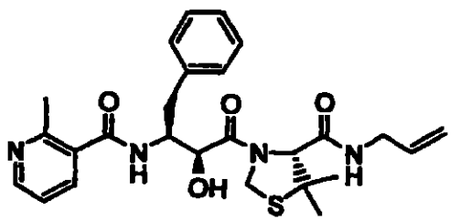
Sólido blanco $^1$H NMR (DMSO-$d_6$) δ 8.89 (d, *J*= 7 9, 1H), 8 66 (d, *J*= 4.2, 1H), 8.39 (t, *J*= 6.54, 1H), 7.89 (m, 2H), 7 32-7.32 (m, 9H), 5.68 (d, *J*= 7.3, 1H), 5.03 (dd, *J*= 9 7, 8.3, 2H), 4.56 (m, 3H), 4 40 (d, *J*= 7.5, 1H), 4 35 (d, *J*= 7 5, 1H), 4 21 (d, *J*= 6.7, 1H), 2.87-2.67 (m, 2H), 2 25 (s, 3H), 1.49 (s, 3H), 1 34 (s, 3H); análisis ($C_{30}H_{34}N_4O_4S$•0.5 $H_2O$•0.5 MeCN) calculado C (64.61), H (6 39), N (10.94), hallado C (65.02), H (6 58), N (10.90) HRMS (ESI) *m/z* calculado para547 2372, hallado 547.2379.

**Ejemplo B48: N-{(1S,2S)-1-bencil-3-[5,5-dimetil-4-(2-metil-bencilcarbamoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-nicotinamida**



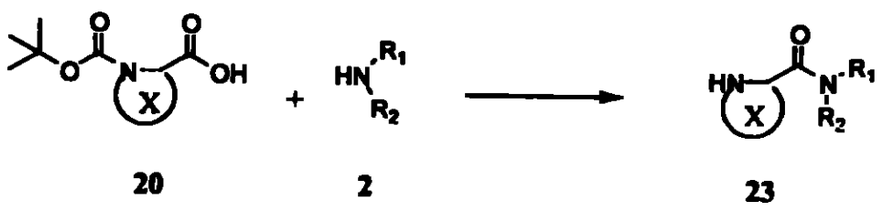
Sólido blanco: $^1$H NMR (DMSO-$d_6$) δ 8 89 (d, *J*= 7 9, 1H), 8 66 (d, *J*= 4.2, 1H), 8 39 (t, *J*= 6.54, 1H), 7.89 (m, 2H), 7.32-7.12 (m, 9H), 5.68 (d, *J*= 7.28, 1H), 5.03 (dd, *J*= 9.7, 8 3, 2H), 4.56(m, 3H), 4 40 (d, *J*= 7.5, 1H), 4 35 (d, *J*= 7.5, 1H), 4.21 (d, *J*= 6.7, 1H), 2.87-2.67 (m, 2H), 2 25 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H); análisis ($C_{30}H_{34}N_4O_5S$•1 3 $H_2O$) calculado C (61.42), H (6.32), N (9.49), hallado C (61.64), H (6.17), N (9 12). HRMS (ESI) *m/z* calculado para 563 2326, hallado 563.2328.

**Ejemplo B49: N-[(1S,2S)-3-(4-alilcarbamoil-5,5-dimetil-tiazolidino-3-il)-1-bencil-2-hidroxi-3-oxo-propil]-2-metil-nicotinamida**

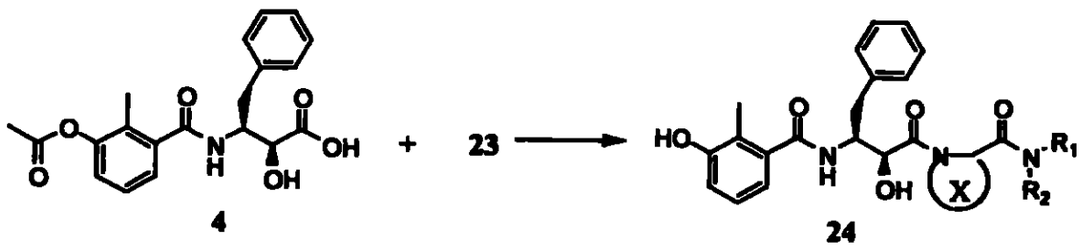


Sólido blanco: $^1$H NMR (DMSO-$d_6$) δ 8.58 (m, 1H), 8.29 (d, *J*= 7 54, 1H), 7.78 (d, *J*=7.88, 2H), 7 32-7.12 (m, 7H), 5 78 (m, 1H), 5.18 (dd, *J*= 9.7, 8.3, 2H), 4 56 (m, 3H), 4.40 (m, 4H), 2.87-2 67 (m, 2H), 2.25 (s, 3H), 1.49 (s, 3H), 1 34 (s, 3H); análisis ($C_{26}H_{32}N_4O_4S$•0.5 $H_2O$•0.5 TFA) calculado C (57.68), H (6.66), N (8.31), hallado C (57 66), H (6.18), N (8 77) HRMS (ESI) *m/z* calculado para 497 2232, hallado 497 2223.

**Métodos Generales C**



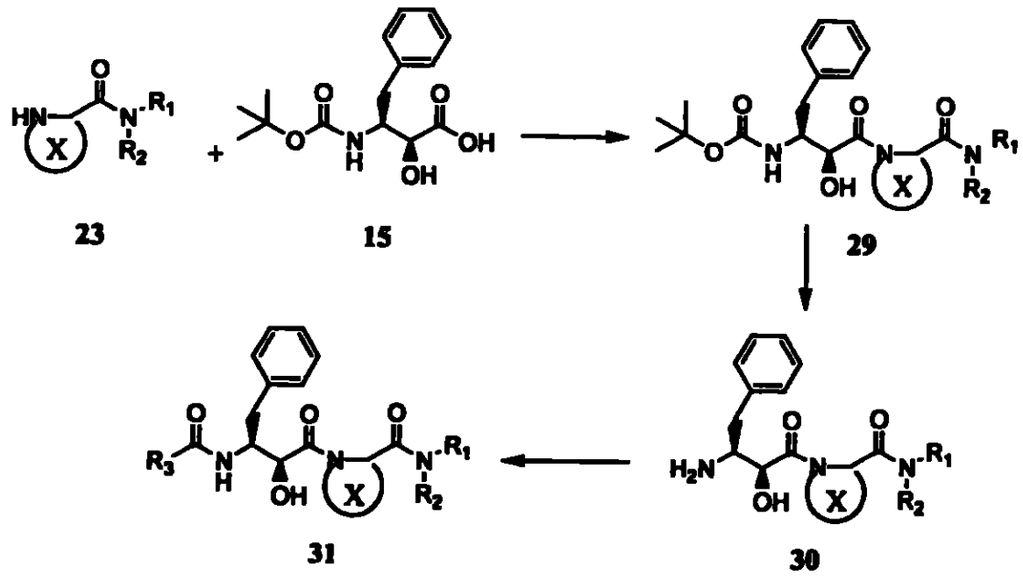
20 2 23



4 24

La síntesis de compuestos con la estructura general **24** es como sigue Los ácidos carboxílicos boc-protegidos **20a-f** se acoplan a las aminas **2** requeridas para producir amino amidas **23** usando un proceso de dos pasos El proceso incluye tratamiento de **20** con **2** en la presencia de difenil clorofosfato o EDCI, seguido por exposición a HCl o ácido metanosulfónico Los compuestos finales **24** se obtienen por un acoplamiento mediado por DCC de **23** y **4** seguido por desprotección del fenol P2 Los compuestos finales se purificaron por cromatografía de destello o HPLC preparativa

**Método General Adicional C**



23 15 29

31 30

La síntesis de compuestos de la estructura general **31** (donde P2 no es 2-metil-3-hidroxi benzamida) es como sigue. Amino amidas de la estructura general **23** se acoplaron al intermedio ácido Boc **15** usando condiciones de acoplamiento DCC. El intermedio resultante **29** se desprotegió bajo condiciones ácidas para producir amina de la estructura general **30**. Los compuestos finales se obtuvieron por modificación de amina **30** por métodos descritos en sección **Métodos Generales B** para producir P2 amidas y ureas.

**Métodos usados para síntesis de compuestos con variaciones P1.**

Acoplamiento EDCI – A una solución de ácido, amina y HOBT en $CH_2Cl_2$ se agregó EDCI y la solución se agitó durante la noche a temperatura ambiente. La solución se concentró *in vacuo* y el residuo se disolvió en acetato de etilo y una pequeña porción de agua La solución se lavó con $NH_4Cl$ saturado (2x), $NaHCO_3$ saturado (2x), salmuera (1x), se secó con $MgSO_4$ y se concentró *in vacuo*. El crudo se usó sin más purificación a menos que se indique lo contrario.

Acoplamiento DCC - Una solución de ácido, amina y HOBT se preparó en acetato de etilo A la solución se agregó entonces DCC en una solución de EtOAc a 0°C y la mezcla se agitó durante la noche a temperatura ambiente. La mezcla se filtró y el filtrado se concentró *in vacuo*. El residuo se disolvió en acetato de etilo lavado con $NH_4Cl$ saturado (1x), $NaHCO_3$ saturado (1x), salmuera (1x), se secó sobre $Na_2SO_4$ y se concentró *in vacuo*. El crudo se usó sin más purificación a menos que se indique lo contrario

Desprotección 4N HCl Boc – A una solución de amina Boc en dioxano se agregó 4N HCl solución en dioxano y la solución se agitó durante la noche a temperatura ambiente La solución se vertió en $NaHCO_3$ saturado y el producto se extrajo en acetato de etilo La solución orgánica se lavó con salmuera, se secó sobre $Na_2SO_4$ y se concentró *in vacuo*. El crudo se usó sin más purificación a menos que se indique lo contrario

Desprotección $MeSO_3H$ Boc - A una solución de amina Boc en

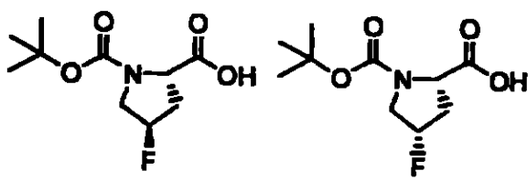
acetato de etilo a 0 °C se agregó ácido metanosulfónico y la solución se agitó 3-6 h a temperatura ambiente. La solución se enfrió a 0°C y se agregó suficiente $NaHCO_3$ saturado para extinguir el ácido. La solución se diluyó con acetato de etilo, se lavó con $NaHCO_3$ saturado y salmuera, se secó sobre $Na_2SO_4$ y se concentró *in vacuo*. El crudo se usó sin más purificación a menos que se indique lo contrario

Desprotección de acetato fenólico KCN - Una solución de acetato fenólico y KCN en etanol se calentó a 50°C durante la noche. La solución se concentró *in vacuo* El residuo se purificó por cromatografía de destello eluida con 0 a 5% metanol en $CH_2Cl_2$ a menos que se indique lo contrario

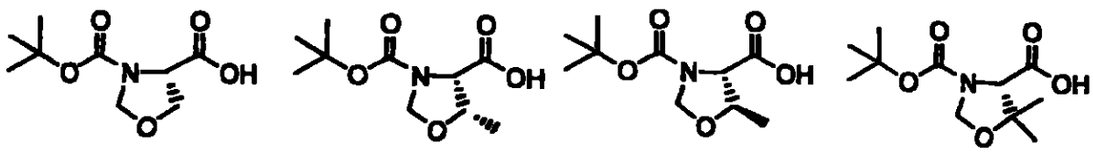
Desprotección de acetato fenólico NaOMe/MeOH – desprotección de acetato fenólico 0.5 N $NaOCH_3$/MeOH - Una solución de acetato fenólico en EtOAc y metanol se enfrió a 0°C en un baño helado. Seguidamente se agregó gota a gota 0 5 N $NaOCH_3$/MeOH y luego se agitó a 0 °C durante 1 5-2 hrs luego de la adición Entonces se agregó EtOAc adicional, el 15 N HCl (4 5 eq.) se agregó gota a gota. Se separaron las bases y las capas orgánicas se lavaron con 2 5% $Na_2CO_3$ solución acuosa, luego con 0 1 N HCl/salmuera (2·1), seguida con salmuera, se secaron con $MgSO_4$ y se concentraron *in vacuo*. El residuo resultante se sometió a cromatografía de destello de gel de sílice para proporcionar el producto deseado a menos que se indique lo contrario.

Desprotección de acetato fenólico HCl/MeOH - A una solución de acetato fenólico en metanol se agregó 4N HCl en dioxano y la solución se agitó a temperatura ambiente aprox 4 h. La solución se concentró *in vacuo*. El residuo se purificó por cromatografía de destello eluida con 0 a 5% metanol en $CH_2Cl_2$ a menos que se indique lo contrario.

**Fragmentos de la estructura general 20.**



**20b** **20c**



**20c** **20d** **20e** **20f**

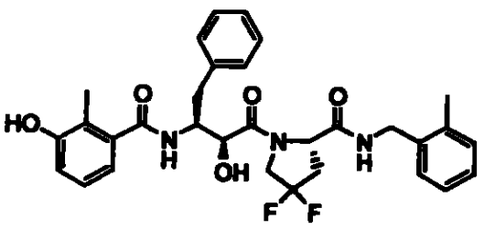
Fuente de Ácidos Boc-carboxílicos 20a-f

Boc-ácidos **20a** y **20b** se prepararon siguiendo el procedimiento de Demange, L , Ménez, A.; Dugave, C. *Tet Lett* **1998,** *39,* 1169.

Boc-ácidos **20c, 20d, 20e** y **20f** se prepararon siguiendo el procedimiento de Karanewsky, D , y colegas, *J Med Chem* **1990,** *33,* 1459

**Método Específico C**

**Ejemplo C1: ácido (S)-4,4-difluoro-1-[(2S,3S)-2-hidroxi-3-(3-hidroxi-2-metil-benzoilamino)-4-fenil-butiril]-pirrolidino-2-carboxílico 2-metil-bencilamida.**

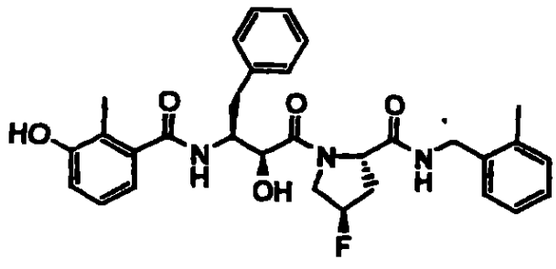


El compuesto del título se preparó de acuerdo con los Métodos Generales usando el correspondiente ácido pirrolidínico Boc-protegido (0.96 g, 3 8 mmol), o-metilbencil amina (0 57 mL, 4.6 mmol), HOBT (0.62 g 4 6 mmol), EDCI (0 88 g, 4.6 mmol), $CH_2Cl_2$ (50 mL) para producir la Boc-amida cruda (MS-APCI (*m/z*+)· 355, 255) (1.35 g, 3.8 mmol). El Boc se retiró usando la desprotección general 4N HCl Boc, 4N HCl en 1,4-dioxano

(5 mL), 1,4-dioxano (5 mL) El resultado fue un amino amida de estructura general **23** Rendimiento aislado· 0.79 g (71%, 2 pasos). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.02 (t, 1H), 7.24-7.14 (m, 4H), 4.55 (t, 1H), 4 35 (dd, 1H), 4.30 (dd, 1H), 3.73 (m, 2H), 2 94 (m, 2H), 2.52 (m, 1H), 2 27 (s, 3H); $^{19}$F NMR (376 MHz, DMSO-$d_6$)· δ -95 3 (dq. $J$= 235, 15 Hz, 1F), -96.5 (dq, $J$= 235, 12 Hz, 1F), MS-APCI *(m/z+)* 255.

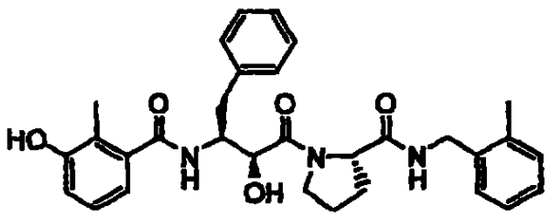
Amino amida **23** (100 mg, 0.34 mmol) se acopló a ácido carboxílico **4** (140 mg, 0.38 mmol) usando el método general de acoplamiento DCC bosquejado más arriba. HOBT (51 mg, 0 38 mmol), DCC (78 mg, 0.38 mmol), TEA (50 µL, 0.36 mmol), $CH_2Cl_2$ (10 mL). El crudo se purificó por cromatografía eluida con 10% cetona en $CH_2Cl_2$. Rendimiento aislado 0 13 g (63%) MS-APCI (*m/z+*). 608 Este material se sometió a las condiciones generales de desprotección de acetato fenólico KCN (130 mg, 0 21 mmol), KCN (1 mg, 15 µmol), etanol (10 mL) El crudo se precipitó de éter dietílico y acetato de etilo con hexanos a -78 °C. Rendimiento aislado. 0-10 g (84%). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9 37 (s, 1H), 8 36 (t, 1 H), 8 16 (d, 1H), 7 32-7 09 (m, 9H), 6.93 (t, 1H), 6.76 (d, 1H), 6 54 (d, 1H), 5.49 (d, 1H), 4.66 (dd, 1H), 4.34-4.15 (m, 6H), 2 85-2 67 (m, 3H), 2.40 (m, 1H), 2 22 (s, 3H), 1.79 (s, 3H); $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -98 7 (m, 2F), MS-APCI (*m/z+*) 566; HPLC Pureza. 100%, Rf (min.) 19 01; análisis $C_{31}H_{33}N_3O_5F_2$-0.3 $H_2O$ C, H, N calculado: C65 21, H5.93, N7.36; hallado· C65.11, H5 90, N7.17.

**Ejemplo C2: ácido (2S,4R)-4-fluoro-1-[(2S,3S)-2-hidroxi-3-(3-hidroxi-2-metil-benzoilamino)-4-fenil-butiril]-pirrolidino-2-carboxílico 2-metil-bencilamida**



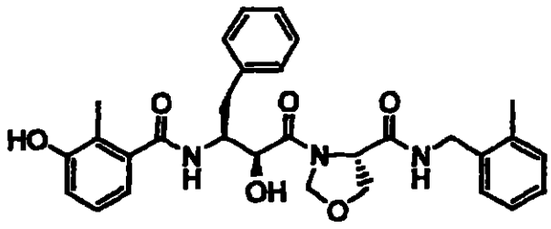
Material aislado se sometió a cromatografía de destello de gel de sílice, eluyendo con EtOAc/hexanos (50/50) luego con EtOAc EtOAc/hexanos (4.1) para proporcionar el compuesto del título $^1$H NMR (400 MHz, DMSO-$d_6$)· δ 9 37 (s, 1H), 8.46 (t, 1H), 8.21 (d, 1H), 7.34 (d, 2H), 7.26 (d, 2H), 7.21 (t, 2H), 7.15-7.07 (m, 3H), 6.94 (t, 1H), 6.76 (d, 1H), 6.56 (d, 1H), 5.51 + 5.38 (bs + bs, 1H), 5 06 (d, 1H), 4 58 (t, 1H), 4 45 (dd, 1H), 4 35-4 27 (m, 2H), 4 21-4.09 (m, 3H), 3 94-3 91 + 3.84-3.81 (m + m, 1H), 2.69 (d, 2H), 2.23 (s, 3H), 2.19-2.01 (m, 1H), 1.83 (s, 3H), MS-APCI (*m/z*+) 548; HPLC· Rf (mm.) 18 72; pureza: 96% Análisis $C_{31}H_{34}N_3O_5F$•03 $H_2O$ calculado: 67.33, 6.31, 7 60, hallado: 67 37, 6 25, 7.35.

**Ejemplo C3: ácido (2S,4S)-4-fluoro-1-[(2S,3S)-2-hidroxi-3-(3-hidroxi-2-metil-benzoilamino)-4-fenil-butiril]-pirrolidino-2-carboxílico 2-metil-bencilamida**



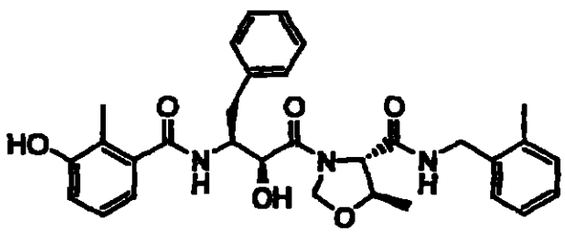
Material aislado se sometió a cromatografía de destello de gel de sílice, eluyendo con EtOAc/hexanos (50/50) luego con EtOAc para proporcionar el compuesto del título. $^1$H NMR (400 MHz, DMSO-$d_6$)· δ 9 37 (s, 1H), 8 21 (d, 1H), 7.96 (t, 1 H), 7.29 (d, 2H), 7 23 (t, 2H), 7.18-7.13 (m, 2H), 7.10-7 04 (m, 3H), 6 90 (t, 1H), 6.75 (d, 1H). 6 52 (d, 1H), 5.55 (d, 1H), 5.45 + 5 32 (bs + bs, 1H), 4.54 (d, 1H), 4.42-4.36 (m, 1H), 4 29-4.40 (m, 5H), 2.98 (t, 1H), 2.73 (t, 1H), 2.32-2.21 (m, 2H), 2.19 (s, 3H), 1.78 (s, 3H); MS-APCI (*m/z*+) 548, HPLC: Rf (min.) 18.21; pureza. 99%; análisis $C_{31}H_{34}N_3O_5F$•0.5 $H_2O$ calculado: 66 89, 6.34, 7 55, hallado: 66.85, 6 22, 7 41

**Ejemplo C4: ácido (S)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-oxazolidino-4-carboxílico 2-metil-bencilamida**



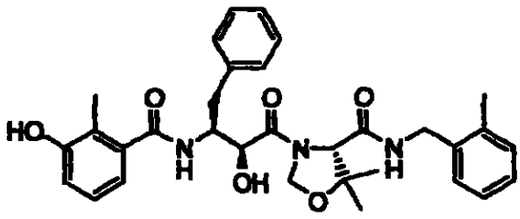
Sólido blanco, $^1$H NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8 80 (dd, *J*= 8.8, 4.8, 1H), 8 30 (t, *J*= 5.5, 1H), 8 12 (d, *J*= 8.6, 1H), 7-30-7.13 (m, 9H), 6.96 (t, *J*= 7.9, 1H), 6 76 (d, *J*= 7.9, 1H), 6 55 (d, *J*= 7 2, 1H), 5.74 (d, *J*= 8.8, 1H), 5 31 (d, *J*= 3.8, 1H), 5.23 (d, *J*= 4.2, 1H), 4.49 (dd, *J*= 6.6, 6 5, 1H), 4 33-4 11 (m, 5H), 2.94-2.68 (m, 2H), 2.24 (s, 3H), 1.78 (s, 3H), HRMS (ESI) *m/z* calculado para $C_{30}H_{34}N_3O_6$ $(M + H)^+$ 532.2448, hallado 532.2450

**Ejemplo C5: ácido (4S,5R)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5-metil-oxazolidino-4-carboxílico 2-metil-bencilamida**



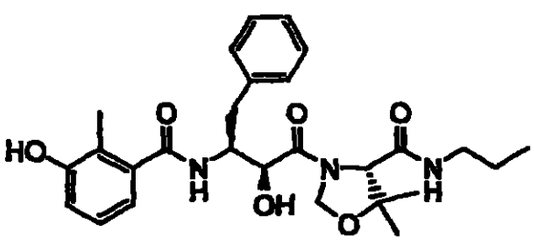
Sólido blanco; $^1$H NMR (DMSO-$d_6$) δ 9.38 (s, 1H), 8 51 (t, *J*= 6 0, 1H), 8.15 (d, *J*= 8 4, 1H), 7.33-7 13 (m, 9H), 6 96 (t, *J*= 7.7, 1H), 6.79 (d, *J*= 8.2, 1H), 6 58 (d, *J*= 7 3, 1H), 5.69 (d, *J*= 5.7, 1H), 5.50 (d, *J*= 4 6, 1H), 5.10 (d, *J*=4.8, 1H), 4.39-4 22 (m, 4H), 4.11-4.01 (m, 2H), 2 90 (m, 1H), 2.74 (m, 1H), 2.27 (s, 3H), 1 82 (s, 3H), 1.37 (d, *J*= 5 9, 1H), HRMS (ESI) *m / z* calculado para $C_{31}H_{36}N_3O_6$ $(M + H)^+$ 546.2604, hallado 546.2595.

**Ejempl C6: ácido (S)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-oxazolidino-4-carboxílico 2-metil-bencilamida**



Sólido blanco; $^1$H NMR (DMSO-$d_6$) δ 9.34 (s, 1H), 8 32 (t, *J*= 5.8, 1H), 8.11 (*J*= 9.0, 1H), 7 31-7 10 (m, 9H), 6.93 (t, *J*= 7 9, 1H), 6.76 (d, *J*= 8.1, 1H), 6 55 (d, *J*= 6.5, 1H), 5.73 (d, *J*= 4 0, 1H), 5 46 (d, *J*= 4.1, 1H), 5.23 (d, *J*= 3.9, 1H), 4.39-4.32 (m, 2H), 4 18 (m, 3H), 2 92 (m, 1H), 2.69 (m, 1H), 2.27 (s, 3H), 1 81 (s, 3H), 1.28 (s, 3H), 1-18 (s, 3H), HKMS (ESI) *m / z* calculado para $C_{32}H_{38}N_3O_6$ $(M + H)^+$ 560 2761, hallado 560.2759, análisis calculado para $C_{32}H_{37}N_3O_6 \cdot 0.5\ H_2O$. C, 67.59, H, 6 74; N, 7 39. Hallado C, 67.74; H, 6 75; N, 7.16

**Ejemplo C7: ácido (S)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-oxazolidino-4-carboxílico propilamida**

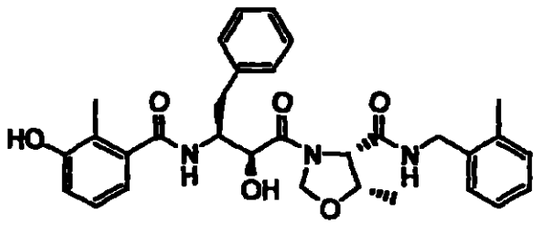


$^1$H NMR (DMSO-$d_6$) δ 9 37 (s, 1H), 8 12 (d, *J*= 9 3, 1H), 7.93 (t, *J*= 5 6, 1H), 7.34-7.18 (m, 5H), 6.96 (t, *J*= 8.1, 1H), 6.79 (d, *J*= 8.1, 1H), 6 56 (d, *J*= 7.1, 1H), 5.73 (d, *J* =6 2, 1H), 5 44 (d, *J*= 4.0, 1H), 5.24 (d, *J*= 3 8, 1H), 4 36 (m, 1H), 4 18 (m, 1H), 4 11 (s, 1H), 3.10-2 92 (m, 3H), 2.75-2.66 (m, 1H), 1 80 (s, 3H), 1.46-1.39 (m, 2H), 1 31 (s, 3H), 1.22 (s, 3H), 0 86 (t, *J*=

213

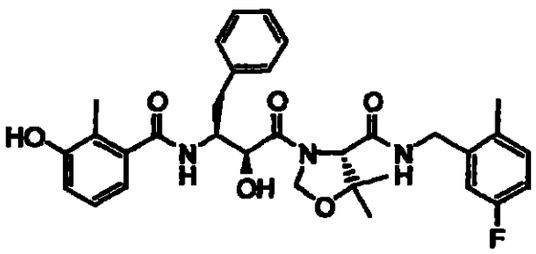
7.2, 3H); HRMS (ESI) *m / z* calculado para $C_{27}H_{36}N_3O_6$ $(M + H)^+$ 498 2604, hallado 498.2590

**Ejemplo C8: ácido (4S,5S)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5-metil-oxazolidino-4-carboxílico 2-metil-bencilamida**



Sólido blanco; $^1$H NMR (DMSO-$d_6$) δ 9.36 (s, 1H), 8.26 (t, *J*= 5 5, 1H), 8.09 (d, *J*= 8 8, 1H), 7.30-7 08 (m, 9H), 6.93 (t, *J*=7.7, 1H), 6 76 (d, *J*= 7 9, 1H), 6.56 (d, *J*= 7.5, 1H), 5 72 (d, *J*= 6.4, 1H), 5 55 (d, *J*= 3.7, 1H), 5 08 (d, *J*= 3.8, 1H), 4 40-4 33 (m, 3H), 4.26-4 11 (m, 3H), 3.10-2.89 (m, 1H), 2 78-2.67 (m, 1H), 2.26 (s, 3H), 1 78 (s, 3H), 1 15 (d, *J*= 6.2, 3H), HRMS (ESI) *m/z* calculado para $C_{31}H_{36}N_3O_6$ $(M + H)^+$ 546.2604, hallado 546.2592.

**Ejemplo C9: ácido (S)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-oxazolidino-4-carboxílico 5-fluoro-2-metil-bencilamida**

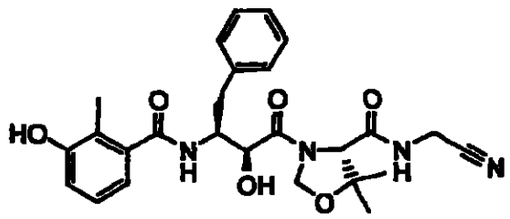


Sólido blanco, $^1$H NMR (DMSO-$d_6$) δ 9.35 (s, 1H), 8.41 (t, *J*= 5.6, 1H), 8.12 (d, *J*= 8.9, 1H), 7 28-7 08 (m, 8H), 6.95-6.90 (m, 1H), 6.76 (d, *J*= 8.1, 1H), 6.55 (d, *J*= 7.2, 1H), 5.78 (d, *J*= 6 1, 1H), 5 47 (d, *J*= 3.8, 1H), 5 24 (d, *J*= 3.8, 1H), 4.40-4.25 (m, 2H), 4.20-4.30 (m, 3H), 3.00-2 60 (m, 2H), 2.22 (s, 3H), 1.77 (s, 3H), 1.30 (s, 3H), 1.19 (s, 3H), análisis calculado para

214

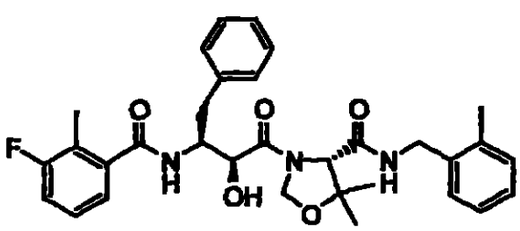
$C_{32}H_{36}N_3O_6F$: C, 66.54, H, 6.28; N, 7 27. Hallado: C, 66.37; H, 6.20; N, 7.21.

**Ejemplo C10: ácido (S)-3-((2S,3S)-2-hidroxi-3-{[1-(3-hidroxi-2-metil-fenil)-metanoil]-amino}-4-fenil-butanoil)-5,5-dimetil-oxazolidino-4-carboxílico cianometil-amida**



Sólido blanco, $^1$H NMR (DMSO-$d_6$) δ 9 36 (s, 1H), 8.72 (t, *J*= 5.3, 1H), 8 11 (d, *J*= 9 0, 1H), 7 29-7 16 (m, 5H), 6 94 (t, *J*= 7.7, 1H), 6.76 (d, *J*= 8.1, 1H), 6.50 (d, *J*= 7.5, 1H), 5 85 (d, *J*= 6.0, 1H), 5 49 (d, *J*= 4 0, 1H), 5.23 (d, *J*= 3 9, 1H), 4 35 (m, 1H), 4 18-4 12 (m, 3H), 4.11 (s, 1H), 2.92 (m, 1H), 2.70 (m, 1H), 1.76 (s, 3H), 1.29 (s, 3H), 1.19 (s, 3H); HRMS (ESI) *m / z* calculado para $C_{26}H_{31}N_4O_6$ (M + H) 495.2244, hallado 495 2239.

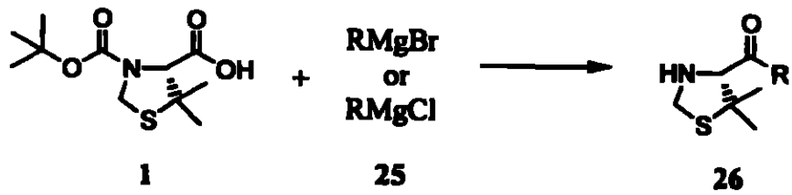
**Ejemplo C11: ácido (S)-3-((2S,3S)-3-{[1-(3-fluoro-2-metil-fenil)-metanoil]-amino}-2-hidroxi-4-fenil-butanoil)-5,5-dimetil-oxazolidino-4-carboxílico 2-metil-bencilamida**



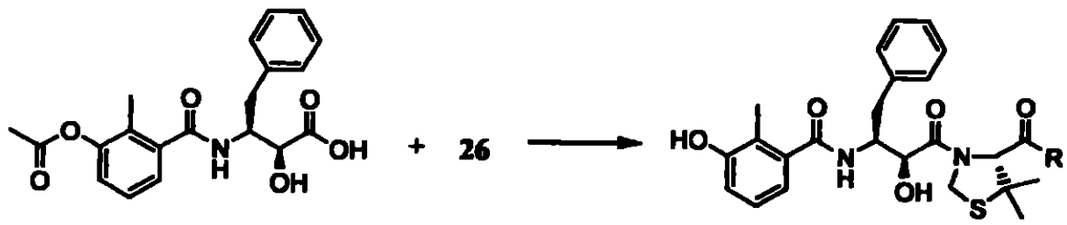
$^1$H NMR (DMSO-$d_6$) δ 8 34 (m, 2H), 7.30-7 13 (m, 11H), 6.95 (d, *J*= 7 1, 1H), 5.82 (d, *J*=6.4, 1H), 5.45 (d, *J*= 3 9, 1H), 5.23 (d, *J*= 4.0, 1H), 4 38-4.31 (m, 2H), 4.18-4.15 (m, 3H), 2.96 (m, 1H), 2.67 (m, 1H), 2.26 (s, 3H), 1.87 (s, 3H), 1.28 (s, 3H), 1.18 (s, 3H), HRMS (ESI) *m / z* calculado para

$C_{32}H_{37}N_3O_5F$ $(M + H)^+$ 562.2717, hallado 562.2713

**Métodos Generales D**




1 25 26

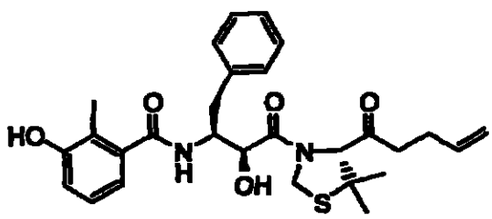


4 27

La síntesis de compuestos con la estructura general **27** es como sigue. El ácido tiazolidino carboxílico boc-protegido **1** se convierte en amino-cetonas **26** con reactivos de Grignard requeridos **25** en la presencia de cloruro de oxalilo. Los compuestos finales **27** se obtienen por un acoplamiento mediado por DCC de **26** y **4** seguido por desprotección del fenola P2. Los compuestos finales se purificaron por cromatografía de destello o HPLC preparativa.

**Método Específico D**

**Ejemplo D1: *N*-[(1S,2S)-1-Bencil-3-((R)-5,5-dimetil-4-pent-4-enoil-tiazolidino-3-il)-2-hidroxi-3-oxo-propil]-3-hidroxi-2-metil-benzamida**



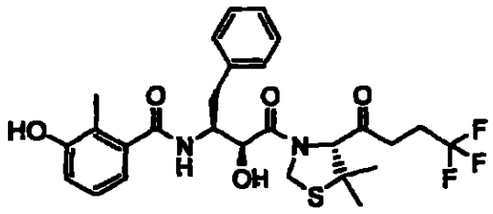
El compuesto del título se preparó en la siguiente forma Ácido (R)-5,5-dimetil-tiazolidino-3,4-dicarboxílico 3-*tert*-butil éster **1** (1.0 g, 3 80 mmol) se disolvió en benzeno (10 mL) y se enfrió a 0°C con agitación magnética

Se agregaron dos gotas de DMF seguidas por una adición gota a gota de cloruro de oxalilo (0 33 mL, 3.80 mmol) Una vez cesó la evolución de gas, la solución se concentró a un residuo amarillo/rojo. El material se disolvió en THF seco (10 mL) y se enfrió a -78 °C con agitación magnética. El reactivo de Grignard, bromuro de 3-butenilmagnesio (7 7 mL, 3.80 mmol) se agregó gota a gota durante 10 min. El resultado se agitó a -78 °C durante 1h luego a -55 °C durante 30 min. La reacción se extinguió a -55°C con solución $NH_4Cl$ saturado (3 mL) y luego se vertió en $H_2O$ (50 mL) La mezcla se extrajo con EtOAc (2 x 50 mL). Los orgánicos combinados se lavaron con salmuera (1 x 100 mL), se secaron sobre $Na_2SO_4$, se filtraron, y se concentraron El resultado fue la aminocetona **26** que era lo suficientemente pura para usar en el paso subsiguiente. El aceite transparente **26** (0.24 g, 1 15 mmol) se disolvió en EtOAc (10 mL) Se agregó AMB-AHPBA **4** (0.40 g, 1 09 mmol) seguido por HOBt (0 15 g, 1.09 mmol). La mezcla se agitó a temperatura ambiente 1h, luego se enfrió a 0°C DCC (0.24 g, 1.15 mmol) se agregó lentamente como solución en EtOAc (6 mL). La mezcla se calentó a temperatura ambiente y se agitó durante la noche. La mezcla se filtró y el filtrado se lavó con 1N HCl (30 mL), $NaHCO_3$ saturado (10 mL), salmuera (10 mL), se secó sobre $Na_2SO_4$ y se concentró para producir un sólido blanco crudo (contaminado con DCU). El DCU se retiró por cromatografía de destello (30% a 50% EtOAc en hexanos) para proporcionar un sólido blanco, el cual se disolvió en MeOH (2 mL) y se trató con 4N HCl en 1,4-dioxano (0.26 mL, 1.1 mmol). La reacción se agitó a temperatura ambiente durante la noche, luego se dividió en partes entre 1N HCl (10 mL) y EtOAc (10 mL). La capa orgánica se lavó con $NaHCO_3$ saturado (1 x 25 mL) se secó sobre $Na_2SO_4$, se filtró, y se concentró a un residuo que se purificó por cromatografía de destello (60% EtOAc en hexanos) para proporcionar el compuesto del título como un sólido amorfo blanco. $^1H$ NMR (DMSO-$d_6$) δ 9 36 (s, 1H), 8.23 (d, *J*= 8.1, 1H), 7.35-7.14 (m, 5H), 6.96 (t, *J*= 7 5, 1H), 6 78 (d, *J*= 8 2, 1H), 6.52 (d, *J*= 7.5, 1H), 5 81-5 69 (m, 2H), 5.32 (d, *J*= 9 7, 1H), 5 11-5.91 (m, 3H), 4 40 (m, 3H), 2.89-2.61 (m, 4H), 2.37-2.14 (m, 2H), 1 81 (s, 3H), 1.55 (s,

3H), 1 30 (s, 3H), análisis calculado para $C_{28}H_{34}N_2O_5S$: C, 65.86; H, 6 71, N, 5.49. Hallado: C, 65.52; H, 6 55, N, 5.81

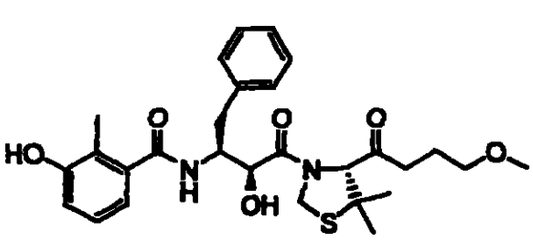
Los siguientes ejemplos se sintetizaron usando el método específico bosquejado anteriormente empleando el reactivo de Grignard apropiado para el compuesto deseado.

**Ejemplo D2: N-{1-bencil-3-[5,5-dimetil-4-(4,4,4-trifluoro-butanoil)-tiazolidino-3-il]-2-hidroxi-3-oxo-propil}-3-hidroxi-2-metil-benzamida**



$^1$H NMR (DMSO-$d_6$) δ 9.34 (s, 1H). 8.16 (d, 1H, *J*= 8.6), 7.29-6.49 (m, 8H) 5.88 (d, 1H, *J*= 6 1), 5 33 (d, 1H, *J*= 9.5), 5 10 (d, 1H, *J*= 9.5), 4.56 (s br, 3H), 2.98-2.57 (m, 6H), 1.74 (s, 3H), 1.55 (s, 3H), 1 30 (s, 3H), HRMS (ESI) *m / z* calculado para $C_{27}H_{32}N_2O_5SF_3$ (M + H)$^+$ 553.1984, hallado 553.1984; análisis calculado para $C_{27}H_{31}N_2O_5SF_3$•0.5$H_2O$: C, 58 59; H, 5.66; N, 5 06, S, 5 79. Hallado: C, 58.96; H, 6.02; N, 5 58; S, 5.33.

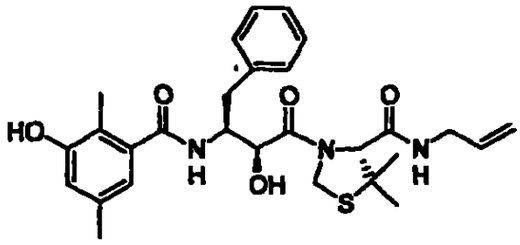
**Ejemplo D3: N-{1-bencil-2-hidroxi-3-[4-(4-metoxi-butanoil)-5,5-dimetil-tiazolidino-3-il]-3-oxo-propil}-3-hidroxi-2-metil-benzamida**



$^1$H NMR (DMSO-$d_6$) δ 9 34 (s, 1H), 8 18 (d, 1H, *J*= 8.2), 7.32-6.51 (m, 8H), 5.56 (d, 1H, *J*= 7.8), 5.26 (d, 1H, *J*= 9.5). 5.08 (d, 1H, *J*= 9.5), 4 45-4 38 (m, 2H), 4.36 (s, 1H), 3.15 (s, 3H), 2.93-2.61 (m, 2H), 1.87-1 00 (m,

6H), 1 80 (s, 3H), 1.55 (s, 3H), 1.36 (s, 3H), HRMS (ESI) *m / z* calculado para $C_{28}H_{37}N_2O_6S$ $(M + H)^+$ 529.2165, hallado 529.2372, análisis calculado para $C_{28}H_{36}N_2O_6S \cdot 0.5H_2O$· C, 62.55; H, 6.94; N, 5 21; S, 5 96. Hallado C, 62.89; H, 7 32; N, 5.96, S, 5.59

**Ejemplo D4: ácido (R)-3-[(2S,3S)-2-hidroxi-3-(3-hidroxi-2,5-dimetil-benzoilamino)-4-fenil-butiril]-5,5-dimetil-tiazolidino-4-carboxílico alilamida**

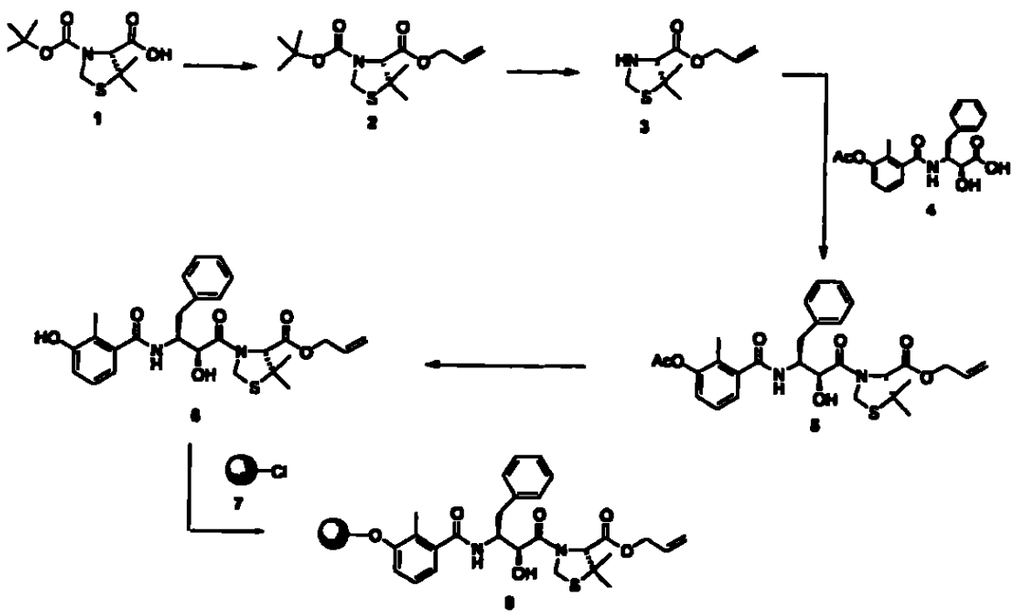


Sólido blanco. $^1$H NMR (DMSO-$d_6$) δ 9.23 (s, 1H), 8 09 (m, 2H). 7.35 - 7 17 (m, 5H), 6.60 (s, 1H), 6.37 (s, 1H), 5 82-5.68 (m, 1H), 5 41 (br s, 1H), 5 20 (dd, 1H, *J*= 1 6, 17.2), 5.11 (d, 1H, *J* = 9 2), 5.02 (dd, 1H, *J*= 1.5, 10.2), 5 00 (d, 1H, *J*= 9.1), 4.46- 4.37 (m, 3H), 3.79 (ddd, 1H, *J*= 5 3, 5.5, 15.9), 3.63 (ddd, 1H, *J*= 5.4 5.3, 15.9), 2.82 (dd, 1H, *J*=0 3, 13.9), 2 71 (dd, *1H, J*= 10.7, 13.6), 2.16 (s, 3H), 1 76 (s, 3H), 1.51 (s, 3H), 1 36 (s, 3H), HRMS (ESI) *m / z* calculado para $C_{28}H_{36}N_3O_5S$ $(M + H)^+$ 526 6670, hallado 526.2376; análisis calculado para $C_{28}H_{35}N_3O_5S \cdot 0.3\ H_2O$ C, 63.32, H, 6.76; N, 7.91, Hallado: C, 63.35 ;H, 6 70; N, 7.71

**Enfoque de Química Combinatoria a Inhibidores P2' de Proteasa VIH**

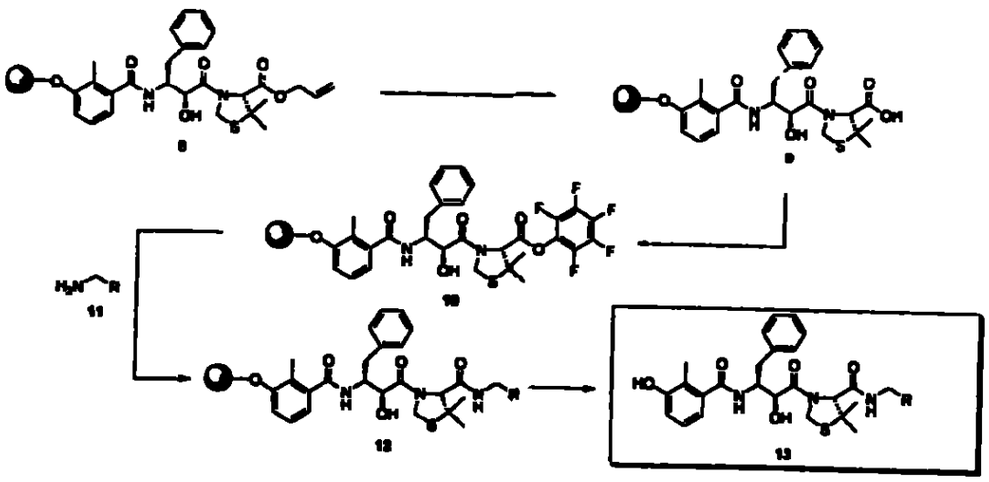
Método General E

**Esquema I**



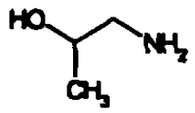
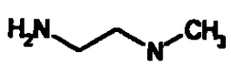
El bloque de construcción combinatorio, **8**, se prepara usando los siguientes métodos El ácido tiazolidino carboxílico boc-protegido, **1**, se trata con bromuro de alilo en la presencia de $NaHCO_3$ para producir el éster alílico de tiazolidina boc-protegido, **2**. La desprotección del éster alílico boc-protegido, **2**, con HCl (g) en EtOAc produce la sal HCl de la amina del éster alílico de tiazolidina, **3**, el cual se trata con TEA y se acopla a **4** en la presencia de HOBT y DCC para producir el bloque de construcción precursor, **5**. La desprotección del bloque de construcción, **5**, con 4N HCl produce el fenol, **6**. La carga del bloque de construcción, **6**, en glóbulos activados de tritil cloruro poliestireno enlazado cruzadamente, **7**, se llevó a cabo en la siguiente manera El alcohol tritílico enlazado cruzadamente con poliestireno se activó al cloruro de tritilo, **7**, por tratamiento con 20% cloruro de acetilo en $CH_2Cl_2$ anhidro a temperatura ambiente. Los glóbulos de cloruro de tritilo se combinaron con el fenol **6** en la presencia de una base de Hunig en $CH_2Cl_2$ anhidro para producir los glóbulos de poliestireno cargados en un sustrato **8**. Los intermedios se purificaron por cromatografía de destello o HPLC preparativa.

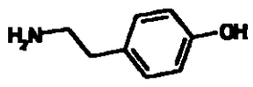
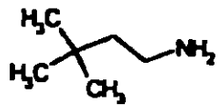
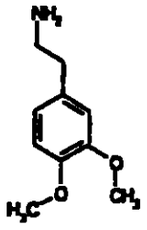
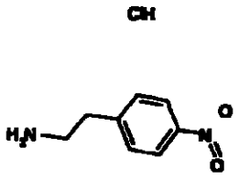
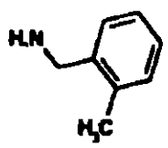
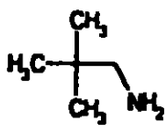
**Esquema II**



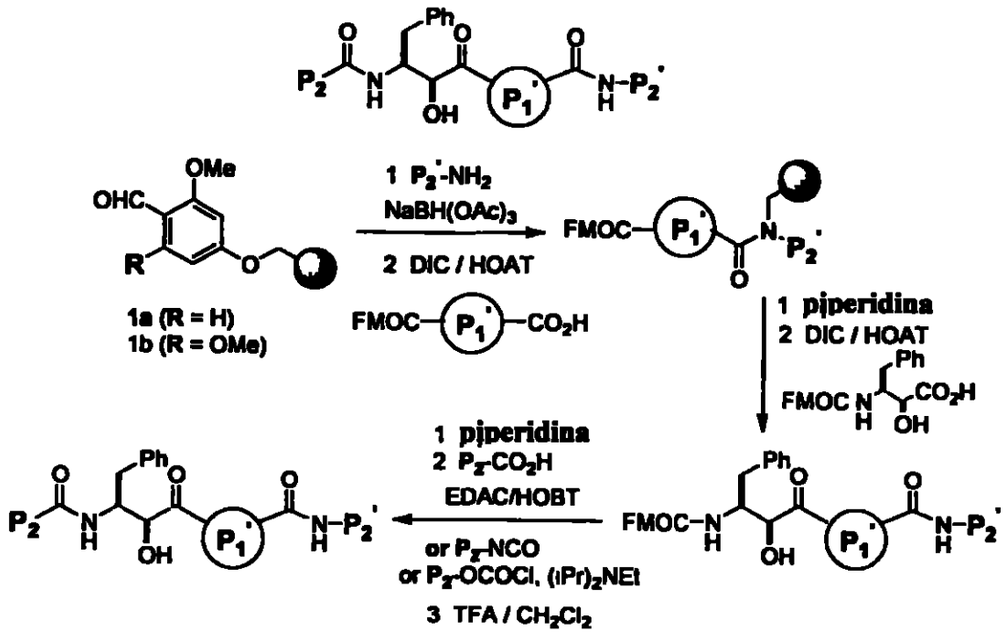
La síntesis de la biblioteca combinatoria de proteasa VIH se llevó a cabo en la siguiente forma El éster alílico se retiró por tratamiento con $Pd[PPh_3]_4$ y NMM en THF anhidro para producir carboxilato 9, el cual se trató con pentafluorofenol, pentafluorofenol trifluoromacetato de etilo y piridina en DMF para producir el pentafluoro éster, 10 El pentafluoro éster 10 se trató con varias aminas primarias en un formato de 96-pozos para producir amidas 12 Los productos finales se dividieron de las coronas de polistireno con TFA para producir productos 13. Cada producto se analizó por LCMS y HPLC La siguiente tabla tipifica compuestos sintetizados por este método combinatorio.

**Tabla 1**

| P2' | Masa Esperada (LCMS) | Masa Observada | % Inhibición |
|---|---|---|---|
|  | 529 | 552($Na^+$) | 38 |
|  | 528 | 529($MH^+$) | 4 |

| | | | |
|---|---|---|---|
|  | 591 | 614($Na^+$) | 18 |
|  | 555 | 578($Na^+$) | 19 |
|  | 635 | 658($Na^+$) | 5 |
|  | 656 | 656($MH^+$) | 8 |
|  | 575 | 598($Na^+$) | 86 |
|  | 541 | 564($Na^+$) | 63 |
|  | 529 | 552($Na^+$) | 49 |

**Esquema 3: Síntesis de Fase Sólida de Inhibidores de Proteasa VIH (Análogos AG 1776)**




La síntesis combinatoria de fase sólida de inhibidores de proteasa VIH se realizó usando la Tecnología de Clasificación Dirigida IRORI Resina comercial 4-formil-3-metoxifenoximetil polistireno **1a** (PS-MB-CHO, Argonaut Technologies) o resina 4-formil-3, 5-dimetoxifenoximetil polistireno **1b** (resina PL-FDMP, Polymer Laboratories) se cargó en Minikans individuales.

Paso A. Aminación Reductora Con Aminas $P_2$'

A matraces separados que contenían los MiniKans clasificados se agregó DCM (3 mL/MiniKan) Se agregaron la amina primaria apropiada $P_2$' (3 eq), triacetoxiborohidruro de sodio (5 eq), y ácido acético (3 eq), y las mezclas se pusieron bajo argón, se agitaron con ventilación periódica a temperatura ambiente durante 1 -2 horas, y se hicieron reaccionar durante la noche. Para la resina **1a**, los filtrados se vertieron y los MiniKans se lavaron con DCM, MeOH (2x), DCM (2x), $Et_3N$/DCM (1:3, 3x), DCM (2x), MeOH (3x), y DCM (4x). Para la resina **1b**, se empleó una secuencia de lavado de DCM, MeOH (2x), DCM (2x), $Et_3N$/DCM (1:3, 3x), DCM (2x), DMF, 1M NaOH/DMF (1:5, 3x), DMF (3x), MeOH (3x), y DCM (3x). Las MiniKans se secaron bajo vacío y se tomaron en el Paso B.

Paso B. Acoplamiento de Péptido Con Aminoácidos $P_1'$

A matraces separados que contenían los MiniKans clasificados se agregó DMF (3 mL/MiniKan) El aminoácido apropiado FMOC-protegido (2.5 eq) y 1-hidroxi-7-azabenzotriazol (HOAT) (3 eq) se agregaron y mezclaron hasta que se disolvieron, y se agregó 1,3-diisopropilcarbodiimida (DIC) (3 eq). Los recipientes se pusieron bajo argón y se agitaron a temperatura ambiente durante la noche. Los filtrados se vertieron, y los MiniKans se lavaron con DMF (3x), MeOH (3x), DCM (2x), y DMF (2x). Las MiniKans se tomaron directamente en Paso C.

Paso C Desprotección FMOC

Un recipiente de MiniKans en DMF y piperidina (25%) con un volumen total de reacción de 3 mL/MiniKan se agitó bajo argón a temperatura ambiente durante 45 minutos. Se retiró el filtrado, y se repitió el procedimiento de reacción Los MiniKans se filtraron y lavaron con DMF (3x), MeOH (2x), DCM (3x), y DMF, y se tomaron directamente en Paso D

Paso D Acoplamiento de Péptido Con FMOC-APNS

FMOC-Alofenilnorstatina (APNS) (3 eq) se agregó al matraz de MiniKans en DMF (3 mL/MiniKan). Luego de la disolución, se agregaron HOAT (3.5 eq) y DIC (3.5 eq). La mezcla se puso bajo argón y se agitó a temperatura ambiente durante la noche. La reacción se filtró y los MiniKans se lavaron con DMF (3x), MeOH (3x), DCM (3x), y DMF. La desprotección FMOC se llevó a cabo como en Paso C, y los MiniKans se lavaron con DMF (3x), MeOH (2x), DCM (3x), se secaron bajo vacío y se tomaron en Paso E o F.

Paso E. Acoplamiento de Péptido Con Ácidos $P_2$

A matraces separados que contenían los MiniKans clasificados en DMF (3 mL/MiniKan) se agregó el ácido $P_2$ apropiado (3 eq), hidrato

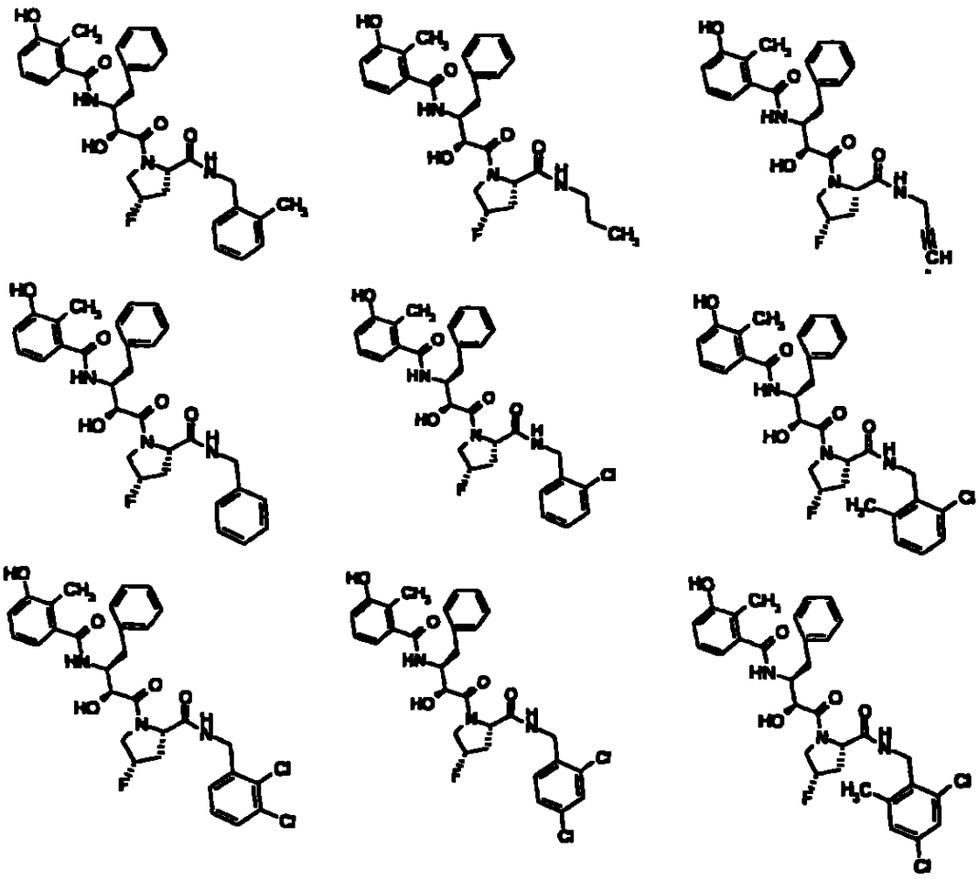
224

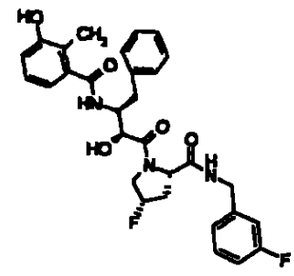
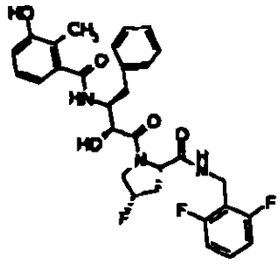
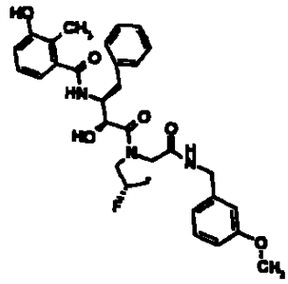
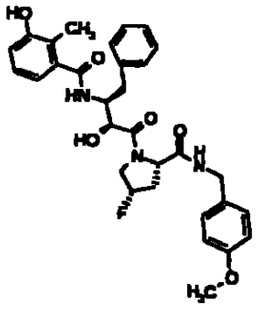
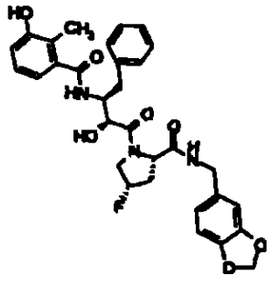
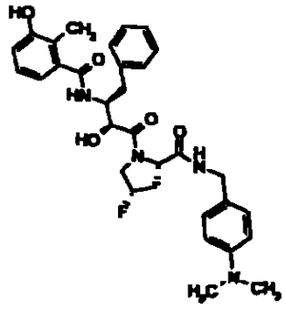
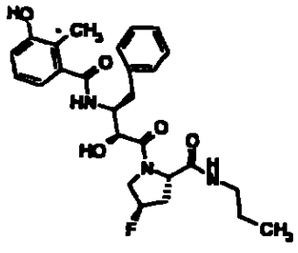
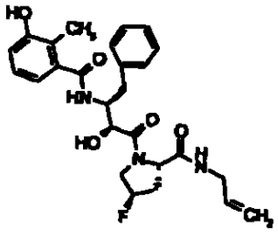
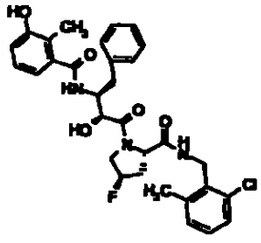
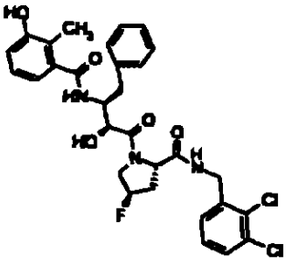
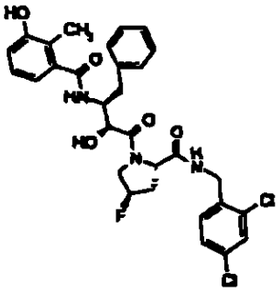
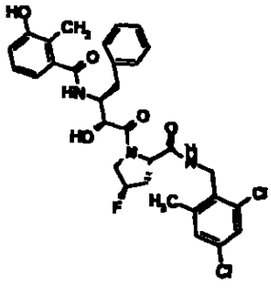
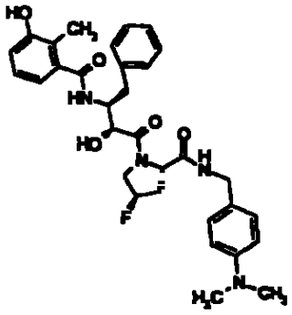
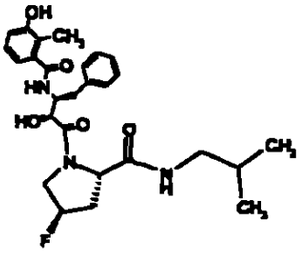
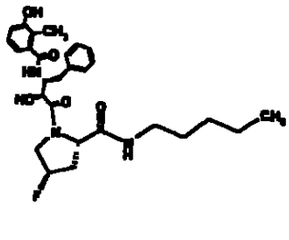
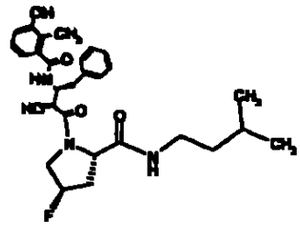
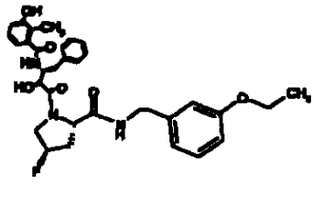
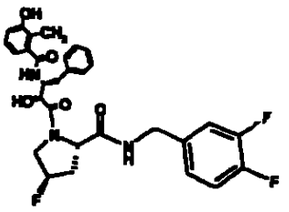
HOBT (4 eq), y (3-(dimetilamino)propil)etilcarbodiimida clorhidrato (EDAC) (3 5 eq). La reacción se agitó bajo argón a temperatura ambiente durante 3 horas. Luego de la filtración, los MiniKans se lavaron con DMF (3x), MeOH (3x), y DCM (3x), se secaron bajo vacío, y se tomaron en Paso G

Paso F. Escisión y Procesamiento de los Análogos de VIH

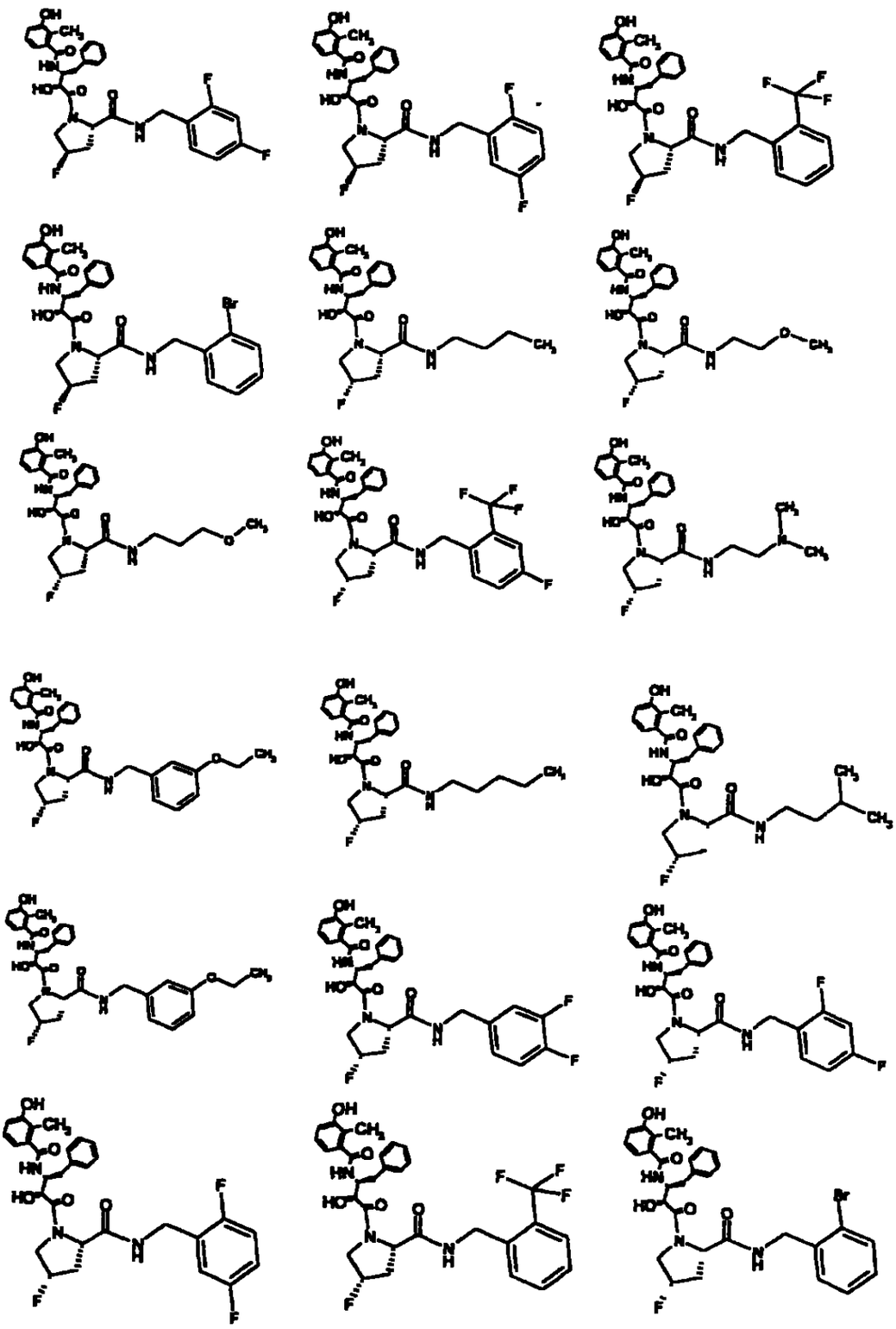
Los MinKans individuales se clasificaron en bastidores de escisión y se agregó una solución de 25% TFA en DCM (3 mL/MinKan). Los bastidores se agitaron durante 1.5 horas Se recogieron los filtrados individuales y los enjuagues DCM, se concentraron, y purificaron por HPLC para proporcionar los compuestos finales

**Tabla 2**

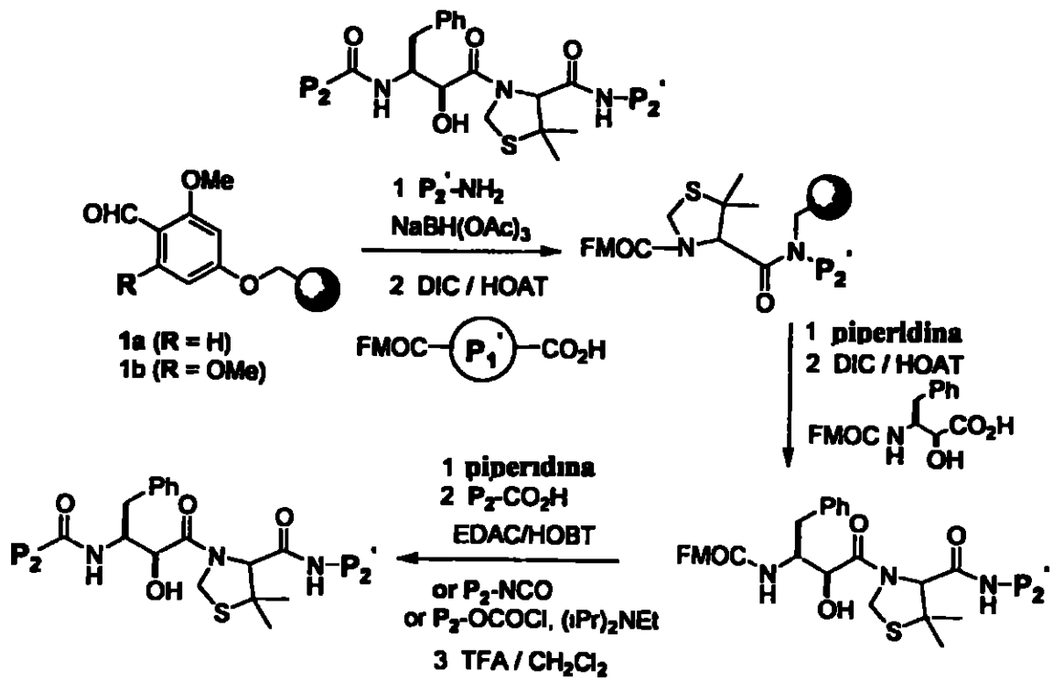


225



**Esquema 3: Síntesis de Fase Sólida de Inhibidores de Proteasa VIH**




**Esquema 3 Experimental**

La síntesis combinatoria de fase sólida de inhibidores de proteasa VIH se llevó a cabo empleando Tecnología de Clasificación Dirigida IRORI. Resina comercial 4-formil-3-metoxifenoximetil polistireno **1a** (PS-MB-CHO, Argonaut Technologies) o resina 4-formil-3,5-dimetoxifenoximetil polistireno **1b** (PL-FDMP, Polymer Laboratories) se cargó en Minikans individuales

Paso A. Aminación Reductora Con Aminas $P_2'$

A matraces separados que contenían MiniKans clasificados se agregó DCM (3 mL/MiniKan) Se agregaron la amina primaria apropiada $P_2'$ (3 eq), triacetoxiborohidruro de sodio (5 eq), y ácido acético (3 eq), y las mezclas se pusieron bajo argón, se agitaron con ventilación periódica a temperatura ambiente durante 1 -2 horas, y se hicieron reaccionar durante la noche Para la resina **1a**, se vertieron los filtrados y los MiniKans se lavaron con DCM, MeOH (2x), DCM (2x), $Et_3N$/DCM (1:3, 3x), DCM

(2x), MeOH (3x), y DCM (4x) Para la resina **1b**, se empleó una secuencia de lavado de DCM, MeOH (2x), DCM (2x), $Et_3N$/DCM (1·3, 3x), DCM (2x), DMF, 1M NaOH/DMF (1·5, 3x), DMF (3x), MeOH (3x), y DCM (3x). Los MiniKans se secaron bajo vacío y se tomaron en Paso B.

Paso B. Acoplamiento de Péptido Con Aminoácidos $P_1'$

A matraces separados que contenían los MiniKans clasificados se agregó DMF (3 mL/MiniKan). Se agregaron el aminoácido apropiado FMOC-protegido (2 5 eq) y 1 -hidroxi-7-azabenzotriazol (HOAT) (3 eq) y se mezclaron hasta que se disolvieron y se agregó 1,3-diisopropilcarbodiimida (DIC) (3 eq). Los recipientes se pusieron bajo argón y se agitaron a temperatura ambiente durante la noche Se vertieron los filtrados, y los MiniKans se lavaron con DMF (3x), MeOH (3x), DCM (2x), y DMF (2x). Los MiniKans se tomaron directamente en Paso C.

Paso C. Desprotección FMOC

Un recipiente de MiniKans en DMF y piperidina (25%) con un volumen total de reacción de 3 mL/MiniKan se agitó bajo argón a temperatura ambiente durante 45 minutos. Se eliminó el filtrado, y se repitió el procedimiento de reacción. Se filtraron los MiniKans y se lavaron con DMF (3x), MeOH (2x), DCM (3x), y DMF, y se tomaron directamente en Paso D.

Paso D. Acoplamiento de Péptido Con FMOC-APNS

FMOC-Alofenilnorstatina (APNS) (3 eq) se agregó al matraz de MiniKans en DMF (3 mL/MiniKan). Luego de la disolución, se agregaron HOAT (3.5 eq) y DIC (3.5 eq). La mezcla se puso bajo argón y se agitó a temperatura ambiente durante la noche La reacción se filtró y los MiniKans se lavaron con DMF (3x), MeOH (3x), DCM (3x), y DMF La desprotección FMOC se llevo a cabo como en Paso C, y los MiniKans se lavaron con DMF (3x), MeOH (2x), DCM (3x), se secaron bajo vacío y se tomaron en Paso E o F

229

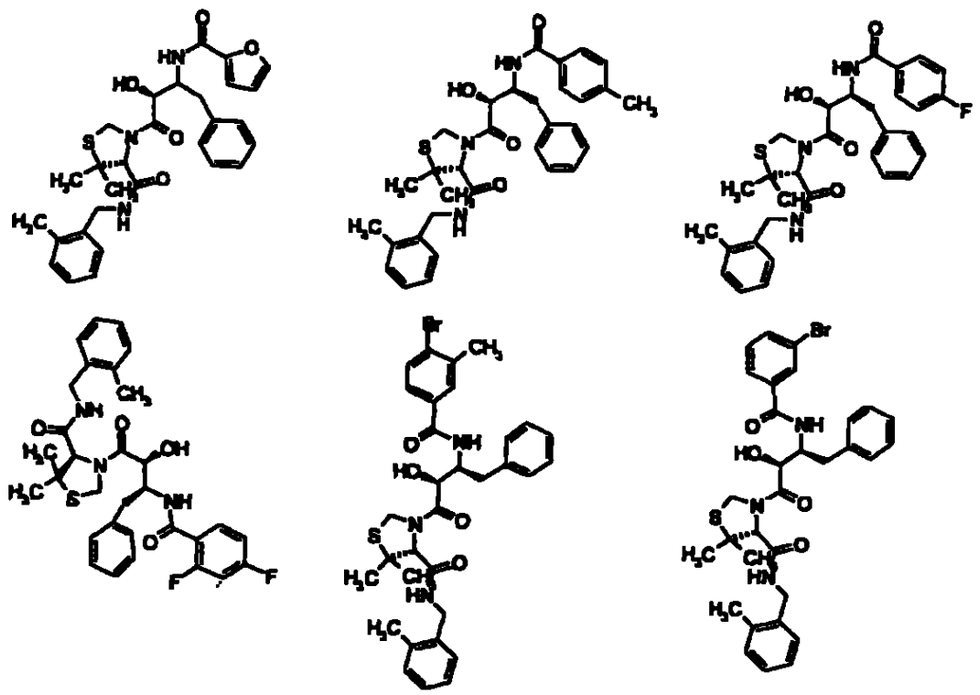
Paso E Acoplamiento de Péptido Con Ácidos $P_2$

A matraces separados que contenían los MiniKans clasificados en DMF (3 mL/MiniKan) se agregó el ácido apropiado $P_2$ (3 eq), HOBT hidrato (4 eq), y (3-(dimetilamino)propil)etilcarbodiimida clorhidrato (EDAC) (3.5 eq). La reacción se agitó bajo argón a temperatura ambiente durante 3 horas. Después de la filtración, los MiniKans se lavaron con DMF (3x), MeOH (3x), y DCM (3x), se secaron bajo vacío, y se tomaron en Paso G.

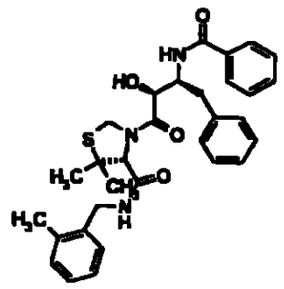
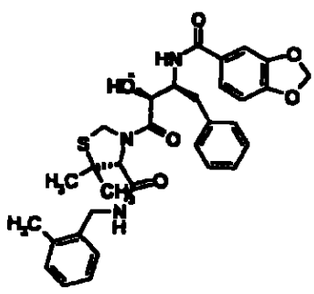
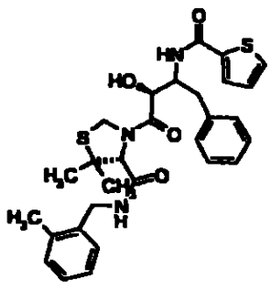
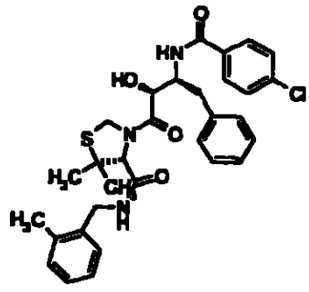
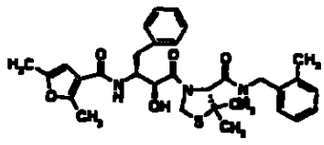
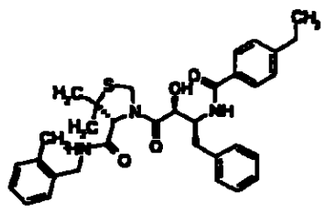
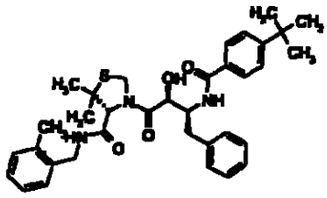
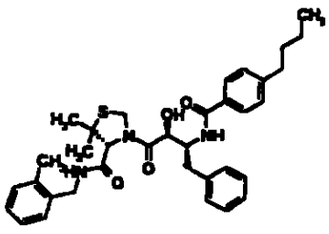
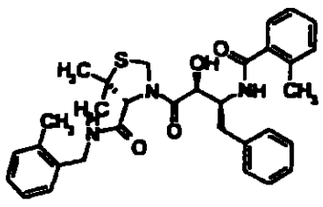
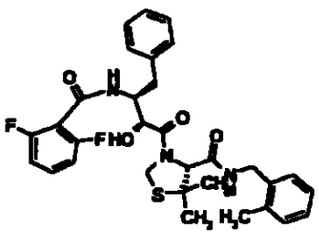
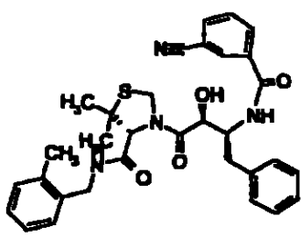
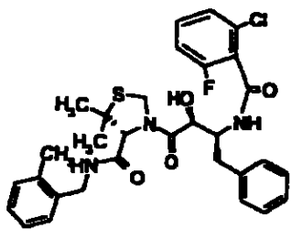
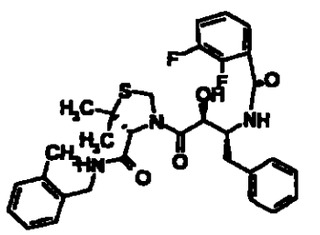
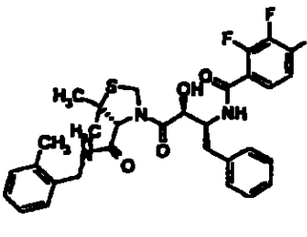
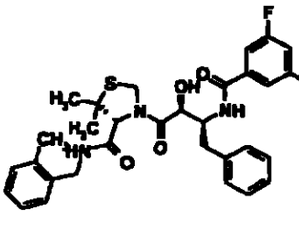
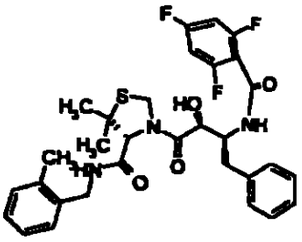
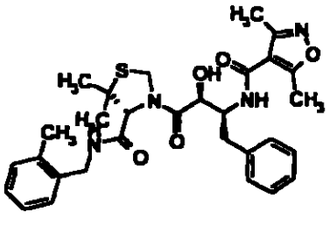
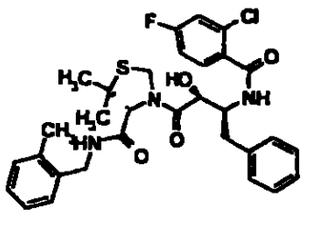
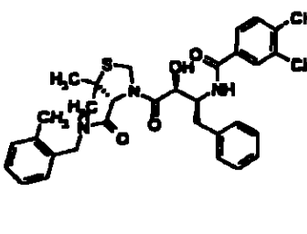
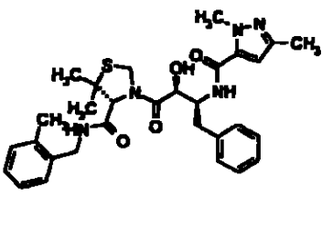
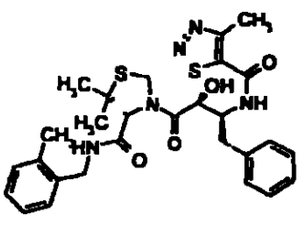
Paso F. Escisión y Procesamiento de los Análogos de VIH

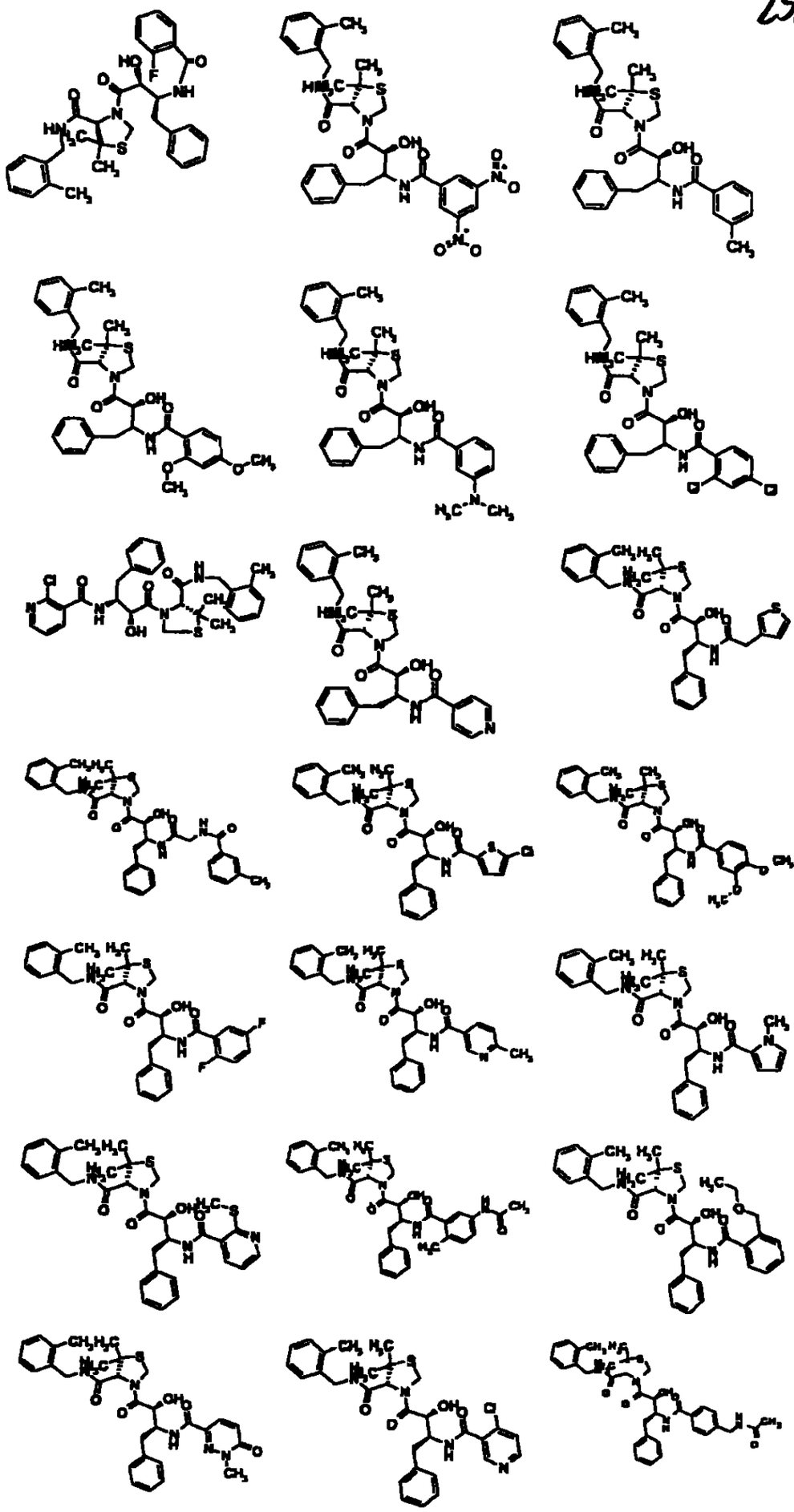
Los MinKans individuales se clasificaron en bastidores de escición y se agregó una solución de 25% TFA en DCM (3 mL/MinKan). Los bastidores se agitaron durante 1 5 horas. Se recolectaron los filtrados individuales y los enjuagues DCM, se concentraron, y se purificaron por HPLC para proporcionar los compuestos finales.

**Tabla 3**



230



232

## EVALUACIÓN BIOLÓGICA

Células y Virus

Líneas de células T, CEM-SS, y MT-2, y virus VIH-1 RF y VIH-1 NL4-3 (pNL4-3) se obtuvieron de los National Institutes of Health (AIDS Research and Reference Reagent Program, Bethesda, MD) VIH-1 NL4-3(184V/L90M) se derivó de un aislado clínico que exhibía las sustituciones I84V y L90M asociadas con la resistencia a inhibidor de proteasa, por clonación de un fragmento amplificado por transcriptasa reversa –reacción de cadena de polimerasa en los sitios únicos de restricción Age I y Spe I de pNL4-3

Análisis de Inhibición de Efecto Citopático (CPE)

Se midió la capacidad de los compuestos para proteger células contra la infección VIH mediante el método de reducción de tinte MTT, esencialmente como se describe (véase Pauwels, R Balzarini, J. Baba, M. Snoeck, R Schols, D. Herdewijn, P. Desmyter, J. y De Clercq, E. 1988, "Rapid and automated tetrazolium-based colorimetric assay for the detection of anti-HIV compuestos,". *J Virol Methods*, 20 309-321 y Weislow, O S. Kiser, R. Fine, D.L. Bader, J. Shoemaker, R.H. y Boyd, M R. 1989 "New soluble-formazan assay for HIV-1 cytopathic effects. application to high-flux screening of synthetic and natural products for AIDS-antiviral activity". *J Natl Cancer Inst* 81:577-586). Las células en cuestión se infectaron con el virus de ensayo con una moi (multiplicidad de infección) de 0.025 a 0 819 o se infectaron simuladamente sólo con medio y se agregaron a 2 x $10^4$ células por pozo en placas de 96 pozos que contenían diluciones semilogarítmicas de los compuestos de ensayo Seis días más tarde se agregaron 50 µl de XTT (1mg/ml XTT tetrazolio, 0.02 nM fenazina metosulfato) a los pozos y la placa se incubó nuevamente durante cuatro horas. Se cuantificó la viabilidad, determinada por la cantidad de XTT formazan producido, espectrofotométricamente por absorción a 450 nm. Los datos de los análisis CPE se expresaron como el porcentaje de

formazan producido en células tratadas con compuesto comparados con el formazan producido en pozos de células no infectadas, libres de compuesto. La concentración efectiva del cincuenta por ciento ($EC_{50}$) se calculó como la concentración de compuesto que ocasionó un aumento en el porcentaje de producción de formazan en células infectadas, tratadas con compuesto al 50% de la producida por células no infectadas, libres de compuesto. La concentración de citotoxicidad del 50% ($CC_{50}$) se calculó como la concentración de compuesto que disminuyó el porcentaje de formazan producido en células no infectadas, tratadas con compuesto al 50% de la producida en células no infectadas, libres de compuesto. El índice terapéutico se calculó dividiendo la citotoxicidad ($CC_{50}$) por la actividad antiviral ($EC_{50}$)

Análisis de Susceptibilidad

Los compuestos se ensayaron en estudios de susceptibilidad fenotípica en Virologic, Inc , (véase Petropoulos C J., Parkin N T., Limoli K L., Lie Y S., Wrin T., Huang W., Tian H., Smith D , Winslow G.A., Capon DJ, Whitcomb JM. 2000, "A novel phenotypic drug susceptibility assay for human immunodeficiency virus type 1," *Antimicrob Agents Chemother* 44(4):920-928) o usando el estudio descrito aquí Células MT-2 se infectaron con VIH-1 NL4-3 o VIH-1 NL4-3(I84V/L90M) y se incubaron en la presencia de diluciones 0 5 log en serie de compuestos de ensayo. Tres días más tarde, se recolectaron los sobrenadantes de cultivo y se analizó la producción de virus, determinado por p24 ELISA La inhibición porcentual se calculó como la concentración p24 en muestras tratadas con compuesto comparadas con controles infectados, libres de compuesto. La inhibición de la replicación viral se determina midiendo la reducción en p24 VIH presente en el sobrenadante de cultivo, usando un kit Beckman-Coulter p24 HIV-1 Ag EIA y siguiendo el protocolo suministrado. La absorción se lee en un lector de microplaca MRX (Dynex Technologies). La $EC_{50}$ se calculó como la concentración de compuesto que ocasionó una disminución en la producción de p24 por células

234

infectadas, tratadas con compuesto al 50% de la producida por células infectadas, libres de compuesto.

Análisis RET de Proteasa VIH-1

Los $K_i$'s de los inhibidores de proteasa VIH-1 se determinaron usando un análisis transferencia de energía de resonancia (RET) Una forma mutante de esta enzima (Q7S) se emplea para este ensayo porque es más estable contra auto-proteólisis que la proteína tipo silvestre. Esta enzima se purifica primero parcialmente como cuerpos de inclusión de lisado de células. Luego se solubiliza en 8M urea y se pasa a través de una columna Q-Sepharose (Pharmacia) para purificación adicional. Para replegar esta proteína, muestras que contienen Q7S se dializan en 50mM fosfato de sodio pH 7.0, 50mM NaCl, 10mM DTT, y 10% glicerol

El sustrato peptídico disponible en el comercio (Molecular Probes Cat. # H-2930) RE(EDANS)SQNYPIVQK(DABCIL)R se utiliza para evaluar la actividad y $K_i$'s Este péptido se escinde cuantitativamente por VIH -1 Pr en el enlace Tyr-Pro. El fluoroforo EDANS absorbe a 340nm y emite a 490nm. La reacción se lleva a cabo en una placa de 96 pozos en un volumen total de 100µL y se ejecuta durante 12 minutos a 37C condiciones de estado de equilibrio con sustrato 5µM y 2nM concentración de enzima dímero activo. El valor de literatura Km para este sustrato y enzima es 103 +/- 8µM (véase Matayoshi, y colegas, "Novel Fluorogenic Substrates for Assaying Retroviral Proteases by Resonance Energy Transfer, " *Science* 247, 954 (1990)). El amortiguador para esta reacción es 0.1M acetato de sodio pH 4 8, 1M NaCl, 1mM EDTA, 5mM ditiotreitol, 10% sulfóxido de dimetilo y 1mg/ml albúmina de suero bobino. Se ajustan las curvas de inhibición usando la ecuación de enlace estrecho de Morrison

| Ejemplo No. | Prom. $K_i$ (nM) | Prom. Ave CPE $EC_{50}$ (mM) | $EC_{50}$ ó $IC_{50}$(mM) |
|---|---|---|---|
| A3 | 1.7 | 0.37 | |

| | | | |
|---|---|---|---|
| A4 | 4.1 | 0.591 | |
| A5 | 2 | 0.433 | |
| A6 | 0.22 | 0.036 | |
| A7 | 0.49 | 0.104 | 0.832 |
| A8 | 0.23 | 0.036 | |
| A9 | 4 | 0.565 | |
| A10 | 51 | > 1 | |
| A11 | 19 | 0 93 | |
| A12 | 1 7 | 1.09 | |
| A13 | 44.1 | > 1 | |
| A14 | 0 44 | 0.052 | 0.071 * |
| A15 | 10.9 | 0 13 | |
| A16 | 0 63 | 0.134 | |
| A17 | < 0 1 | 0 045 | 0.102* |
| A18 | 0 38 | 0.193 | |
| A19 | 10 | 0 442 | |
| A20 | 0.13 | 0.037 | 0.147* |
| A21 | 1.9 | 0 717 | |
| A22 | 0.32 | 0.061 | 0.226* |
| A23 | 0 65 | 0.072 | |
| A24 | 0.18 | 0.104 | 0 831 |
| A25 | 5 8 | 0 248 | |
| A26 | 0.38 | 0.119 | 0.321* |
| A27 | 0 62 | 0 072 | |
| A28 | < 0 1 | 0 041 | |
| A29 | < 0.1 | 0.117 | |
| A30 | 1 1 | 0.507 | 0 829* |
| A31 | < 0.1 | 0.041 | |
| A32 | < 0 1 | 0.045 | 0 486 |
| A33 | < 0.1 | 0.577 | |
| A34 | < 0 1 | 0 036 | |
| A35 | < 0.1 | 0 017 | 0.063 |
| A36 | 0.59 | 0 519 | |
| A37 | 0.13 | 0.161 | |
| A38 | 0 17 | 0 078 | 0.401 |
| A39 | 0.27 | 0.367 | |
| A40 | 1 2 | 0 275 | |
| A41 | 1.6 | 0.527 | |
| A42 | 0 23 | 0 126 | 0 307 |
| A43 | 0.35 | 0.561 | |
| A44 | 0.14 | 0.022 | 0.472 |
| A45 | 0.51 | 0.165 | |
| A46 | 0 31 | 0 091 | 0 79 |
| A47 | 2.3 | 1.813 | |

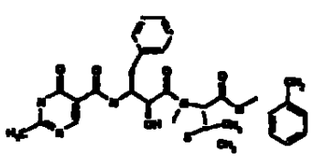
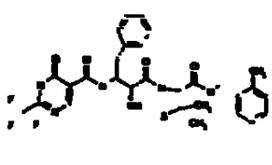
| | | | |
|---|---|---|---|
| A48 | 0.19 | 0.417 | |
| A49 | 1.2 | 0.13 | |
| A50 | 0.26 | 0.224 | |
| A51 | 1 3 | 0 667 | |
| A52 | 37 | | |
| B1 | 2.5 | 0.905 | |
| B2 | 0.78 | 0.369 | |
| B3 | 4 | 0 409 | |
| B8 | 0.31 | 0 095 | 0.405* |
| B4 | 1.7 | 0.551 | |
| B5 | 1.6 | 0.508 | |
| B6 | 1.6 | 0.589 | |
| B7 | 1 9 | 0.68 | |
| B8 | 1.5 | 0.552 | |
| B10 | < 0 1 | 1 1 | |
| B11 | 1.2 | 1.175 | 1 716* |
| B12 | 0 45 | 1 398 | |
| B13 | 19%@64nM | | |
| B14 | 3.7 | 3 054 | |
| B15 | 2 | 1.086 | |
| B16 | < 0.1 | 0 298 | 1 754 |
| B17 | 0.42 | 0.534 | 1.579 |
| BI8 | 0.29 | 0 457 | |
| B19 | < 0.1 | 0.124 | 1.369 |
| B20 | 2.1 | 0.427 | |
| B21 | 4.6 | 0.598 | |
| B22 | 1.8 | 1.613 | |
| B23 | 0.42 | 1.42 | |
| B24 | 5.5 | 2 316 | |
| B25 | 2.7 | 1.794 | |
| B26 | 2.9 | 1.712 | |
| B27 | 3.5 | | |
| B28 | 153 | | |
| B29 | 0.12 | 1.256 | |
| B30 | 1 1 | 1 227 | |
| B31 | 1.5 | 1.316 | |
| B32 | 4.9 | | |
| B33 | 1.2 | 1.286 | |
| B34 | | | |
| B35 | | | |
| B36 | < 0 1 | 0 615 | |
| B37 | 0 11 | 0 736 | |
| B38 | | | |
| B39 | 0.16 | | |

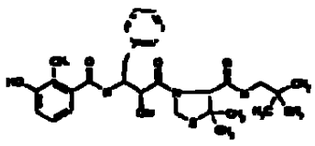
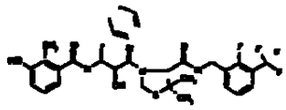
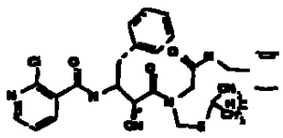
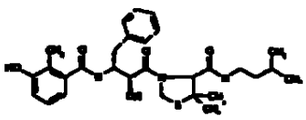
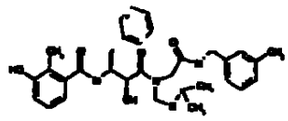
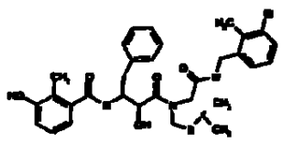
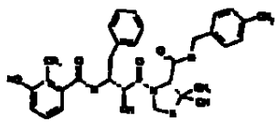
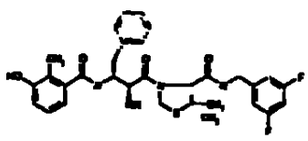
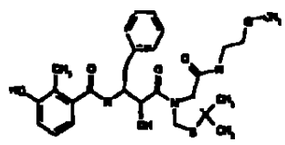
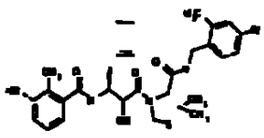
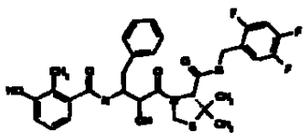
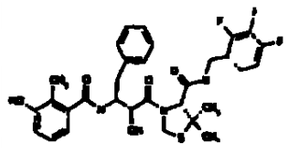
237

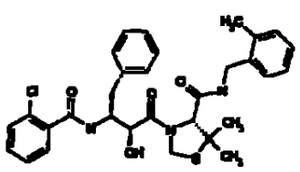
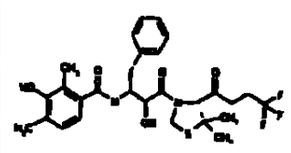
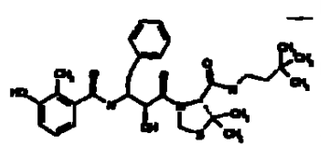
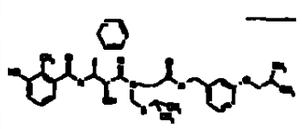
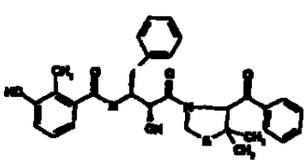
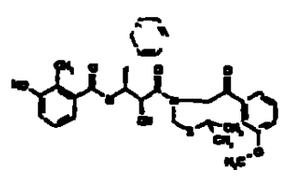
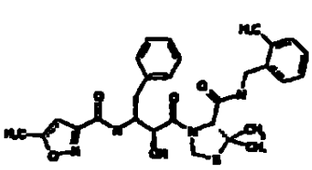
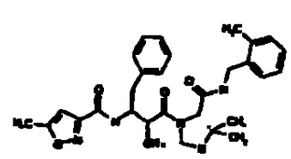
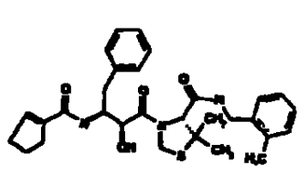
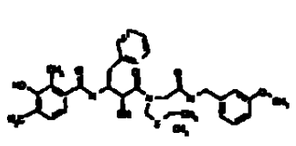
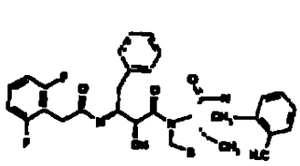
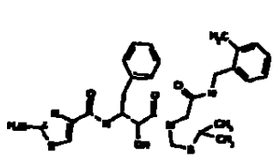
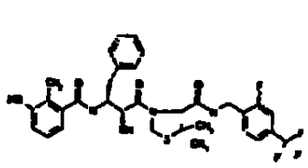
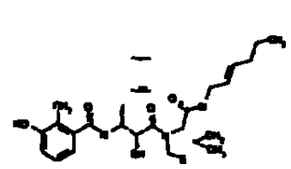
| | | | |
|---|---|---|---|
| B40 | 2.8 | 1.396 | |
| B41 | 0.15 | | |
| B42 | 0 73 | | |
| B43 | 0 2 | | |
| B44 | 0.76 | 0.629 | |
| B45 | 19 7 | | |
| B46 | 12.5 | | |
| B47 | 6.9 | | |
| B48 | 12 | < 3.2 | |
| B49 | 17.2 | | |
| C1 | 0.38 | 0.627 | 0.427 |
| C3 | 1 3 | 0.5 | |
| C4 | 4.2 | | |
| C4 | 69 | | |
| C5 | 3.2 | | |
| C6 | < 0.1 | 0.164 | 1.475 |
| C7 | 7 9 | | |
| C8 | 0.26 | 0.447 | |
| C9 | 0.34 | 0 233 | |
| C10 | 36 | | |
| C11 | 1 1 | 1.562 | |
| Dl | <0 01 | 0.052 | 0.601 |
| D3 | 0.5 | 0.162 | 1.954 |
| D4 | 0 7 | 0 016 | 1 954 |

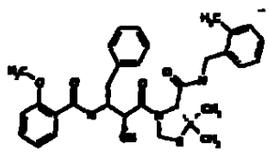
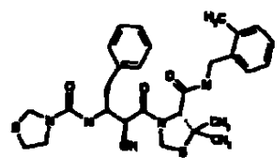
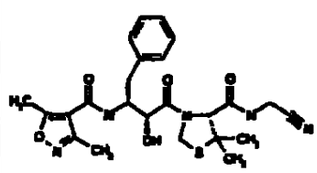
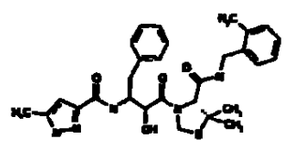
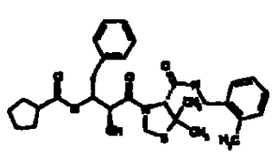
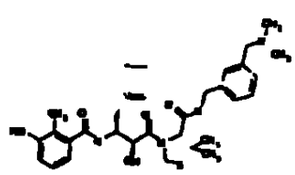
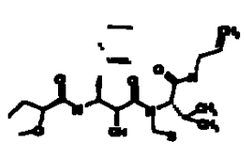
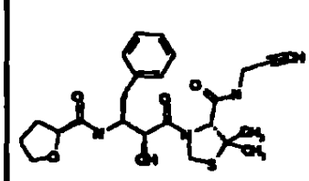
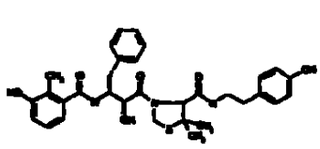
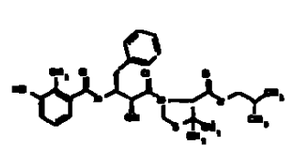
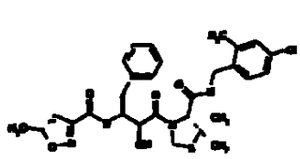
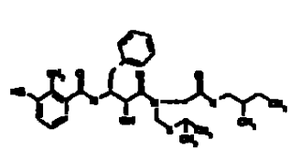
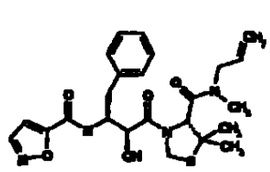
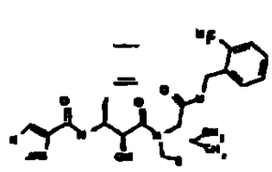
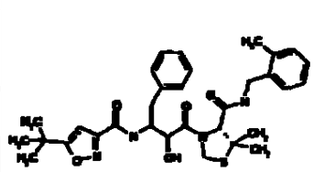
* Los datos $IC_{50}$ (mM) se determinaron en Virologic Inc contra los virus 461, 84V, 90M

Los siguientes compuestos se han preparado de acuerdo con los procedimientos descritos aquí y han demostrado la actividad anotada·

| ESTRUCTURA MOL. | $K_I$ | $EC_{50}$ | ESTRUCTURA MOL. | $K_I$ | $EC_{50}$ |
|---|---|---|---|---|---|
|  | 209 | 10 |  | 1700 | 10 |

| ESTRUCTURA MOL. | $K_i$ | $EC_{50}$ | ESTRUCTURA MOL. | $K_i$ | $EC_{50}$ |
|---|---|---|---|---|---|
|  | 0.1 | 0.053 |  | 62 | |
|  | 0.75 | | | | |
|  | 0 1 | 0.072 |  | 1.5 | 0.076 |
|  | 0.2 | 0.113 |  | 0 73 | 0.141 |
|  | 0.36 | 0.144 |  | 0.24 | 0.158 |
| | | |  | 0 26 | 0 207 |
|  | 0 17 | 0 289 |  | 0 11 | 0 334 |

| ESTRUCTURA MOL. | $K_i$ | $EC_{50}$ | ESTRUCTURA MOL. | $K_i$ | $EC_{50}$ |
|---|---|---|---|---|---|
|  | 0.2 | 0.585 |  | 9.6 | 0.723 |
|  | 4.7 | 1 064 |  | 1 1 | 1 114 |
|  | 2.5 | 1.221 |  | 7.4 | |
|  | 2.6 | 1.3095 |  | 2.6 | 1.3095 |
|  | 3.4 | |  | 3.7 | 1 332 |
|  | 72 | |  | 2.03 | 1 378 |
|  | 11.1 | 1.401 |  | 2 06 | 1 416 |

| ESTRUCTURA MOL. | $K_i$ | $EC_{50}$ | ESTRUCTURA MOL. | $K_i$ | $EC_{50}$ |
|---|---|---|---|---|---|
|  | 2 1 | 1 488 |  | 14 | 1 512 |
|  | 18 5 | |  | 19 5 | 3 |
|  | 12 1 | |  | 10.5 | 3.2 |
|  | 17 3 | 3 303 |  | 16 8 | 3.745 |
|  | 13 1 | |  | 0 1 | |
|  | 28 | 4.132 |  | 0 1 | |
|  | 24.6 | 4 951 |  | 55.8 | 10 |
|  | 214 | 10 | | | |

241

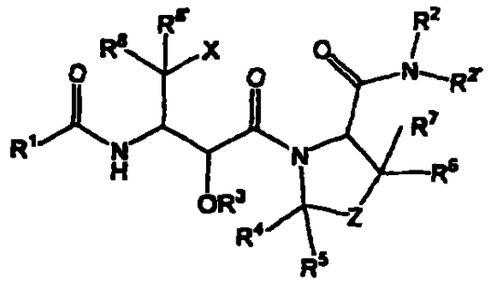
Los siguientes compuestos se han preparado de acuerdo con los procedimientos descritos aquí y han demostrado la actividad anotada:

Si bien la invención se ha descrito en términos de incorporaciones preferidas y ejemplos específicos, aquellas personas expertas en el arte reconocerán que pueden hacerse varios cambios y modificaciones mediante experimentación de rutina sin apartarse del espíritu y la órbita de la invención Por consiguiente, la invención debe entenderse como no limitada por la anterior descripción detallada, sino como definida por las reivindicaciones adjuntas y sus equivalentes.

242

REIVINDICAMOS

1. Un compuesto que tiene la Fórmula I:



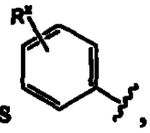
I

en donde.

$R^1$ es un grupo carbocíclico o heterocíclico mono-cíclico de 5 o 6 miembros, en donde dicho grupo carbocíclico o heterocíclico es saturado, parcialmente insaturado o completamente insaturado y es no sustituido o sustituido por uno o más sustituyentes apropiados,

$R^2$ es un grupo alquilo sustituido, un grupo alquenilo sustituido o no sustituido, un grupo alquinilo sustituido o no sustituido, un grupo fenilo sustituido, un grupo fenilalquilo sustituido, un grupo fenilalquenilo sustituido o no sustituido o un grupo fenilalquinilo sustituido o no sustituido,

$R^{2'}$ es H o un grupo $C_1$-$C_4$ alquilo sustituido o no sustituido;

X es  , en donde $R^x$ es H o uno o más sustituyentes apropiados;

Z es S, O, SO, $SO_2$, $CH_2$ o CFH;

$R^3$ es H o un grupo $C_1$-$C_4$ alquilo sustituido o no sustituido;

$R^4$, $R^5$, $R^6$ y $R^7$ se seleccionan independientemente de H o un grupo $C_1$-$C_6$ alquilo; y

$R^8$ y $R^{8'}$ se seleccionan independientemente de H, halo, un grupo $C_1$-$C_4$ alifático o un grupo alifático $C_1$-$C_4$ halo-sustituido,

243

donde cualquiera de dichos grupos alquilo, alquenilo o alquinilo sustituido se sustituyen por uno o más sustituyentes apropiados

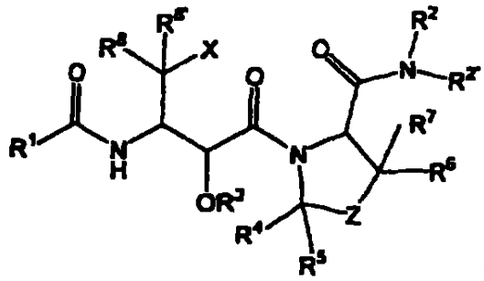
con la condición que dicho grupo heterocicloalquilo, heterocicloalquenilo o heteroarilo mono-cíclico de 5- ó 6-miembros contenga por lo menos dos heteroátomos cuando $R^2$ es un grupo fenilo sustituido, un grupo fenilalquilo sustituido, un grupo fenilalquenilo sustituido o no sustituido o un grupo fenilalquinilo sustituido o no sustituido; o

con la condición que dicha fracción alquilo, alquenilo o alquinilo de dicho grupo fenilalquilo, fenilalquenilo o fenilalquinilo sustituido se sustituya por uno o más sustituyentes seleccionados de halo o aceto; o

con la condición que dicho grupo fenilo sustituido o fracción fenilo de dicho grupo fenilalquilo, fenilalquenilo o fenilalquinilo sustituido se sustituya por uno o más sustituyentes apropiados distintos de halo o metilo,

o profármaco, metabolito farmacéuticamente activo, o solvato farmacéuticamente aceptable de los mismos.

2. Un compuesto que tiene la Fórmula I.



I

en donde:

$R^1$ es un grupo cicloalquilo monocíclico de 5 ó 6 miembros, cicloalquenilo, arilo, heterocicloalquilo, heterocicloalquenilo o heteroarilo, donde dicho grupo cicloalquilo, cicloalquenilo, arilo, heterocicloalquilo, heterocicloalquenilo o heteroarilo no se sustituye o se sustituye con uno o más sustituyentes independientemente seleccionados de alquilo, haloalquilo, amino, ciano, halógeno, hidroxilo, alcoxi, haloalcoxi,

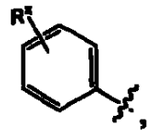
alquilenedioxi, di-haloalquilenodioxi, ariloxi, cicloalcoxi, cicloalquilalcoxi, cicloalqueniloxi, cicloalquenilalcoxi, heterocicloalcoxi, heterocicloalquilalcoxi, heterocicloalqueniloxi, heterocicloalquenilalcoxi, heteroariloxi, alquilcarboniloxi, arilcarboniloxi, heteroarilcarboniloxi, alquilamino, dialquilamino, aceto, alquilsulfonilo, arilsulfonilo, alquilcarbonilamino, alquiltio, haloalquiltio y ariltio, en donde cualquiera de las fracciones alquilo, alquileno, arilo, cicloalquilo, heterocicloalquilo, heteroarilo presentes en los anteriores sustituyentes se sustituyen adicionalmente por uno o más grupos independientemente seleccionados de grupos alquilo, haloalquilo, arilo, nitro, amino, alquilamino, dialquilamino, halógeno, hidroxilo, alcoxi, haloalcoxi, ariloxi, mercapto, alquiltio, haloalquiltio y ariltio;

$R^2$ es un grupo alquilo sustituido, un grupo alquenilo sustituido o no sustituido, o un grupo alquinilo sustituido o no sustituido, en donde dicho grupo alquilo, alquenilo o alquinilo es un grupo de cadena recta o ramificada, y

donde dicho grupo alquilo, alquenilo o alquinilo sustituido se sustituye por uno o más sustituyentes independientemente seleccionados de grupos amino, ciano, halógeno, hidroxilo, alcoxi, haloalcoxi, ariloxi, cicloalcoxi, cicloalquilalcoxi, cicloalqueniloxi, cicloalquenilalcoxi, heterocicloalcoxi, heterocicloalquilalcoxi, heterocicloalqueniloxi, heterocicloalkenlalcoxi, heteroariloxi, alquilamino, dialquilamino, alquilsulfonilo, arilsulfonilo, alquilsulfenilo, arilsulfenilo, alquiltio, haloalquiltio, ariltio y heteroariltio, en donde cualquiera de las fracciones alquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo o heteroarilo presentes en los sustituyentes anteriores se sustituyen adicionalmente por uno o más grupos independientemente seleccionados de grupos alquilo, haloalquilo, halógeno, hidroxilo, alcoxi, haloalcoxi, alquiltio y haloalquiltio;

$R^{2'}$ es H, metilo, etilo o propilo, donde dicho metilo, etilo o propilo no se sustituye o se sustituye por halo o hidroxilo,

245

X es  , en donde $R^x$ es H o uno o más sustituyentes independientemente seleccionados de halógeno, alquilo, haloalquilo, alcoxi, haloalcoxi, hidroxilo, alquilenodioxi, di-haloalquilenodioxi, alquilamino, dialquilamino, alquiltio y haloalquiltio;

Z es S, O, SO, $SO_2$, $CH_2$ ó CFH;

$R^3$ es H;

$R^4$, $R^5$, $R^6$ y $R^7$ se seleccionan independientemente de H o metilo; y

$R^8$ y $R^{8'}$ se seleccionan independientemente de H, halógeno, metilo, monohalo-metilo, dihalo-metilo y tri-halometilo;

o un profármaco, metabolito farmacéuticamente activo o sal farmacéuticamente activa o solvato de los mismos.

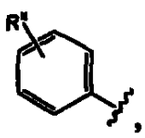
3 El compuesto de acuerdo con la reivindicación 2, en donde:

$R^1$ es fenilo, pirrolilo, pirrolidinilo, isoxazolilo, pirazolilo, tiazolilo, tetrahidrofuranilo, furanilo, tienilo o tetrahidropiridazinilo, donde dicho fenilo, pirrolilo, pirrolidinilo, isoxazolilo, pirazolilo, tiazolilo, tetrahidrofuranilo, furanilo, tienilo o tetrahidropiridazinilo no se sustituye o sustituye con uno o más sustituyentes independientemente seleccionados de alquilo, haloalquilo, halógeno, e hidroxilo;

$R^2$ es un grupo alquilo sustituido, un grupo $C_1$-$C_6$ alquenilo sustituido o no sustituido, un grupo $C_1$-$C_6$ alquinilo sustituido o no sustituido, en donde dicho grupo alquilo, alquenilo o alquinilo es un grupo de cadena recta o ramificada, y

donde dicho grupo alquilo, alquenilo o alquinilo sustituido se sustituye por uno o más sustituyentes independientemente seleccionados de ciano, halógeno y alquilamino;

$R^{2'}$ es H, metilo o etilo;

X es  , en donde $R^x$ es H, halógeno, o alcoxi,

Z es S, O, $CH_2$ ó CFH;

246

$R^3$, $R^4$, $R^5$, $R^8$ y $R^{8'}$ son cada uno H; y

$R^6$ y $R^7$ se seleccionan independientemente de H o metilo;

o un profármaco, metabolito farmacéuticamente activo o sal farmacéuticamente activa o solvato de los mismos

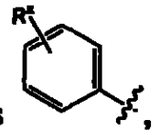
4 El compuesto de acuerdo con la reivindicación 2, en donde·

$R^1$ es fenilo, donde dicho fenilo se sustituye con uno o más sustituyentes independientemente seleccionados de alquilo, halógeno o hidroxilo;

$R^2$ es un grupo $C_1$-$C_6$ alquenilo o un grupo $C_1$-$C_6$ alquinilo, en donde dicho grupo alquenilo o alquinilo es un grupo de cadena recta o ramificada, y

donde dicho grupo alquenilo o alquinilo no se sustituye o se sustituye por uno o más sustituyentes halógeno;

$R^{2'}$ es H;

X es  , en donde $R^x$ es H,

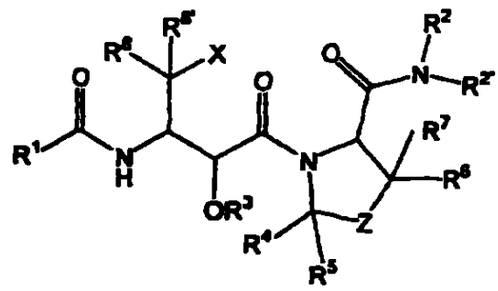
Z es S;

$R^3$, $R^4$, $R^5$, $R^8$ y $R^{8'}$ son cada uno H, y

$R^6$ y $R^7$ son cada uno metilo;

o un profármaco, metabolito farmacéuticamente activo o sal farmacéuticamente activa o solvato de los mismos

5 Un compuesto que tiene la Fórmula I



I

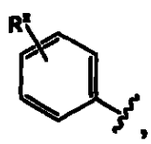
en donde

$R^1$ es un grupo cicloalquilo, cicloalquenilo, arilo, heterocicloalquilo, heterocicloalquenilo o heteroarilo mono-cíclico de 5 ó 6 miembros, donde dicho grupo cicloalquilo, cicloalquenilo, arilo, heterocicloalquilo, heterocicloalquenilo o heteroarilo no se sustituye o se sustituye con uno o más sustituyentes independientemente seleccionados de alquilo, haloalquilo, amino, ciano, halógeno, hidroxilo, alcoxi, haloalcoxi, alquilenodioxi, dihaloalquilenodioxi, ariloxi, cicloalcoxi, cicloalquilalcoxi, cicloalqueniloxi, cicloalquenilalcoxi, heterocicloalcoxi, heterocicloalquilalcoxi, heterocicloalqueniloxi, heterocicloalquenilalcoxi, heteroariloxi, alquilcarboniloxi, arilcarboniloxi, heteroarilcarboniloxi, alquilamino, dialquilamino, aceto, alquilsulfonilo, arilsulfonilo, alquilcarbonilamino, alquiltio, haloalquiltio y ariltio, en donde cualquiera de las fracciones alquilo, alquileno, arilo, cicloalquilo, heterocicloalquilo, heteroarilo presentes en los anteriores sustituyentes se sustituyen por uno o más grupos independientemente seleccionados de grupos alquilo, haloalquilo, arilo, nitro, amino, alquilamino, dialquilamino, halógeno, hidroxilo, alcoxi, haloalcoxi, ariloxi, mercapto, alquiltio, haloalquiltio y ariltio,

$R^2$ es un grupo fenilo sustituido, un grupo fenilalquilo sustituido, un grupo fenilalquenilo sustituido o no sustituido o un grupo fenilalquinilo sustituido o no sustituido;

donde dicha fracción alquilo, alquenilo o alquinilo de dicho grupo fenilalquilo, fenilalquenilo o fenilalquinilo es una fracción de cadena recta o ramificada,

$R^{2'}$ es H, metilo, etilo o propilo, donde dicho metilo, etilo o propilo no se sustituye o sustituye con halo o hidroxilo;

X es  , en donde $R^x$ es H o uno o más sustituyentes independientemente seleccionados de halógeno, alquilo, haloalquilo, alcoxi, haloalcoxi, hidroxilo, alquilenodioxi, di-haloalquilenodioxi, alquilamino,

dialquilamino, alquiltio y haloalquiltio;

Z es S, O, SO, $SO_2$, $CH_2$ ó CFH,

$R^3$ es H,

$R^4$, $R^5$, $R^6$ y $R^7$ se seleccionan independientemente de H o metilo; y

$R^8$ y $R^{8'}$ se seleccionan independientemente de H, halógeno, metilo, monohalo-metilo, dihalo-metilo y tri-halometilo,

con la condición que dicho grupo heterocicloalquilo, heterocicloalquenilo o heteroarilo mono-cíclico de 5 ó 6 miembros contiene por lo menos dos heteroátomos, o

con la condición que dicha fracción alquilo, alquenilo o alquinilo de dicho grupo fenilalquilo sustituido, fenilalquenilo o fenilalquinilo se sustituye por uno o más sustituyentes seleccionados de halo o aceto, o

con la condición que dicho grupo fenilo sustituido o fracción fenilo de dicho grupo fenilalquilo sustituido, fenilalquenilo o fenilalquinilo se sustituye por uno o más sustituyentes distintos de halo o metilo, donde dichos uno o más sustituyentes se seleccionan independientemente de grupos haloalquilo, hidroxialquilo, alcoxialquilo, cicloalcoxialquilo, alquilcarbonilalquilo, haloalcoxialquilo, ariloxialquilo, alquiltioalquilo, haloalquiltioalquilo, ariltioalquilo, cianoalquilo, aminoalquilo, alquilaminoalquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, heteroarilo, nitro, amino, ciano, hidroxilo, alcoxi, haloalcoxi, alqueniloxi, alquiniloxi, alquilenodioxi, ariloxi, cicloalcoxi, cicloalquilalcoxi, cicloalqueniloxi, cicloalquenilalcoxi, heterocicloalcoxi, heterocicloalquilalcoxi, heterocicloalkenoxi, heterocicloalquenilalcoxi, heteroariloxi, alquilcarbonilo, alquiloxicarbonilo, alquilcarboniloxi, arilcarbonilo, arilcarboniloxi, ariloxicarbonilo, cicloalquilcarbonilo, cicloalquilcarboniloxi, cicloalquioxicarbonilo, heteroarilcarbonilo, heteroarilcarboniloxi, heteroariloxicarbonilo, heterocicloalquilcarbonilo, heterocicloalquilcarboniloxi, heterocicloalquioxicarbonilo, carboxil. carbamoilo, formilo, aceto, tioaceto, sulfo, alquilamino, cicloalquilamino, arilamino, heterocicloalquilamino, heteroarilamino, dialquilamino, alquilaminocarbonilo,

cicloalquilaminocarbonilo, arilaminocarbonilo, heterocicloalquilaminocarbonilo, heteroarilaminocarbonilo, dialquilaminocarbonilo, alquilaminotiocarbonilo, cicloalquilaminotiocarbonilo, arilaminotiocarbonilo, heterocicloalquilaminotiocarbonilo, heteroarilaminotiocarbonilo, dialquilaminotiocarbonilo, alquilsulfonilo, arilsulfonilo, alquilsulfenilo, arilsulfenilo, alquilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, heterocicloalquilcarbonilamino, heteroarilcarbonilamino, alquiltiocarbonilamino. cicloalquiltiocarbonilamino, ariltiocarbonilamino, heterocicloalquiltiocarbonilamino, heteroariltiocarbonilamino, alquilsulfoniloxi, arilsulfoniloxi, alquilsulfonilamino, arilsulfonilamino, mercapto, alquiltio, haloalquiltio, ariltio y heteroariltio, en donde cualquiera de las fracciones alquilo, alquileno, arilo, cicloalquilo, heterocicloalquilo, o heteroarilo presentes en los anteriores sustituyentes no se sustituyen o se sustituyen por uno o más grupos independientemente seleccionados de alquilo, haloalquilo, halógeno, hidroxilo, alcoxi, haloalcoxi, alquiltio y haloalquiltio,

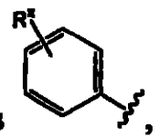
o un profármaco, metabolito farmacéuticamente activo o sal farmacéuticamente activa o solvato de los mismos

6 El compuesto de acuerdo con la reivindicación 5, en donde:

$R^1$ es fenilo, pirrolilo, pirrolidinilo, isoxazolilo, pirazolilo, tiazolilo, tetrahidrofuranilo, furanilo, tienilo o tetrahidropiridazinilo, donde dicho fenilo, pirrolilo, pirrolidinilo, isoxazolilo, pirazolilo, tiazolilo, tetrahidrofuranilo, furanilo, tienilo o tetrahidropiridazinilo no se sustituye o se sustituye con uno o más sustituyentes independientemente seleccionados de alquilo, haloalquilo, halógeno, e hidroxilo;

$R^2$ es un grupo fenilalquilo sustituido, donde dicha fracción alquilo de dicho grupo fenilalquilo sustituido es una fracción alquilo de cadena recta o ramificada;

$R^{2'}$ es H, metilo, etilo o propilo, donde dicho metilo, etilo o propilo no se sustituye o se sustituye con hidroxilo;

X es  , en donde $R^x$ es H, halógeno, o alcoxi,

Z es S, O, $CH_2$ ó CFH;

$R^3$, $R^4$, $R^5$, $R^8$ y $R^{8'}$ son cada uno H, y

$R^6$ y $R^7$ se seleccionan independientemente de H o metilo,

con la condición que $R^1$ se selecciona de isoxazolilo, pirazolilo, tiazolilo o tetrahidropiridazinilo, donde dicho grupo es isoxazolilo, pirazolilo, tiazolilo o tetrahidropiridazinilo no se sustituye o se sustituye con uno o más sustituyentes independientemente seleccionados de alquilo, haloalquilo, halógeno, e hidroxilo cuando $R^2$ es un grupo fenilalquilo sustituido o no sustituido o

con la condición que $R^1$ se seleccione de fenilo, pirrolilo, pirrolidinilo, isoxazolilo, pirazolilo, tiazolilo, tetrahidrofuranilo, furanilo, tienilo o tetrahidropiridazinilo cuando $R^2$ es un grupo fenilalquilo sustituido y dicha fracción fenilo de dicho grupo fenilalquilo sustituido comprende uno o más sustituyentes distintos de halo o metilo, donde dichos uno o más sustituyentes se seleccionan independientemente de haloalquilo, amino, hidroxilo, alcoxi, haloalcoxi, alquilenodioxi, di-haloalquilenodioxi, cicloalquilalquiloxi, dialquilamino, alquilsulfonil y alquiltio;

o un profármaco, metabolito farmacéuticamente activo o sal farmacéuticamente activa o solvato de los mismos.

7. El compuesto de acuerdo con la reivindicación 5, en donde

$R^1$ es fenilo, donde dicho fenilo se sustituye con uno o más sustituyentes independientemente seleccionados de metilo, halógeno o hidroxilo;

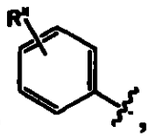
$R^2$ es un grupo fenilalquilo sustituido, donde dicha fracción alquilo de dicho grupo fenilalquilo sustituido es una fracción alquilo de cadena recta o ramificada,

donde dicha fracción fenilo de dicho grupo fenilalquilo sustituido comprende uno o más sustituyentes distintos de halo o metilo, donde dichos

251

uno o más sustituyentes se seleccionan independientemente de trifluorometilo, amino, hidroxil, $C_1$-$C_4$ alcoxi, alquilenodioxi, di-fluoro-alquilenodioxi, ciclopropilmetoxi, di-metil-amino, metanosulfonilo y metiltio,

$R^2$ es H, metilo o etil

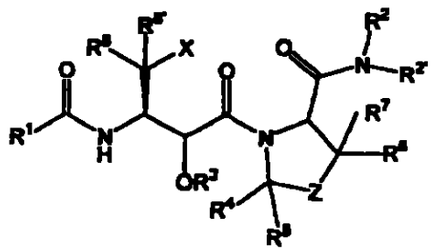
X es  , en donde $R^x$ es H;

Z es S ó O; y

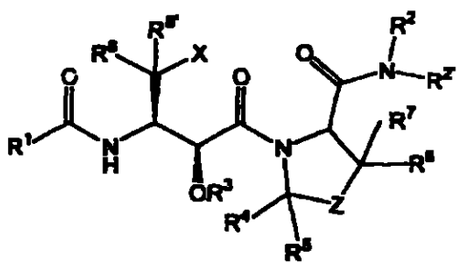
$R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$ y $R^{8'}$ son cada uno H,

o un profármaco, metabolito farmacéuticamente activo o sal farmacéuticamente activa o solvato de los mismos.

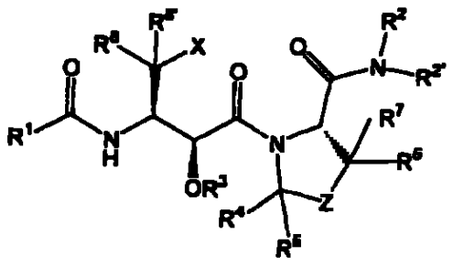
8. El compuesto, profármaco, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o solvato farmacéuticamente aceptable de acuerdo con una cualquiera de las reivindicaciones1, 2 ó 5, que tiene la fórmula.



9. El compuesto, profármaco, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o solvato farmacéuticamente aceptable de acuerdo con una cualquiera de las reivindicaciones1, 2 ó 5, que tiene la fórmula:



10. El compuesto, profármaco, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o solvato farmacéuticamente aceptable de acuerdo con una cualquiera de las reivindicaciones1, 2 ó 5, que tiene la fórmula.



11 Una composición farmacéutica que comprende
una cantidad terapéuticamente efectiva de por lo menos un agente VIH seleccionado de compuestos, profármacos, sales farmacéuticamente aceptables, metabolitos farmacéuticamente activos, y solvatos farmacéuticamente aceptables definidos en una cualquiera de las reivindicaciones 1,2 ó 5; y

un portador, diluyente, vehículo o excipiente farmacéuticamente aceptable.

12. La composición farmacéutica de acuerdo con la reivindicación 11, en donde la composición comprende además una cantidad terapéuticamente efectiva de por lo menos un agente de tratamiento de infección VIH /SIDA seleccionado del grupo conformado por agentes antivirales VIH/SIDA, inmunomoduladores, y agentes anti-infecciosos.

13. La composición farmacéutica de acuerdo con la reivindicación 12, en donde la composición comprende además una cantidad terapéuticamente efectiva de por lo menos un agente antiviral seleccionado del grupo conformado por inhibidores de transcriptasa reversa de VIH no nucleósidos e inhibidores de transcriptasa reversa VIH nucleósidos

253

14. La composición farmacéutica de acuerdo con la reivindicación 13, que comprende además una cantidad terapéuticamente efectiva de por lo menos un inhibidor de proteasa VIH

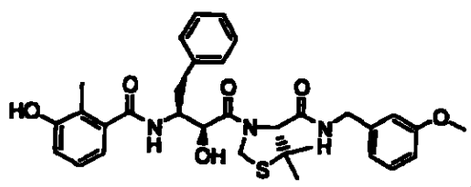
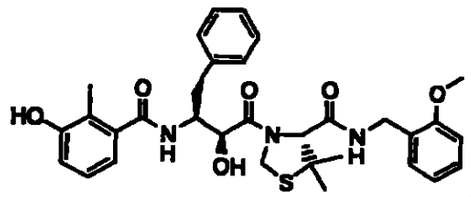
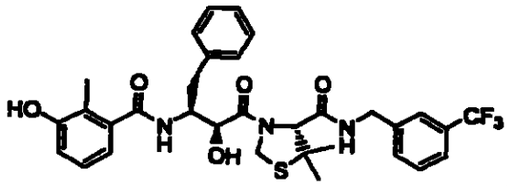
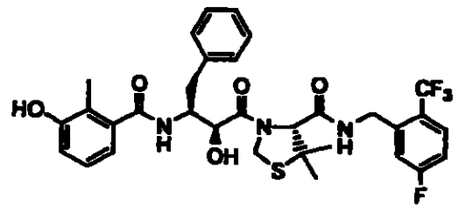
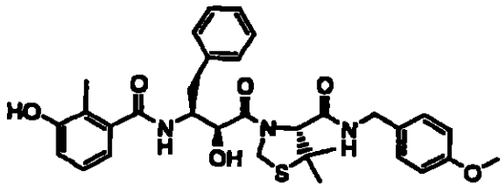
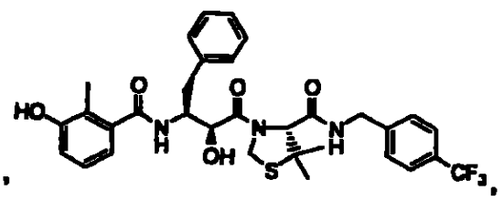
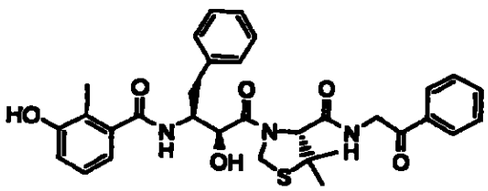
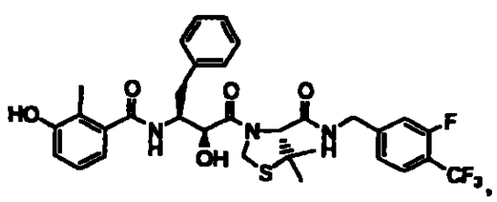
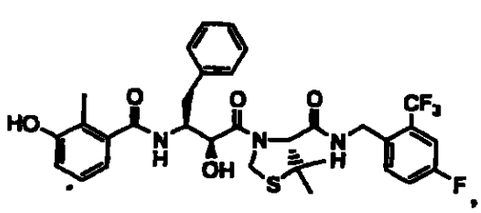
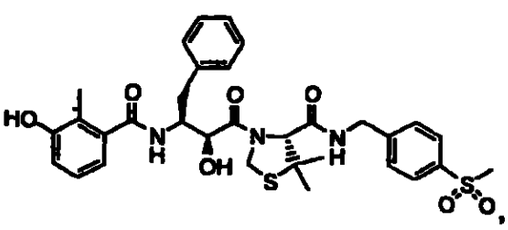
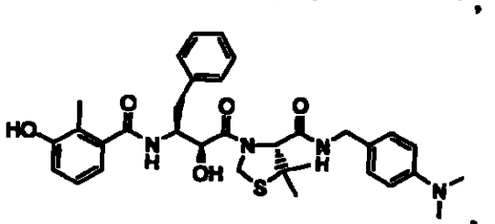
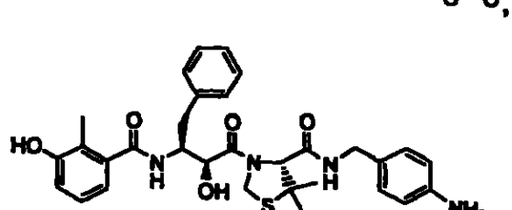
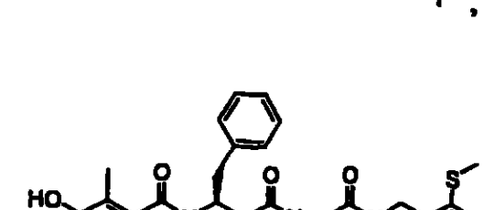
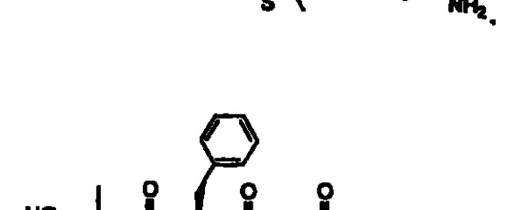
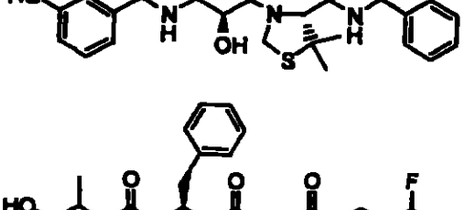
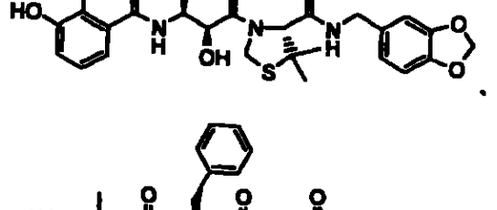
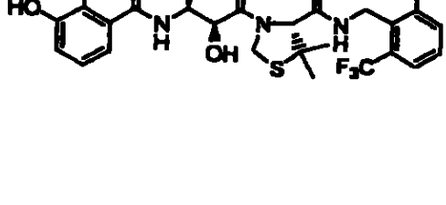
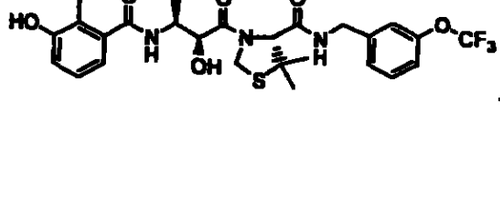
15. Un método de tratar una condición patológica de un mamífero mediada por actividad de proteasa VIH, que comprende administrar a un mamífero necesitado de ello una cantidad terapéuticamente efectiva de por lo menos un compuesto, profármaco, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o solvato farmacéuticamente aceptable definidos en una cualquiera de las reivindicaciones 1, 2 ó 5

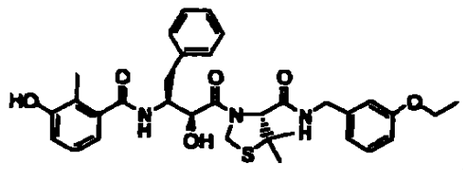
16. Un método de inhibir la actividad de protease VIH en un sujeto necesitado de ello, que comprende poner en contacto la proteasa VIH con una cantidad efectiva de por lo menos un compuesto, profármaco, sal farmacéuticamente aceptable, metabolito farmacéuticamente activo, o solvato farmacéuticamente aceptable definidos en una cualquiera de las reivindicaciones 1, 2 ó 5.

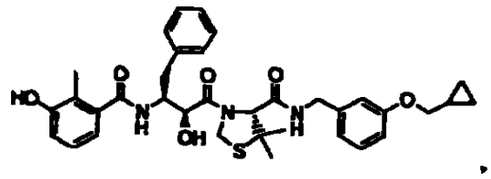
17. Un método de prevenir o tratar infección por VIH en un sujeto necesitado de ello que comprende administrar al sujeto una cantidad terapéuticamente efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1, 2 ó 5.

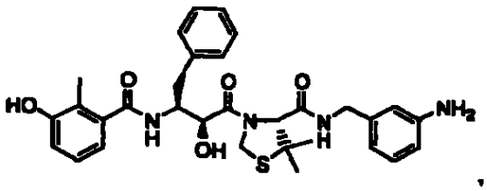
18. El método de acuerdo con la reivindicación 17, en donde el compuesto se administra en combinación con una cantidad terapéuticamente efectiva de por lo menos un agente de tratamiento de infección VIH/SIDA seleccionado del grupo conformado por agentes antivirales VIH/SIDA, inmunomoduladores, y agentes anti-infecciosos

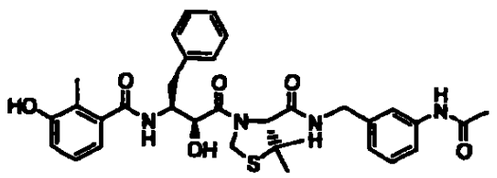
19. Un compuesto seleccionado de

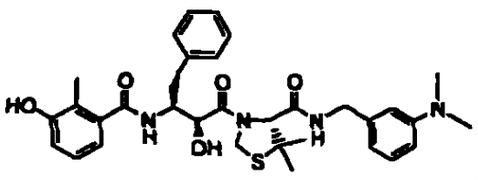

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

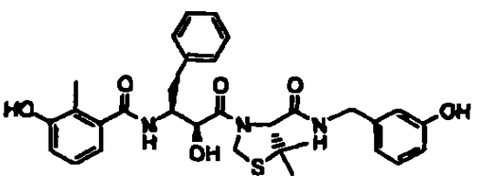


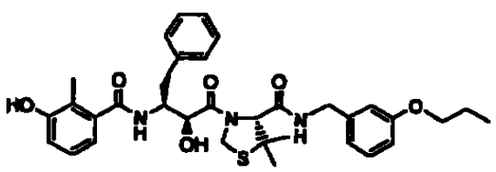


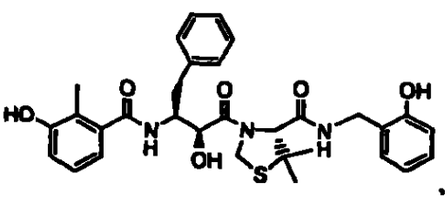


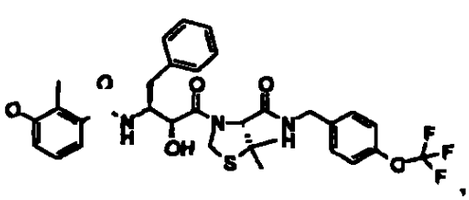


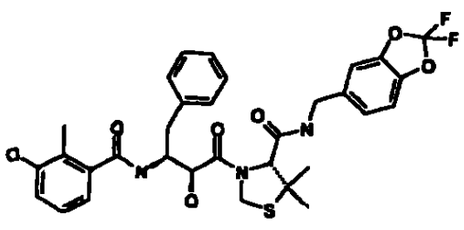


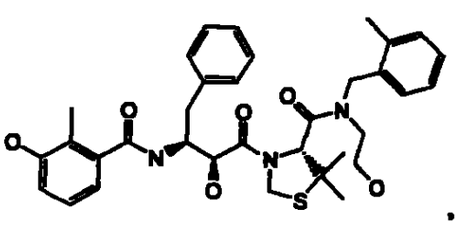


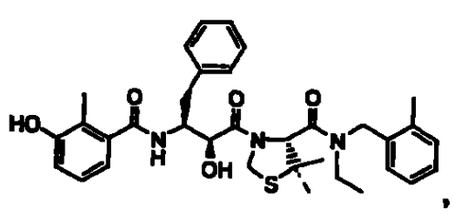


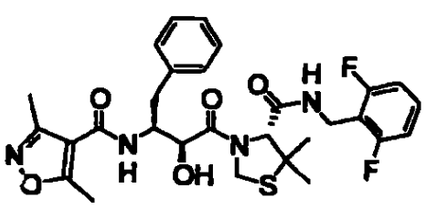


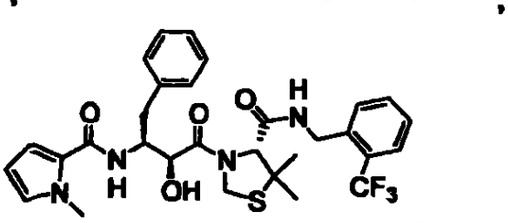


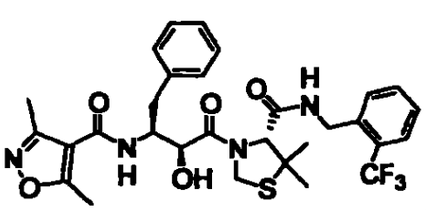


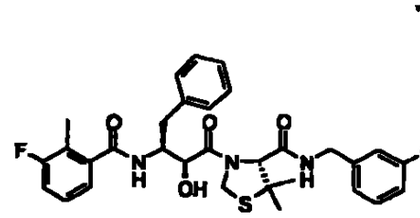


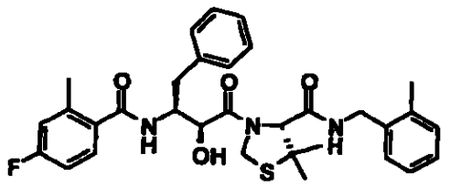


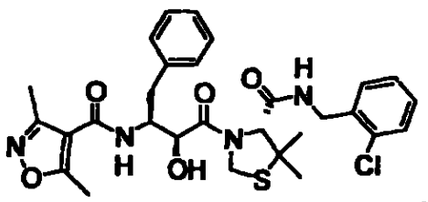


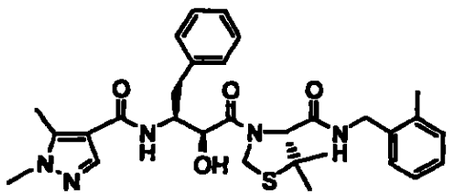


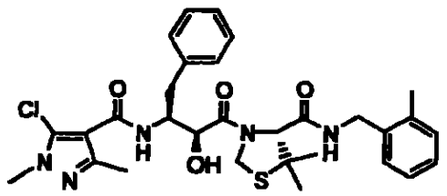


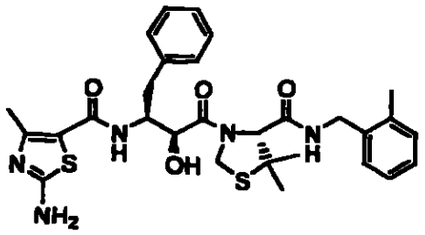


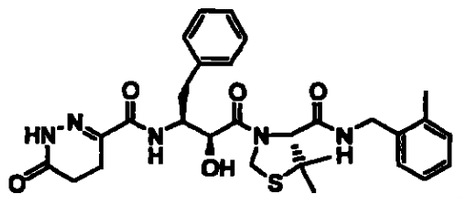


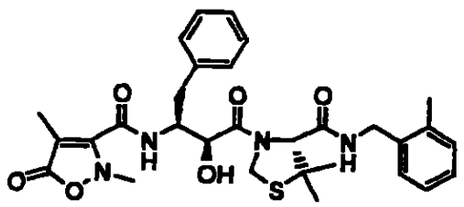


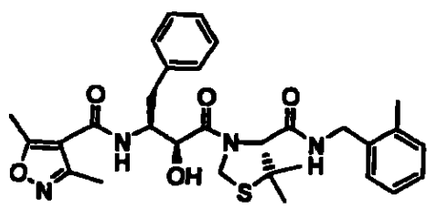


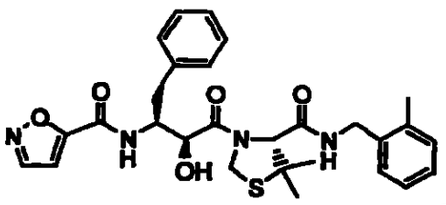


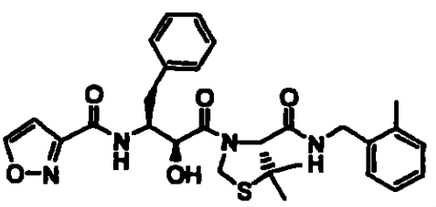


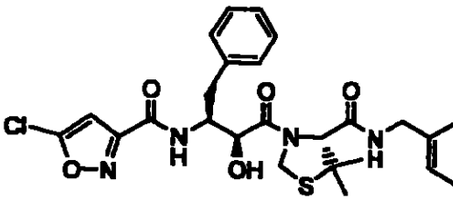


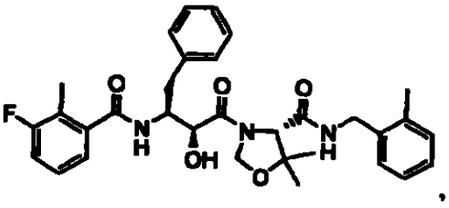


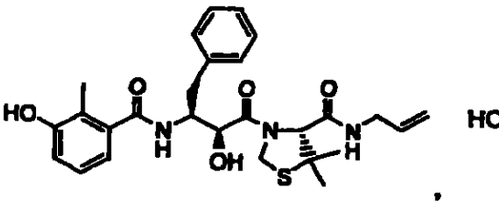


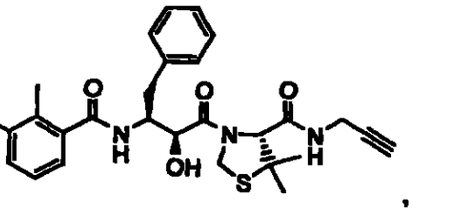


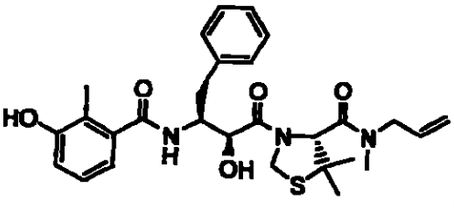


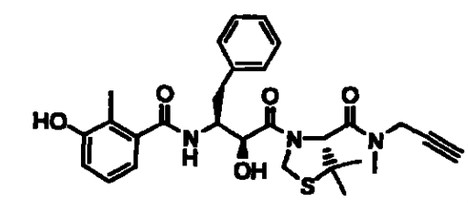


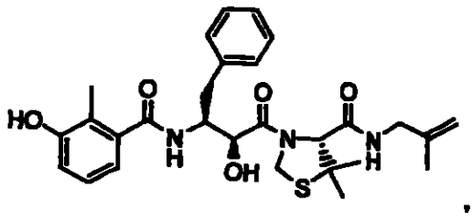
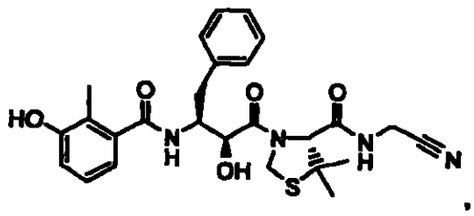
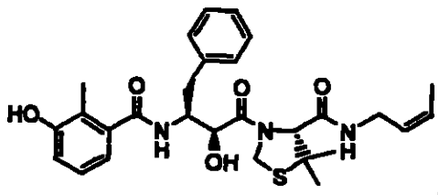
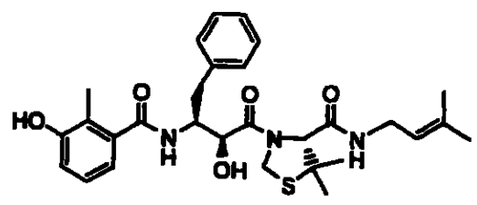
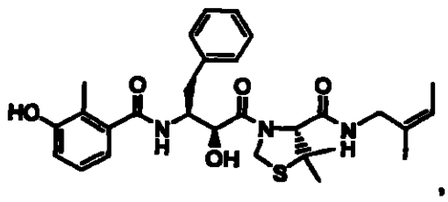
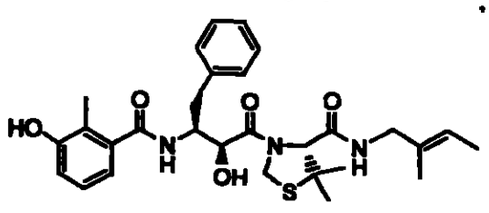
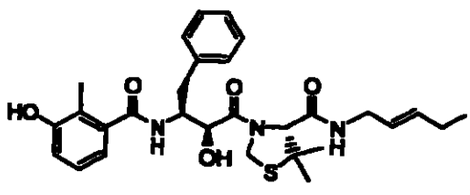
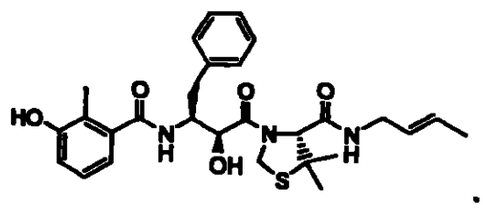
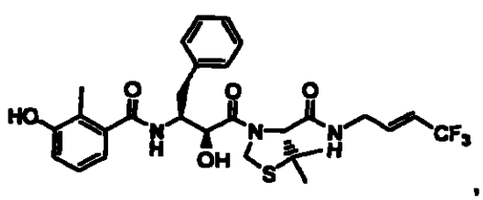
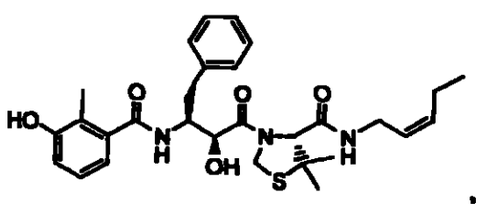
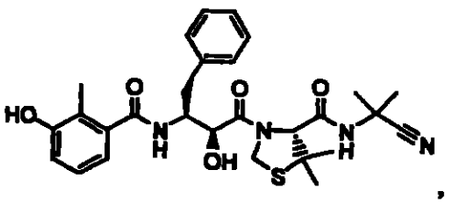
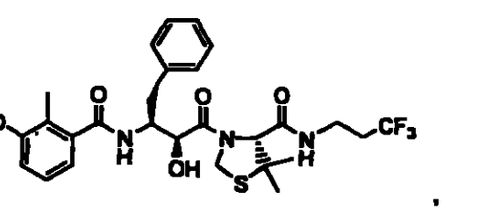
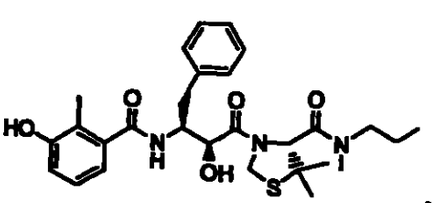
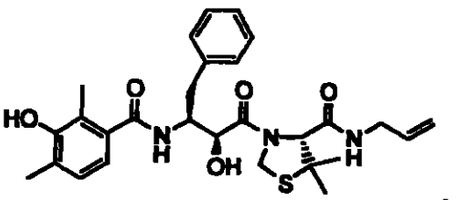
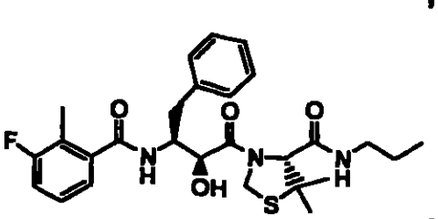
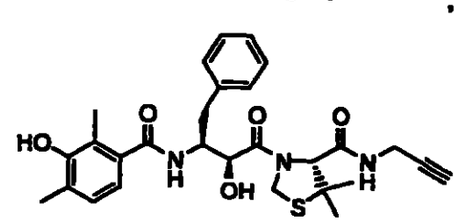




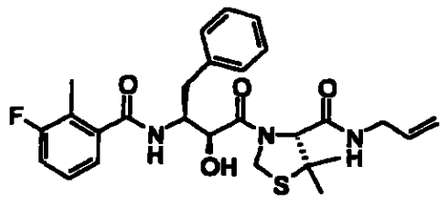


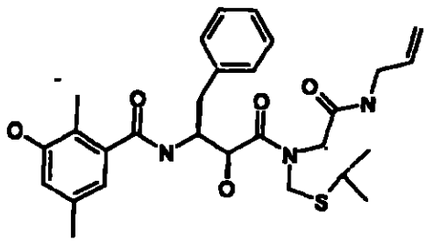


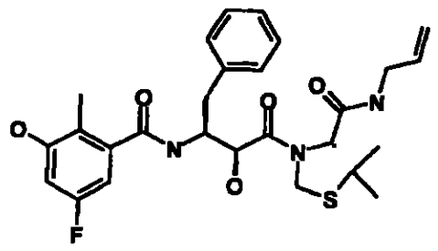


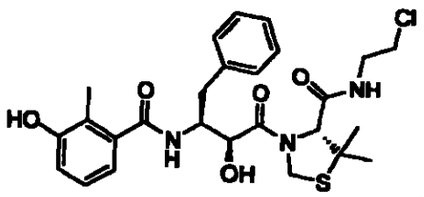

















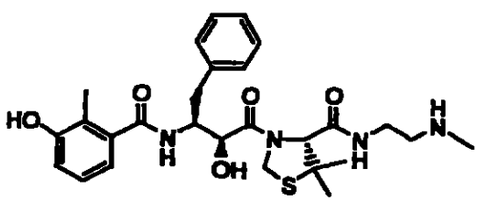


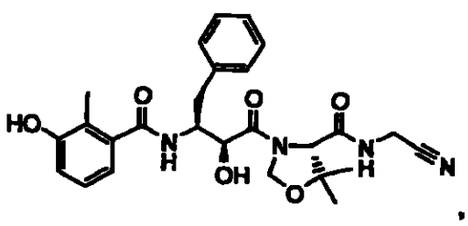


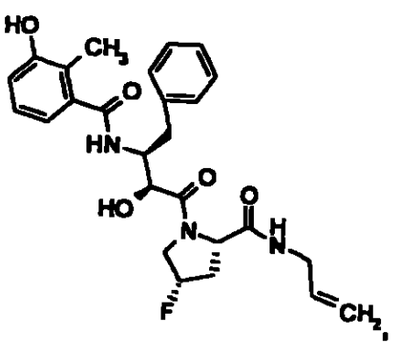


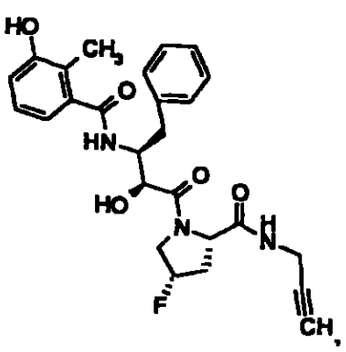


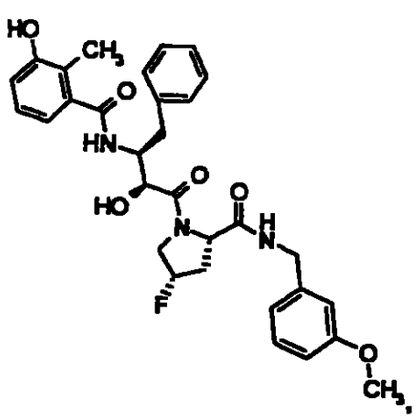


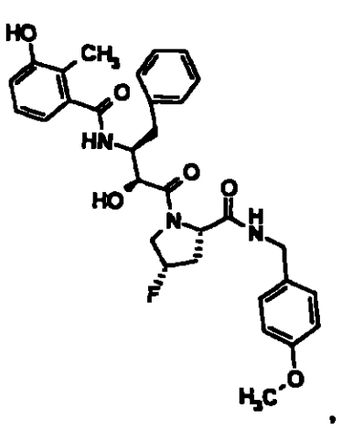


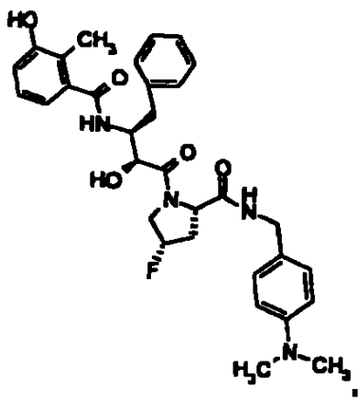


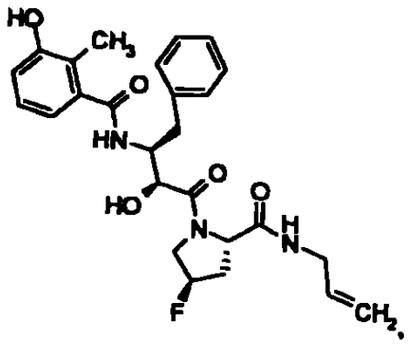


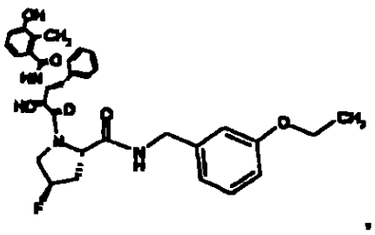


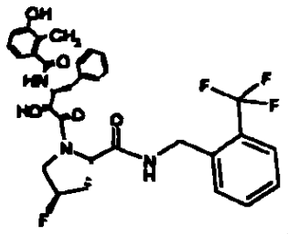


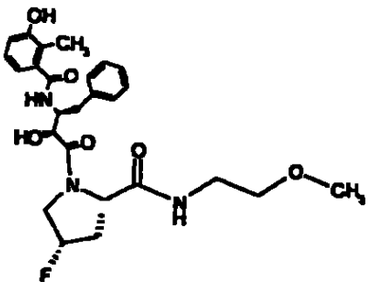


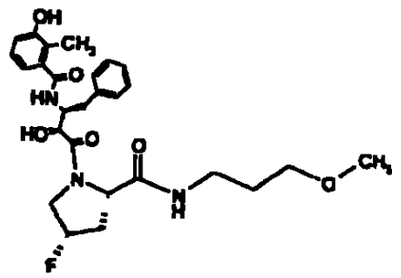


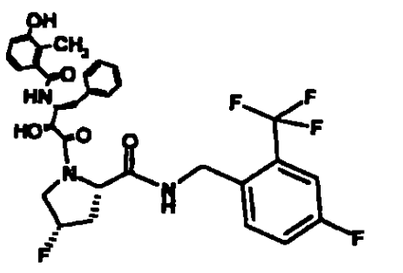


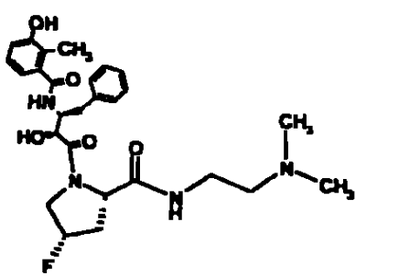


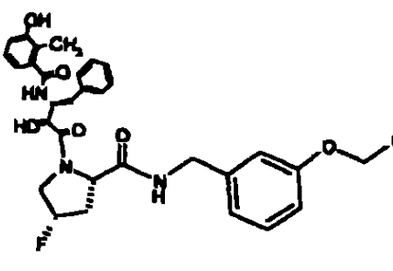


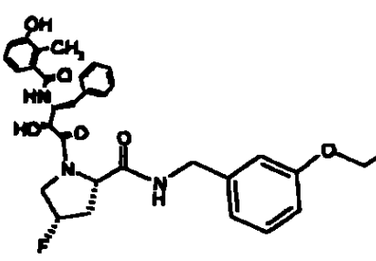


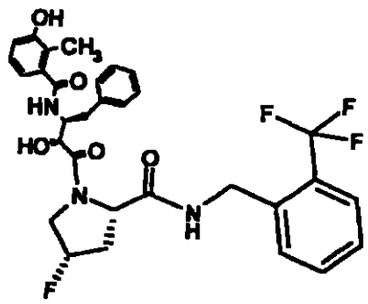












y los profármacos, metabolitos farmacéuticamente activos, y sales farmacéuticamente aceptables y solvatos del mismo.

For receiving Office Use Only

# PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

| | |
|---|---|
| International Application No. | 261 |
| International Filing Date | |
| Name of receiving Office and "PCT International Application" | |
| Applicant's or agent's file reference *(If desired) (12 characters maximum)* | 02521 000213.PC |

**Box No I TITLE OF INVENTION**

HIV PROTEASE INHIBITORS, COMPOSITIONS CONTAINING THE SAME, THEIR PHARMACEUTICAL USES AND MATERIALS FOR THEIR SYNTHESIS

**Box No. II APPLICANT** ☐ This person is also inventor

Name and address *(Family name followed by given name for a legal entity full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

AGOURON PHARMACEUTICALS, INC
10350 North Torrey Pines Road
La Jolla, California 92037
US

Telephone No (858) 622-3000

Facsimile No (858) 622-3297

Teleprinter No

Applicant's registration No with the Office

State *(that is, country)* of nationality US

State *(that is, country)* of residence US

This person is applicant for the purposes of ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

**Box No III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

Name and address. *(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CANON-KOCH, Stacie S
5940 La Jolla Messa Drive
La Jolla, California 92137
US

This person is
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below)*

Applicant's registration No with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence

This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

**Box No. IV AGENT OR COMMON REPRESENTATIVE, OR ADDRESS FOR CORRESPONDENCE**

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as. ☒ agent ☐ common representative

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*

MANDRA, Raymond R.
FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, NY 10112-3801
US
(continued on page 8)

Telephone No. (212) 218-2100

Facsimile No. (212) 218-2200

Teleprinter No.

Agent's registration No. with the Office
34,382

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

262

**Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS**

*If none of the following sub-boxes is used this sheet is not to be included in the request*

Name and address *(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ALEXANDER, Therese N
6557 Thornwood Street
San Diego, California 92111
US

This person is
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence

This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BARVIAN, Mark
1225 Olivia Avenue
Ann Arbor, MI 48104
US

This person is.
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence.

This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BOLTON, Gary
4800 Hillway Ct.
Ann Arbor 48105
US

This person is
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence

This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BOYER, Fredrick E.
482 Pleasant Ridge Drive
Canton Township, MI 48188
US

This person is.
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence

This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

263

**Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS**

*If none of the following sub-boxes is used, this sheet is not to be included in the request.*

Name and address *(Family name followed by given name for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is country) of residence if no State of residence is indicated below.)*

BURKE, Benjamin J
5761 Campanile Way
San Diego, California 92115
US

This person is
- [ ] applicant only
- [ ] applicant and inventor
- [x] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence

This person is applicant for the purposes of
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

HOLLER, Tod
2381 Placid Way
Ann Arbor, MI 48105
US

This person is
- [ ] applicant only
- [ ] applicant and inventor
- [X] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence

This person is applicant for the purposes of Box
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is country) of residence if no State of residence is indicated below.)*

JEWELL, Tanya M
12604 Torrey Bluff Dr #400
San Diego, CA 92130
US

This person is.
- [ ] applicant only
- [ ] applicant and inventor
- [x] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence

This person is applicant for the purposes of
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is country) of residence if no State of residence is indicated below.)*

PRASAD JOSYULA, Vara
3129 Fawn Meadow Court
Ann Arbor, Michigan 48105
US

This person is
- [ ] applicant only
- [ ] applicant and inventor
- [x] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence

This person is applicant for the purposes of
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

[x] Further applicants and/or (further) inventors are indicated on another continuation sheet.

264

**Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS**

*If none of the following sub-boxes is used, this sheet is not to be included in the request*

Name and address *(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KUCERA, David J
14099 Recuerdo Drive
Del Mar, California 92014
US

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [x] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LINTON, Maria A
11320 Red Cedar Drive
San Diego, California 92131
US

This person is
- [ ] applicant only
- [ ] applicant and inventor
- [x] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is country) of residence if no State of residence is indicated below.)*

MACHAK, Jeff
12980 Easton Court
Shelby Township, MI 48315
US

This person is
- [ ] applicant only
- [ ] applicant and inventor
- [x] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is country) of residence if no State of residence is indicated below.)*

MITCHELL, Lennert J
520 N Woodlawn Avenue
Chula Vista, California 91910
US

This person is.
- [ ] applicant only
- [ ] applicant and inventor
- [x] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

[ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

**Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS**

*If none of the following sub-boxes is used, this sheet is not to be included in the request*

265

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MURPHY, Sean T
7716 Dover Drive
Ypsilanti, MI 48197
US

This person is
[ ] applicant only
[ ] applicant and inventor
[X] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

REICH, Siegfried H
311 Glenmont Drive
Solana Beach, CA 92075
US

This person is:
[ ] applicant only
[ ] applicant and inventor
[X] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SKALITZKY, Donald J
4269 Taos Drive
San Diego, CA 92117
US

This person is.
[ ] applicant only
[ ] applicant and inventor
[X] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

TATLOCK, John H
13153Dressage Lane
San Diego, CA 92130
US

This person is
[ ] applicant only
[ ] applicant and inventor
[X] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

[ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

**Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS**

*If none of the following sub-boxes is used, this sheet is not to be included in the request.*

266

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

VARNEY, Michael D
738 Barbara Avenue
Solana Beach, CA 92075

This person is
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

VIRGIL, Scott C
3950 Mahaila Avenue, Apt, S23
San Diego, CA 92122
US

This person is
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

WEBBER, Stephen E.
3531 Millikan Avenue
San Diego, CA 92122
US

This person is
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

WORLAND, Stephen T
727 Hoska Drive
Del Mar, CA 92014
US

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

**Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS**

*If none of the following sub-boxes is used, this sheet is not to be included in the request.*

267

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MELNICK, Michael
3613 Weeburn Court
Ann Arbor, Michigan 48108
US

This person is
- [ ] applicant only
- [ ] applicant and inventor
- [X] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is country)* of residence:

This person is applicant for the purposes of
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

- [ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

268

**Box No. V DESIGNATION OF STATES** *Mark the applicable check boxes; at least one must be marked.*

The following designations are hereby made under Rule 4 9(a)

**Regional Patent**

[x] **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

[x] **EA** Eurasian Patent AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

[x] **EP** European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

[x] **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on the dotted line)* . . . . . .

**National Patent** *(if other kind of protection or treatment desired, specify on dotted line)*

[x] AE United Arab Emirates
[x] AG Antigua and Barbuda
[x] AL Albania
[x] AM Armenia
[x] AT Austria
[x] AU Australia
[x] AZ Azerbaijan
[x] BA Bosnia and Herzegovina
[x] BB Barbados
[x] BG Bulgaria
[x] BR Brazil
[x] BY Belarus
[x] BZ Belize
[x] CA Canada
[x] CH & LI Switzerland and Liechtenstein
[x] CN China
[x] CO Colombia
[x] CR Costa Rica
[x] CU Cuba
[x] CZ Czech Republic
[x] DE Germany
[x] DK Denmark
[x] DM Dominica
[x] DZ Algeria
[x] EC Ecuador
[x] EE Estonia
[x] ES Spain
[x] FI Finland
[x] GB United Kingdom
[x] GD Grenada
[x] GE Georgia
[x] GH Ghana
[x] GM Gambia
[x] HR Croatia
[x] HU Hungary
[x] ID Indonesia
[x] IL Israel
[x] IN India
[x] IS Iceland
[x] JP Japan
[x] KE Kenya
[x] KG Kyrgyzstan
[x] KP Democratic People's Republic of Korea
[x] KR Republic of Korea
[x] KZ Kazakhstan
[x] LC Saint Lucia
[x] LK Sri Lanka
[x] LR Liberia
[x] LS Lesotho
[x] LT Lithuania
[x] LU Luxembourg
[x] LV Latvia
[x] MA Morocco
[x] MD Republic of Moldova
[x] MG Madagascar
[x] MK The Former Yugoslav Republic of Macedonia
[x] MN Mongolia
[x] MW Malawi
[x] MX Mexico
[x] MZ Mozambique
[x] NO Norway
[x] NZ New Zealand
[x] OM Oman
[x] PH Philippines
[x] PL Poland
[x] PT Portugal
[x] RO Romania
[x] RU Russian Federation
[x] SD Sudan
[x] SE Sweden
[x] SG Singapore
[x] SI Slovenia
[x] SK Slovakia
[x] SL Sierra Leone
[x] TJ Tajikistan
[x] TM Turkmenistan
[x] TN Tunisia
[x] TR Turkey
[x] TT Trinidad and Tobago
[x] TZ United Republic of Tanzania
[x] UA Ukraine
[x] UG Uganda
[ ] US United States of America
[x] UZ Uzbekistan
[x] VN Viet Nam
[x] YU Yugoslavia
[x] ZA South Africa
[x] ZM Zambia
[x] ZW Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

[ ] [ ] [ ]
[ ] [ ] [ ]

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4 9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

269

**Supplemental Box** *If the Supplemental Box is not used, this sheet need not be included in the request.*

1 *If in any of the Boxes, except Boxes Nos VIII(i) to (v) for which a special continuation box is provided the space is insufficient to furnish all the information in such case, write "Continuation of Box No. " [indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular*

*(i) If more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below,*

*(ii) If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked. in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, European or OAPI patent) for the purposes of which the named person is applicant,*

*(iii) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, European or OAPI patent) for the purposes of which the named person is inventor,*

*(iv) If, in addition to the agent(s) indicated in Box No. IV, there are further agents in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV,*

*(v) If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part" in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application,*

*(vi) If, in Box No. VI, there are more than five earlier applications whose priority is claimed in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI*

2 *If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

FITZPATRICK, Joseph M. (Registration No. 17,398), SCINTO, Lawrence P (Registration No. 18,973), BRUNET William J (Registration No. 20,430), BAECHTOLD, Robert L. (Registration No. 20,860), O'BRIEN, John A. (Registration No. 24,367), ERAUER, John A. (Registration No. 24,613), RINK, Henry J (Registration No. 25,499), BAXTER, Peter (Registration, No. 26,947), ZUPCIC, Anthony M. (Registration No. 29,270), BAKER, Charles P (Registration No. 26,782), ROBBINS, Steven J. (Registration No. 22,291), VASSALLO, Edward E. (Registration No. 28,117), CLAYTON, Ronald A. (Registration No. 26,718), STAHL, Lawrence A. (Registration No. 30,110), BAUER, Laura A. (Registration No. 29,767), DIANA, Leonard P (Registration No. 29,296), KALLAS, Nicholas N (Registration No. 31,530), WANNIEKY, William M. (Registration No. 28,573), PERRY Lawrence S (Registration No. 31,869), FISCHER, Robert H. (Registration No. 30,051), WRIST Christopher Philip (Registration No. 32,078), JACOBS, Gary M. (Registration No. 28,861), O'NEILL, Michael K. (Registration No. 32,622), HAAS, Bruce C. (Registration No. 32,734), REED, Scott K. (Registration No. 32,433), MALPEDE, Scott D. (Registration No. 32,533), ZULLOW, Fredrick M. (Registration No. 32,452), OLSEN, Warren E. (Registration No. 27,280), WARNER, Steven E. (Registration No. 33,326), O'CONNELL, Thomas J (Registration No. 33,302), CUBERT Jack S (Registration No. 24,245), WILLIAMSON, Mark A. (Registration No. 33,628), DUDEK, Jean K. (Registration No. 30,936), MANDRA, Raymond R. (Registration No. 34,382), CONDE, Dominick A. (Registration No. 33,856), RAZZANO, Pasquale A. (Reg. No. 35,512), BEHRINGER, John W (Registration No. 33,686), KLINE, Robert C. (Registration No. 17,739), SANDONATO, Michael P (Registration No. 35,345), CARLIN, John D. (Registration No. 37,292), GLUECK, Daniel E. (Registration No. 37,838), RAGUBA, Joseph W (Registration No. 38,886), KLOCK, Brian L. (Registration No. 36,570), MAHER, Anne M. (Registration No. 38,201), WEIGLER, Bruce M. (Registration No. 35,409), TAYLOR, Errol B. (Registration No. 39,851), SHARROTT, Douglas (Registration No. 39,832), SMITH, Lelia M. (Registration No. 39,578), HOLOWACZ, Elizabeth F (Registration No. 42,667), DELUCIA, Frank A., Jr (Registration No. 42,476), DALKE, David P (Registration No. 40,989), QUINN, Carole A. (Registration No. 39,000), HAUGHEY III, Edmund J (Registration No. 44,769), OLIVER, Justin J. (Registration No. 44,986), YU-JAHNES, Lock Sze (Registration No. 38,667), PENSABENE, Marc J (Registration No. 37,416), DUCHENE, Dennis A. (Registration No. 40,595), EMETT, Edward A. (Registration No. 42,746), MIR, Brandon (Registration No. 43,591), HADLEY, Jason (Registration No. 46,009), RATLIFF II, Preston (Registration No. 43,634), WISCHHUSEN, Carl B. (Registration No. 43,279), BELISLE, Stephen E. (Registration No. 46,546), BERSCHADSKY, Jonathan (Registration No. 44,551), THURLOW Peter (Registration No. 47,138), ROBERTS, Simon (Registration No. 47,342), FRASER, Steven W (Registration No. 45,086), DERZKO, Natalie M. (Registration No. 48,102), KHOO, Carol K. (Registration No. 44,270), PINSKY Douglas W (Registration No. 44,994), TSU, Victor (Registration No. 44,165), SHATZ, Howard D (Registration No. 47,036), DIPERNA, Raymond (Registration No. 44,063), BARON Jacob K. (Registration No. 48,961), CALLAGHAN, Edward J. (Registration No. 46,594), KONDOUDIS, Michael E. (Registration No. 43,798), LOH, Christopher E. (Registration No. 46,000), and OKUN, Jason M. (Registration No. 48,512), TAFFY, Joseph (Registration No. 50,973), KLANTSCHI, Fritz (Registration No. 50,333), ALY Amr O. (Registration No. 50,525) and MICKELSEN, Andrew D. (Registration No. 50,957) all of:

*FITZPATRICK, CELLA, HARPER & SCINTO*
*30 Rockefeller Plaza*
*New York, New York 10112-3801*
*United States of America*



*See Notes to the request form*

270

**Box No. VI PRIORITY CLAIM**

The priority of the following earlier application(s) is hereby claimed

| Filing date of earlier application *(day/month/year)* | Number of earlier application | Where earlier application is | | |
|---|---|---|---|---|
| | | national application. country | regional application * regional Office | international application receiving Office |
| item (1) (11/06/2001) 11 JUNE 2001 | 60/297,460 | US | | |
| item (2) (11/06/2001) 11 JUNE 2001 | 60/297,729 | US | | |
| item (3) | | | | |
| item (4) | | | | |
| item (5) | | | | |

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as

☐ all items ☒ item (1) ☒ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* *Where the earlier application is an ARIPO application, it is madatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4 10(b)(ii)*

**Box No. VII INTERNATIONAL SEARCHING AUTHORITY**

**Choice of International Searching Authority (ISA)** *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen the two-letter code may be used)*
ISA/EPO

**Request to use results of earlier search, reference to that search** *(if an earlier search has been carried out by or requested from the International Searching Authority)*

Date *(day/month/year)* Number Country *(or regional Office)*

**Box No. VIII DECLARATIONS**

| The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)* | | Number of declarations |
|---|---|---|
| ☐ | Box No. VIII (i) Declaration as to the identity of the inventor | |
| ☐ | Box No VIII (ii) Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | |
| ☐ | Box No. VIII (iii) Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | |
| ☐ | Box No. VIII (iv) Declaration of inventorship (only for the purposes of the designation of the United States of America) | |
| ☐ | Box No VIII (v) Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | |

271

## Box No IX CHECK LIST, LANGUAGE OF FILING

This international application contains

(a) the following number of sheets in paper form

| | |
|---|---|
| request (including declaration sheets) | 11 |
| description (exclusing sequence listing part) | 142 |
| claims | 19 |
| abstracts | 1 |
| drawings | |
| Sub-total number of sheets | 173 |
| sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form see (b) below)* | |
| Total number of sheets | 173 |

(b) sequence listing part of description filed in computer readable form

(i) ☐ only (under Section 801(a)(i))

(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*

This international application is accompanied by the following items(s) *(mark the applicable check-boxes below and indicate in right column the number of each items)*

Number of items

1 ☒ fee calculation sheet

2 ☐ original separate power of attorney

3 ☐ original general power of attorney

4. ☐ copy of general power of attorney; reference number, if any

5 ☐ statement explaining lack of signature

6 ☐ priority document(s) identified in Box No. VI as item(s)

7 ☐ translation of international application into *language)*

8 ☐ separate indications concerning deposited microorganism or other biological material

9 ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))

(i) ☐ copy submitted or the purposes of international search under Rule 13*ter* only (and not as part of the international application)

(ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*

(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column

10 ☐ other *(specify)*

**Figure of the drawings which should accompany the abstract**

**Language of filing of the international application.** English

## Box No X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

*Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).*

Raymond R. Mandra -Agent

For receiving Office use only

| | | |
|---|---|---|
| 1 Date of actual receipt of the purported international application | | 2 Drawings ☐ received. ☐ not received. |
| 3 Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application | | |
| 4 Date of timely receipt of the required corrections under PCT Article 11(2): | | |
| 5 International Searching Authority specified by the applicant: ISA/ | 6. ☐ Transmittal of search copy delayed until search fee is paid | |

For International Bureau use only

Date of receipt of the record copy by the International Bureau

PATENT COOPERATION TREATY

# PCT

2727

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | FOR FURTHER ACTION | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below |
|---|---|---|
| 02521 000213 PC | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/US 02/18548 | 11/06/2002 | 11/06/2001 |
| Applicant | | |
| AGOURON PHARMACEUTICALS, INC | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1 Basis of the report

a With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2 [ ] Certain claims were found unsearchable (See Box I)

3. [ ] Unity of invention is lacking (see Box II)

4 With regard to the title,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows.

5 With regard to the abstract,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6 The figure of the drawings to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

# INTE NATIONAL SEARCH REPORT

National Application No
PCT/US 02/18548 273

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/06 A61K31/425 C07D417/12 C07D403/12 C07D207/16 A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data

C DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | MIMOTO T ET AL "Structure-Activity Relationship of Small-Sized HIV Protease Inhibitors Containing Allophenylnorstatine" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY WASHINGTON, US, vol 42, no. 10, 24 April 1999 (1999-04-24), pages 1789-1802, XP002192452 ISSN. 0022-2623 cited in the application * see the whole document; in particular compound no. 21h * | 1-19 |

-/—

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 5 September 2002 | 13/09/2002 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Lauro, P |

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document with indication where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | PATENT ABSTRACTS OF JAPAN<br>vol. 1998, no 12,<br>31 October 1998 (1998-10-31)<br>& JP 10 182601 A (JAPAN ENERGY CORP),<br>7 July 1998 (1998-07-07)<br>* see RN=210878-37-8,<br>RN=210878-41-4,RN=210878-44-7,<br>RN=210878-47-0 *<br>abstract | 1-19 |
| X | EP 0 751 145 A (JAPAN ENERGY CORP)<br>2 January 1997 (1997-01-02)<br>cited in the application<br>the whole document | 1-19 |
| X | US 6 222 043 B1 (FUKAZAWA TOMINAGA ET AL)<br>24 April 2001 (2001-04-24)<br>* see the whole document, in particular<br>formula (IV) and (VI) * | 1-19 |

# INTE NATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/18548 275

| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|---|
| JP 10182601 | A | 07-07-1998 | NONE | | |
| EP 0751145 | A | 02-01-1997 | AU | 705193 B2 | 20-05-1999 |
| | | | AU | 5628596 A | 06-02-1997 |
| | | | CA | 2179935 A1 | 31-12-1996 |
| | | | EP | 0751145 A2 | 02-01-1997 |
| | | | JP | 10025242 A | 27-01-1998 |
| | | | NO | 962748 A | 02-01-1997 |
| | | | US | 5962640 A | 05-10-1999 |
| | | | US | 6222043 B1 | 24-04-2001 |
| | | | US | 5932550 A | 03-08-1999 |
| | | | ZA | 9605472 A | 27-01-1997 |
| US 6222043 | B1 | 24-04-2001 | AU | 705193 B2 | 20-05-1999 |
| | | | AU | 5628596 A | 06-02-1997 |
| | | | CA | 2179935 A1 | 31-12-1996 |
| | | | EP | 0751145 A2 | 02-01-1997 |
| | | | JP | 10025242 A | 27-01-1998 |
| | | | NO | 962748 A | 02-01-1997 |
| | | | US | 5962640 A | 05-10-1999 |
| | | | US | 5932550 A | 03-08-1999 |
| | | | ZA | 9605472 A | 27-01-1997 |

276

*The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below*

IPEA/ EP

# PCT

**CHAPTER II**

## DEMAND

under Article 31 of the Patent Cooperation Treaty

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated)

| For International Preliminary Examining Authority use only | |
|---|---|
| Identification of IPEA | Date of receipt of DEMAND |

| Box No I IDENTIFICATION OF THE INTERNATIONAL APPLICATION | | Applicant's or agent's file reference 02521 000213 PC |
|---|---|---|
| International application No PCT/US02/18548 | International filing date *(day/month/year)* 11 JUNE 2002 (11.06 02) | (Earliest) Priority date *(day/month/year)* 11 JUNE 2001 (11 06 01) |

Title of invention

HIV PROTEASE INHIBITORS, COMPOSITIONS CONTAINING THE SAME, THEIR PHARMACEUTICAL USES AND MATERIALS FOR THEIR SYNTHESIS

Box No. II APPLICANT(S)

| Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)* | Telephone No (858) 622-3000 |
|---|---|
| AGOURON PHARMACEUTICALS, INC<br>10350 North Torrey Pines Road<br>La Jolla, California 92037<br>US | Facsimile No (858) 622 3297 |
| | Teleprinter No |
| | Applicant's registration No with the Office |

| State *(that is, country)* of nationality | State *(that is, country)* of residence |
|---|---|
| US | US |

Name and address *(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country.)*

| State *(that is, country)* of nationality | State *(that is, country)* of residence |
|---|---|

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*

| State *(that is, country)* of nationality | State *(that is, country)* of residence |
|---|---|

☐ Further applicants are indicated on a continuation sheet.

International application No
PCT/US02/18548

**Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*

MANDRA ,Mandra R.
Fitzpatrick, Cella, Harper & Scinto
30 Rockefeller Plaza
New York, New York 10112-3801
US

Telephone No (212) 218-2100

Facsimile No (212) 218-2200

Teleprinter No

Agent's registration No with the Office
34,382

[ ] Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent

**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION**

Statement concerning amendments:*

1 The applicant wishes the international preliminary examination to start on the basis of:

[X] the international application as originally filed

the description
[ ] as originally filed
[ ] as amended under Article 34

the claims
[ ] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings
[ ] as originally filed
[ ] as amended under Article 34

2 [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed

3 [ ] The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 of a notice from the applicant that he does not wish to make such amendments (Rule 69 1(d)) *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended

Language for the purposes of international preliminary examination ENGLISH

[X] which is the language in which the international application was filed

[ ] which is the language of a translation furnished for the purposes of international search.

[ ] which is the language of publication of the international application.

[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

**Box No. V ELECTION OF STATES**

278

International application No
PCT/US02/18548

**Box No. VI CHECK LIST**

The demand is accompanied by the following elements, in the language referred to in Box No IV, for the purposes of international preliminary examination.

| | | | For International Preliminary Examining Authority use only: received | not received |
|---|---|---|---|---|
| 1 | translation of international application | sheets | ☐ | ☐ |
| 2 | amendments under Article 34 | sheets | ☐ | ☐ |
| 3 | copy (or, where required, translation) of amendment under Article 19 | sheets | ☐ | ☐ |
| 4 | copy (or, where required, translation) of statement under Article 19 | sheets | ☐ | ☐ |
| 5 | letter | sheets | ☐ | ☐ |
| 6 | other *(specify)* | sheets | ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

| | | | | |
|---|---|---|---|---|
| 1 | ☒ | fee calculation sheet | 5 ☐ | statement explaining lack of signature |
| 2 | ☐ | original separate power of attorney | 6 ☐ | sequence listing in computer readable form |
| 3 | ☐ | original general power of attorney | 7 ☐ | other *(specify)* |
| 4 | ☐ | copy of general power of attorney, reference number, if any | | |

**Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE**

*Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such a capacity is not obvious from reading the demand).*

Raymond R Mandra-Agent

**For International Preliminary Examining Authority use only**

| | | | |
|---|---|---|---|
| 1 | Date of actual receipt of DEMAND | | |
| 2 | Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b) | | |
| 3 | ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply | ☐ | The applicant has been informed accordingly |
| 4 | ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5 | | |
| 5 | ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82 | | |

**For International Bureau Use Only**

Demand received from IPEA on.



*See Notes to the demand form*

# INTERNATI NAL SEARCH REPORT

In ernal Application No
PCT/US 02/18548 279

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/06 A61K31/425 C07D417/12 C07D403/12 C07D207/16
A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | MIMOTO T ET AL: "Structure-Activity Relationship of Small-Sized HIV Protease Inhibitors Containing Allophenylnorstatine" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, no. 10, 24 April 1999 (1999-04-24), pages 1789-1802, XP002192452 ISSN: 0022-2623 cited in the application * see the whole document; in particular compound no. 21h * | 1-19 |

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 5 September 2002 | 13/09/2002 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Lauro, P |

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | PATENT ABSTRACTS OF JAPAN<br>vol. 1998, no. 12,<br>31 October 1998 (1998-10-31)<br>& JP 10 182601 A (JAPAN ENERGY CORP),<br>7 July 1998 (1998-07-07)<br>* see RN=210878-37-8,<br>RN=210878-41-4,RN=210878-44-7,<br>RN=210878-47-0 *<br>abstract | 1-19 |
| X | EP 0 751 145 A (JAPAN ENERGY CORP)<br>2 January 1997 (1997-01-02)<br>cited in the application<br>the whole document | 1-19 |
| X | US 6 222 043 B1 (FUKAZAWA TOMINAGA ET AL)<br>24 April 2001 (2001-04-24)<br>* see the whole document; in particular<br>formula (IV) and (VI) * | 1-19 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

In ternal Application No
PCT/US 02/18548

230

| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|---|
| JP 10182601 | A | 07-07-1998 | NONE | | |
| EP 0751145 | A | 02-01-1997 | AU | 705193 B2 | 20-05-1999 |
| | | | AU | 5628596 A | 06-02-1997 |
| | | | CA | 2179935 A1 | 31-12-1996 |
| | | | EP | 0751145 A2 | 02-01-1997 |
| | | | JP | 10025242 A | 27-01-1998 |
| | | | NO | 962748 A | 02-01-1997 |
| | | | US | 5962640 A | 05-10-1999 |
| | | | US | 6222043 B1 | 24-04-2001 |
| | | | US | 5932550 A | 03-08-1999 |
| | | | ZA | 9605472 A | 27-01-1997 |
| US 6222043 | B1 | 24-04-2001 | AU | 705193 B2 | 20-05-1999 |
| | | | AU | 5628596 A | 06-02-1997 |
| | | | CA | 2179935 A1 | 31-12-1996 |
| | | | EP | 0751145 A2 | 02-01-1997 |
| | | | JP | 10025242 A | 27-01-1998 |
| | | | NO | 962748 A | 02-01-1997 |
| | | | US | 5962640 A | 05-10-1999 |
| | | | US | 5932550 A | 03-08-1999 |
| | | | ZA | 9605472 A | 27-01-1997 |

92 859

281

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

**(Rationalised Report according to the Notice of the President of the EPO published in the OJ 11/2001)**

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| 02521.000213 PC | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/US 02/ 18548 | 11/06/2002 | 11/06/2001 |
| International Patent Classification (IPC) or national classification and IPC | | |
| C07D277/06 | | |
| Applicant | | |
| AGOURON PHARMACEUTICALS, INC. | | |

1 This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36

2 This REPORT consists of a total of 2 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT)

These annexes consists of a total of _____ sheets.

3 This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 07/01/2003 | 22/04/2003 |
| Name and mailing address of the IPEA/ | Authorized officer |
| European Patent Office<br>D-80298 Munich<br>Tel. (+49-89) 2399-0, Tx: 523656 epmu d<br>Fax: (+49-89) 2399-4465 | GELLIE B R<br><br>Tel. (+49-89) 2399 2828 |

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)

## I. Basis of the report

The basis of this international preliminary examination is the application as originally filed

## V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims does not appear to meet the criteria mentioned in Article 33(1) PCT, i e does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references)

# PATENT COOPERATION TREATY

283

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

RECEIVED

# PCT

To:
Mandra, Mandra R.
FITZPATRICK CELLA HARPER & SCINTO
30 Rockefeller Plaza
New York, NY 10112-3801
ETATS-UNIS D'AMERIQUE

2003 FEB -4 A 10:31

FITZPATRICK, CELLA, HARPER & SCINTO

## WRITTEN OPINION

(PCT Rule 66)

| | |
|---|---|
| | Date of mailing *(day/month/year)* 30/01/2003 |
| Applicant's or agent's file reference 02521.000213.PC | REPLY DUE within 2 / 00 months/days from the above date of mailing |
| International application No. PCT/US 02/ 18548 | International filing date *(day/month/year)* 11/06/2002 |
| Priority date *(day/month/year)* 11/06/2001 | |
| International Patent Classification (IPC) or both national classification and IPC C07D277/06 | |
| Applicant AGOURON PHARMACEUTICALS, INC. | |

1 This written opinion is the first drawn up by this International Preliminary Examining Authority

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

FILE NO. 2521.0213PCT
ATTORNEY DFG
DUE DATE 3/30/03
DOCKETED VMG 2/4/03

3 The applicant is hereby invited to reply to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3
For the form and the language of the amendments, see Rules 66.8 and 66.9

**Also** For an additional opportunity to submit amendments, see Rule 66.4
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 11/10/2003

| | |
|---|---|
| Name and mailing address of the IPEA/<br>European Patent Office<br>D-80298 Munich<br>Tel. (+49-89) 2399-0, Tx. 523656 epmu d<br>Fax. (+49-89) 2399-4465 | Authorized officer<br>Examiner<br>Formalities officer<br>(incl. extension of time limits)<br>Tel. (+49-89) 2399 2828 |

Form PCT/IPEA/408 (cover sheet) (march 2002)

## I. Basis of the opinion

1 The basis of this written opinion is the application as originally filed

## V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

1 In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims does not appear to meet the criteria mentioned in Article 33(1) PCT, i e does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claims references)

2 If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out

NB Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested

285

02521 000213 PC INTERNATIONAL APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE AS RECEIVING OFFICE (RO/US)

| | | |
|---|---|---|
| In re Application of | ) | |
| | | Authorized Officer Corbeira, M. |
| Stacie S Canon-Koch et al | ) | |
| Application No PCT/US02/18548 | ) | |
| Filed 11 June 2002 | ) | |
| For HIV PROTEASE INHIBITORS, COMPOSITIONS CONTAINING THE SAME, THEIR PHARMACEUTICAL USES AND MATERIALS FOR THEIR SYNTHESIS | ) | September 16, 2002 |

Commissioner for Patents
BOX PCT
Attn RO/US
Washington, D C 20231

SUBMISSION OF REQUEST SUBSTITUTE SHEET

Sir

In reference to the above-identified International Patent Application, Applicant hereby submits a substitute sheet of the Request filed on 11 June 2002 to correct the filing date of U S. Provisional Application No 60/297,729 The correct date of filing for U S. Provisional Application No. 60/297,729 is 12 June 2001 Attached hereto is said substitute sheet

286

If the Authorized Officer has any questions, the Officer is invited to contact Applicant's agent at the telephone number listed below All correspondence should be directed to the below-listed address

Respectfully submitted,

Raymond R. Mandra
Agent for Applicant

FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112-3801
Facsimile (212) 218-2200
Telephone. (212) 218-2100

NY_MAIN 280288 v 1

**Box No. VI PRIORITY CLAI**

The priority of the following earlier application(s) is hereby claimed.

| Filing date of earlier application *(day/month/year)* | Number of earlier application | Where earlier application is | | |
|---|---|---|---|---|
| | | national application. country | regional application.* regional Office | international application. receiving Office |
| item (1) (11/06/2001) 11 JUNE 2001 | 60/297,460 | US | | |
| item (2) (12/06/2001) 12 JUNE 2001 | 60/297,729 | US | | |
| item (3) | | | | |
| item (4) | | | | |
| item (5) | | | | |

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as:

☐ all items ☒ item (1) ☒ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii))*

**Box No. VII INTERNATIONAL SEARCHING AUTHORITY**

**Choice of International Searching Authority (ISA)** *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen, the two-letter code may be used)*:

ISA/EPO

**Request to use results of earlier search, reference to that search** *(if an earlier search has been carried out by or requested from the International Searching Authority)*

Date *(day/month/year)* Number Country *(or regional Office)*

**Box No. VIII DECLARATIONS**

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*

Number of declarations

| | | |
|---|---|---|
| ☐ | Box No. VIII (i) | Declaration as to the identity of the inventor |
| ☐ | Box No. VIII (ii) | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent |
| ☐ | Box No. VIII (iii) | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application |
| ☐ | Box No. VIII (iv) | Declaration of inventorship (only for the purposes of the designation of the United States of America) |
| ☐ | Box No. VIII (v) | Declaration as to non-prejudical disclosures or exceptions to lack of novelty |

# UNITED STATES RECEIVING OFFICE

| International Application No | PCT/US02/18548 |
|---|---|
| Attorney's Docket No | 02521 000213 PC |

I. Certification Under 37 CFR 1 10 (if applicable)

| | |
|---|---|
| Express Mail mailing number | Date of Deposit |

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1 10 on the date indicated above and is addressed to Commissioner for Patents, Washington, D C 20231

| | |
|---|---|
| Signature of person mailing correspondence | Typed or printed name of person mailing correspondence |

II ☐ New International Application

| TITLE | | Earliest priority date (Day/Month/Year) |
|---|---|---|
| | | |

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied (Note: check as many boxes as apply)

A ☐ The invention disclosed was not made in the United States

B ☐ There is no prior U S application relating to this invention.

C ☐ The following prior U S application(s) contain subject matter which is related to the invention disclosed in the attached international application *(Note: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority)*

| | | | |
|---|---|---|---|
| Application No | | filed on | |
| Application No | | filed on | |

D ☐ The present international application ☐ is identical to ☐ contains less subject matter than that found in the prior U.S application(s) identified in paragraph C above

E ☐ The present international application ☐ contains additional subject matter not found in the prior U S application(s) identified in paragraph C, above. The additional subject matter is found on pages [ ] and ☐ DOES NOT ALTER ☐ MIGHT BE CONSIDERED TO ALTER the general nature of the invention in a manner which would require the U S application to have been made available for inspection by the appropriate defense agencies under 35 U.S C. 181 and 37 CFR 5 1. See 37 CFR 5 15

III. ☐ A Response to An Invitation from the RO/US. The following document(s) is/are enclosed

A ☐ A Request for An Extension of Time to File a Response.

B ☐ A Power of Attorney (General or Regular)

C ☐ Replacement pages

| | | | | | |
|---|---|---|---|---|---|
| pages | | of the request (PCT/RO/101) | pages | | of the figures |
| pages | | of the description | pages | | of the abstract |
| pages | | of the claims | | | |

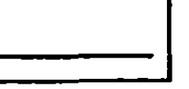
D ☐ Submission of Priority Documents

| | | | |
|---|---|---|---|
| Priority document | | Priority document | |

E ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex.

IV. ☐ A Request for Rectification Under PCT 91 ☐ A Petition ☐ Sequence Listing Diskette

V. ☒ Other (please specify) Submission of Request Substitute Sheet

| | | |
|---|---|---|
| The person signing this form is the | ☐ Applicant | Raymond R Mandra<br>Typed name of signer |
| | ☒ Attorney/Agent (Reg. No ) 34,382 |  <br>Signature |
| | ☐ Common Representative | |

U.S. Department of Commerce Patent and Trademark Office

Form 8118

02521.000213 PC
Aft 19 Amends 11/13/02
Wth 10/31/02

289

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

# PCT

## INVITATION TO CORRECT PRIORITY CLAIM

(PCT Rules 4.10, 26*bis*.1, 26*bis*.2(a) and (b))

To:

MANDRA, Raymond, R.
Fitzpatrick, Cella, Harper & Scinto
30 Rockefeller Plaza
New York, NY 10112-3801
ETATS-UNIS D'AMERIQUE

| | |
|---|---|
| Date of mailing (*day/month/year*) 22 October 2002 (22.10.02) | |
| Applicant's or agent's file reference 02521.000213 PC | REPLY DUE See item 1 |
| International application No. PCT/US02/18548 | International filing date (*day/month/year*) 11 June 2002 (11.06.02) |
| Applicant AGOURON PHARMACEUTICALS, INC. | |

The applicant is hereby invited, within the time limit indicated below, to correct, by a notice submitted to the International Bureau, defects in the priority claim(s), as indicated in the Annex.

1 Time limit to respond to this invitation (Rule 26*bis*.1(a)):

– within 16 months from the (earliest) priority date; or

– if the (earliest) priority date is changed as a result of the correction or addition of the (earliest) priority claim, within 16 months from that (earliest) priority date so changed,

whichever expires first, provided that such a notice may, in any event, be submitted until the expiration of four months from the international filing date.

Failure to respond to this invitation within the prescribed time limit may result in the priority claim concerned to be considered, for the purposes of the procedure under the PCT, not to have been made (Rule 26*bis*.2(b)).

2. In the case where multiple priorities have been claimed, this invitation relates to the following priority claim(s):

| | | |
|---|---|---|
| US | 11 June 2001 (11.06.01) | 60/297,460 |

3 A copy of this invitation is being sent to the receiving Office.

| | |
|---|---|
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland | Authorized officer<br>Miguel CORBEIRA |
| Facsimile No. (41-22) 740.14.35 | Telephone No. (41-22) 338.83.38 direct x 9201 |

Form PCT/IB/316 (January 2000)

ANNEX TO FORM PCT/IB/316

International application No.
PCT/US02/18548 290

The International Bureau has found the following defects in the priority claim(s):

1 Failure to Comply with the Requirements of Rule 4.10

a. ☐ National application

- ☐ Missing indication of the filing date of the earlier application.
- ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
- ☐ Missing indication of the number of the earlier application.*
- ☐ Missing indication of the country party to the Paris Convention for the Protection of Industrial Property, or of the Member of the World Trade Organization that is not party to that Convention, in which the earlier national application was filed.
- ☐ The country indicated is neither a party to the Paris Convention for the Protection of Industrial Property nor a Member of the World Trade Organization

b. ☐ Regional application

- ☐ Missing indication of the filing date of the earlier application.
- ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
- ☐ Missing indication of the number of the earlier application.*
- ☐ Missing indication of the authority entrusted with the granting of regional patents under the applicable regional patent treaty
- ☐ The authority indicated as the authority entrusted with the granting of regional patents does not grant regional patents.
- ☐ The priority claim in relation to the ARIPO application does not indicate either at least one country party to the Paris Convention for the Protection of Industrial Property, or at least one Member of the World Trade Organization, for which the earlier application was filed.

c. ☐ International application

- ☐ Missing indication of the filing date of the earlier application.
- ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
- ☐ Missing indication of the number of the earlier application.*
- ☐ Missing indication of the receiving Office with which it was filed.

2. Inconsistency with the Corresponding Indications in the Priority Document*

a. ☒ Inconsistency with regard to the filing date of the earlier application.
The request indicates: 11 June 2001
The priority document indicates: 12 June 2001

b. ☐ Inconsistency with regard to the number of the earlier application.
The request indicates:
The priority document indicates:

c. ☐ Inconsistency with regard to the country party to the Paris Convention for the Protection of Industrial Property or the Member of the World Trade Organization in which the national application was filed.
The request indicates:
The priority document indicates:

d. ☐ Inconsistency with regard to the authority entrusted with the granting of regional patents under the applicable regional patent treaty:
The request indicates:
The priority document indicates:

e. ☐ Inconsistency with regard to the receiving Office with which the international application was filed.
The request indicates:
The priority document indicates:

* Even if this defect is not corrected in response to this invitation, the priority claim concerned will not be considered not to have been made (Rule 26*bis*.2(b)).

02521 0213 PCT
DFG
DMND CH II 1/11/03
WMS 12/31/02

# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

# PCT

## NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47 1(c), first sentence)

To

RECEIVED
2002 DEC 31 A 10:23

MANDRA, Raymond, B.
Fitzpatrick, Cella, Harper & Scinto
30 Rockefeller Plaza
New York, NY 10112
ETATS-UNIS D'AMERIQUE

| | |
|---|---|
| Date of mailing (day/month/year)<br>19 December 2002 (19 12 02) | |
| Applicant s or agent s file reference<br>02521 000213 PC | IMPORTANT NOTICE |

| International application No | International filing date (day/month/year) | Priority date (day/month/year) |
|---|---|---|
| PCT/US02/018548 | 11 June 2002 (11 06 02) | 11 June 2001 (11 06 01) |

Applicant
AGOURON PHARMACEUTICALS, INC

1 Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice

KP, KR

In accordance with Rule 47 1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s)

2 The following designated Offices have waived the requirement for such a communication at this time

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49 1(a-*bis*))

3 Enclosed with this notice is a copy of the international application as published by the International Bureau on 19 December 2002 (19 12 02) under No. WO 02/100845.

4. **TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase**

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant s Guide*, Volume II, National Chapters, all available from WIPO s Internet site, at http://www wipo.int/pct/en/index html

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's sole responsibility to monitor all these time limits.

| | |
|---|---|
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland | Authorized officer<br>Judith Zahra |
| Facsimile No.(41-22) 740 14.35 | Telephone No.(41-22) 338 91 11 |

Form PCT/IB/308 (April 2002)

521.0213PCT
Res Written Opinion 3/30/03
DFG 3/3/03
WMG 3/3/03

292

# PATENT COOPERATION TREATY

## PCT

## NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis 1 and 26bis 2 and Administrative Instructions, Sections 402 and 409)

From the INTERNATIONAL BUREAU

To

RECEIVED
2003 MAR -3 A 11:34

MANDRA, Raymond, R
Fitzpatrick, Cella, Harper & Scinto
FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, NY 10112-3801
United States of America

| | |
|---|---|
| Date of mailing (day/month/year)<br>11 February 2003 (11 02 03) | |
| Applicant's or agent's file reference<br>02521 000213 PC | IMPORTANT NOTIFICATION |
| International application No.<br>PCT/US02/18548 | International filing date (day/month/year)<br>11 June 2002 (11 06 02) |
| Applicant<br>AGOURON PHARMACEUTICALS, INC | |

The applicant is hereby notified of the following in respect of the priority claim(s) made in the international application

1 [X] **Correction of priority claim.** In accordance with the applicant's notice received on 18 September 2002 (18 09 02), the following priority claim has been corrected to read as follows

US 12 June 2001 (12 06 01) 60/297,729

- [ ] even though the indication of the number of the earlier application is missing.
- [ ] even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document

2 [ ] **Addition of priority claim.** In accordance with the applicant's notice received on , the following priority claim has been added

- [ ] even though the indication of the number of the earlier application is missing
- [ ] even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document

3. [ ] As a result of the correction and/or addition of (a) priority claim(s) under items 1 and/or 2, the (earliest) priority date is

4. [ ] **Priority claim considered not to have been made.**
   - [ ] The applicant failed to respond to the invitation under Rule 26bis 2(a) (Form PCT/IB/316) within the prescribed time limit.
   - [ ] The applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a)
   - [ ] The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.

   The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis 2(c) and the PCT Applicant's Guide, Volume I, Annex B2(IB).

5. [ ] In case where multiple priorities have been claimed, the above item(s) relate to the following priority claim(s)

6 A copy of this notification has been sent to the receiving Office and
- [ ] to the International Searching Authority (where the international search report has not yet been issued).
- [X] the designated Offices (which have already been notified of the receipt of the record copy)

| | |
|---|---|
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland | Authorized officer<br>Sean TAYLOR (Fax 338 9090) |
| Facsimile No. (41-22) 740.14.35 | Telephone No. (41-22) 338 9811 |

29383649

# State of California

## SECRETARY OF STATE

## *APOSTILLE*

*(Convention de La Haye du 5 octobre 1961)*

1 *Country United States of America*
*This public document*

2 *has been signed by BILL JONES*

3 *acting in the capacity of SECRETARY OF STATE*

4 *bears the seal/stamp of the*
*State of California*

## *CERTIFIED*

5 *At SAN DIEGO, California* 6 *The 12TH day of APRIL, 2001*

7 *by Deputy Secretary of State, State of California*

8 *No 47332*

9 *Stamp/Seal*

10 *Signature*

Notaría Cuarenta en esta ciudad
cotejo la presente fotocopia
que concuerda con el original
que se ha tenido a la vista.
Fecha DIC. 1 2003
NOTARIA CUARENTA
Abogado Carlos Zuleta
Bogotá, D.C. - Colombia

BILL JONES
Secretary of State

BY Marsh C. Collins

NP-24 A (Rev 1-98)

294

# State of California

## SECRETARY OF STATE

I, BILL JONES, Secretary of State of the State of California, hereby certify:

That GREGORY J. SMITH, whose name appears on the annexed certificate, was on FEBRUARY 7TH, 2001, the duly elected, qualified and acting ASSESSOR/RECORDER/CLERK of the County of SAN DIEGO, in said State.

That the seal affixed thereto is the seal of said County; that the signature thereon appears to be the signature of GREGORY J. SMITH and that the annexed certificate is in due form and by proper officer.

IN WITNESS WHEREOF, I execute this certificate and affix the Great Seal of the State of California this 7TH day of FEBRUARY 2001

Notario Cubano de este distrito
Notario Cubano de este distrito
DIC. 1 2003
NOTARIO CUARENTA

BILL JONES
Secretary of State

Deputy

NP-24 A (Rev 1-96)

OSP 96 21838

# Gregory J. Smith

## COUNTY OF SAN DIEGO

## ASSESSOR / RECORDER / COUNTY CLERK

**Assessor's Office**
1600 Pacific Highway, Room 103
San Diego, CA 92101-2480
Tel. (619) 236-3771 • Fax (619) 557-4056

www.sdarcc.com

**Recorder/County Clerk's Office**
1600 Pacific Highway, Room 260
P.O. Box 121750 • San Diego, CA 92112-1750
Tel (619) 237-0502 • Fax (619) 557-4155

I, GREGORY J SMITH, Assessor/Recorder/County Clerk of the County of San Diego, State of California, having by law a Seal, DO HEREBY CERTIFY that

BONNIE ACOSTA whose name is subscribed to the oath or Certificate of Proof or Acknowledgement of the annexed instrument and thereon written, was at the time of taking such oath, or Proof or Acknowledgement, a Notary Public, in and for said County, duly commissioned and sworn and duly authorized by the laws of said State to take the same and administer oaths and to take the Acknowledgements and Proofs of Deeds and other instruments in writing to be recorded in this State I am acquainted with the handwriting of such Notary Public and believe that the signature to said oath or Certificate of Proof Acknowledgement is genuine I further certify that under the laws of the State of California the said oath or Certificate of Proof or Acknowledgement is required to be under seal, but the impression of said seal is not required by the laws of the State of California to be filed in my office or in any other place.

DATED: February 7, 2001 Witness by hand

GREGORY J SMITH, County Assessor/Recorder/

En la Notaría Cuarenta de este Círculo se cotejó la presente fotocopia que coincide con el original que se ha tenido a la vista
Fecha DIC 1 2003
NOTARIO CUARENTA
Agueda Castillo Zarate
Bogotá, D.C., Colombia

*Branch Offices Available To Serve You*

**Chula Vista**
"F" Street, Suite 200
Vista, CA 91910-2646
(619) 498-2200

**El Cajon**
198 West Main Street, Suite 101
El Cajon, CA 92020-3316
(619) 401-5700

**Kearny Mesa**
5473 Kearny Villa Road, 3rd Floor
San Diego, CA 92123-1142
(858) 505-6262

**San Marcos**
334 Via Vera Cruz, Suite 150
San Marcos, CA 92069-2638
(760) 510-6500

2521 0194 Colombia

296

# Brigard & Castro

SANTA FE DE BOGOTA - COLOMBIA

## PODER

(nosotros)

domiciliado(s) en

Nombro(amos) a **RAMIRO CASTRO DUQUE** y/o **HECTOR GOMEZ MEJIA**, de Santafé de Bogotá, Colombia apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía en cualquier instancia o recurso la obtención de patentes de invención registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio, elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como oposiciones al registro de marcas, acciones de caducidad, cancelación y nulidad, acciones reivindicatorias acciones derivadas de la obtención o explotación de licencias, acciones de competencia desleal, demandas penales, acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares

A este efecto lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos, pagar impuestos, cuotas y gravámenes prescritos por la ley, renunciar o desistir a derechos concedidos o en curso de concesión recibir toda clase de documentos y valores, dando el descargo respectivo, y en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer y la de sustituirlo en todo o en parte y revocar sustituciones Asimismo nombro(amos) a **RAMIRO CASTRO DUQUE** y/o **HECTOR GOMEZ MEJIA**, domiciliado(s) en la Carrera 7 No 16-56, Piso 2, mis (nuestros) apoderados en Colombia para recibir notificaciones y designar apoderados judiciales o extrajudiciales

Otorgado y firmado en

hoy de de

Firma

Nombre

Cargo

## POWER OF ATTORNEY

I (We) Agouron Pharmaceuticals, Inc.

domiciled in

10350 North Torrey Pines Road, La Jolla, California 92037, USA

Hereby appoint **RAMIRO CASTRO DUQUE** and/or **HECTOR GOMEZ MEJIA** of Santafé de Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models, registration of commercial names and emblems, registration of copyright and contracts related thereto certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above, to prepare, prosecute and register licenses of any kind, to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions such as oppositions to the registration of trademarks, caducity, cancellation and nullity actions, claim actions derived from the obtaining or exploitation of licenses action of unfair competition penal demands actions of indemnities for damages claims or observations on patent applications, models, industrial designs and utility models, in the exercise of preventive measures and in other actions or similar proceedings

To that effect they hereby empowered to file applications, formulate descriptions, amendments protests declarations oppositions, cancellations, nullities, appeals and claims, to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting to receive all kinds of documents and valuables, giving the respective release of receipt and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers

This power includes the faculty to ratify or confirm desist settle and compromise on my (our) behalf and to substitute this power in whole or in part and to revoke substitutions At the same time I (We) hereby appoint **RAMIRO CASTRO DUQUE** and/or **HECTOR GOMEZ MEJIA** domiciled in Carrera 7 No 16-56, Piso 2, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys

Notaría Cuarenta de este círculo certifica que el presente fósforo es copia fiel tomada de original que se ha tenido a la vista.
Fecha DIC. 1 2003
NOTARIA CUARENTA
Agustín Castillo Zimic
Santafé de Bogotá, D.C., Colombia

Signed and signed in La Jolla, California

this 23rd day ____ of January 2001

Signature

Name Gary E Friedman

Title Senior Vice-President

2521 0194 Colombia

297

## CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento debidamente juramentado declaró y dijo que él es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado, que el declarante está autorizado por dicha compañía para conferir este poder, que el sello estampado por el al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad

Estado de
con fecha

y que quien confiere el presente poder es su representante

Notario Público (sello)

## NOTARIAL CERTIFICATE (CORPORATION)

On this 23rd day of January of 2001
personally appeared before me Gary E. Fnedman

to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the

Senior Vice-President

of

Agouron Pharmaceuticals, Inc.

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof and that the purpose for which this instrument is granted is included within the corporate purpose of company

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company

State of California
under date of 23 January 2001

and that he (she) who grants the present power of attorney is its Representative

BONNIE ACOSTA
Comm. # 1263927
NOTARY PUBLIC-CALIFORNIA
San Diego County
My Comm. Expires Dec. 6, 2004

Public Notary (Seal)

## CERTIFICADO NOTARIAL PERSONA NATURAL

Hoy de de , compareció(eron)
ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan

En la Notaría Cuarenta de este círculo se obtuvo la presente fotocopia que coincide con el original que se ha tenido a la vista
Fecha DIC. 1 2003 2
NOTARIA CUARENTA
Agustín Castillo Zárate
Santafé de Bogotá, D.C. Colombia

Notario Público (sello)

## NOTARIAL CERTIFICATE NATURAL PERSON

On this day of of
personally appeared before me
Gary E Fnedman

who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed

Notary Public (Seal)

LEGALIZACION ANTE CONSUL COLOMBIANO ES REQUERIDA

LEGALIZATION BEFORE COLOMBIAN CONSUL IS REQUIRED

299

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03108298 00000000 Folios: 298
Fecha (AMD): 2003-12-10 17:01:16
Tramite : 911 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

298

# REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

| | USUARIO | RADICADOR |
|---|---|---|
| PATENTE DE INVENCIÓN ✓ MODELO DE UTILIDAD | ( ) | ( ) |
| - Indicacion de que se solicita la concesion de una patente | | ( ) |
| - Datos de identificacion del solicitante o de la persona que se presenta la solicitud | | ( ) |
| - Descripcion de la invención | | ( ) |
| Dibujos de ser estos pertinentes | | ( ) |
| Comprobante de Pago de las tasas establecidas | | |
| COMPLETA ( ) INCOMPLETA | ( ) | ( ) |
| DISEÑO INDUSTRIAL ( ) | | |
| - Indicacion de que se solicita el registro de Diseño Industrial | ( ) | ( ) |
| - Datos de identificación del solicitante o de la persona que presenta | ( ) | ( ) |
| - la solicitud | | |
| - Representacion grafica y fotografica del Diseño Industrial o muestra del Material que incorpora el diseño | ( ) | ( ) |
| Comprobante de pago de las tasas establecidas | ( ) | ( ) |
| COMPLETA ( ) INCOMPLETA | ( ) | ( ) |
| ESQUEMA DE TRAZADO ( ) | | |
| - Indicacion de que solicita el registro de un Esquema de trazado | ( ) | ( ) |
| - Datos de identificación del solicitante o de la persona que presenta La solicitud | ( ) | ( ) |
| Representacion grafica del esquema de trazado | ( ) | ( ) |
| Comprobante de pago de las tasas establecidas | ( ) | ( ) |
| COMPLETA ( ) INCOMPLETA | ( ) | ( ) |

Firma Responsable ANDREA ROSE

Fecha

380

299

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

01302

**Doctor:** **Oficio N°**
Ramiro Castro Duque
Apoderado
Agouron Pharmaceutcals Inc

| | | |
|---|---|---|
| **ASUNTO:** | Radicación N° | 03 108298 |
| | Solicitud internacional | PCT/US2002/18548 |
| | Fecha inicio fase nacional | 11/01/2004 |
| | Trámite | 011 |
| | Evento | 379 |
| | Actuación | 430 |
| | Folios | 001 |

Como resultado del examen de forma, realizado con fundamento el 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:

☐ La solicitud no contiene la copia del documento en que consta la cesón del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

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 N° 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 06 FEB. 2004

202065