OlarteRaisbeck

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Trámite: 340 PATENTE CIVIL Cve: 378 FASE NACIONAL
Actividad: 440 PRESENTACION Folios: 242

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

P2007/000200

SOLICITUD DE:

(1)

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: SCHERING CORPORATION

Dirección: 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 E.U.A.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: Kenilworth E.U.A.

Teléfono: _____ Fax: _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número _____

(3) **REPRESENTANTE O APODERADO**

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Dirección: World Trade Center Torre A, Calle 100 Nº. 8A-37 Piso 10
Teléfono: 601-7700 Fax: 601-7799
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IDENTIFICACIÓN
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número 79.782.747 Btá
TP 74.295

(4) **INVENTOR (ES) (72)**

Nombre: VER PAGINA ADJUNTA

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2006/022918 Fecha Junio 12, 2006

Publicación Internacional No. WO 2006/138264 Fecha Diciembre 28, 2006

(6) **Título (54)** INHIBIDORES DE ASPARTIL PROTEASAS

(7) **Clasificación Internacional (51):** C07D 487/04, A61K 31/519, A61P 25/28

(8) **Prioridad** SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Junio 14, 2005	60/690.537

(9) *Comprobante de pago No.* **07-98.630** **Fecha:** Diciembre 4 de 2007

(10) ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. **Ver Expediente 06-029.040. Adjunto Copia Simple**
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud Internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar Internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) FIGURA CARACTERÍSTICA:

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Bta T.P. 74.295

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Estados Unidos de América
Nacionalidad: India

5

Y COMERCIO

CIONES
NACIONAL

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 98,639
: DICIEMBRE 4 DE 2007

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
OLARTE RAISBER	CONSIGNACION	BANCO POPULAR	050-00110-6	4022B6500	03/12/2007	6,123,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50009-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	492,000.00
		TOTAL : $	492,000.00

SON: CUATROCIENTOS NOVENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

6

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SCHERING CORPORATION

APOSTILLA

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

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

CERTIFICADO

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

PODER DE REPRESENTACIÓN

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

CERTIFICADO NOTARIAL

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

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

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

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

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

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

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

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

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

CERTIFIED

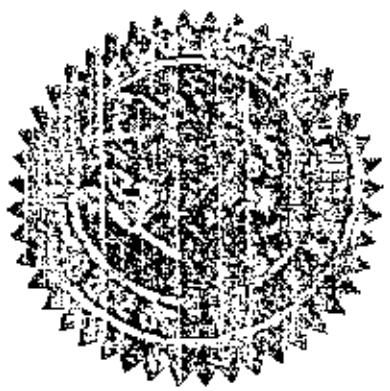
5. AT TRENTON, NEW JERSEY

6. THE 29TH DAY OF AUGUST 2003

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

8. NO. A180345

9. SEAL/STAMP:



10. SIGNATURE

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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Power of Attorney

The undersigned,
SCHERING CORPORATION

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

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

Poder

El suscrito,

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

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

Signature/Firma: _____

Edward B. Mazey, Senior Legal Director

Date/Fecha: August 7, 2003

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

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
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Notarial Certification

On this date, August 7, 2003

The undersigned Notary Public certifies:

1. That Edward H. Mazer

of legal age and domiciled in 119 Greenwood Drive, Millburn, New Jersey 07041, U.S.A. signed the foregoing document.

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

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

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

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

Power of Attorney, dated November 4, 2002.

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

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

de

4. Que

con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

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

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

PUBLIC (Signature):

Marguerite La Corte

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

VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application SCHERING CORPORATION is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from ZHU, Zhaoning to SCHERING CORPORATION, dated 09 June 2006 (09.06.2006)
VIII-2-1(iv)		an assignment from MCKITTRICK, Brian to SCHERING CORPORATION, dated 09 June 2006 (09.06.2006)
VIII-2-1(iv)		an assignment from STAMFORD, Andrew to SCHERING CORPORATION, dated 09 June 2006 (09.06.2006)
VIII-2-1(iv)		an assignment from GREENLEE, William, J. to SCHERING CORPORATION, dated 09 June 2006 (09.06.2006)
VIII-2-1(iv)		an assignment from LIU, Xiaoxiang to SCHERING CORPORATION, dated 09 June 2006 (09.06.2006)
VIII-2-1(iv)		an assignment from MANDAL, Mihirbaran to SCHERING CORPORATION, dated 09 June 2006 (09.06.2006)
VIII-2-1(iv)		an assignment from VOIGT, Johannes, H. to SCHERING CORPORATION, dated 09 June 2006 (09.06.2006)
VIII-2-1(iv)		an assignment from VOIGT, Johannes, H. to SCHERING CORPORATION, dated 09 June 2006 (09.06.2006)

VIII-3-1	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(ii) and 51bis.1(a)(ii)) Name	in relation to this international application SCHERING CORPORATION is entitled to claim priority of earlier application No. 60/690,537 by virtue of the following:
VIII-3-1(v)		an assignment from ZHU, Zhaoning to SCHERING CORPORATION, dated 06 February 2006 (06.02.2006)
VIII-3-1(v)		an assignment from MCKITTRICK, Brian to SCHERING CORPORATION, dated 06 February 2006 (06.02.2006)
VIII-3-1(v)		an assignment from STAMFORD, Andrew to SCHERING CORPORATION, dated 06 February 2006 (06.02.2006)
VIII-3-1(v)		an assignment from GREENLEE, William, J. to SCHERING CORPORATION, dated 06 February 2006 (06.02.2006)

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

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
28 December 2006 (28.12.2006)

(10) International Publication Number
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C07D 487/04 (2006.01) *A61P 25/28* (2006.01)
A61K 31/519 (2006.01)

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PCT/US2006/022918

(22) International Filing Date: 12 June 2006 (12.06.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/690,537 14 June 2005 (14.06.2005) US

(71) Applicant *(for all designated States except US)*: **SCHERING CORPORATION** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ZHU, Zhaoning** [US/US]; 6 Cypress Court, Plainsboro, New Jersey 08536 (US). **MCKITTRICK, Brian** [US/US]; 14 Millbrook Road, New Vernon, New Jersey 07976 (US). **STAMFORD, Andrew** [AU/US]; 27 Overlook Road, Chatham Township, New Jersey 07928 (US). **GREENLEE, William, J.** [US/US]; 115 Herrick Avenue, Teaneck, New Jersey 07666 (US). **LIU, Xiaoxiang** [CN/US]; 551 Cleveland Avenue, Rivervale, New Jersey 07675 (US). **MANDAL, Mihirbaran** [IN/US]; 181 Spruce Mill Lane, Scotch Plains, New Jersey 07076 (US). **VOIGT, Johannes, H.** [DE/US]; 10 Willow Street, Cranford, New Jersey 07016 (US). **STRICKLAND, Corey** [US/US]; 825 Newmans Lane, Martinsville, New Jersey 08836 (US).

(74) Agent: **LEE, William, Y.**; SCHERING-PLOUGH CORPORATION, Patent Department, K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 (US).

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

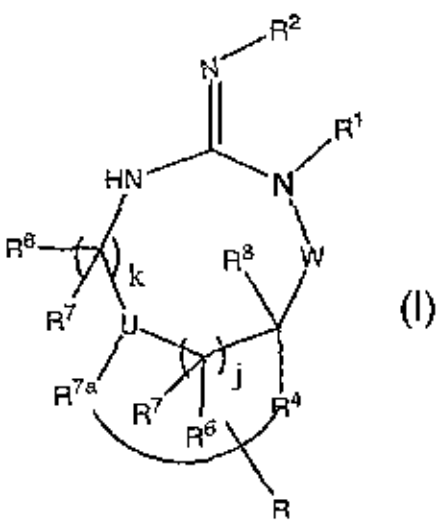
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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

(54) Title: ASPARTYL PROTEASE INHIBITORS



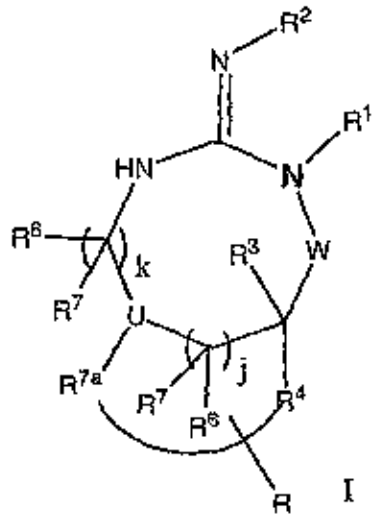
(I)

(57) Abstract: Disclosed are compounds of the formula (I) or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, wherein j, k, U, W, R, R^1, R^2, R^3, R^4, R^6, R^7 and R^{7a} are as described above in the specification. Also disclosed is the method of inhibiting aspartyl protease, and in particular, the methods of treating cardiovascular diseases, cognitive and neurodegenerative diseases. Also disclosed are methods of treating cognitive or neurodegenerative diseases using the compounds of formula (I) in combination with a cholinesterase inhibitor or a muscarinic m1 agonist or m_2 antagonist.

WO 2006/138264 A2

ABSTRACT

Disclosed are compounds of the formula I



I

or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, wherein j, k, U, W, R, R^1, R^2, R^3, R^4, R^6, R^7 and R^{7a} are as described above in the specification.

Also disclosed is the method of inhibiting aspartyl protease, and in particular, the methods of treating cardiovascular diseases, cognitive and neurodegenerative diseases. Also disclosed are methods of treating cognitive or neurodegenerative diseases using the compounds of formula I in combination with a cholinesterase inhibitor or a muscarinic m_1 agonist or m_2 antagonist.

ASPARTYL PROTEASE INHIBITORS

FIELD OF THE INVENTION

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

BACKGROUND

There are a number of aspartic proteases known to date, including pepsin A and C, renin, BACE, BACE 2, Napsin A, and cathepsin D, which have been implicated in pathological conditions. The role of renin-angiotensin system (RAS) in regulation of blood pressure and fluid electrolyte has been well established (Oparil, S, etal. N Engl J Med 1974; 291:381-401/446-57). The octapeptide Angiotensin-II, a potent vasoconstrictor and stimulator for release of adrenal aldosterone, was processed from the precursor decapeptide Angiotensin-I, which in turn is processed from angiotensinogen by the renin enzyme. Angiotensin-II is also found to play roles in vascular smooth muscle cell growth, inflammation, reactive oxygen species generation and thrombosis and influence atherogenesis and vascular damage. Clinically, the benefit of interruption of the generation of angiotensin-II through antagonism of conversion of angiotensin-I has been well known and there are a number of ACE inhibitor drugs on the market. The blockade of the earlier conversion of angiotensinogen to angiotensin-I, i.e.the inhibition of renin enzyme, is expected to have similar but not identical effects. Since renin is an aspartyl protease whose only natural substrate is angiotensinogen, it is believed that there would be less frequent adverse effect for controlling high blood pressure and related symptoms regulated by angiotensin-II through its inhibition.

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

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

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

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

Accumulated biochemical and genetic evidence supports a central role of Aβ in the etiology of AD. For example, Aβ has been shown to be toxic to neuronal cells in vitro and when injected into rodent brains. Furthermore inherited forms of early-onset

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AD are known in which well-defined mutations of APP or the presenilins are present. These mutations enhance the production of Aβ and are considered causative of AD.

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

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

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

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

Compounds that act as aspartyl protease inhibitors are described, for example in application USSN 11/010,772, filed on December 13, 2004, herein incorporated by reference.

WO/9304047, herein incorporated by reference, describes compounds having a quinazolin-2-(thi)one nucleus. The document alleges that the compounds described therein are inhibitors of HIV reverse transcriptase.

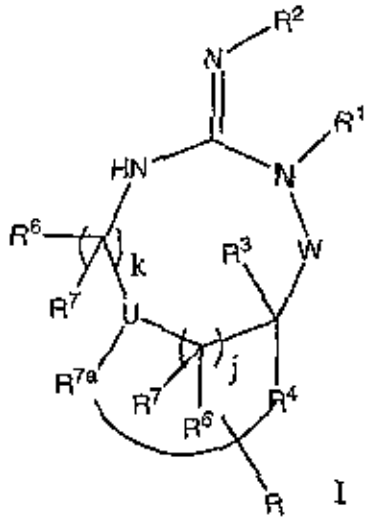
US Publication No. US 2005/0282826 A1, herein incorporated by reference, describes diphenylimidazopyrimidine or –imidazole amines, which are said to be useful for the therapeutic treatment, prevention or amelioration of a disease or disorder characterized by elevated β-amyloid deposits or β-amyloid levels in a patient. Disease states mentioned in the publication include Alzheimer's disease, mild cognative impairment, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, cerebral amyloid angiopathy and degenerative dementia.

US Publication No. US 2005/0282825 A1, herein incorporated by reference, describes amino-5,5-diphenylimidazolones, which are said to be useful for the therapeutic treatment, prevention or amelioration of a disease or disorder characterized by elevated β-amyloid deposits or β-amyloid levels in a patient. Disease states mentioned in the publication include Alzheimer's disease, mild cognative impairment, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, cerebral amyloid angiopathy and degenerative dementia.

Other publications that disclosed compounds that are useful for treating Alzherimer's disease include WO 2006/044492, which discloses spiropiperidine compounds that are said to be inhibitors of β-secretase, and WO 2006/041404, which discloses substituted amino compounds that are said to be useful for the treatment or prophylaxix of Aβ related pathologies. Both these publications are incorporated by reference.

SUMMARY OF THE INVENTION

The present invention relates to compounds having the structural formula I



I

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

j is 0 or 1;

k is 0 or 1, provided that when k is 1, U cannot be -N-;

W is a bond, -C(=S)-, –S(O)-, -$S(O)_2$-, -C(=O)-, -O-, -$C(R^6)(R^7)$-, -$N(R^5)$-, -$C(R^6)(R^7)C(=O)$-, or -$C(=N(R^5))$-;

U is –N- or -$C(R^6)$-;

R is 1 to 5 R^{21} groups;

R^1, R^2 and R^5 are independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, –OR^{16}, -CN, -$C(=NR^{11})R^8$, -$C(O)R^8$, -$C(O)OR^9$, -$S(O)R^{10}$, -$S(O)_2R^{10}$, -$C(O)N(R^{11})(R^{12})$, -$S(O)N(R^{11})(R^{12})$, -$S(O)_2N(R^{11})(R^{12})$, -NO_2, -$N=C(R^8)_2$ and –$N(R^{11})(R^{12})$, provided that R^1 and R^5 are not both selected from -NO_2, -$N=C(R^8)_2$ and –$N(R^{11})(R^{12})$;

R^3, R^6 and R^7 are independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl,

cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, aryiheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, halo, $-CH_2-O-Si(R^9)(R^{10})(R^{19})$, -SH, -CN, $-OR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^{11})(R^{12})$, $-SR^{19}$, $-S(O)N(R^{11})(R^{12})$, $-S(O)_2N(R^{11})(R^{12})$, $-N(R^{11})(R^{12})$, $-N(R^{11})C(O)R^8$, $-N(R^{11})S(O)R^{10}$, $-N(R^{11})S(O)_2R^{10}$, $-N(R^{11})C(O)N(R^{12})(R^{13})$, $-N(R^{11})C(O)OR^9$ and $-C(=NOH)R^8$;

R^4 and R^{7a} are independently selected from the group consisting of a bond, alkylene, arylalkylene, heteroarylalkylene, cycloalkylalkylene, heterocycloalkylalkylene, arylcycloalkylalkylene, heteroarylcycloalkylalkylene, arylheterocycloalkylalkylene, heteroarylheterocycloalkylalkylene, cycloalkylene, arylcycloalkylene, heteroarylcycloalkylene, heterocycloalkylene, aryiheterocycloalkylene, heteroarylheterocycloalkylene, alkenylene, arylalkenylene, cycloalkenylene, arylcycloalkenylene, heteroarylcycloalkenylene, heterocycloalkenylene, arylheterocycloalkenylene, heteroarylheterocycloalkenylene, alkynylene, arylalkynylene, arylene, cycloalkylarylene, heterocycloalkylarylene, cycloalkyenylarylene, cycloalkenylarylene, heterocycloalkenylarylene, heteroarylene, cycloalkylheteroarylene, heterocycloalkylheteroarylene, cycloalkenylheteroarylene and heterocycloalkenylheteroarylene, with the proviso that both R^4 and R^{7a} are not both a bond;

R^4 and R^{7a} together can be a C_1 to C_8 carbon chain, wherein, optionally, one, two or three ring carbons can be replaced by –O-, -C(O)-, -C(S)-, -S-, -S(O)-, $-S(O)_2-$ or $-N(R^5)-$, and R^4 and R^{7a} together with the carbon atoms to which they are attached, form a 3 to 8 membered ring, optionally substituted by R, with the following provisos:

that when at least one of the carbons is replaced by –O-, -C(O)-, -C(S)-, -S-, -S(O)- ,-$S(O)_2$-or $-N(R^5)-$, then the number of carbons in the R^4 and R^{7a} portion of the chain that bonds with U is b, wherein b is 0 to 5, and the number of carbons that are in the R^4 and R^{7a} portion of the chain that bonds with the carbon of $-C(R^3)-$ is c, wherein c is 0 to 5;

that when j is 0 or 1, at least one of the ring carbons must be replaced by -O-, -C(O)-, -C(S)-, -S-, -S(O)- ,–$S(O)_2$-or –$N(R^5)$-;

that when j is 0 or 1 and only one ring carbon is replaced with –O-, -C(O)-, -C(S)-, -S-, -S(O)- ,–$S(O)_2$-or –$N(R^5)$-, R^4 and R^{7a} cannot form a cycloalkylether;

R^8 is independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, -OR^{15}, -$N(R^{15})(R^{16})$, -$N(R^{15})C(O)R^{16}$, -$N(R^{15})S(O)R^{16}$, -$N(R^{15})S(O)_2R^{16}$, -$N(R^{15})S(O)_2N(R^{16})(R^{17})$, -$N(R^{15})S(O)N(R^{16})(R^{17})$, -$N(R^{15})C(O)N(R^{16})(R^{17})$ and -$N(R^{15})C(O)OR^{16}$;

R^9 is independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, and heterocycloalkenylheteroaryl;

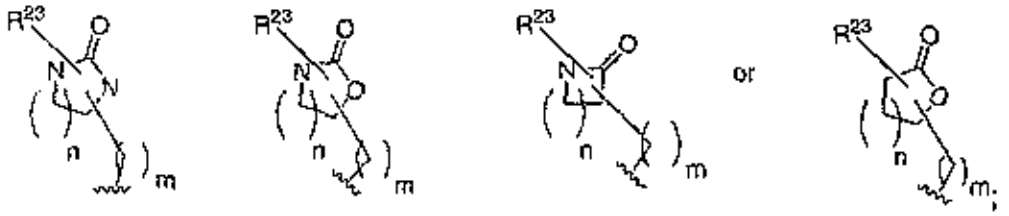
R^{10} is independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl,

cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl and $-N(R^{15})(R^{16})$;

R^{11}, R^{12} and R^{13} are independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, $-C(O)R^{8}$, $-C(O)OR^{9}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-C(O)N(R^{15})(R^{16})$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$ and $-CN$;

R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, R^{18}-alkyl, R^{18}-arylalkyl, R^{18}-heteroarylalkyl, R^{18}-cycloalkylalkyl, R^{18}-heterocycloalkylalkyl, R^{18}-arylcycloalkylalkyl, R^{18}-heteroarylcycloalkylalkyl, R^{18}-arylheterocycloalkylalkyl, R^{18}-heteroarylheterocycloalkylalkyl, R^{18}-cycloalkyl, R^{18}-arylcycloalkyl, R^{18}-heteroarylcycloalkyl, R^{18}-heterocycloalkyl, R^{18}-arylheterocycloalkyl, R^{18}-heteroarylheterocycloalkyl, R^{18}-alkenyl, R^{18}-arylalkenyl, R^{18}-cycloalkenyl, R^{18}-arylcycloalkenyl, R^{18}-heteroarylcycloalkenyl, R^{18}-heterocycloalkenyl, R^{18}-arylheterocycloalkenyl, R^{18}-heteroarylheterocycloalkenyl, R^{18}-alkynyl, R^{18}-arylalkynyl, R^{18}-aryl, R^{18}-cycloalkylaryl, R^{18}-heterocycloalkylaryl, R^{18}-cycloalkenylaryl, R^{18}-heterocycloalkenylaryl, R^{18}-heteroaryl, R^{18}-cycloalkylheteroaryl, R^{18}-heterocycloalkylheteroaryl, R^{18}-cycloalkenylheteroaryl, and R^{18}-heterocycloalkenylheteroaryl; or

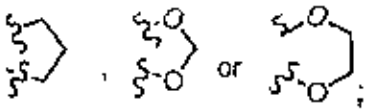
R^{15}, R^{16} and R^{17} are



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

R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, *arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl,* heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, *arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl,* arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, *heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl,* heterocycloalkenylheteroaryl, $-NO_2$, halo, HO-alkoxyalkyl, $-CF_3$, -CN, alkyl-CN, $-C(O)R^{19}$, -C(O)OH, $-C(O)OR^{19}$, $-C(O)NHR^{20}$, $-C(O)NH_2$, $-C(O)NH_2$-$C(O)N(alkyl)_2$, *$-C(O)N(alkyl)(aryl)$, $-C(O)N(alkyl)(heteroaryl)$,* $-SR^{19}$, *$-S(O)_2R^{20}$, $-S(O)NH_2$,* $-S(O)NH(alkyl)$, $-S(O)N(alkyl)(alkyl)$, $-S(O)NH(aryl)$, $-S(O)_2NH_2$, $-S(O)_2NHR^{19}$, $-S(O)_2NH(heterocycloalkyl)$, $-S(O)_2N(alkyl)_2$, $-S(O)_2N(alkyl)(aryl)$, $-OCF_3$, -OH, $-OR^{20}$, *-O-heterocycloalkyl, -O-cycloalkylalkyl, -O-heterocycloalkylalkyl,* $-NH_2$, *$-NHR^{20}$,* $-N(alkyl)_2$, $-N(arylalkyl)_2$, -N(arylalkyl)-(heteroarylalkyl), $-NHC(O)R^{20}$, $-NHC(O)NH_2$, $-NHC(O)NH(alkyl)$, $-NHC(O)N(alkyl)(alkyl)$, $-N(alkyl)C(O)NH(alkyl)$, *$-N(alkyl)C(O)N(alkyl)(alkyl)$,* *$-NHS(O)_2R^{20}$, $-NHS(O)_2NH(alkyl)$,* $-NHS(O)_2N(alkyl)(alkyl)$, $-N(alkyl)S(O)_2NH(alkyl)$ and $-N(alkyl)S(O)_2N(alkyl)(alkyl)$;

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



R^{19} is alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl,

arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl or heterocycloalkenylheteroaryl;

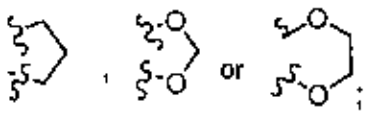
R^{20} is halo substituted aryl, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl or heterocycloalkenylheteroaryl,

and wherein each of the alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, in R, R^1, R^2, R^3, R^4, R^5, R^6, R^7; R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13}

are independently unsubstituted or substituted by 1 to 5 R^{21} groups independently selected from the group consisting of alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, halo, -CN, $-C(=NR^{11})R^{15}$, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-CH(R^{15})(R^{16})$,

$-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-R^{15}$; $-CH_2N(R^{15})(R^{16})$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-S(O)R^{15}$, $-N_3$, $-NO_2$ and $-S(O)_2R^{15}$;

and wherein each of the alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl and heterocycloalkenylheteroaryl groups in R^{21} are independently unsubstituted or substituted by 1 to 5 R^{22} groups independently selected from the group consisting of alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, halo, $-CF_3$, -CN, $-C(=NR^{11})R^{15}$, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, -alkyl-$C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-N_3$, $-NO_2$, $-S(O)R^{15}$ and $-S(O)_2R^{15}$;

or two R^{21} or two R^{22} moieties on adjacent carbons can be linked together to form  ;

and when R^{21} or R^{22} are selected from the group consisting of –C(=NOR^{15})R^{16}, -N(R^{15})C(O)R^{16}, -CH$_2$-N(R^{15})C(O)R^{16}, -N(R^{15})S(O)R^{16}, -N(R^{15})S(O)$_2$R^{16}, -CH$_2$-N(R^{15})S(O)$_2$R^{16}, -N(R^{15})S(O)$_2$N(R^{16})(R^{17}), -N(R^{15})S(O)N(R^{16})(R^{17}), -N(R^{15})C(O)N(R^{16})(R^{17}), -CH$_2$-N(R^{15})C(O)N(R^{16})(R^{17}), -N(R^{15})C(O)OR^{16} and -CH$_2$-N(R^{15})C(O)OR^{16}, R^{15} and R^{16} together can be a C_2 to C_4 chain *wherein, optionally, one, two or three ring carbons can be replaced by –C(O)-* or –N(H)- and R^{15} and R^{16}, together with the atoms to which they are attached, form a 5 to 7 membered ring, optionally substituted by R^{23};

R^{23} is 1 to 5 groups independently selected from the group consisting of alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, halo, -CN, -OR^{24}, -C(O)R^{24}, -C(O)OR^{24}, -C(O)N(R^{24})(R^{25}), -SR^{24}, -S(O)N(R^{24})(R^{25}), -S(O)$_2$N(R^{24})(R^{25}), –C(=NOR^{24})R^{25}, -P(O)(OR^{24})(OR^{25}), -N(R^{24})(R^{25}), -alkyl-N(R^{24})(R^{25}), -N(R^{24})C(O)R^{25}, -CH$_2$-N(R^{24})C(O)R^{25}, -N(R^{24})S(O)R^{25}, -N(R^{24})S(O)$_2$R^{25}, -CH$_2$-N(R^{24})S(O)$_2$R^{25}, -N(R^{24})S(O)$_2$N(R^{25})(R^{26}), -N(R^{24})S(O)N(R^{25})(R^{26}), -N(R^{24})C(O)N(R^{25})(R^{26}), -CH$_2$-N(R^{24})C(O)N(R^{25})(R^{26}), -N(R^{24})C(O)OR^{25}, -CH$_2$-N(R^{24})C(O)OR^{25}, -S(O)R^{24} and -S(O)$_2$R^{24}; and wherein each of the alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl,

heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl and heterocycloalkenylheteroaryl groups in R^{23} are independently unsubstituted or substituted by 1 to 5 R^{27} groups independently selected from the group consisting of alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, halo, $-CF_3$, -CN, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, alkyl-$C(O)OR^{24}$, $-C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, -alkyl-$N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$, $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$, $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$, $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ and $-S(O)_2R^{24}$;

R^{24}, R^{25} and R^{26} are independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, R^{27}-alkyl, R^{27}-arylalkyl, R^{27}-heteroarylalkyl, R^{27}-cycloalkylalkyl, R^{27}-heterocycloalkylalkyl, R^{27}-arylcycloalkylalkyl, R^{27}-heteroarylcycloalkylalkyl, R^{27}-arylheterocycloalkylalkyl, R^{27}-heteroarylheterocycloalkylalkyl, R^{27}-cycloalkyl, R^{27}-arylcycloalkyl, R^{27}-heteroarylcycloalkyl, R^{27}-heterocycloalkyl, R^{27}-arylheterocycloalkyl, R^{27}-heteroarylheterocycloalkyl, R^{27}-alkenyl, R^{27}-arylalkenyl, R^{27}-cycloalkenyl, R^{27}-arylcycloalkenyl, R^{27}-heteroarylcycloalkenyl, R^{27}-heterocycloalkenyl,

R^{27}-arylheterocycloalkenyl, R^{27}-heteroarylheterocycloalkenyl, R^{27}-alkynyl, R^{27}-arylalkynyl, R^{27}-aryl, R^{27}-cycloalkylaryl, R^{27}-heterocycloalkylaryl, R^{27}-cycloalkenylaryl, R^{27}-heterocycloalkenylaryl, R^{27}-heteroaryl, R^{27}-cycloalkylheteroaryl, R^{27}-heterocycloalkylheteroaryl, R^{27}-cycloalkenylheteroaryl and R^{27}-heterocycloalkenylheteroaryl;

R^{27} is 1-5 substituents independently selected from the group consisting of alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, $-NO_2$, halo, $-CF_3$, -CN, alkyl-CN, $-C(O)R^{28}$, -C(O)OH, $-C(O)OR^{28}$, $-C(O)NHR^{29}$, $-C(O)N(alkyl)_2$, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(heteroaryl), $-SR^{28}$, $-S(O)_2R^{29}$, $-S(O)NH_2$, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl), $-S(O)_2NH_2$, $-S(O)_2NHR^{28}$, $-S(O)_2NH(aryl)$, $-S(O)_2NH(heterocycloalkyl)$, $-S(O)_2N(alkyl)_2$, $-S(O)_2N(alkyl)(aryl)$, -OH, $-OR^{29}$, -O-heterocycloalkyl, -O-cycloalkylalkyl, -O-heterocycloalkylalkyl, $-NH_2$, $-NHR^{29}$, $-N(alkyl)_2$, $-N(arylalkyl)_2$, -N(arylalkyl)(heteroarylalkyl), $-NHC(O)R^{29}$, $-NHC(O)NH_2$, -NHC(O)NH(alkyl), -NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl), $-NHS(O)_2R^{29}$, $-NHS(O)_2NH(alkyl)$, $-NHS(O)_2N(alkyl)(alkyl)$, -N(alkyl)$S(O)_2$NH(alkyl) and $-N(alkyl)S(O)_2N(alkyl)(alkyl)$;

R^{28} is alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl or heterocycloalkenylheteroaryl;

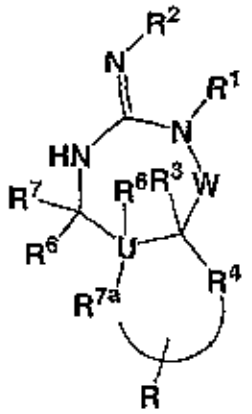
R^{29} is alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl or heterocycloalkenylheteroaryl;

R^{30} is alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl or heterocycloalkenylheteroaryl;

and

R^{31} is alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl;

with the following proviso, that when U, $R^{7a}$and R^4 cyclize to form the following bicyclic structure:



W cannot be a bond.

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

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

More specifically, the invention comprises: the method of treating a cardiovascular disease such as hypertension, renal failure, congestive heart failure or another disease modulated by renin inhibition; the method of treating Human Immunodeficiency Virus; the method of treating a cognitive or neurodegenerative disease such as Alzheimer's Disease; the method of inhibiting plasmepsins I and II for treatment of malaria; the method of inhibiting Cathepsin D for the treatment of Alzheimer's Disease, breast cancer, and ovarian cancer; and the method of inhibiting protozoal enzymes, for example inhibition of plasmodium falciparnum, for the treatment of fungal infections. Said method of treatment comprise administering at least one compound of formula I to a patient in need of such treatment. In particular, the invention comprises the method of treating Alzheimer's Disease comprising administering at least one compound of formula I to a patient in need of such treatment.

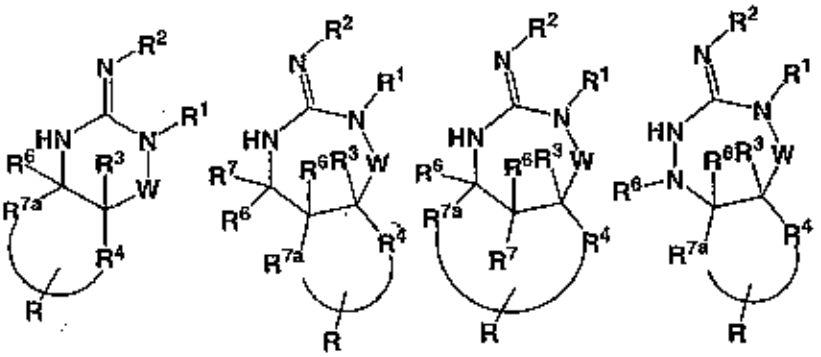
In another aspect, the invention comprises the method of treating Alzheimer's Disease comprising administering to a patient in need of such treatment a combination of at least one compound of formula I and a cholinesterase inhibitor or a muscarinic m_1 agonist or m_2 antagonist.

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

DETAILED DESCRIPTION:

In general, it is understood that divalent groups are to be read left to right.

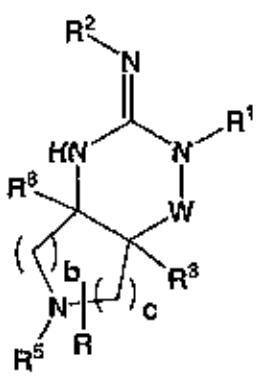
Preferred compounds of formula I wherein R, R^1, R^2, R^3, R^4, R^6, R^7, R^{7a} and W are as defined above include the following structures:



I II III IV

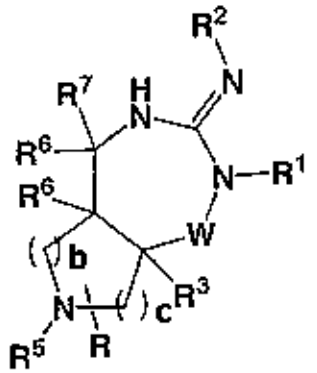
provided that in structure II, W is not a bond.

Compounds of formula I wherein R, R^1, R^2, R^3, R^5, R^6, R^7 and W are as defined above also include the following structures:



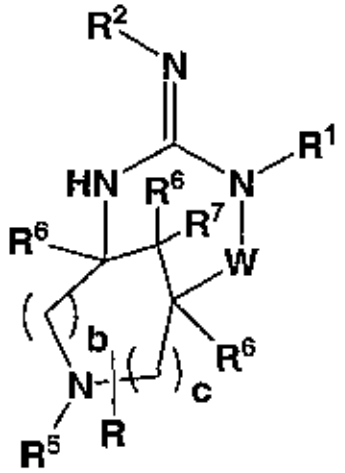
wherein b is 1 to 5 and c is 0 to 5.

or



wherein R, R^1, R^2, R^3, R^5, R^6, R^7 and W, wherein b is 1 to 5 and c is 0 to 5

or

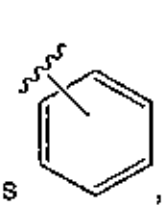
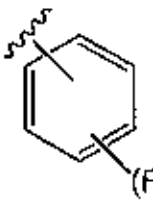
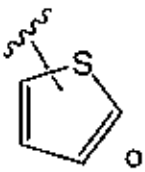


wherein R, R^1, R^2, R^3, R^5, R^6, R^7 and W are as defined above, b is 1 to 4 and c is 0 to 4.

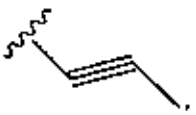
Preferred compounds of formula I are those compounds wherein R^1 is alkyl or more preferably, R^1 is methyl.

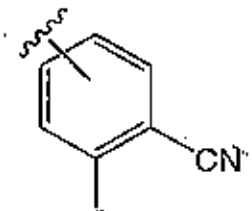
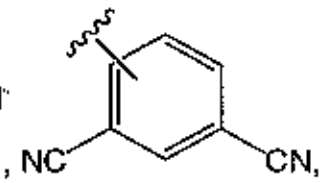
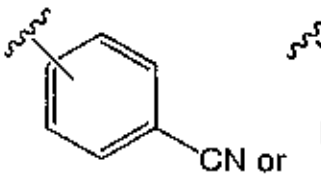
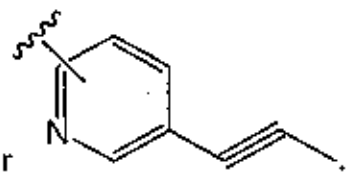
More preferred compounds of the invention are those of formula I wherein R^2 is H.

Another group of preferred compounds of formula I are those compounds wherein R^6 is aryl, $(R^{21})_{1-5}$-aryl, heteroaryl or $(R^{21})_{1-5}$-heteroaryl

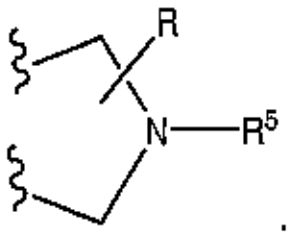
or even more preferably, R^6 is  ,  ,  or  .

Preferred compounds of formula I are those compounds wherein R^{21} is –CN, halo, aryl, $(R^{22})_{1-2}$-aryl, heteroaryl or $(R^{22})_{1-2}$-heteroaryl.

Preferred compounds of formula I are those compounds wherein R^{22} is –CN, halo or alkyne, or more preferably, R^{22} is F or  .

Preferred compounds of formula I are those compounds wherein wherein R^{21} is  ,  ,  or  .

More preferred compounds of formula I are those compounds wherein W is -C(O)-.

Another group of preferred compounds of formula I are those compounds wherein R^4 and R^{7a} form R^4 and R^{7a} form  .

Preferred compounds of formula I are those compounds wherein R is halo, more preferably where R is F.

Preferred compounds of formula I are those compounds wherein

R is H or halo;

R^1 is alkyl;

R^2 is H;

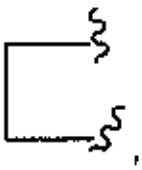
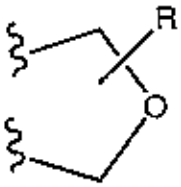
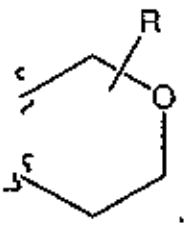
R^6 is R^{21}-aryl;

R^{21} is R^{22}-aryl;

R^{22} is halo or CN;

W is -C(O)-;

and

R^4 and R^{7a} form  ,  or  .

Another group of preferred compounds of formula I are those compounds wherein

R^1 is alkyl;

R^2 is H;

R^6 is R^{21}-aryl;

R^{21} is R^{22}-aryl;

R^{22} is halo or CN;

W is -C(O)-;

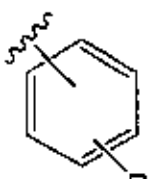
and

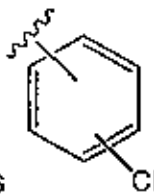
R^4 and R^{7a} form  .

An even further group of preferred compounds of formula I are those compounds wherein

R^1 is methyl;

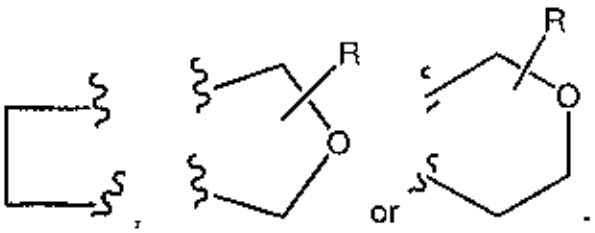
R^2 is H;

R^6 is  ;

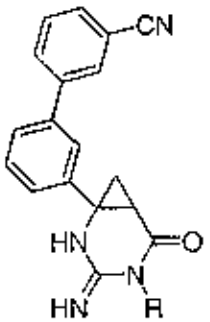
R^{21} is  ;

W is -C(O)-;

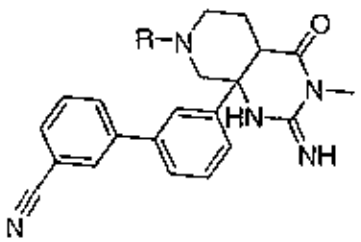
and

R^4 and R^{7a} form  .

In a group of preferred compounds of formula I are those compounds having the structure:

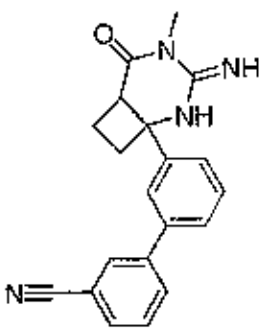


or

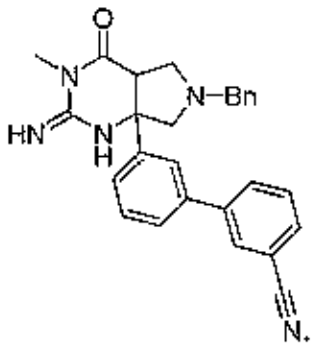


wherein R is defined herein.

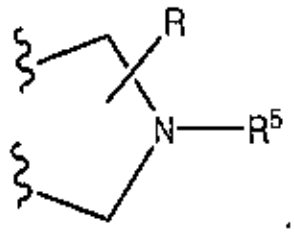
The following preferred compounds of formula I have the following structures;



and

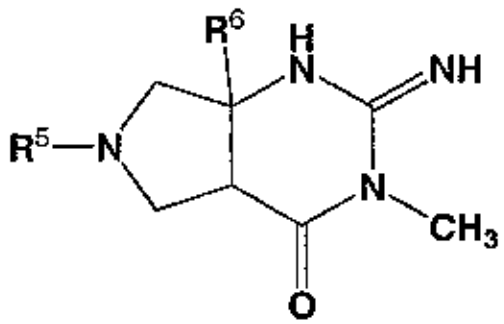


An further group of preferred compounds of formula I are those compounds



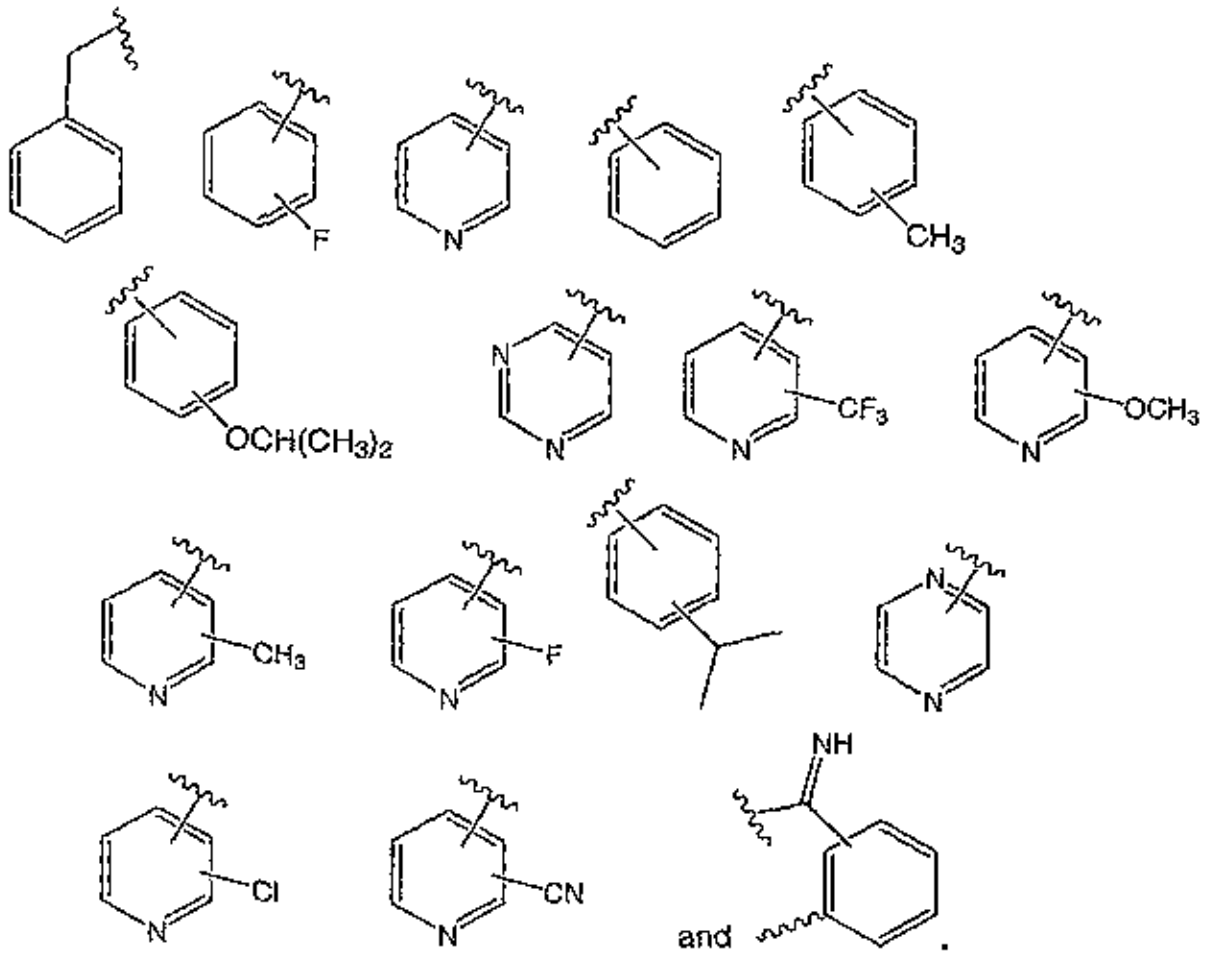
where R^4 and R^{7a} form .

A further group of preferred compounds of formula I are those compounds having the following structure

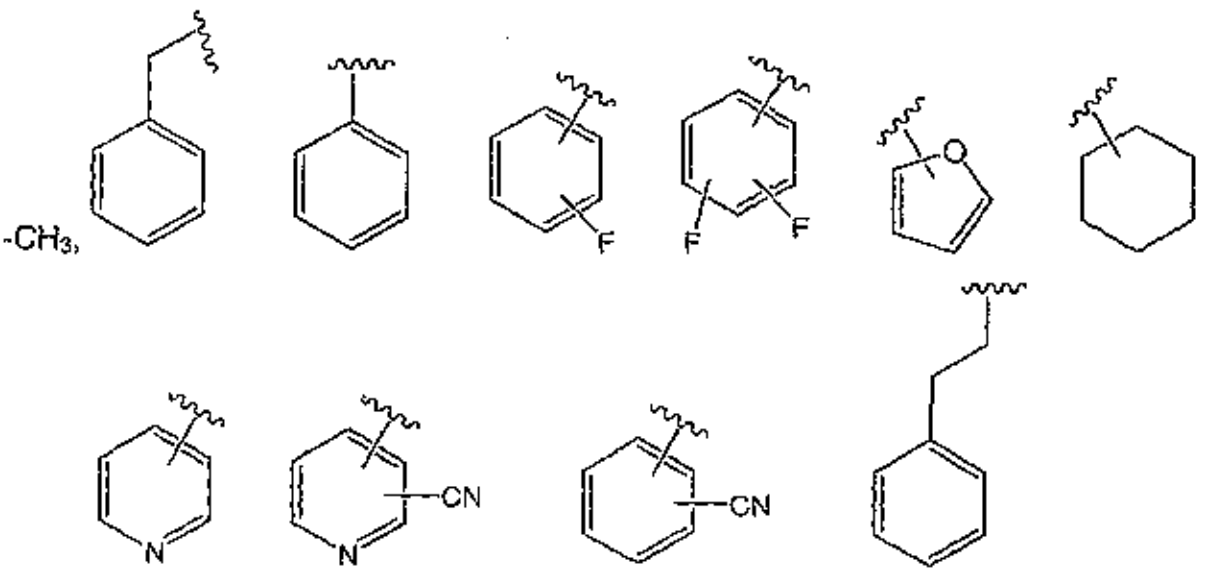


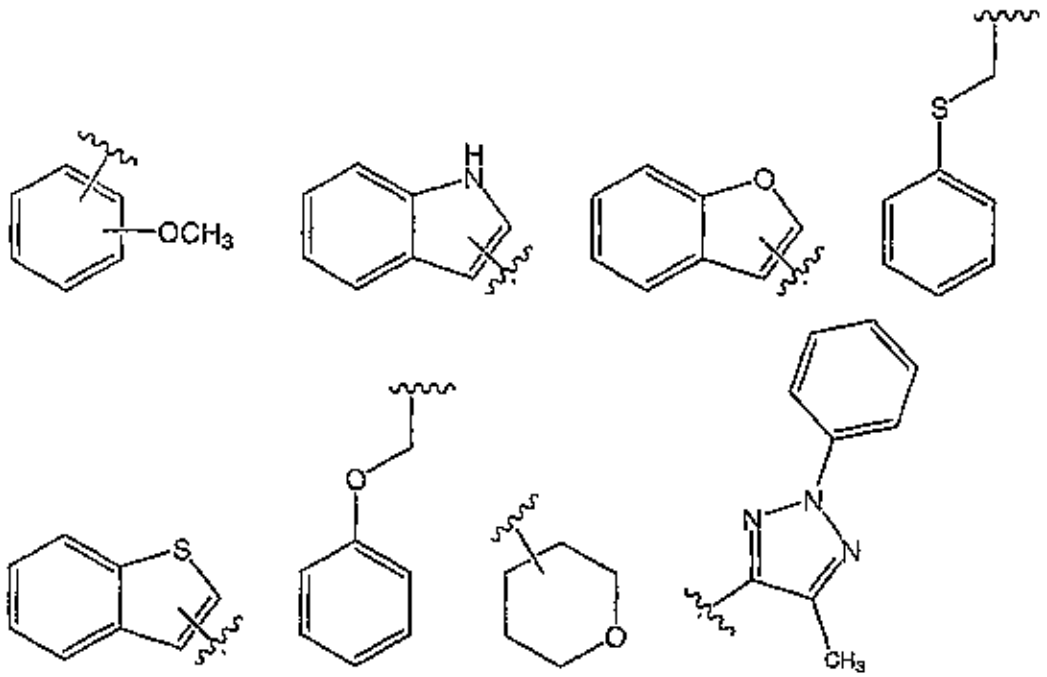
wherein R^5 and R^6 are as defined as above.

A group of preferred compounds of formula I are those compounds where R^5 is independently selected from the group consisting of arylalkyl, aryl, heteroaryl, $-C(=NR^{11})R^8$, $-C(O)R^8$, $-C(O)OR^9$, aryl-R^{21} and heteroaryl-R^{21}, or more preferably, R^5 is

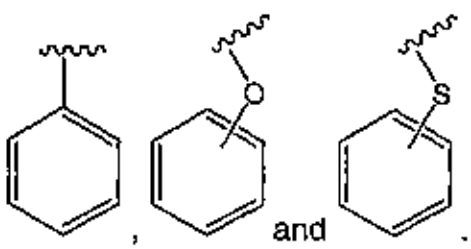


An even further group of preferred compounds of formula I are those compounds where R^8 or R^9 is independently selected from the group consisting of, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, R^{18}-alkyl, R^{18}-aryl, and R^{18}-heteroaryl; or even more preferably, R^8 or R^9 is independently selected from the group consisting of





and

An even further group of preferred compounds of formula I are those compounds where R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, halo, $-CF_3$, -CN, $-SR^{19}$ and $-OR^{20}$, or even more preferably, R^{18} is 1-5 substituents independently selected from the group consisting of halo, -CN, $-OCH(CH_3)_2$, $-OCH_3$, $-CH_3$,  and .

An even further group of preferred compounds of formula I are those compounds wherein R^{21} is 1-5 substituents independently selected from the group consisting of halo, $-OCH(CH_3)_2$, $-CH_3$, $-CF_3$, $-OCH_3$, $-CH(CH_3)_2$ and –CN.

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

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

"Patient" includes both human and animals.

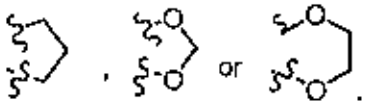
"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, heptyl, nonyl and decyl. R^{21}-substituted alkyl groups include fluoromethyl, trifluoromethyl and cyclopropylmethyl .

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

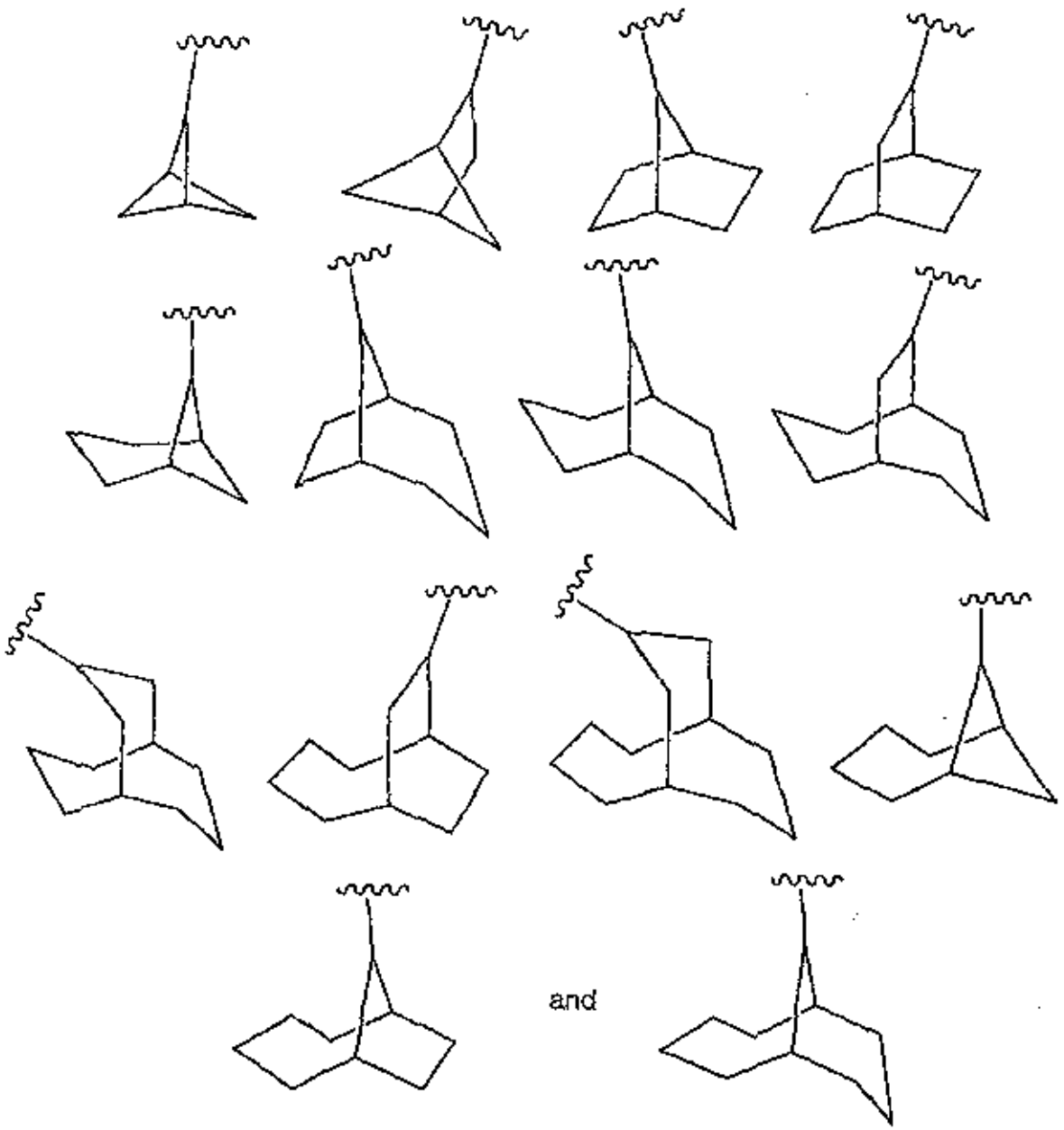
"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl, 3-methylbutynyl, n-pentynyl, and decynyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The

aryl group can be optionally substituted with one or more substituents (e.g., R^{18}, R^{21}, R^{22}, etc.) which may be the same or different, and are as defined herein or two substituents on adjacent carbons can be linked together to form  . Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one to four of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more R^{21} substituents which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 15 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more R^{21} substituents which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalin, norbornyl, adamantyl and the like. Further non-limiting examples of cycloalkyl include the following



and

"Cycloalkylether" means a non-aromatic ring of 3 to 15 atoms comprising an oxygen atom and 2 to 14 carbon atoms. Ring carbon atoms can be substituted, provided that substituents adjacent to the ring oxygen do not include halo or substituents joined to the ring through an oxygen, nitrogen or sulfur atom.

"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 15 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. The cycloalkenyl ring can be optionally substituted with one or more R^{21} substituents which may be the same or different, and are as defined above. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. Non-limiting examples of suitable monocyclic

cycloalkenyls include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

"Heterocyclenyl" (or "heterocycloalkenyl") means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic azaheterocyclenyl groups include 1,2,3,4- tetrahydropyridyl, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridyl, 1,4,5,6-tetrahydropyrimidyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, and the like. Non-limiting examples of suitable oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, fluorodihydrofuranyl, and the like. Non-limiting example of a suitable multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Non-limiting examples of suitable monocyclic thiaheterocyclenyl rings include dihydrothiophenyl, dihydrothiopyranyl, and the like.

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

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

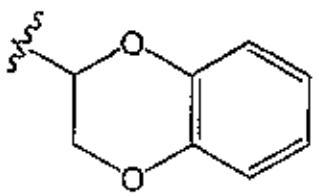
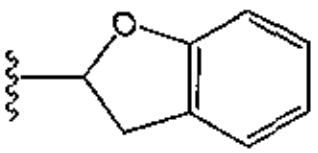
"Heterocyclyl" (or heterocycloalkyl) means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which 1-3, preferably 1 or 2 of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The

heterocyclyl can be optionally substituted by one or more R^{21} substituents which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

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

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

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


and


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

Similarly, "heteroarylalkyl" "cycloalkylalkyl" and "heterocycloalkylalkyl" mean a heteroaryl-, cycloalkyl- or heterocycloalkyl-alkyl- group in which the heteroaryl, cycloalkyl, heterocycloalkyl and alkyl are as previously described. It is also understood that the terms "arylcycloalkylalkyl", "heteroarylcycloalkylalkyl", "arylheterocycloalkylalkyl", "heteroarylheterocycloalkylalkyl", "heteroarylcycloalkyl", "heteroarylheterocycloalkyl", "arylcycloalkenyl", "heteroarylcycloalkenyl", "heterocycloalkenyl", "arylheterocycloalkenyl", "heteroarylheterocycloalkenyl",

"cycloalkylaryl", "heterocycloalkylaryl", "heterocycloalkenylaryl", "heterocycloalkylheteroaryl", "cycloalkenylaryl" "cycloalkenylheteroaryl", "heterocycloalkenylaryl" and "heterocycloalkenylheteroaryl" similarly represented by the combination of the groups aryl-, cycloalkyl-, alkyl-, heteroaryl-, heterocycloalkyl-, cycloalkenyl- and heterocycloalkenyl- as previously described. Preferred groups contain a lower alkyl group. The bond to the parent moiety is through the alkyl.

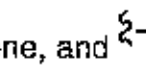
"Acyl" means an H-C(O)-, alkyl-C(O)-, alkenyl-C(O)-, alkynyl-C(O)- or cycloalkyl-C(O)- group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl,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

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

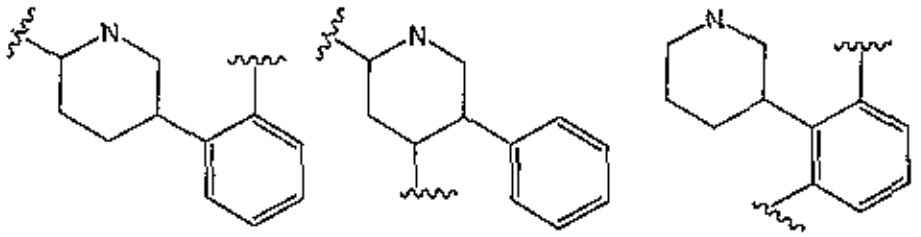
"Alkoxyalkyl" means a group derived from an alkoxy and alkyl as defined herein. The bond to the parent moiety is through the alkyl.

"Arylalkenyl" means a group derived from aryl and alkenyl as defined herein. Preferred arylalkenyls are those wherein aryl is phenyl and the alkenyl consists of about 3 to about 6 atoms. The arylalkenyl can be optionally substituted by one or more R^{27} substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

"Arylalkynyl" means a group derived from aryl and alkynyl as defined herein. Preferred arylalkynyls are those wherein aryl is phenyl and the alkynyl consists of about 3 to about 6 atoms. The arylalkynyl can be optionally substituted by one or more R^{27} substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

The suffix "ene" on alkyl, aryl, hetercycloalkyl, etc. indicates a divalent moiety, e.g., $-CH_2CH_2-$ is ethylene, and  is para-phenylene.

It is understood that multicyclic divalent groups, for example, arylheterocycloalkylene, can be attached to other groups via bonds that are formed on either ring of said group. For example,



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

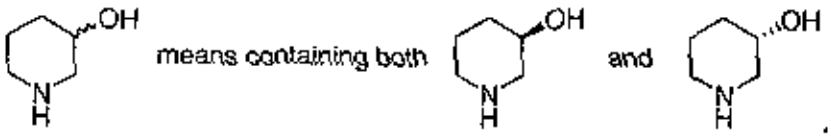
Substitution on a cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, or heteroarylalkyl moiety includes substitution on the ring portion and/or on the alkyl portion of the group.

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

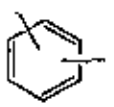
With reference to the number of moieties (e.g., substituents, groups or rings) in a compound, unless otherwise defined, the phrases "one or more" and "at least one" mean that there can be as many moieties as chemically permitted, and the determination of the maximum number of such moieties is well within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

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

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

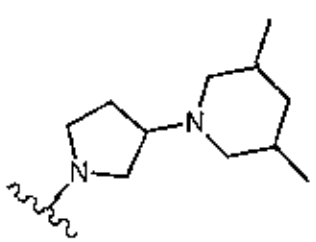


Lines drawn into the ring systems, such as, for example:



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

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



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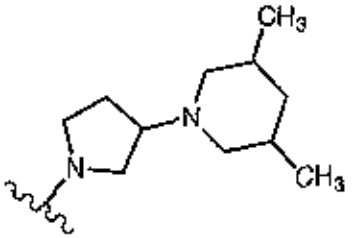
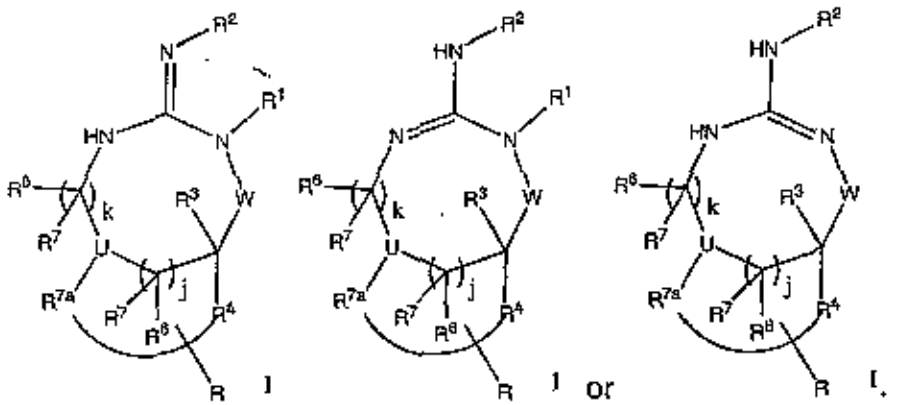
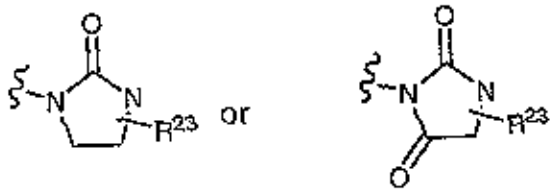


It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples, structural formulae, and any Tables herein is assumed to have the hydrogen atom or atoms to satisfy the valences.

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



When, R^8, for example is, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, and R^{16} and R^{17} form a ring, the molety formed, is, for example



Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and

in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (e.g, a drug precursor) that is transformed *in vivo* to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C_1–C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-*crotonolactonyl*, *gamma-butyrolacton*-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a compound of Formula (I) contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1$-$C_6)alkyl)_2$ or glycosyl (the

radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of Formula (I) incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently $(C_1$-$C_{10})$alkyl, $(C_3$-$C_7)$ cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, $(C_1$-$C_6)$alkyl or benzyl, —$C(OY^2)Y^3$ wherein Y^2 is $(C_1$-$C_4)$ alkyl and Y^3 is $(C_1$-$C_6)$alkyl, carboxy $(C_1$-$C_6)$alkyl, amino$(C_1$-$C_4)$alkyl or mono-N—or di-N,N-$(C_1$-$C_6)$alkylaminoalkyl, —$C(Y^4)Y^5$ wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N-$(C_1$-$C_6)$alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

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

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

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

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formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization. Acids (and bases) which are generally considered suitable for the formation of pharmaceutically useful salts from basic (or acidic) pharmaceutical compounds are discussed, for example, by S. Berge *et al, Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al, The Practice of Medicinal Chemistry* (1996), Academic Press, New York; in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website); and P. Heinrich Stahl, Camille G. Wermuth (Eds.), *Handbook of Pharmaceutical Salts: Properties, Selection, and Use,* (2002) Int'l. Union of Pure and Applied Chemistry, pp. 330-331. These disclosures are incorporated herein by reference thereto.

Exemplary acid addition salts include acetates, adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, methyl sulfates, 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pamoates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, bisulfates, sulfates, sulfonates (such as those mentioned herein), tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) undecanoates, and the like.

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

bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

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

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrugs of the inventive compounds.

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

Compounds of formula I can be made using procedures known in the art. The following reaction schemes show typical procedures, but those skilled in the art will recognize that other procedures can also be suitable.

In the Schemes and in the Example below, the following abbreviations are used:

room temperature: r.t.

high pressure liquid chromatography: HPLC

reverse-phase HPLC: RP-HPLC

liquid chromatography mass spectrometry: LCMS

mass spectrometry: MS

polytetrafluoroethylene: PTFE

hour: h

minute: min

retention time: tR

ethyl: Et

methyl: Me

benzyl: Bn

lithium diisopropylamide: LDA

1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride: EDCI

DIEA means N, N-diisopropylethylamine

ethyl acetate: EtOAc

N,N-dimethylformamide: DMF

methanol: MeOH

Ethanol: EtOH

acetonitrile: CH_3CN

acetic acid: AcOH

magnesium sulfate: $MgSO_4$

copper iodide: CuI

diisopropylamine: iPr_2NH

Dichlorobis(triphenylphosphine)palladium: $PdCl_2(PPh_3)_2$

ammonium hydroxide: NH_4OH

trifluoroacetic acid: TFA

benzyloxycarbonyl: Cbz

tert-butoxycarbonyl: Boc

DCM: Dichloromethane

TMSCHN$_2$: *Trimethylsilyldiazomethane*

Teoc-OSu:O-Trimethylsilylethoxycarbonyl N-hydroxylsuccinate

TBAF: Tetrabutylammonium Flouride

THF: Tetrahydrofurane

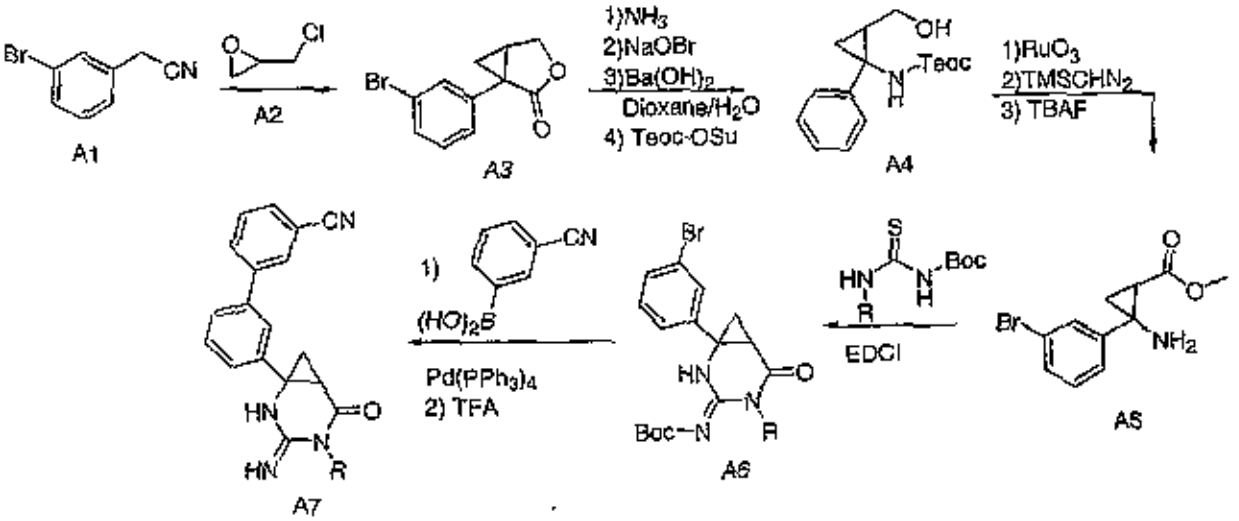
MCPBA: meta-Chloroperbenzoic acid

TsOH:Toluenesulfonic acid.

PhIO: iodosobenzene

Pb(OAc)$_4$: *Lead tetra-acetate*

Method A.



Method A, Step 1

A literature procedure is adapted (Y. Kazuta, et.al. Bioorganic & Medicinal Chemistry, 10 (2002), 3829-3848). Thus, to a suspension of $NaNH_2$ (22.0 mmol) in benzene (20 mL) is added a solution of 3-bromophenylacetonitrile (10 mmol) in benzene (10 ml) at 0ºC, and the reaction is stirred at r.t. for 2h. After the solvent is evaporated the residue is chromatographed to give product A3.

Method A, Step 2

A similar literature procedure is adapted (Casadio, S. et.al. Bollettino Chimico Farmaceutico (1978), 117(6), 331-42). Compound A3 is dissolved in 7N NH_3/MeOH and the solution is heated in a sealed tube to 70 0ºC for 1 h. before the solvent is evaporated. The result amide (10 mmol) redissolved in MeOH is treated with aq NaOBr (5 eq) overnight before the reaction mixture is partitioned between DCM/water. The organic layer is washed with brine and dried with Na_2SO_4 and evaporated to give the crude cyclic carbamate which is hydrolyzed with $Ba(OH)_2$ in dioxane/water under heat overnight to give the aminoalcohol. The solution is cooled to r.t. and its pH is adjusted to 9 using aq $NaHSO_4$ before TEOC-OSu (1.1 eq) is added. The reaction is stirred for 5 h before the solution is partitioned between DCM/water. The organic solution is washed with brine and dried over Na_2SO_4 and subsequently evaporated to give crude product which is purified via a silica gel column to compound A4.

Method A, Step 3,

A literature procedure is adapted (Tetrahedron Letters 2003). To a mixture of A4 in CCl_4/Acetonitrile/H_2O(5/5/1) is added $RuCl_3$(0.1 eq), $NaIO_4$ (10 eq) and $NaHCO_3$ (10 eq) and the reaction is stirred overnight before the mixture is acidified to pH 3 and partitioned in DCM/water. The organic layer is dried and solvent evaporated to give the aminoacid product which is dissolved in MeOH and treated with $TMSCHN_2$ to give the corresponding aminoester after evaporation of the solvent. The aminoester is treated with 1 N TBAF in THF for 20 min before the reaction mixture is diluted with Ether and filtered through a silica gel pad to give the amino ester product A5.

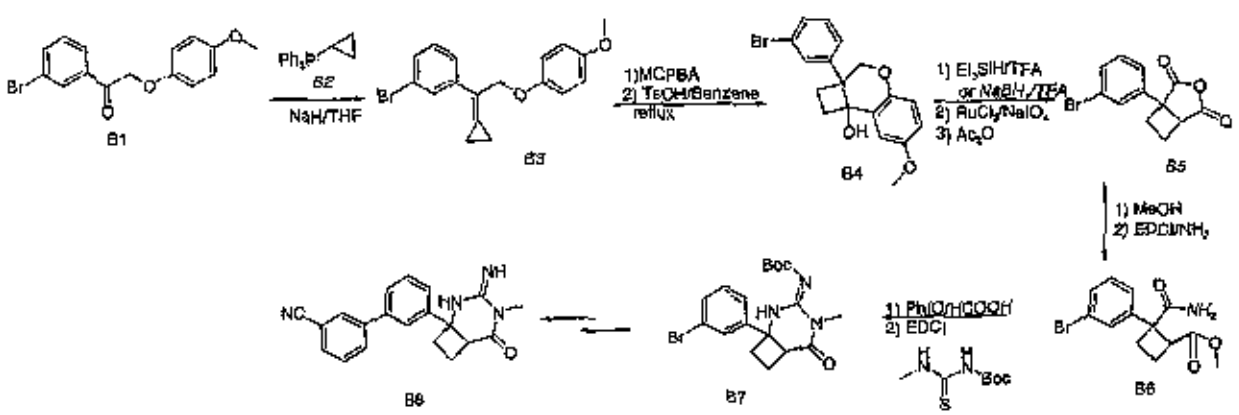
Method A, Step 4,

To a DMF solution of A5 is added N-methyl-N'-Boc-thiourea (1 eq) followed by addition of EDCI (1eq) and DIEA (2 eq) and the solution is stirred overnight. The solvent is evaporated under vacuum and residue chromatographed to give the boc-ed iminopyrimidinone A6.

Method A, Step 5.

A mixture of compound A6, 3-cyanophenylboronic acid, Fibrecat (4.26% of Pd, 0.7 g) and 1N aq. K_2CO_3 (0.5 mL) in tert-butanol (10 mL) is heated at 110 °C for 15 min. After cooling, the reaction mixture is transferred to a pre-packed Si-Carbonate column and eluted with MeOH/CH_2Cl_2 (1:1). The eluant is collected and concentrated under reduced pressure to give a crude product which is purified by silica gel chromatography (20-50% EtOAc/hexanes gradient) to yield the product. After treatment of the product with 30% TFA in DCM for 20 min followed by evaporation of solvent, product A7 is obtained.

Method B



Method B, Step1:

A literature procedure is adapted (Bernard, A. et.al Tetrahedron (2004), 60(2), 449-457). Compound B1 (1g) and B2 (1.1 eq) in anhydrous THF is treated with NaH (1.5 eq) and the mixture is stirred at r.t. overnight. After evaporation of solvent the residue is purified via silica gel column to give compound B3.

Method B, Step 2:

A mixture of compound B3 (1g), MCPBA (2eq) and $NaHCO_3$ (5 eq) is stirred overnight before it is diluted with DCM and washed with aq $NaHCO_3$, brine and dried. The solvent is evaporated to give a crude epoxide. This crude producte is dissolved in anhydrous benzene and 100 mg of p-toluenesulfonic acid is added. The reaction is refluxed overnight before it is cooled to r.t., washed with aq $NaHCO_3$ and concentrated to give product B4.

Method B, Step 3;

A solution of B4 (1 g) in 20% TFA in DCM is treated with triethylsilane(3eq) or with $NaBH_4$. After removal of the volatiles, the residue is chromatographed to give a product which is dissolved in a mixture of CCl_4/Acetonitrile/water (5/5/1) and $RuCl_3$ (0.1 eq)/$NaIO_4$ (10 eq). The reaction mixture is stirred over night before the solid is filtered and the liquid mixture is concentrated. The residue is stirred with 10 ml acetic anhydride for 30 min before the volatile is evaporated to give a crude product B5.

Method B, Step 4.

The crude product anhydride is redissolved in MeOH. The reaction is refluxed for 1 h and solvent evaporated. The residue is redissolved in DMF followed by addition of NH_4Cl (5 eq) and EDCI hydrochloric salt (1.5 eq) and DIEA (5 eq). The reaction mixture is stirred overnight before it is partitioned in DCM/Water. The organic layer is dried, solvent evaporated and the residue is chromatographed to give the primary amide B6.

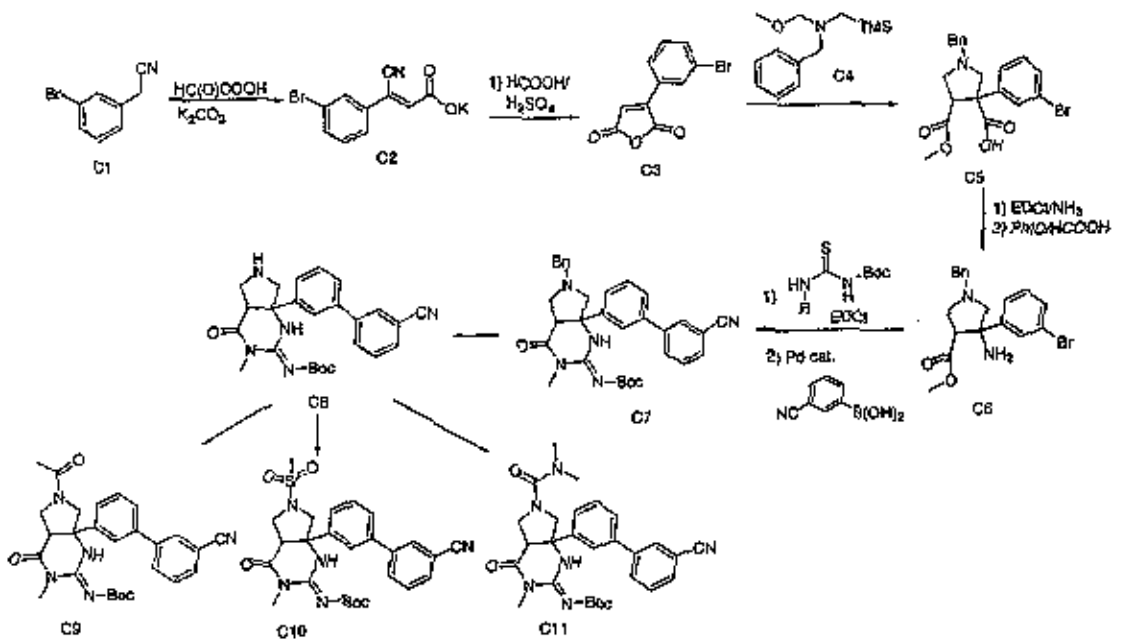
Method B, Step 5.

To a solution of B6 in acetonitrile/water/formic acid (3/1/6) is added PhIO (2 eq) and the mixture is stirred overnight before said mixture is made basic (pH 10) using aq Na_2CO_3 and partitioned between DCM and water. The organic layer is dried and solvent evaporated. The residue is redissolved in DMF and EDCI (1.1 eq), N-methyl-N'-Boc-thiourea (1.1 eq) and DIEA (2 eq) is added. The reaction is stirred overnight before it is partitioned between DCM and water. The organic layer is washed with brine and dried over Na_2SO_4 and solvent evaporated. The residue is purified with a silica gel column to give product B7.

Method B, Step 6

Product B8 is obtained using method similar to Method A step 5.

Method C



Method C, Step 1.

A literature procedure is adapted (JOC, 1993, (58), 7916). To a solution of 36 g of m-bromophenylacetonitrile and glyoxaldehyde (44.4ml 50% aq solution) in 350 ml of MeOH is added 63 g (2.5 eq) of K_2CO_3 and the reaction mixture is stirred at r.t. for 4 h. The solid is filtered and washed with ether before it is resuspended in cold water and stirred vigorously for 1 h. The white solid is filtered to give crude product C2.

Method C, Step2;

The crude product C2 (50 g) is dissolved in 400 ml of formic acid and 40 ml conc. sulfuric acid and the solution is refluxed overnight. After the reaction is cooled down, the mixture is poured into ice water and the solid filtered to give product C3.

Method C, Step 3;

To a solution of C3 (0.27 g) and C4 (1.0 eq) in 3 ml of anhydrous DCM is added 0.5 of TFA and the solution is stirred at r.t. overnight. After removal of solvent, the residue is purified using a reverse phase C-18 column to give product C5.

Method C, Step 4.

Compound C6 is obtained using a procedure similar to Method B, step 5

Method C. Step 5.

Product C7 is obtained using procedure similar to Method A step 4,5.

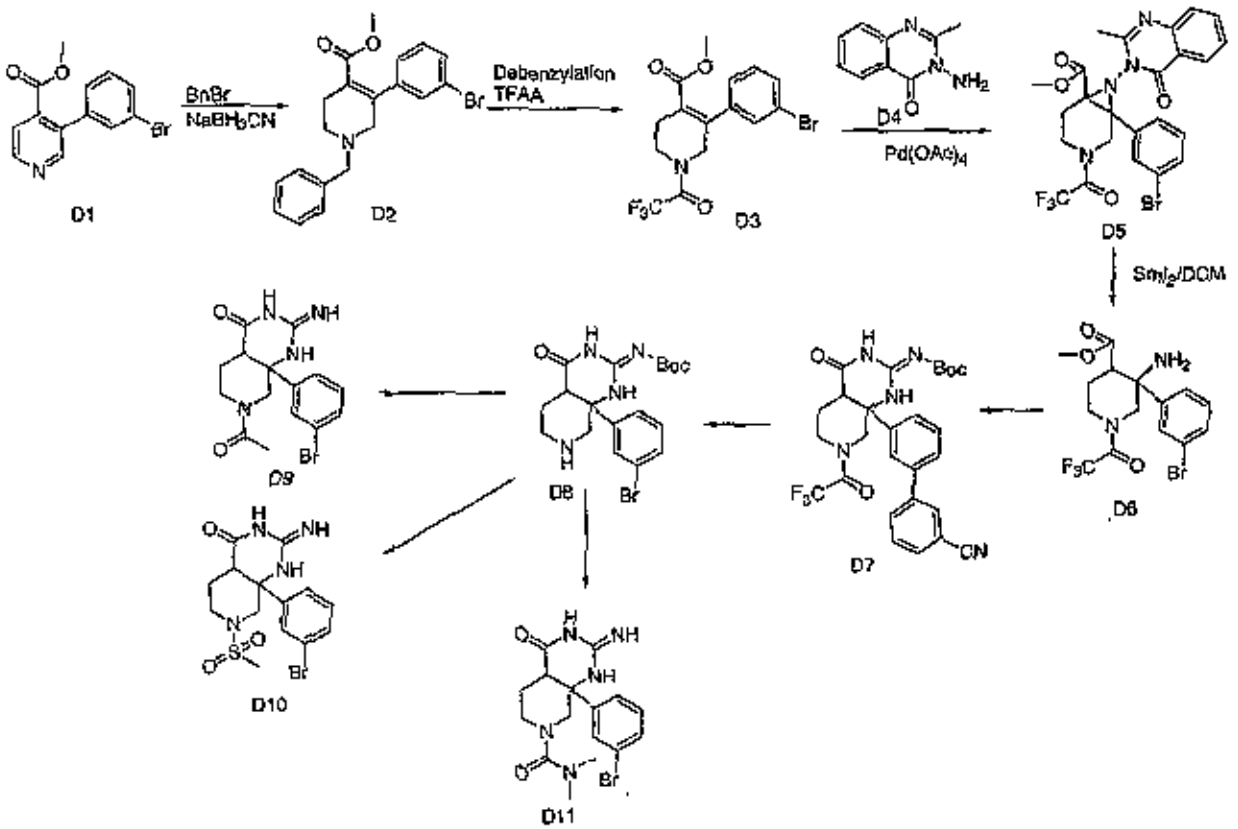
Method C, Step 6

Compound C8 is obtained through debenzylation of C7 under Pd hydrogenation conditions.

Method C, Step 7,8,9

Conventional amide, sulfonamide and urea formation conditions are used for compound C9, C10 and C11.

Method D



Method D, Step 1

A literature procedure is used for generation of compound D2 and D3 (Gwaltney, S. et.al Bioorganic & Medicinal Chemistry Letters (2003), 13(7), 1359-1362). 3-m-bromophenylisonicotinic acid methyl ester (D1) is treated with BnBr in DCM for 3 h at 50 ºC before it is cooled to r.t. and $NaBH_3CN$ (6 eq) is added. The reaction is stirred overnight *before it is diluted with DCM and washed with water and* brine. The residue after removal of organic solvent is purified via a silica gel column to afford D2.

Method D, Step 2.

Compound D2 is treated with 1-Chloroethylchloroformate in DCM for 2 h at r.t. before it is quenched with MeOH. After dilution with DCM, the reaction mixture is washed with aq Na_2CO_3. The organic layer is dried and solvent evaporated to give a crude product which is treated with Trifluroacetic anhydride (2 eq) and *TEA (2 eq) in DCM. The reaction is stirred for 1 h before it is quenched* with water and the DCM solution is dried and concentrated to give compound D3 after purification.

Method D, Step 3

A literature procedure is adapted (**Selective aziridination of olefinic esters.** Deshmukh, M.; Chavan, P.; Kharade, D Monatshefte fuer Chemie (1994), 125(6-7), 743-6). To a DCM solution of D3 and D4 (1.2 eq) is added Lead tetraacetate (2 eq) and the reaction is stirred overnight before it is diluted with DCM and washed with aq $NaHCO_3$, brine. The DCM layer is dried and solvent evaporated. The residue is chromatographed to give compound D5.

Method D, Step 4

A literature procedure is adapted (Atkinson, R et.al. Tetrahedron Letters (2002), 43(11), 2083-2085). To a THF solution of D5 is added SmI2 in THF (4 eq) before the reaction is quenched with water and reaction is adjusted to pH 9. The reaction mixture is partitioned between DCM and water. The organic solution is dried and solvent evaporated to give crude product D6.

Method D, Step 5.

Product D7 is obtained using a procedure similar to Method A Step 4 followed by Method Step 5 for the Suzuki coupling.

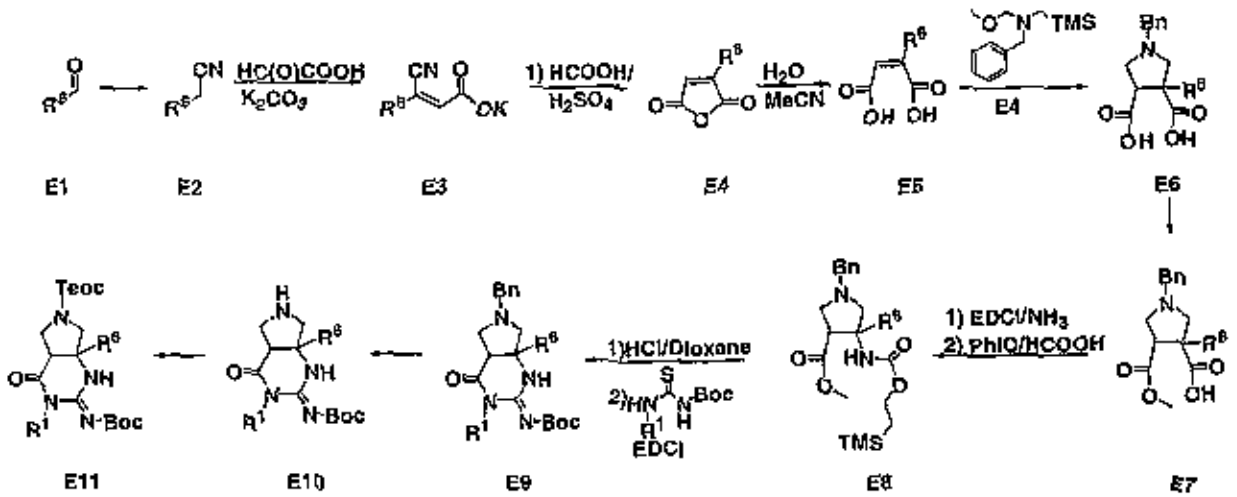
Method D, Step 6,

Compound D8 is obtained by treatment of D7 with 2N ammonia in MeOH.

Method D, Step 7, 8 and 9

Conventional amide, sulfonamide and urea formation procedures are used for generation of D9, D10 and D11 after TFA deprotection of the Boc group.

Method E



Method E, Step 1.

To a solution of aldehyde E1 (R^5 = 4-Bromothien-2-yl, 20 g) in 100 mL methanol was added 4 g of $NaBH_4$ at 0°C and the resulting solution was stirred until the reaction was completed at 0°C. To the reaction was quenched with water (100 mL) before the solvent was evaporated. The residue was extracted with ethyl acetate/water, and the organic layers were combined and washed with brine, dried with $MgSO_4$, evaporated to provide a alcohol which was used without further purification.

NMR(H^1, $CDCl_3$) of product alcohol (R^6 = 4-Bromothien-2-yl): δ 7.17, s, 1H; 6.93 s, 1H; 4.80, d (J = 6.0 Hz), 2H; 1.84, t (J = 6.0 Hz), 1 H.

To a solution of the above alcohol in 10 mL CH_2Cl_2 was added 1.2 equiv. of $SOCl_2$ at 0°C. The resulting reaction mixture was stirred at 0°C for 30 min and at rt for 2h. The reaction mixture was extracted with ethyl acetate/water and the organic layers were washed with brine, dried with MgSO4 and evaporated to yield a chloride.

NMR(H^1, $CDCl_3$) of product chloride (R^5 = 4-Bromothien-2-yl): δ 7.15-7.30, m, 2H; 4.73, s, 2H.

To the chloride (4.4 g, 21 mmol) in 50 mL of AcCN was added KCN (3.6 equiv, 5 gm, 76 mmol) and the resulting reaction mixture was stirred at rt for 1 hr before it was heated under reflux until the disappearance of starting. The reaction mixture was diluted with ethyl acetate, filtered and the solid was washed with ethyl acetate. The combined filtrate was washed with water, brine, dried and concentrated. The

residue was chromatographed using ethyl acetate/hexane to give product E2 (R^6 = 4-Bromothien-2-yl, 75%).

NMR (H^1, $CDCl_3$) of E2(R^6 = 4-Bromothien-2-yl): δ 7.18, s, 1H; 7.00, s, 1H, 3.89, s, 2H.

Method E, Step2;

A literature procedure was adapted (JOC, 1993, (58), 7916). To a solution of 4 g of E2(R^6 = 4-Bromothien-2-yl) and glyoxaldehyde (1.5 eq, 50% aq solution) in 50 ml of MeOH was added 6.9 g (2.5 eq) of K_2CO_3 and the reaction mixture was stirred at r.t. for 4 h. The solid was filtered and washed with ether before it was resuspended in cold water and stirred vigorously for 1 h. The white solid is filtered and dried to give crude product E3(R^6 = 4-Bromothien-2-yl) which was used without further purification. A small quantity of E3 was extracted with EtOAc/1N HCl and the organic solution was evaporated to give the corresponding free acid of E3 (R^6 = 4-Bromothien-2-yl).

NMR(H^1, $CDCl_3$) of E3 (R^6 = 4-Bromothien-2-yl) as a free acid: δ 7.69, s, 1H; 7.56, s, 1H; 6.96, s, 1H.

Method E, Step3;

The crude product E3 (R^6 = 4-Bromothien-2-yl) (50 g) was dissolved in 400 ml of formic acid and 40 ml conc. sulfuric acid. The solution was refluxed for 2h. before it was cooled down to rt. The solution was poured into ice water and the solid filtered to give product E4 (R^6 = 4-Bromothien-2-yl) (80 %).

NMR(H^1, $CDCl_3$) of E4 (R^6 = 4-Bromothien-2-yl): δ 7.88, s, 1H; 7.84, s, 1H; 7.09, s, 1H.

Method E, Step 4;

A solution of E4 (R^6 = 4-Bromothien-2-yl) (27 g) in 300 ml mixture of acetonitril and water (10%) was heated at 40°C until the starting material disappeared. The reaction solution was concentrated and the residue dried in vaccuo to give compound E5(R^6 = 4-Bromothien-2-yl) in quantitative yield.

NMR(H^1, $CDCl_3$) of E4 (R^6 = 4-Bromothien-2-yl): δ 7.66, s, 1H; 7.40, s, 1H; 6.42, s, 1H.

Method E, Step 5.

To solution of E5 (R^6 = 4-Bromothien-2-yl) (5 g, 18.17 mmol) in 72 mL anhydrous THF was added E4 (2.0 equiv. 6 mL) at 0°C and the resulting solution was stirred at 0°C for 90 min. before the reaction was quenched with 10 mL 1N HCl at 0°C and the reaction mixture was extracted with ethyl acetate and the organic layers were combined, dried with anhydrous Na_2SO_4, then concentrated to yield 6 g of E6 (R^6 = 4-Bromothien-2-yl), which was used for next step without further purification.

NMR(H^1, CD_3OD) of E6 (R^6 = 4-Bromothien-2-yl): δ 7.45-7.60, m, 7H; 4.49, m, 2H; 4.30, d (J = 12 Hz), 1H; 3.8-4.0, m, 4 H.

Method E, Step 6.

To a oven-dried flask containing E6(R^6 = 4-Bromothien-2-yl) (6 g) was added acetic anhydride (100 mL) at rt. The resulting solution was heated for 30 min at 90°C before the reaction mixture was cooled to rt, poured into a flask containing 500 mL methanol at 0°C and the solution was evaporated to dryness. The crude product was dissolved in 200 mL CH_2Cl_2, washed with 1H HCl, brine, dried with Na_2SO_4 and concentrated to obtain 6 g of product E7 (R^6 = 4-Bromothien-2-yl) as a HCl salt (yield 96%) which was taken for next step without purification.

NMR(H^1, $CDCl_3$) of E7 (R^6 = 4-Bromothien-2-yl): δ 7.10 – 7.60, m, 7H; 4.3, m, 2H; 4.12, d (J = 12 Hz), 1H; 3.7-3.9, m, 4H; 3.6, s, 3H.

Method E. Step 7.

To an oven-dried flask containing Compound E7 (R^6 = 4-Bromothien-2-yl) (4.67gm) in 10 mL toluene was added DPPA (2 equiv, 14.18 mmol, 3 mL) followed by triethyl amine (2.2 equiv, 2.16 mL) at 0°C before the mixture was stirred at rt overnight. To the reaction mixture was added trimethylsilylethanol (4 equiv. 4 mL) and the reaction mixture was refluxed for 1 hr before it was cooled to rt, diluted with ethyl acetate (150 mL), washed with brine, water, dried with Na_2SO_4 and concentrated. The crude product was chromatographed using a silica gel column eluted with (30% ethyl acetate in hexanes) to obtain 1.5 g of E8 (R^6 = 4-Bromothien-2-yl) (40%)

NMR(H^1, $CDCl_3$) of E8 (R^6 = 4-Bromothien-2-yl): δ 7.20-7.40, m, 5H; 7.07, d (J = 1.5 Hz), 1H; 6.94, d (J = 1.5 Hz), 1 H; 4.11, m, 2H; 3.79, AB (J = 11 Hz), 1H; 3.70,

s, 3H; 3.69, AB (J = 11 Hz), 1H; 3.54, AB (J = 10 Hz), 1H; 3.32, t (J = 8 Hz), 1 H; 3.21, AB (J = 10 Hz), 1H; 3.16, t (J = 8 Hz), 1H; 2.88, t (J = 8 Hz), 1H; 0.97, m, 2H; 0.03, s, 9H.

Method E. Step 8.

To a solution of 35.2 g of E8 (R^6 = 4-Bromothien-2-yl) in 200 ml dioxane was added 20 ml of 4N HCl in dioxane at 0 C and the solution was allowed to warm to rt *over 14 h before ether (400 ml) was added.* The white precipitate was collected and washshed with 200 ml of ether, dried in a vacuum oven overnight to give 36.7 g of a HCl salt, which was used without further purification.

NMR(H^1, $CDCl_3$) of the product amine HCl salt (R^6 = 4-Bromothien-2-yl): δ 7.17, d (J = 1.5 Hz), 1H; 6.86, d (J = 6.86 Hz), 1H; 3.65-2.71, m, 1H; 3.45-3.31, m, 6H; 3.29, s, 3H.

To a DMF solution (300 ml) of the HCl salt (76 mmol) was added DIEA (5 eq), and N-methyl-N'-Boc-thiourea (1 eq) followed by addition of EDCI.HCl (1.05 eq) and the solution was stirred at rt for 48 h before it was extracted with EtOAc/water. After removal of organic solvent, the residue was chromatographed via a silica gel column to give product E11(R^6 = 4-thien-2-yl, R^1 = Me).

NMR(H^1, $CDCl_3$) for E11 (R^6 = 4-thien-2-yl, R^1 = Me): δ 7.25-7.34, m, 5 H; 7.15, d (J = 1.5 Hz), 1H; 6.91, d (J = 1.5 Hz), 1H; 3.75, m, 2H; 3.42, m, 1H; 3.34, m, 1H; 3.31, S, 3H; 3.22, AB (J = 10 Hz), 1H; 3.09, AB (J = 10 Hz), 1H; 3.02, M, 1H; 1.54, S, 9H.

Method E. Step 9

To a mixture of DCM solution (10 ml) of E11(R^6 = 4-thien-2-yl, R^1 = Me; 1 g) and potassium carbonate (300 mg) was added 1-chloroethylchloroformate at -15°C and the solution was stirred for 1.5 h at r.t. before the mixture was filtered followed by evaporation of the solvent. The residue was redissolved in 10 ml methanol and the reaction left overnight. After removal of methanol in vaccuo, the residue was chromatographed to give E12 as a solid (R^6 = 4-thien-2-yl, R^1 = Me; 70% yield).

NMR(H^1, $CDCl_3$) for E12(R^6 = 4-thien-2-yl, R^1 = Me): δ 10.30, br, s, 1H; 7.17, d (J = 1.5 Hz), 1H; 6.86, d (J=1.5 Hz), 1H; 3.68, m, 1H; 3.42, d(J = 12 Hz), 1H, 3.31-3.40, m, 3H, 3.29, s, 3H; 1.52, s, 9H.

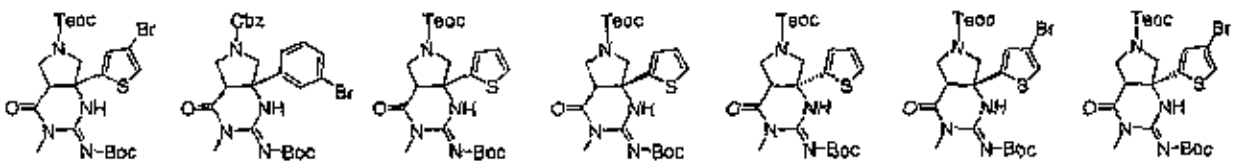
Method E. Step 10

To a solution of 13 g of E12 (R^6 = 4-thien-2-yl, R^1 = Me) in 100 ml DCM was added Teoc-OSu (1.03 eq) and DIEA (1.1 eq) at 0°C. The reaction was stirred until disappearance of E12 (R^6 = 4-thien-2-yl, R^1 = Me) before it was extracted with EtOAc/water. The organic layer was dried and solvent evaporated and the residue chromatographed to give E13 (R^6 = 4-thien-2-yl, R^1 = Me) as an oil.

NMR(H^1, $CDCl_3$) for E13 (R^6 = 4-thien-2-yl, R^1 = Me): *δ 10.40, br, m, 1H; 7.22, br. s, 1H; 6.90, 1H; 4.20, m, 2H; 3.68-4.06, m, 4H; 3.47, m, 1H; 3.30, s, 3H; 1.29, s, 9H; 1.01, m, 2H; 0.03, s, 9H.*

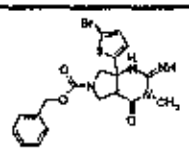
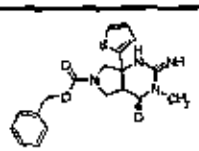
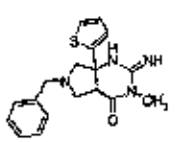
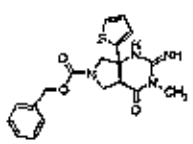
E13 (R^6 = 4-thien-2-yl, R^1 = Me) was resolved using a semi-prep ChiralPak AS column eluted with 50% isopropanol in hexane (50 ml/min): t = 19.3 min, enantiomer I, E19 (R^6 = 4-thien-2-yl, R^1 = Me), [D] = -94° mL g^{-1} dm^{-1} (MeOH, C = 1, 23 °C); t = 39.5 min, enantiomer II, E20 (R^6 = 4-thien-2-yl, R^1 = Me), [D] = +105° mL g^{-1} dm^{-1} (MeOH, C = 1, 23 °C).

The following compounds were produced using similar methods:

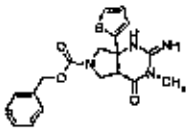


E14 E15 E16 E17 E18 E19 E20

The following compounds were generated *using method similar to* Method E *followed by deprotection of Boc using* 20% TFA in DCM.

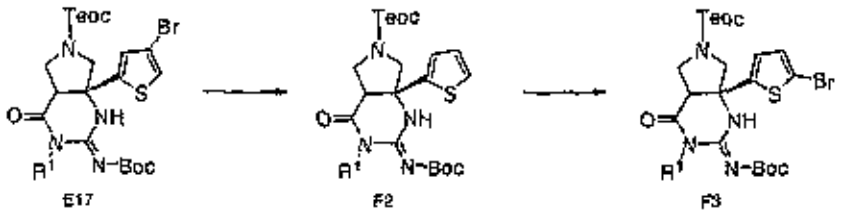
Structure	Obs. Mass	Structure	Obs. Mass
	463.25		385.21
	341.19		385.21

63



385.21

Method F



E17 F2 F3

Method F, Step 1

A MeOH solution (40 ml) of E17(1.8 g, R^1 = Me) was hydrogenated at 1 atm with 0.9 g of 10% Pd/C for 1.5 h. After the solution was adjusted to basic using Et_3N, it was filtered, concentrated and residue chromatographed to give F2 (1.41 g, R^1 = Me).

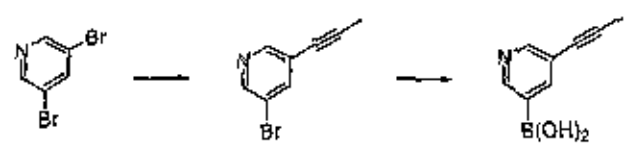
NMR(H^1, $CDCl_3$) for F2 (R^1 = Me): δ 10.40, br, m, 1H; 7.31, br. m, 1H; 6.97-6.99, m,2H; 4.20, m, 2H; 3.68-4.06, m, 4H; 3.50, m, 1H; 3.30, s, 3H; 1.53, s, 9H; 1.01, m, 2H; 0.03, s, 9H.

Method F, Step 2

A DMF solution (15 ml) of F2 (1.41 g, R^1 = Me) was treated with NBS (1.2 eq) and the reaction was stirred overnight before it was extracted using EtOAc/water. The organic solution was evaporated and the residue chromatographed to give F3 (R^1 = Me).

NMR(H^1, $CDCl_3$) for F3 (R^1 = Me): δ 10.39, br, m, 1H; 6.94, d (J = 4 Hz), 1H; 6.76, m,1H; 4.20, m, 2H; 3.68-4.04, m, 4H; 3.43, m, 1H; 3.29, s, 3H; 1.53, s, 9H; 1.01, m, 2H; 0.03, s, 9H.

Method G



G1 G2 G3

Method G, Step 1;

A mixture of G1 (2.5 g), CuI (0.3 eq), palladium tetrakistriphenylphosphine (0.05 eq), TBAF (1 N in THF, 1 eq), TMS-propyne(1 eq) and triethylamine(3.3 eq) in 400 mL of toluene was stirred at rt for 3h before it was extracted with DCM and water. The organic layer was dried, evaporated and the residue chromatographed to give compound G2 in 68% yield.

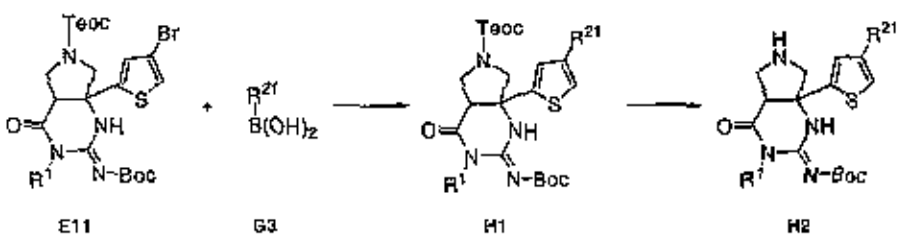
NMR(H^1, $CDCl_3$) for G2: δ 8.54, m, 1H; 8.51, m, 1H; 7.81, m, 1H; 2.08, s, 3H.

Method G. Step 2;

To A 1000 mL flame dried flask charged with anhydrous toluene (1.6 mL/mmol, 188 mL) and anhydrous THF (0.4 mL / mmol47 mL) under nitrogen was added triisopropyl borate (32 mL, 141.36 mmol, 1.2 equiv.) and 3-bromo-3-propynylpyridine (23 gm, 117.8 mmol). The mixture was cooled to -40 °C followed by addition of *n*-Butyllithium (2.5 M in hexanes, 56 mL, 141.36 mmol) via a syringe pump over 1 hr. The mixture was stirred for an additional 0.5 hr while the temperature was held at -40°C before it was warmed to – 20°C followed by addition of 2 N aq. HCl (120 mL). After removal of the organic layer, the pH of the aqueous phase was adjusted to pH7 using a 5 N NaOH solution. A white solid product precipitated as the pH approached 7. The aq. mixture was then saturated with NaCl using solid NaCl, and extracted three times with THF (150 mL). The combined THF extracts were evaporated in vacuo to provide a solid, (18 gm, 95 % yield).

NMR(H^1, $CDCl_3$) for G3: δ 8.67, s, 1H; 8.48, s, 1H; 8.09, s, 1H; 2.06, s, 3H.

Method H



Method H, Step 1,

To a solution of bromide E11(1 g, 1.74 mmol, R^1= Me) and boronic acid G3 (1.5 eq, R^{21} = m-propynylpyridin-3-yl) in 7 mL tBuOH was added dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium(II) dichloromethane (0.15 eq) followed by aqueous K_2CO_3 (1N, 1.5 equiv.). The resulting mixture was heated at 60°C for 1h before it was cooled, diluted with ethyl acetate and washed with water. The organic

layer was dried, concentrated and the residue was chromatographed using a silica gel column eluted with ethyl acetate in hexanes to give H1 (R^1= Me, R^{21} = m-propynylpyridin-3-yl; Yield 90%).

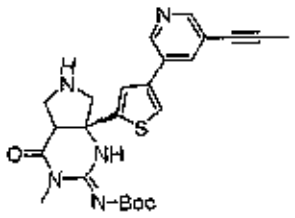
NMR(H^1, $CDCl_3$) for H1(R^1= Me, R^{21} = m-propynylpyridin-3-yl): δ 10.45, br.1H; 8.63, br. s, 1H; 8.53, br. s, 1H; 7.76, br s, 1H; 7.46, br s, 1H; 7.20, m, 1H; 4.20, m, 2H; 3.90-4.13, m, 3H; 3.74, m, 1H; 3.73, m, 1H; 3.31, s, 3H; 2.08, s, 3H; 1.53, s, 9H; 1.01, m, 2H; 0.03, s, 9H.

Method H, Step 2,

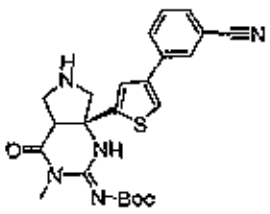
Into a 25 mL flask containing H1 (1gm, 1.64 mmol, R^1= Me, R^{21} = m-propynylpyridin-3-yl) was added 5 mL of 1 M TBAF in THF at 0°C and the solution was stirred at rt for 4h. The reaction mixture was poured into saturated solution of $NaHCO_3$, extracted with ethyl acetate. The organic layer was concentrated and residue purified with 2% MeOH/ CH_2Cl_2 to give H2 (R^1= Me, R^{21} = m-propynylpyridin-3-yl) in 70% yiled.

NMR(H^1, $CDCl_3$) for H2(R^1= Me, R^{21} = m-propynylpyridin-3-yl): δ10.36, s, 1H; 8.65, s, 1H; 8.53, s, 1H; 7.77, s, 1H; 7.43, br s, 1H; 7.18, m, 1H; 3.73, m, 1H; 3.49, m, 2H; 3.40, m, 2H; 3.32, s, 3H; 2.09, s, 3H; 1.54, s, 9H.

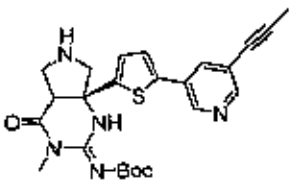
The following compounds were generated using similar method:



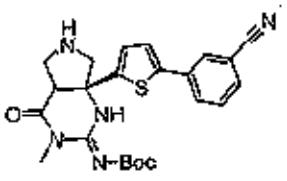
H2



H3



H4



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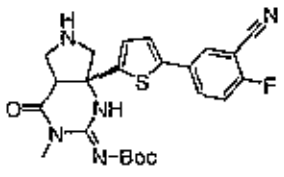
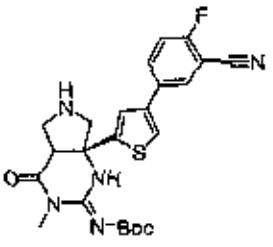
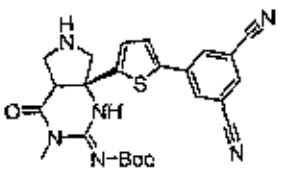


H6



H7



H8

The following compounds were generated using method similar to method H following by deprotection of Boc using 20% TFA in DCM.

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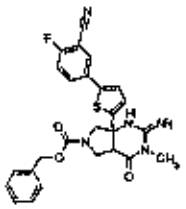
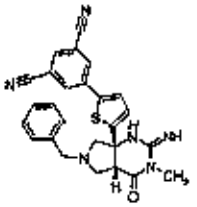
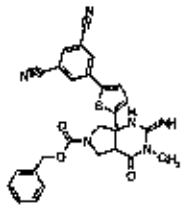
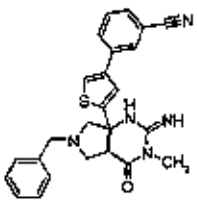
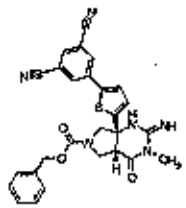
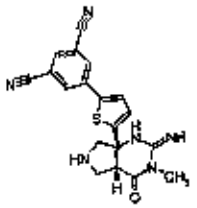
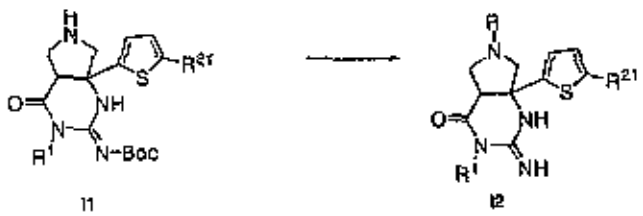
	504.3		467.3
	511.3		NA
	511.3		377.2

Method I



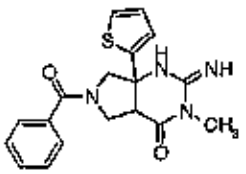
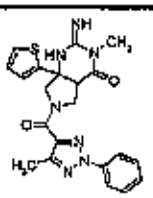
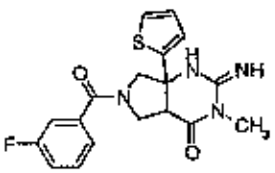
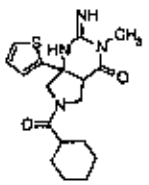
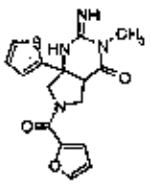
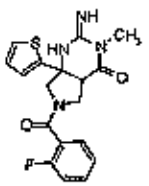
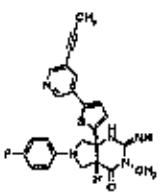
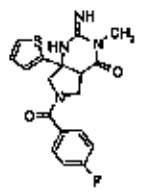
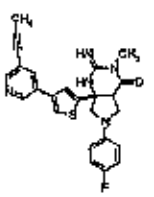
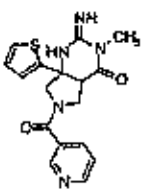
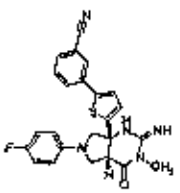
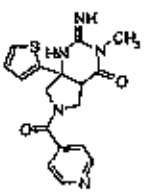
I1 I2

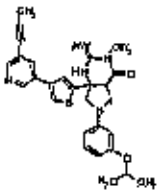
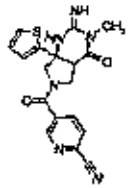
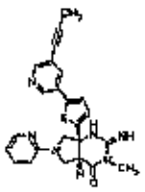
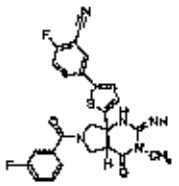
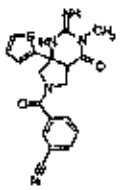
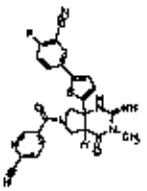
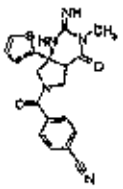
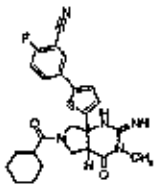
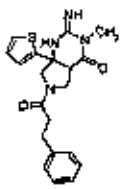
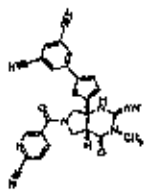
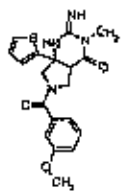
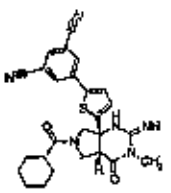
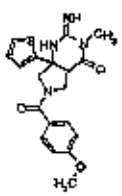
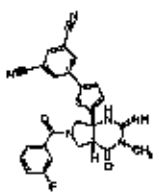
Method I, Step A:

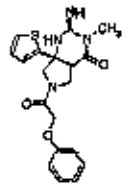
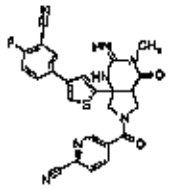
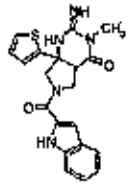
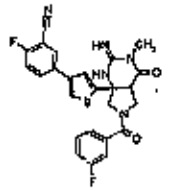
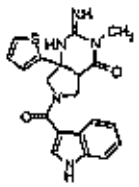
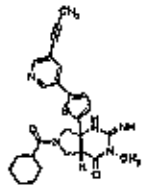
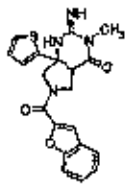
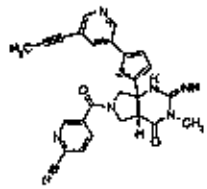
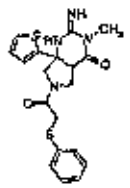
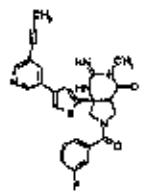
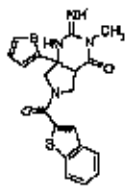
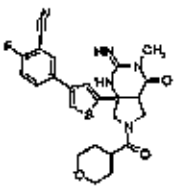
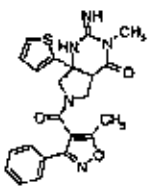
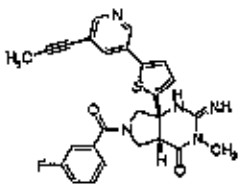
To a DCM (2 ml) solution of I1 (35 mg) was added HOBt (15 mg), m-Fluorobenzoic acid (15.8 mg), DIEA (28 mg) followed by EDCI (21.5 mg) and the solution was stirred for 3 h. before it was extracted with EtOAc. The organic layer was dried, concentrated and residue chromatographed to give a product which was deprotected with 20% TFA/DCM to give product I1 after reverse phase purification.

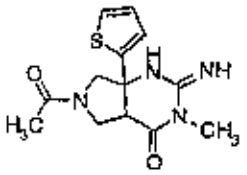
NMR(H^1, $CDCl_3$) for H2(*R = m-F-benzoyl*, R^1= *Me*, R^{21} = *m-propynylpyridin-3-yl*): δ10.71, br s, 1H; 8.85, s, 1H; 8.58, s, 1H; 8.20, s, 1H; 7.01-7.66, m, 6H; 3.80-4.45, m, 5H; 3.38, s, 3H; 2.13, s, 3H.

The following compounds were generated using similar method:

Structure	Obs. Mass	Structure	Obs. Mass
	355.2		436.2
	373.2		361.2
	345.2		373.2
	345.2		373.2
	356.2		356.2
	361.2		356.2

	361.2		381.2
	369.2		492.3
	380.2		500.3
	380.2		480.3
	383.2		507.3
	385.2		487.3
	385.2		499.3

	385.2		500.3
	394.2		492.3
	394.2		476.3
	395.2		496.3
	401.2		488.3
	411.2		482.3
	436.2		488.3



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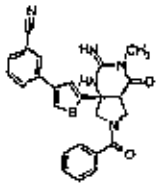

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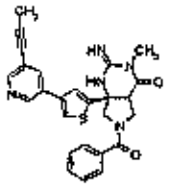

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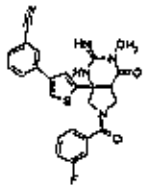

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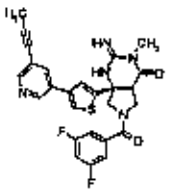


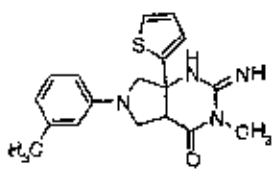
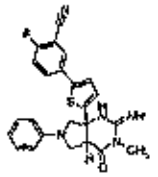
506.3

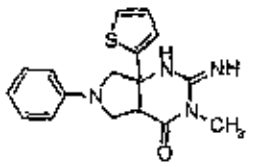
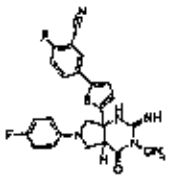
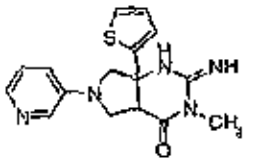
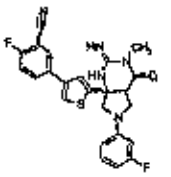
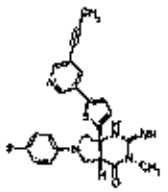
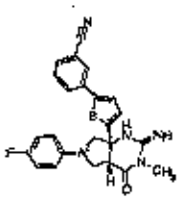
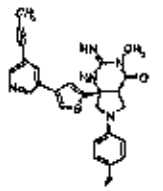
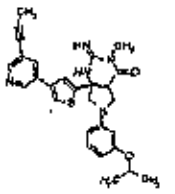
Method J

H2 J1

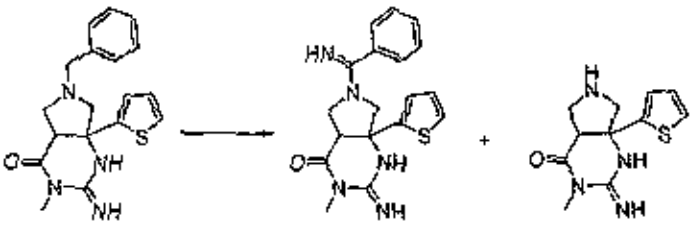
To a DCM solution (2ml) of **H2** (25 mg, R^{21} = m-propynylpyridin-3-yl, R^1 = Me), p-F-phenylboronic acid (20 mg), $Cu(OAc)_2$, and 0.1 ml triethylamine was added preactivated 4 Å molecular sieves (5 micron, 20 mg). The reaction was stirred for 48 h before the solid was filtered and the organic solution concentrated and the residue chromatographed to give a product which was deprotected using 20% TFA/DCM to give J1 (R^{21} = m-propynylpyridin-3-yl, R^1 = Me and R = p-fluorophenyl)after reverse phase purification.

The following compounds were generated using similar method:

Structure	Obs. Mass	Structure	Obs. Mass
	341.2		446.2

	327.2		464.3
	328.2		464.3
	460.3		446.3
	460.3		500.3

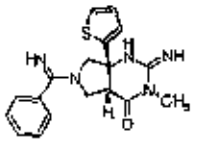
Method K



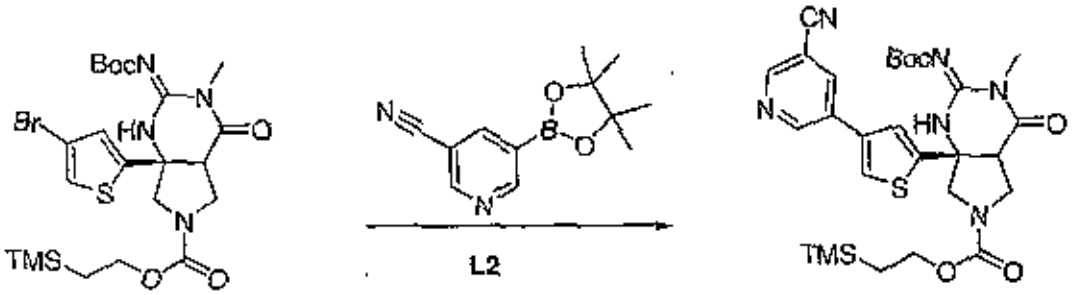
K1 K2 K2

Method K, Step 1.

To a solution of K1 (3.5 g) in 60 ml 1:1 ration of DCM/HOAc was added 1.5 g of NBS at 0°C and the solution was allowed to warm-up to rt. The reaction mixture was pured into a mixture of DCM and sat. K2CO3/Na2SO3 (1:1) and the organic layer was concentrated, residue chromatographed to give K2 (100 mg) and K3 (750 mg).

Structure	Obs. Mass
	354.2

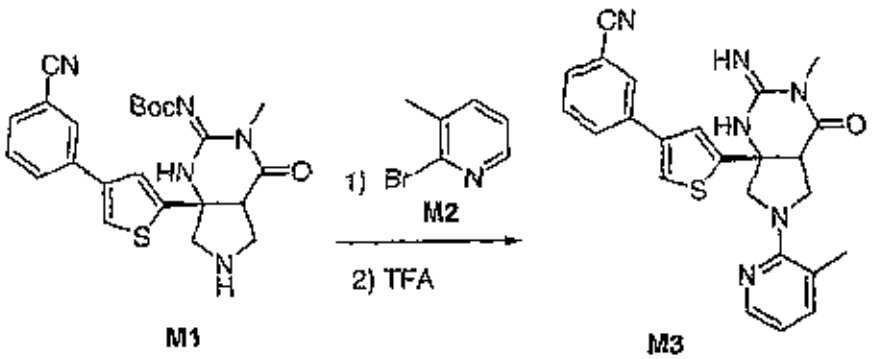
Method L



To a solution of bromide **L1** (500 mg, 0.872 mmol, 1.0 equiv.) and boronic ester (300 mg, 1.30 mmol, 1.5 equiv.) in 3 mL tBuOH were added Tris-(dibenzylideneacetone)dipalladium (0) (119 mg, 0.130 mmol, 0.15 equiv.) and Tri-t-butylphosphonium tetrafluoroborate (119 mg) followed by aqueous K_2CO_3 (1M, 1.30 mL, 1.30 mmol, 1.5 equiv.). The resulting mixture was heated at 60 °C for 1hr and TLC indicated completion of reaction. The reaction mixture was diluted with ethyl acetate and wash with water. The organic layer was dried with MgSO4, concentrated and purified via a silica gel column with ethyl acetate in hexanes.

NMR(H^1, $CDCl_3$) for **L3**: δ10.71, m, 1H; 8.96, s, 1H; 8.80, s, 1H; 8. 40, s, 1H; 7.56, s, 1H; 7.24, s, 1H; 4.17-4.22, m, 2H; 3.87-4.11, m, 3H; 3.71-3..80, m, 1H; 3.50-3.60, m, 1H; 3.30, s, 3H; 1.52, s, 9H; 0.98-1.05, m, 2H; 0.07, s, 9H.

Method M

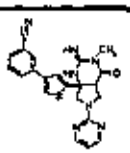
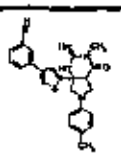
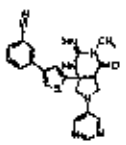
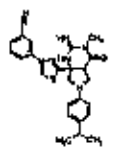
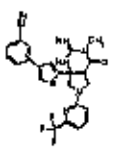
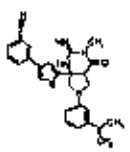
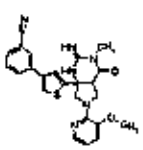
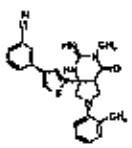


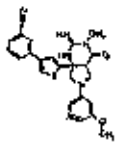
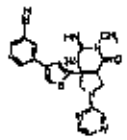
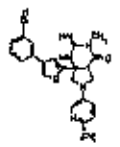
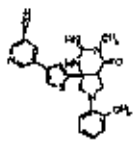
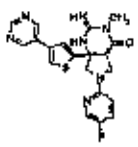
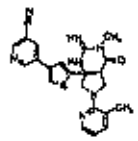
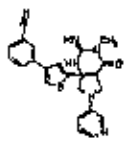
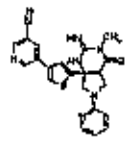
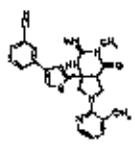
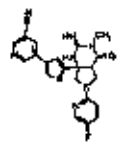
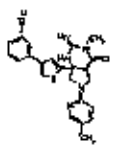
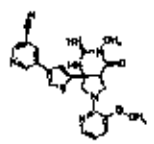
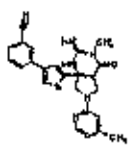
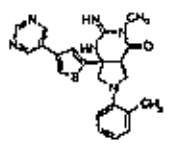
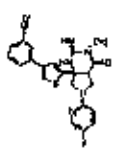
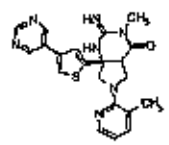
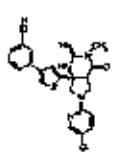
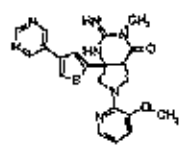
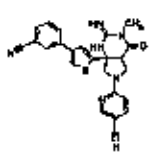
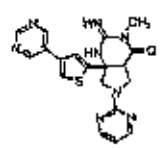
M1 M3

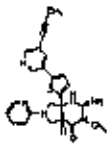
To a solution of amine **M1** (15 mg, 0.033 mmol, 1.0 equiv.) and bromide **M2** (5 equiv.) in 0.250 mL toluene were added Tris(dibenzylideneacetone)dipalladium (0) (3.0 mg, 0.0032 mmol, 0.10 equiv.) and racemic-2,2'-Bis-(diphenylphosphino)-1.1'-binaphthyl (3.0 mg) followed by 12 mg of NaOtBu. The resulting mixture was heated at 70 °C for 12 hr and the crude product was purified via a silica gel column eluted with EtOAc/Hexane to give a product which was treated with 20% TFA in DCM followed by reverse phase HPLC purification to give product **M3**.

NMR(H^1, CD_3OD) for **M3**: δ7.57-8.04, m , 8H; 7.00-7.04, m, 1H; 4.32-4.56, m, 4H; 4.12-4.17, m, 1H; 3.35, s, 3H; 2.55, s, 3H.

The following compounds were generated using method similar to Method M.

Structure	Obs. Mass	Structure	Obs. Mass
	430.2		
	430.2		470.3
	497.3		470.3
	459.3		442.2

	459.3		430.2
	443.2		443.2
	424.2		444.2
	429.2		430.2
	443.2		448.3
	443.2		460.3
			419.2
	447.3		420.2
	463.3		436.2
	*454.3*		407.2



443.2

Human Cathepsin D FRET assay.

The substrate used below has been described **(Y.Yasuda et al., J. Biochem., 125, 1137 (1999)).** Substrate and enzyme are commercially available.

The assay can be run in a 30 µl final volume using a 384 well Nunc black plate. 8 concentrations of compound can be pre-incubated with enzyme for 30 mins at 37° C followed by addition of substrate with *continued incubation at 37° C for 45 mins.* The rate of increase in fluorescence is linear for over 1h and is measured at the end of the incubation period using a *Molecular Devices FLEX station plate reader. Kis are* interpolated from the IC_{50}s using a Km value of 4 µM and the substrate concentration of 2.5 µM.

Reagents

Na-Acetate pH 5

1% Brij-35 from 10% stock (Calbiochem)

DMSO

Purified (>95%) human liver Cathepsin D (Athens Research & Technology Cat# 16-12-030104)

Peptide substrate(Km=4uM) Mca-Gly-Lys-Pro-Ile-Leu-Phe-Phe-Arg-Leu-Lys(Dnp)-D-Arg-NH_2 Bachem Cat # M-2455

Pepstatin is used as a control inhibitor (Ki~0.5 nM) and is available from Sigma.

Nunc 384 well black plates

Final Assay buffer conditions

100 mM Na Acetate pH 5.0

0.02% Brij-35

1% DMSO

Compound can be diluted to 3x final concentration in assay buffer containing 3% DMSO. 10 µl of compound will be added to 10 µl of 2.25 nM enzyme (3x) diluted in assay buffer without DMSO, mixed briefly, spun, and can be incubated at 37° C for 30 mins. 3x substrate (7.5 µM) is prepared in 1x assay buffer without DMSO. 10 µl of substrate will be added to each well mixed and spun briefly to initiate the reaction. Assay plates can be incubated at 37 C for 45 mins and read on 384 compatible fluorescence plate reader using a 328 nm Ex and 393 nm Em.

BACE-1 Cloning, Protein Expression and Purification.

A predicted soluble form of human BACE1 (sBACE1, corresponding to amino acids 1-454) can be generated from the full length BACE1 cDNA (full length human BACE1 cDNA in pCDNA4/mycHisA construct; University of Toronto) by PCR using the advantage-GC cDNA PCR kit (Clontech, Palo Alto, CA). A HindIII/PmeI fragment from pCDNA4-sBACE1myc/His can be blunt ended using Klenow and subcloned into the Stu I site of pFASTBACI(A) (Invitrogen). A sBACE1mycHis recombinant bacmid can be generated by transposition in DH10Bac cells(GIBCO/BRL). Subsequently, the sBACE1mycHis bacmid construct can be transfected into sf9 cells using CellFectin (Invitrogen, San Diego, CA) in order to generate recombinant baculovirus. Sf9 cells are grown in SF 900-II medium (Invitrogen) supplemented with 3% heat inactivated FBS and 0.5X penicillin/streptomycin solution (Invitrogen). Five milliliters of high titer plaque purified sBACEmyc/His virus is used to infect 1L of logarithmically growing sf9 cells for 72 hours. Intact cells are pelleted by centrifugation at 3000xg for 15 minutes. The supernatant, containing secreted sBACE1, is collected and diluted 50% v/v with 100 mM HEPES, pH 8.0. The diluted medium is loaded onto a Q-sepharose column. The Q-sepharose column is washed with Buffer A (20 mM HEPES, pH 8.0, 50 mM NaCl).

Proteins, can be eluted from the Q-sepharose column with Buffer B (20 mM HEPES, pH 8.0, 500 mM NaCl). The protein peaks from the Q-sepharose column are pooled and loaded onto a Ni-NTA agarose column. The Ni-NTA column can be then washed with Buffer C (20 mM HEPES, pH 8.0, 500 mM NaCl). Bound proteins

are then eluted with Buffer D (Buffer C+250 mM imidazole). Peak protein fractions as determined by the Bradford Assay (Biorad, CA) are concentrated using a Centricon 30 concentrator (Millipore). sBACE1 purity is estimated to be ~90% as assessed by SDS-PAGE and Commassie Blue staining. N-terminal sequencing indicates that greater than 90% of the purified sBACE1 contained the prodomain; hence this protein is referred to as sproBACE1.

Peptide Hydrolysis Assay.

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

IC_{50} determinations for inhibitors, (*I*), are determined by measuring the percent change of the relative fluorescence at 665 nm divided by the relative fluorescence at 620 nm, (665/620 ratio), in the presence of varying concentrations of *I* and a fixed concentration of enzyme and substrate. Nonlinear regression analysis of this data can be performed using GraphPad Prism 3.0 software selecting four parameter logistic equation, that allows for a variable slope. Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*Hill Slope)); X is the logarithm of concentration of I, Y is the percent change in ratio and Y starts at bottom and goes to top with a sigmoid shape.

Using the above assay, the K_i values of some of the compounds were determined. The K_i values ranged from 0.1 to 100,000 nM.

Human mature Renin enzyme assay:

Human Renin can be cloned from a human kidney cDNA library and C-terminally epitope-tagged with the V5-6His sequence into *pCDNA3.1*. *pCNDA3.1*-Renin-V5-6His is stably expressed in HEK293 cells and purified to >80% using standard *Ni-Affinity chromatography*. *The prodomain* of the recombinant human renin-V5-6His can be removed by limited proteolysis using immobilized TPCK-trypsin to give mature-human renin. Renin enzymatic activity can be monitored using a commercially available fluorescence resonance energy transfer (FRET) peptide substrate, RS-1 (Molecular Probes, Eugene, OR) in 50 mM Tris-HCl pH 8.0, 100 mM NaCl, 0.1%Brij-35 and 5% DMSO buffer for 40 mins at 30 °Celsius in the presence or absence of different concentrations of test compounds. Mature human Renin is present at approximately 200 nM. Inhibitory activity *is defined as the percent* decrease in renin induced fluorescence at the end of the 40 min incubation compared *to vehicle controls and samples lacking enzyme.*

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

In one aspect of the invention, a combination of *at least one compound of* formula I with at least one muscarinic m_1 agonist or m_2 antagonist can be used. *Examples of m_1 agonists are known in the art.* Examples of m_2 antagonists are also known in the art; in particular, m_2 antagonists are disclosed in US patents 5,883,096; 6,037,352; 5,889,006; 6,043,255; 5,952,349; 5,935,958; 6,066,636; 5,977,138; 6,294,554; 6,043,255; and 6,458,812; and in WO 03/031412, all of which are incorporated herein by reference.

In other aspects of the invention relating to a combination of at least one compound of formula I and at least one other agent, for example a beta secretase inhibitor; a gamma secretase inhibitor; an HMG-CoA reductase *inhibitor such as* atorvastatin, lovastatin, simvastatin, pravastatin, fluvastatin and rosuvastatin; non-steroidal *anti-inflammatory agents such as, but not* necessarily limited to ibuprofen, relafen or naproxen; N-methyl-D-aspartate receptor antagonists such as memantine; anti-amyloid antibodies including humanized monoclonal antibodies; vitamin E;

nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; antibiotics such as doxycycline; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; $GABA_A$ inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity. Preferably, these combinations are directed to the treatment of Alzheimer's Disease.

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

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

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

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

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

Preferably the compound is administered orally.

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

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

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

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

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

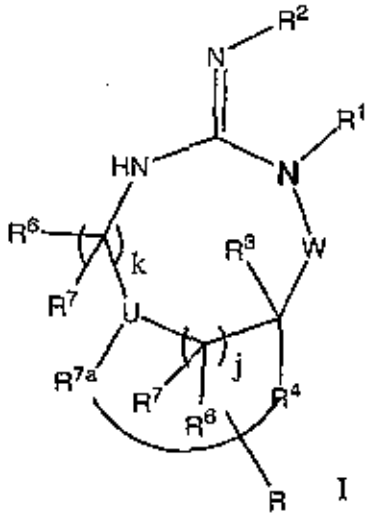
When separate pharmaceutical compositions of a compound of formula I and a cholinesterase inhibitor are to be administered, they can be provided in a kit comprising in a single package, one container comprising a compound of formula I in a pharmaceutically acceptable carrier, and a separate container comprising a

cholinesterase inhibitor in a pharmaceutically acceptable carrier, with the compound of formula I and the cholinesterase inhibitor being present in amounts such that the combination is therapeutically effective. A kit is advantageous for administering a combination when, for example, the components must be administered at different time intervals or when they are in different dosage forms.

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

We claim:

1. A compound having the structural formula I



I

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

j is 0 or 1;

k is 0 or 1, provided that when k is 1, U cannot be -N-;

W is a bond, -C(=S)-, –S(O)-, -$S(O)_2$-, -C(=O)-, -O-, -$C(R^6)(R^7)$-, -$N(R^5)$-, -$C(R^6)(R^7)C(=O)$-, or -$C(=N(R^5))$-;

U is –N- or -$C(R^6)$-;

R is 1 to 5 R^{21} groups;

R^1, R^2 and R^5 are independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, –OR^{15}, -CN, -$C(=NR^{11})R^8$, -$C(O)R^8$, -$C(O)OR^9$, -$S(O)R^{10}$, -$S(O)_2R^{10}$, -$C(O)N(R^{11})(R^{12})$, -$S(O)N(R^{11})(R^{12})$, -$S(O)_2N(R^{11})(R^{12})$, -NO_2, -$N=C(R^8)_2$ and –$N(R^{11})(R^{12})$, provided that R^1 and R^5 are not both selected from -NO_2, -$N=C(R^8)_2$ and –$N(R^{11})(R^{12})$;

R^3, R^6 and R^7 are independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, halo, $-CH_2-O-Si(R^9)(R^{10})(R^{19})$, -SH, -CN, $-OR^9$, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^{11})(R^{12})$, $-SR^{19}$, $-S(O)N(R^{11})(R^{12})$, $-S(O)_2N(R^{11})(R^{12})$, $-N(R^{11})(R^{12})$, $-N(R^{11})C(O)R^8$, $-N(R^{11})S(O)R^{10}$, $-N(R^{11})S(O)_2R^{10}$, $-N(R^{11})C(O)N(R^{12})(R^{13})$, $-N(R^{11})C(O)OR^9$ and $-C(=NOH)R^8$;

R^4 and R^{7a} are independently selected from the group consisting of a bond, alkylene, arylalkylene, heteroarylalkylene, cycloalkylalkylene, heterocycloalkylalkylene, arylcycloalkylalkylene, heteroarylcycloalkylalkylene, arylheterocycloalkylalkylene, heteroarylheterocycloalkylalkylene, cycloalkylene, arylcycloalkylene, heteroarylcycloalkylene, heterocycloalkylene, arylheterocycloalkylene, heteroarylheterocycloalkylene, alkenylene, arylalkenylene, cycloalkenylene, arylcycloalkenylene, heteroarylcycloalkenylene, heterocycloalkenylene, arylheterocycloalkenylene, heteroarylheterocycloalkenylene, alkynylene, arylalkynylene, arylene, cycloalkylarylene, heterocycloalkylarylene, cycloalkyenylarylene, cycloalkenylarylene, heterocycloalkenylarylene, heteroarylene, cycloalkylheteroarylene, heterocycloalkylheteroarylene, cycloalkenylheteroarylene and heterocycloalkenylheteroarylene, with the proviso that both R^4 and R^{7a} are not both a bond;

R^4 and R^{7a} together can be a C_1 to C_8 carbon chain, wherein, optionally, one, two or three ring carbons can be replaced by –O-, -C(O)-, -C(S)-, -S-, -S(O)-, $-S(O)_2-$ or $-N(R^5)-$, and R^4 and R^{7a} together with the carbon atoms to which they are attached, form a 3 to 8 membered ring, optionally substituted by R, with the following provisos:

that when at least one of the carbons is replaced by –O-, -C(O)-, -C(S)-, -S-, -S(O)- ,$-S(O)_2-$or $-N(R^5)-$, then the number of carbons in the R^4 and R^{7a} portion of the chain that bonds with U is b, wherein b is 0 to 5, and the number of carbons that are

in the R^4 and R^{7a} portion of the chain that bonds with the carbon of $-C(R^9)-$ is c, wherein c is 0 to 5;

that when j is 0 or 1, at least one of the ring carbons must be replaced by -O-, -C(O)-, -C(S)-, -S-, -S(O)- ,$-S(O)_2$-or $-N(R^5)$-;

that when j is 0 or 1 and only one ring carbon is replaced with –O-, -C(O)-, -C(S)-, -S-, -S(O)- ,$-S(O)_2$-or $-N(R^5)$-, R^4 and R^{7a} cannot form a cycloalkylether;

R^8 is independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, $-OR^{15}$, $-N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$ and $-N(R^{15})C(O)OR^{16}$;

R^9 is independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, and heterocycloalkenylheteroaryl;

R^{10} is independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl,

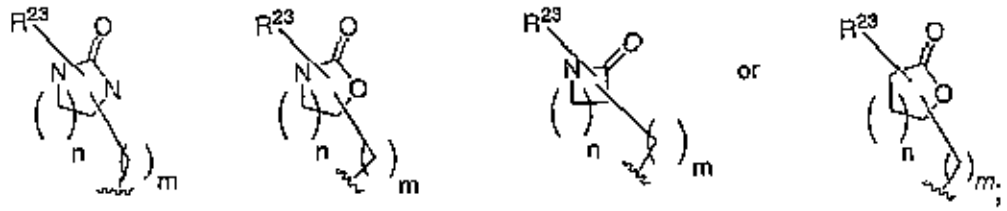
heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl and –N(R^{15})(R^{16});

R^{11}, R^{12} and R^{13} are independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, -C(O)R^8, -C(O)OR^9, -S(O)R^{10}, -S(O)$_2R^{10}$, -C(O)N(R^{15})(R^{16}), -S(O)N(R^{15})(R^{16}), -S(O)$_2$N(R^{15})(R^{16}) and –CN;

R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, R^{18}-alkyl, R^{18}-arylalkyl, R^{18}-heteroarylalkyl, R^{18}-cycloalkylalkyl, R^{18}-heterocycloalkylalkyl, R^{18}-arylcycloalkylalkyl, R^{18}-heteroarylcycloalkylalkyl, R^{18}-arylheterocycloalkylalkyl, R^{18}-heteroarylheterocycloalkylalkyl, R^{18}-cycloalkyl, R^{18}-arylcycloalkyl, R^{18}-heteroarylcycloalkyl, R^{18}-heterocycloalkyl, R^{18}-arylheterocycloalkyl, R^{18}-heteroarylheterocycloalkyl, R^{18}-alkenyl, R^{18}-arylalkenyl, R^{18}-cycloalkenyl, R^{18}-arylcycloalkenyl, R^{18}-heteroarylcycloalkenyl, R^{18}-heterocycloalkenyl, R^{18}-arylheterocycloalkenyl, R^{18}-heteroarylheterocycloalkenyl, R^{18}-alkynyl, R^{18}-arylalkynyl, R^{18}-aryl, R^{18}-cycloalkylaryl, R^{18}-heterocycloalkylaryl, R^{18}-cycloalkenylaryl, R^{18}-heterocycloalkenylaryl, R^{18}-heteroaryl,

R^{18}-cycloalkylheteroaryl, R^{18}-heterocycloalkylheteroaryl, R^{18}-cycloalkenylheteroaryl, and R^{18}-heterocycloalkenylheteroaryl; or

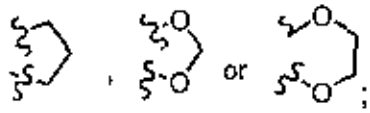
R^{15}, R^{16} and R^{17} are



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

R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, $-NO_2$, halo, HO-alkoxyalkyl, $-CF_3$, -CN, alkyl-CN, $-C(O)R^{19}$, -C(O)OH, $-C(O)OR^{19}$, $-C(O)NHR^{20}$, $-C(O)NH_2$, $-C(O)NH_2$-C(O)N(alkyl)$_2$, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(heteroaryl), $-SR^{19}$, $-S(O)_2R^{20}$, $-S(O)NH_2$, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl), $-S(O)_2NH_2$, $-S(O)_2NHR^{19}$, $-S(O)_2$NH(heterocycloalkyl), $-S(O)_2N(alkyl)_2$, $-S(O)_2N(alkyl)(aryl)$, $-OCF_3$, -OH, $-OR^{20}$, -O-heterocycloalkyl, -O-cycloalkylalkyl, -O-heterocycloalkylalkyl, $-NH_2$, $-NHR^{20}$, $-N(alkyl)_2$, $-N(arylalkyl)_2$, -N(arylalkyl)-(heteroarylalkyl), $-NHC(O)R^{20}$, $-NHC(O)NH_2$, -NHC(O)NH(alkyl), -NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl), $-NHS(O)_2R^{20}$, $-NHS(O)_2$NH(alkyl), $-NHS(O)_2N(alkyl)(alkyl)$, $-N(alkyl)S(O)_2NH(alkyl)$ and $-N(alkyl)S(O)_2N(alkyl)(alkyl)$;

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



R^{19} is alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl,

heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl or heterocycloalkenylheteroaryl;

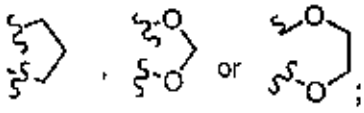
R^{20} is halo substituted aryl, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl or heterocycloalkenylheteroaryl,

and wherein each of the alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, in R, R^1, R^2, R^3, R^4, R^5, R^6, R^7; R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13}

are independently unsubstituted or substituted by 1 to 5 R^{21} groups independently selected from the group consisting of alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl,

cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, halo, -CN, -C(=NR^{11})R^{15}, -OR^{15}, -C(O)R^{15}, -C(O)OR^{15}, -C(O)N(R^{15})(R^{16}), -SR^{15}, -S(O)N(R^{15})(R^{16}), -CH(R^{15})(R^{16}), -S(O)$_2$N(R^{15})(R^{16}), –C(=NOR^{15})R^{16}, -P(O)(OR^{15})(OR^{16}), -N(R^{15})(R^{16}), -alkyl-N(R^{15})(R^{16}), -N(R^{15})C(O)R^{16}, -CH$_2$-N(R^{15})C(O)R^{16}, -CH$_2$-N(R^{15})C(O)N(R^{16})(R^{17}), -CH$_2$-R^{15}; -CH$_2$N(R^{15})(R^{16}), -N(R^{15})S(O)R^{16}, -N(R^{15})S(O)$_2$R^{16}, -CH$_2$-N(R^{15})S(O)$_2$R^{16}, -N(R^{15})S(O)$_2$N(R^{16})(R^{17}), -N(R^{15})S(O)N(R^{16})(R^{17}), -N(R^{15})C(O)N(R^{16})(R^{17}), -CH$_2$-N(R^{15})C(O)N(R^{16})(R^{17}), -N(R^{15})C(O)OR^{16}, -CH$_2$-N(R^{15})C(O)OR^{16}, -S(O)R^{15}, -N$_3$, -NO$_2$ and -S(O)$_2$R^{15};

and wherein each of the alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl and heterocycloalkenylheteroaryl groups in R^{21} are *independently* unsubstituted or substituted by 1 to 5 R^{22} groups independently selected from the group consisting of alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, *heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl,* arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, *heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl,* alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, *heteroarylheterocycloalkenyl, alkynyl,* arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, *heterocycloalkylheteroaryl,* cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, halo, -CF$_3$, -CN, -C(=NR^{11})R^{15}, -OR^{15}, -C(O)R^{15}, -C(O)OR^{15}, -alkyl-C(O)OR^{15}, -C(O)N(R^{15})(R^{16}), -SR^{15}, -S(O)N(R^{15})(R^{16}), -S(O)$_2$N(R^{15})(R^{16}), –C(=NOR^{15})R^{16}, -P(O)(OR^{15})(OR^{16}), -N(R^{15})(R^{16}), -alkyl-N(R^{15})(R^{16}), -N(R^{15})C(O)R^{16}, -CH$_2$-N(R^{15})C(O)R^{16}, -N(R^{15})S(O)R^{16}, -N(R^{15})S(O)$_2$R^{16}, -CH$_2$-N(R^{15})S(O)$_2$R^{16}, -N(R^{15})S(O)$_2$N(R^{16})(R^{17}), -N(R^{15})S(O)N(R^{16})(R^{17}), -N(R^{15})C(O)N(R^{16})(R^{17}), -CH$_2$-N(R^{15})C(O)N(R^{16})(R^{17}), -N(R^{15})C(O)OR^{16}, -CH$_2$-N(R^{15})C(O)OR^{16}, -N$_3$, -NO$_2$, -S(O)R^{15} and -S(O)$_2$R^{15};

or two R^{21} or two R^{22} moieties on adjacent carbons can be linked together to form  ;

and when R^{21} or R^{22} are selected from the group consisting of $-C(=NOR^{15})R^{16}$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$ and $-CH_2-N(R^{15})C(O)OR^{16}$, R^{15} and R^{16} together can be a C_2 to C_4 chain wherein, optionally, one, two or three ring carbons can be replaced by –C(O)- or –N(H)- and R^{15} and R^{16}, together with the atoms to which they are attached, form a 5 to 7 membered ring, optionally substituted by R^{23};

R^{23} is 1 to 5 groups independently selected from the group consisting of alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, halo, -CN, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, $-C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, -alkyl-$N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$, $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$, $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$, $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ and $-S(O)_2R^{24}$; and wherein each of the alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl,

heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl and heterocycloalkenylheteroaryl groups in R^{23} are independently unsubstituted or substituted by 1 to 5 R^{27} groups independently selected from the group consisting of alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, halo, $-CF_3$, -CN, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, alkyl-$C(O)OR^{24}$, $-C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, -alkyl-$N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$, $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$, $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$, $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ and $-S(O)_2R^{24}$;

R^{24}, R^{25} and R^{26} are independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, R^{27}-alkyl, R^{27}-arylalkyl, R^{27}-heteroarylalkyl, R^{27}-cycloalkylalkyl, R^{27}-heterocycloalkylalkyl, R^{27}-arylcycloalkylalkyl, R^{27}-heteroarylcycloalkylalkyl, R^{27}-arylheterocycloalkylalkyl, R^{27}-heteroarylheterocycloalkylalkyl, R^{27}-cycloalkyl, R^{27}-arylcycloalkyl, R^{27}-heteroarylcycloalkyl, R^{27}-heterocycloalkyl, R^{27}-arylheterocycloalkyl, R^{27}-heteroarylheterocycloalkyl, R^{27}-alkenyl, R^{27}-arylalkenyl, R^{27}-cycloalkenyl, R^{27}-arylcycloalkenyl, R^{27}-heteroarylcycloalkenyl, R^{27}-heterocycloalkenyl,

R^{27}-arylheterocycloalkenyl, R^{27}-heteroarylheterocycloalkenyl, R^{27}-alkynyl, R^{27}-arylalkynyl, R^{27}-aryl, R^{27}-cycloalkylaryl, R^{27}-heterocycloalkylaryl, R^{27}-cycloalkenylaryl, R^{27}-heterocycloalkenylaryl, R^{27}-heteroaryl, R^{27}-cycloalkylheteroaryl, R^{27}-heterocycloalkylheteroaryl, R^{27}-cycloalkenylheteroaryl and R^{27}-heterocycloalkenylheteroaryl;

R^{27} is 1-5 substituents independently selected from the group consisting of alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl, $-NO_2$, halo, $-CF_3$, -CN, alkyl-CN, $-C(O)R^{28}$, -C(O)OH, $-C(O)OR^{28}$, $-C(O)NHR^{29}$, $-C(O)N(alkyl)_2$, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(heteroaryl), $-SR^{28}$, $-S(O)_2R^{29}$, $-S(O)NH_2$, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl), $-S(O)_2NH_2$, $-S(O)_2NHR^{28}$, $-S(O)_2NH(aryl)$, $-S(O)_2NH(heterocycloalkyl)$, $-S(O)_2N(alkyl)_2$, $-S(O)_2N(alkyl)(aryl)$, -OH, $-OR^{29}$, -O-heterocycloalkyl, -O-cycloalkylalkyl, -O-heterocycloalkylalkyl, $-NH_2$, $-NHR^{29}$, $-N(alkyl)_2$, $-N(arylalkyl)_2$, -N(arylalkyl)(heteroarylalkyl), $-NHC(O)R^{29}$, $-NHC(O)NH_2$, -NHC(O)NH(alkyl), -NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl), $-NHS(O)_2R^{29}$, $-NHS(O)_2NH(alkyl)$, $-NHS(O)_2N(alkyl)(alkyl)$, -N(alkyl)$S(O)_2$NH(alkyl) and --N(alkyl)$S(O)_2$N(alkyl)(alkyl);

R^{28} is alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl or heterocycloalkenylheteroaryl;

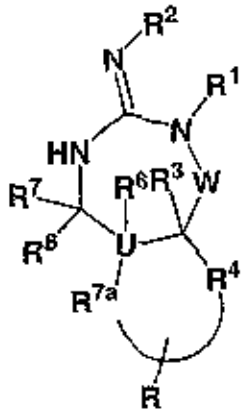
R^{29} is alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl or heterocycloalkenylheteroaryl;

R^{30} is alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl or heterocycloalkenylheteroaryl;

and

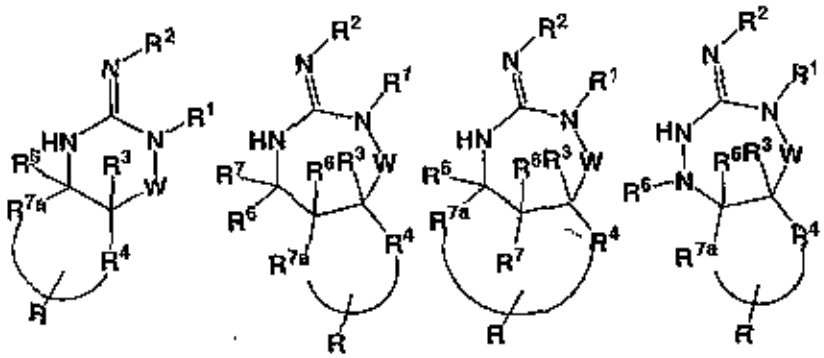
R^{31} is alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylcycloalkylalkyl, heteroarylcycloalkylalkyl, arylheterocycloalkylalkyl, heteroarylheterocycloalkylalkyl, cycloalkyl, arylcycloalkyl, heteroarylcycloalkyl, heterocycloalkyl, arylheterocycloalkyl, heteroarylheterocycloalkyl, alkenyl, arylalkenyl, cycloalkenyl, arylcycloalkenyl, heteroarylcycloalkenyl, heterocycloalkenyl, arylheterocycloalkenyl, heteroarylheterocycloalkenyl, alkynyl, arylalkynyl, aryl, cycloalkylaryl, heterocycloalkylaryl, cycloalkenylaryl, heterocycloalkenylaryl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylheteroaryl, cycloalkenylheteroaryl, heterocycloalkenylheteroaryl;

with the following proviso, that when U, R^{7a} and R^4 cyclize to form the following bicyclic structure:



W cannot be a bond.

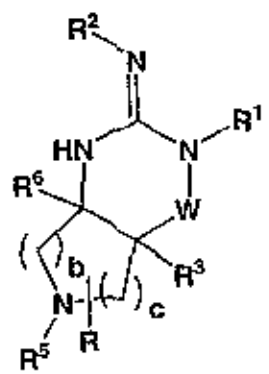
2. A compound of claim 1 having the following structure



I II III IV

wherein R, R^1, R^2, R^3, R^4, R^6, R^7, R^{7a} and W are as defined above, provided that in structure II, W is not a bond.

3. A compound of claim 1 having the following structure



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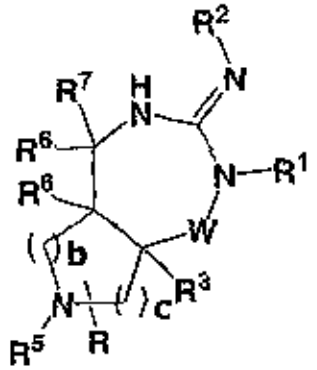
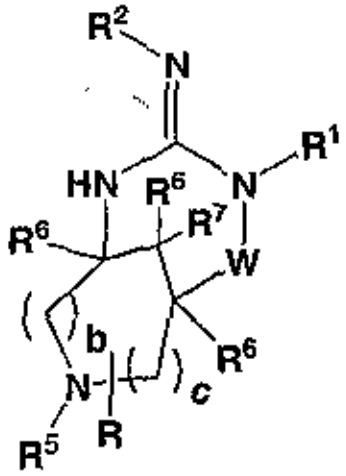
wherein R, R^1, R^2, R^3, R^5, R^6 and W are as defined above, wherein b is 1 to 5 and c is 0 to 5.

4. A compound of claim 1 having the following structure



wherein R, R^1, R^2, R^3, R^5, R^6, R^7 and W are as defined above, wherein b is 1 to 5 and c is 0 to 5.

5. A compound of claim 1 having the following structure



wherein R, R^1, R^2, R^3, R^5, R^6, R^7 and W are as defined above, b is 1 to 4 and c is 0 to 4.

6. A compound of claim 1 wherein R^1 is alkyl.

7. A compound of claim 6 wherein R^1 is methyl.

8. A compound of claim 1 wherein R^2 is H.

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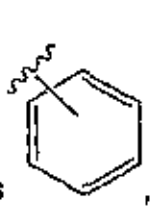
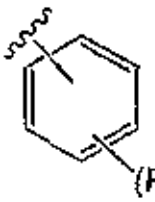
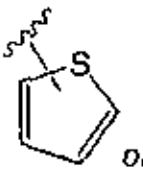
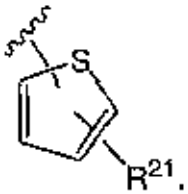
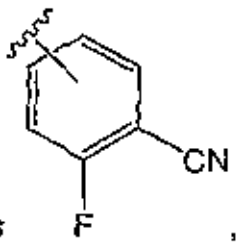
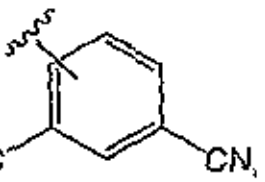
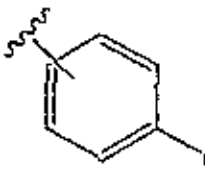
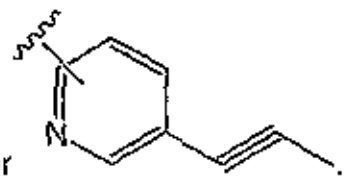
9. A compound of claim 1 wherein R^6 is aryl, $(R^{21})_{1-5}$-aryl, heteroaryl or $(R^{21})_{1-5}$-heteroaryl.

10. A compound of claim 9 wherein R^6 is  ,  ,  or  .

11. A compound of claim 1 wherein R^{21} is –CN, halo, aryl, $(R^{22})_{1-2}$-aryl, heteroaryl or $(R^{22})_{1-2}$-heteroaryl.

12. A compound of claim 11 wherein R^{22} is –CN, halo or alkyne.

13. A compound of claim 12 wherein R^{22} is F or  .

14. A compound of claim 1 wherein R^{21} is  ,  ,  or  .

15. A compound of claim 1 wherein W is -C(O)-.

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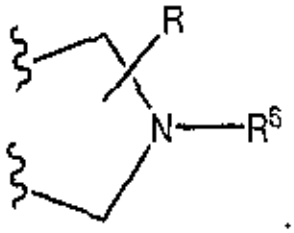
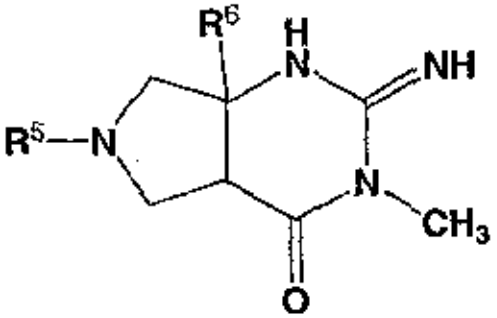
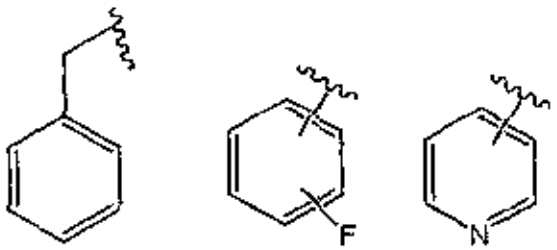
16. A compound of claim 1 wherein R^4 and R^{7a} form  .

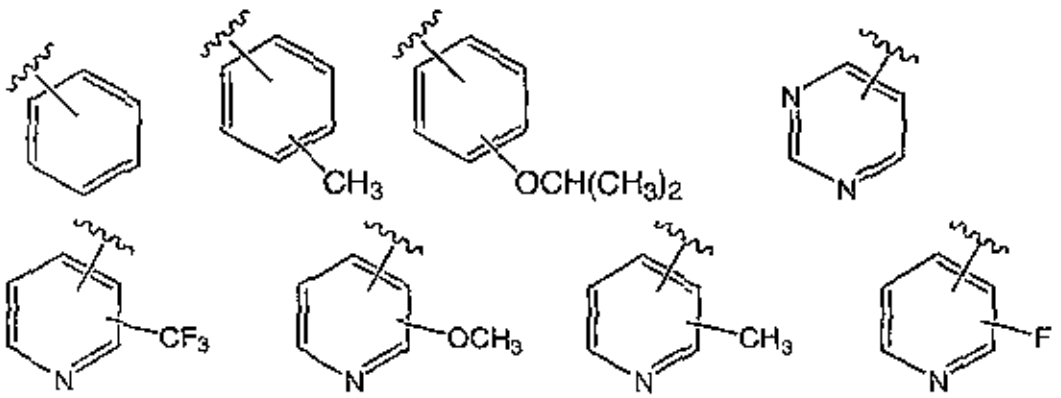
17. A compound of claim 1 having the following structure

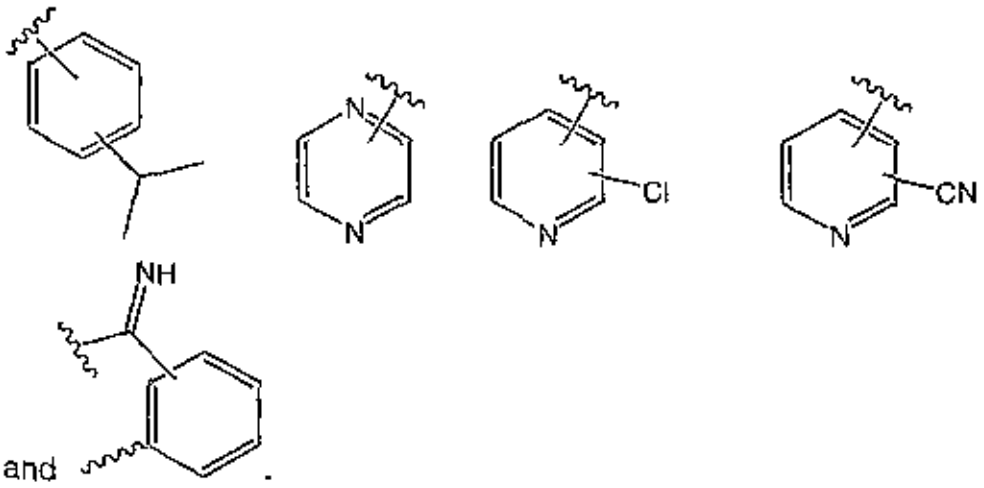


wherein R^5 and R^6 are as defined as above.

18. A compound of claim 17 wherein R^5 is independently selected from the group consisting of arylalkyl, aryl, heteroaryl, $-C(=NR^{11})R^8$, $-C(O)R^8$, $-C(O)OR^9$, aryl-R^{21} and *heteroaryl*-R^{21}.

19. A compound of claim 18 wherein R^5 is 



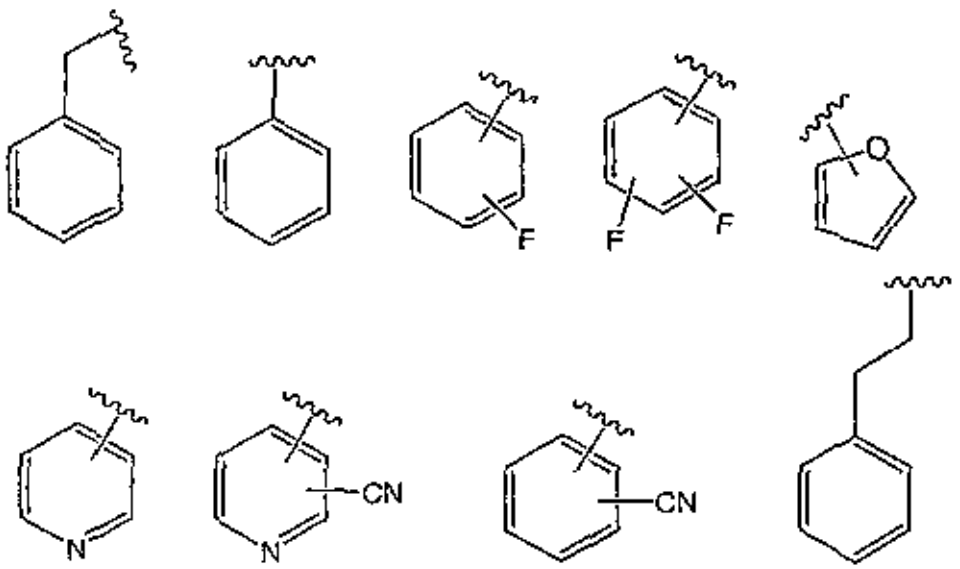


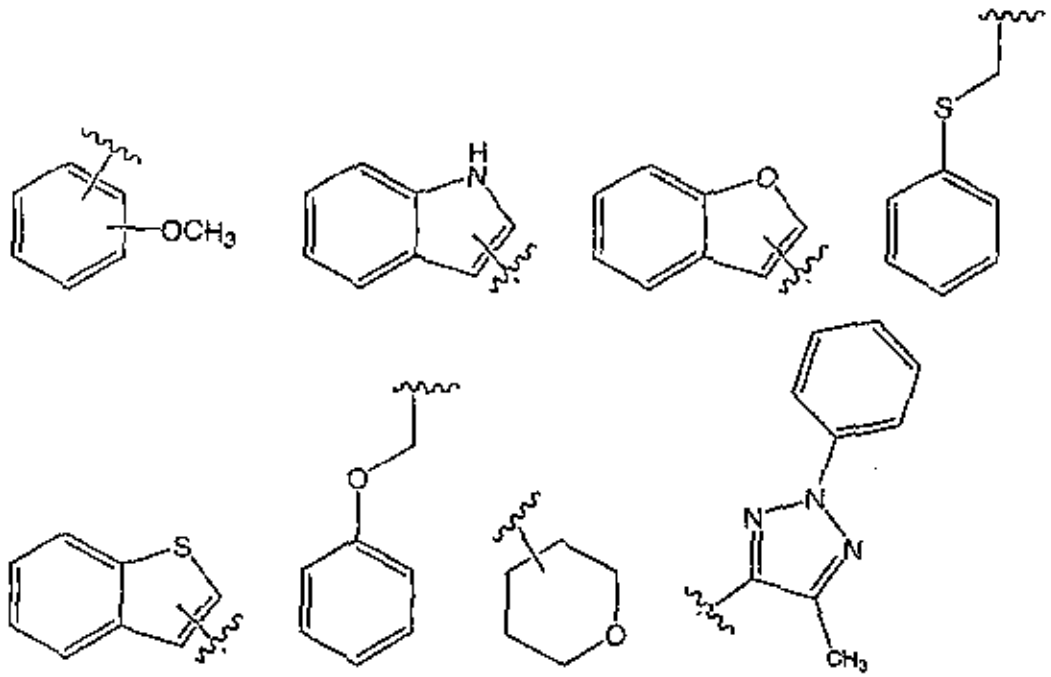
and .

20. A compound of claim 18 wherein R^8 is independently selected from the group consisting of alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, R^{18}-alkyl, R^{18}-aryl, and R^{18}-heteroaryl.

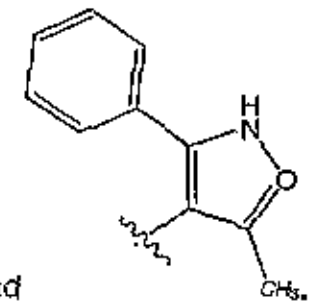
21. A compound of claim 18 wherein R^9 is independently selected from the group consisting of alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, R^{18}-alkyl, R^{18}-aryl, and R^{18}-heteroaryl.

22. A compound of claim 18 wherein R^8 is independently selected from the group consisting of $-CH_3$,

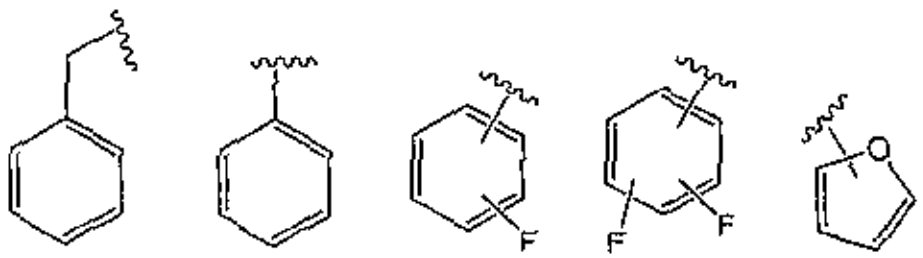


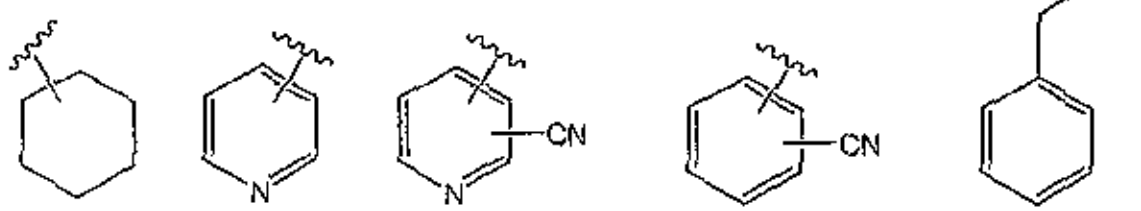


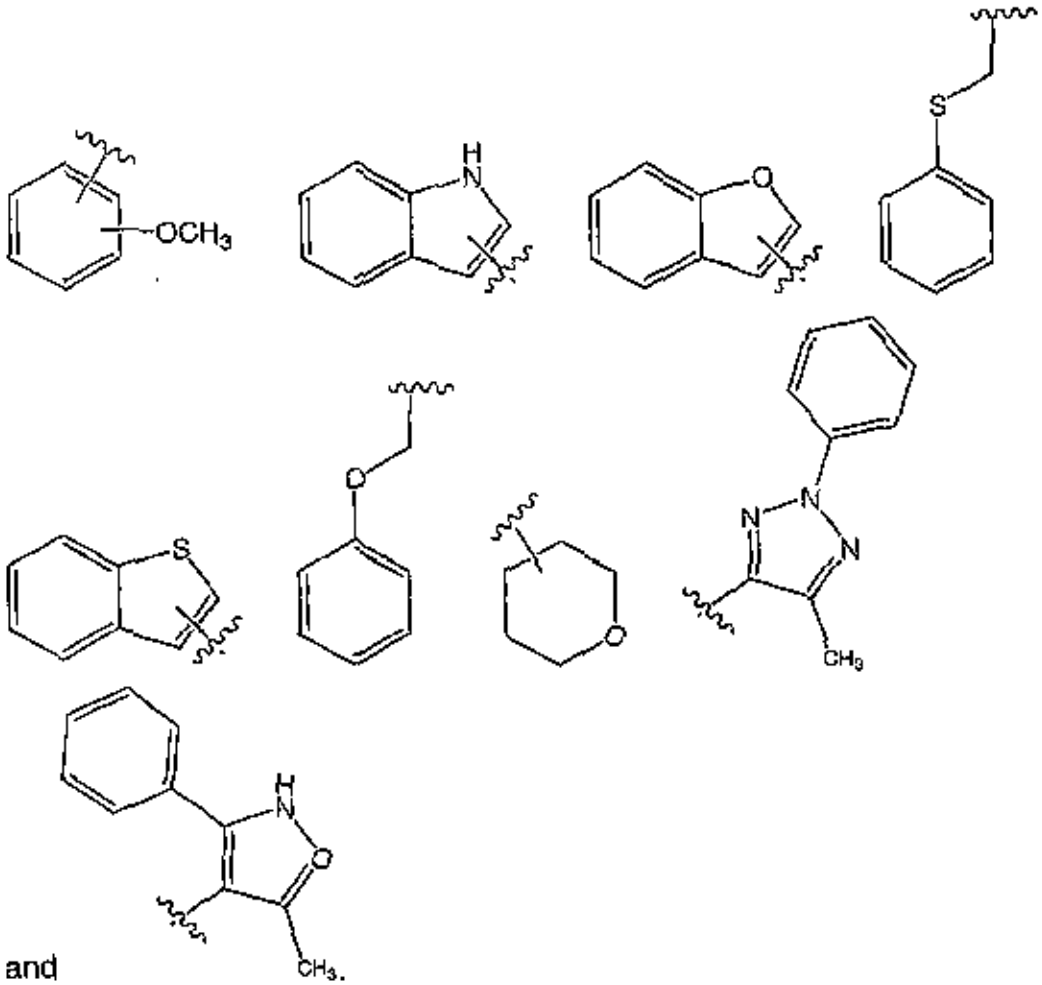
and



23. A compound of claim 18 wherein R^9 is independently selected from the group consisting of $-CH_3$,



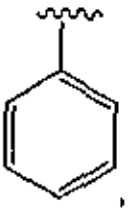
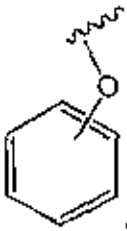


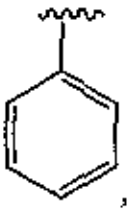
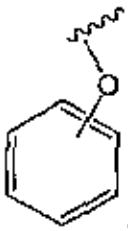


and

24. A compound of claim 20 wherein R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, halo, $-CF_3$, -CN, $-SR^{19}$ and $-OR^{20}$.

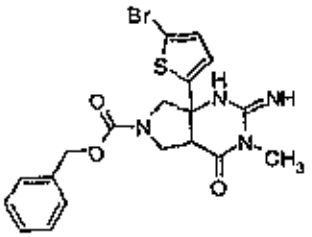
25. A compound of claim 21 wherein R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, halo, $-CF_3$, -CN, $-SR^{19}$ and $-OR^{20}$.

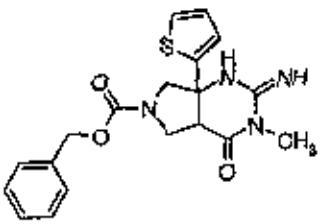
26. A compound of claim 20 wherein R^{18} is 1-5 substituents independently selected from the group consisting of halo, -CN, $-OCH(CH_3)_2$, $-OCH_3$, $-CH_3$,  ,  and  .

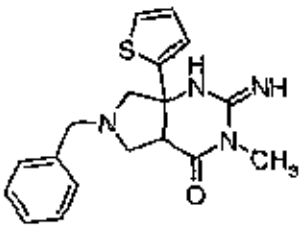
27. A compound of claim 21 wherein R^{18} is 1-5 substituents independently selected from the group consisting of halo, -CN, $-OCH(CH_3)_2$, $-OCH_3$, $-CH_3$,  ,  and  .

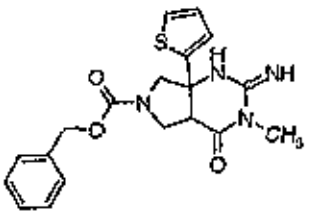
28. A compound of claim 18 wherein R^{21} is 1-5 substituents independently selected from the group consisting of halo, $-OCH(CH_3)_2$, $-CH_3$, $-CF_3$, $-OCH_3$, $-CH(CH_3)_2$ and –CN.

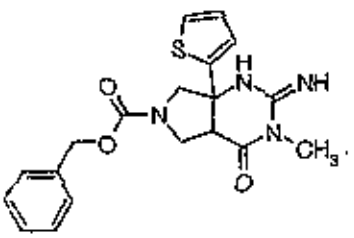
29. A compound selected from the group consisting of:

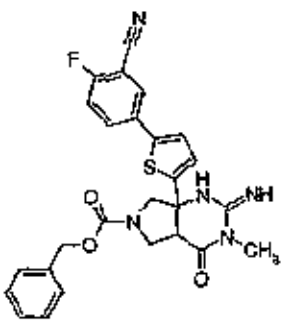


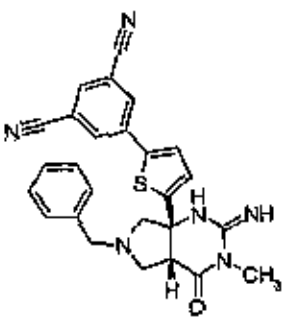


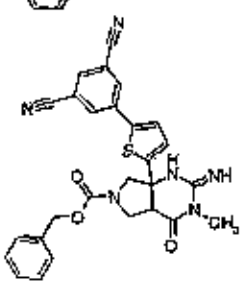


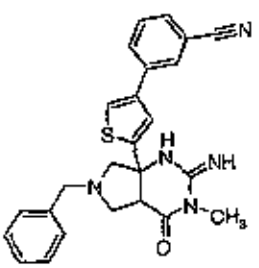


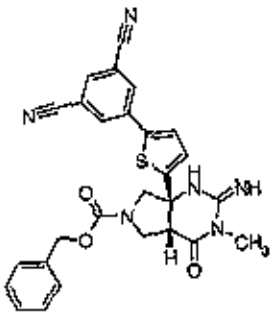


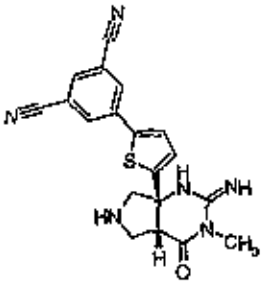


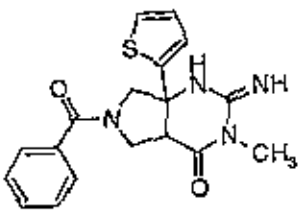


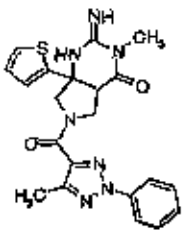


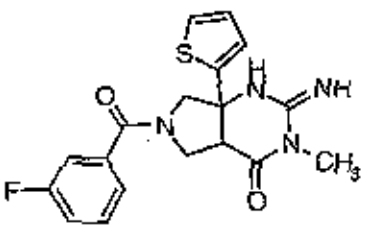


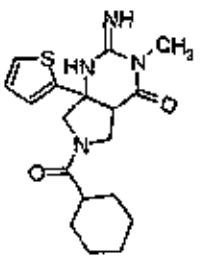


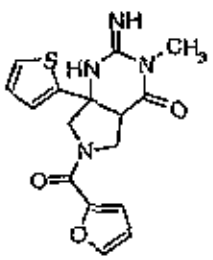


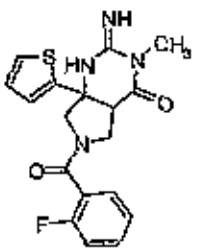


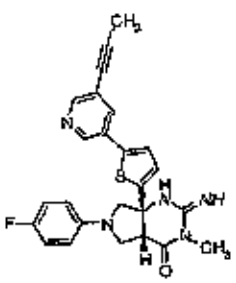


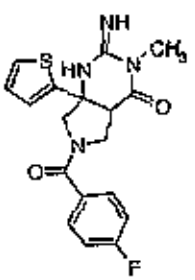


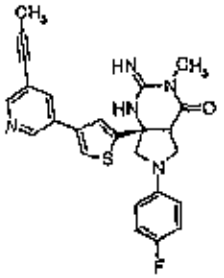


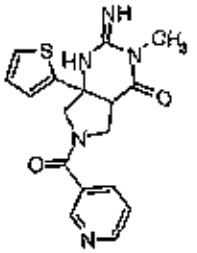


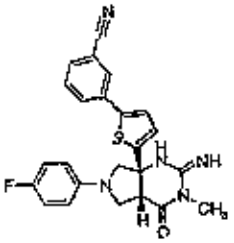


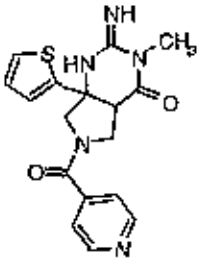


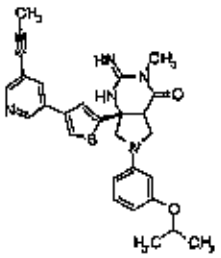


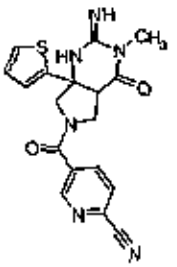


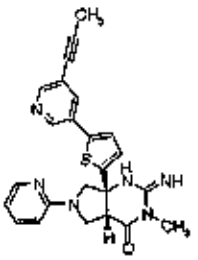


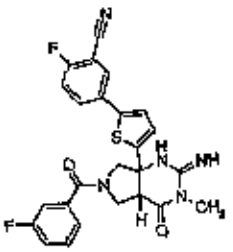


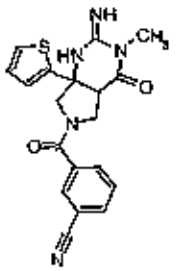


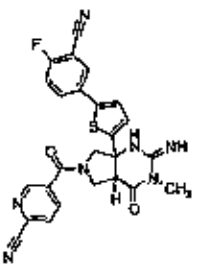


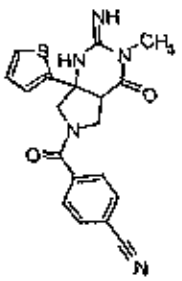


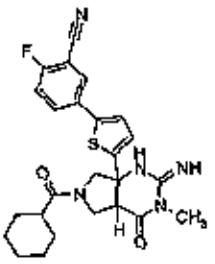


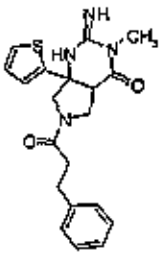


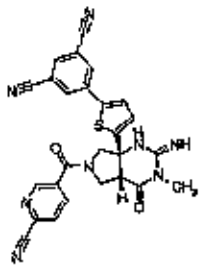


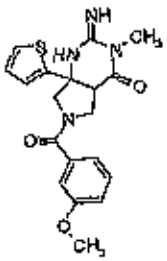


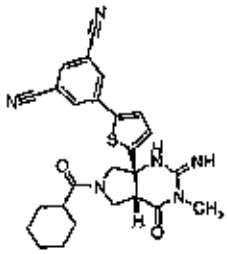


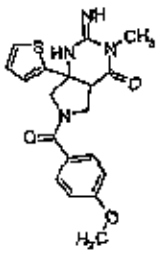


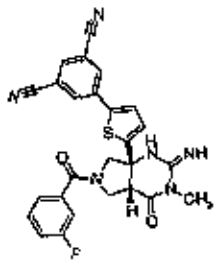


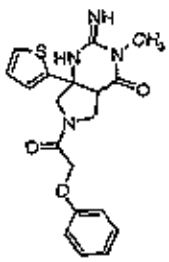


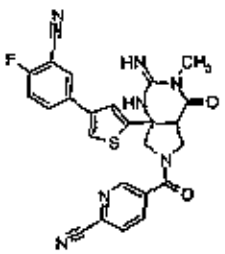


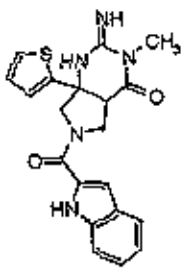


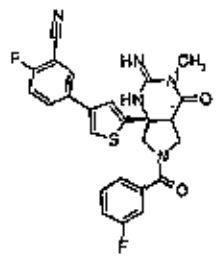


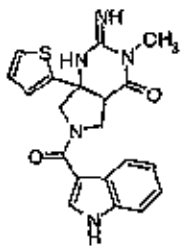


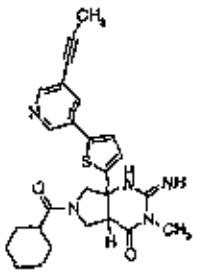


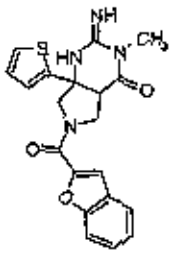


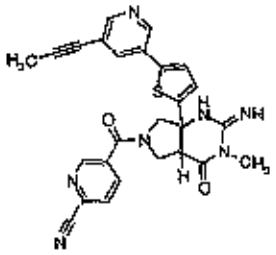


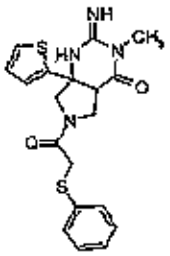


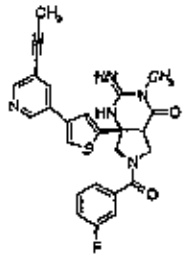


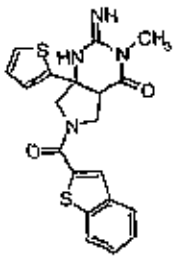


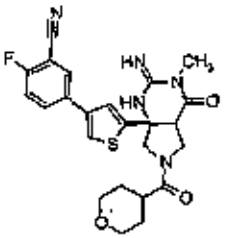


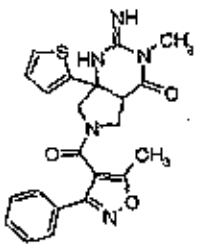


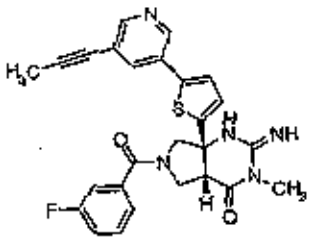


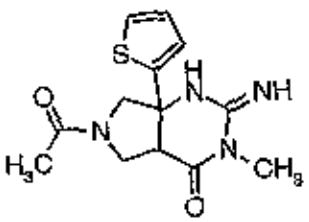


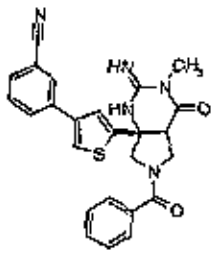


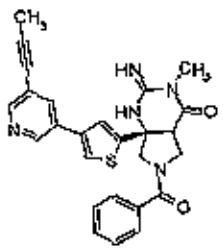


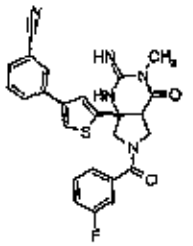


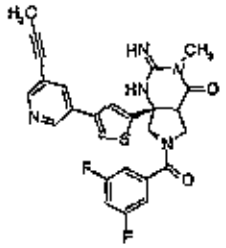


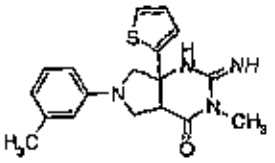


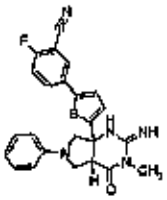


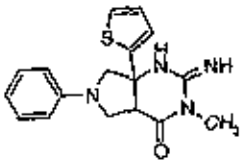


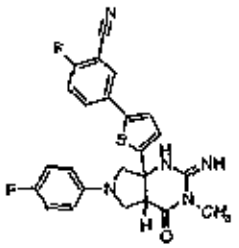


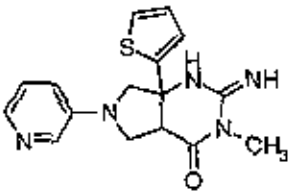


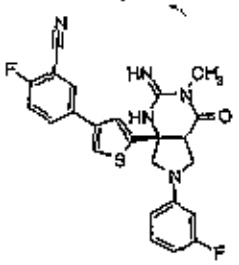


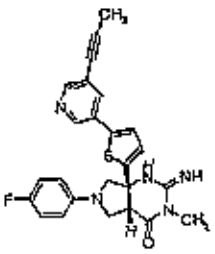


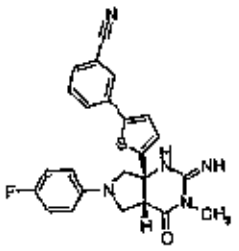


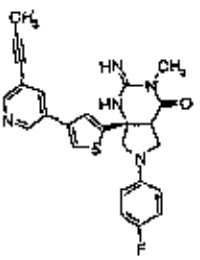


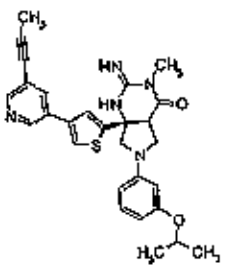


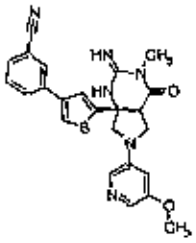


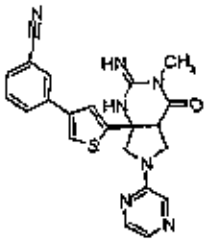


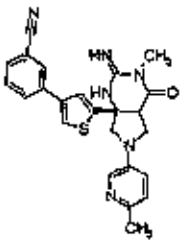


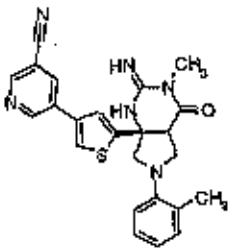


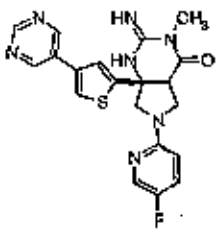


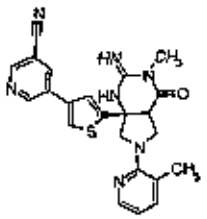


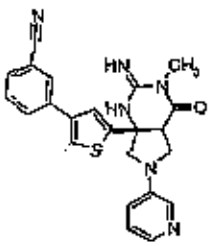


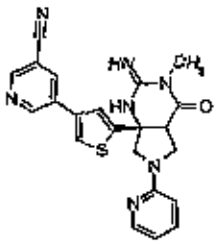


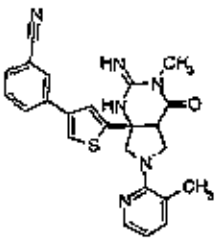


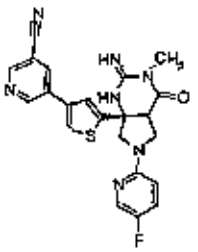


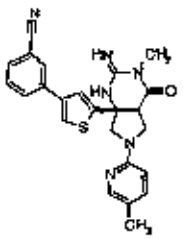


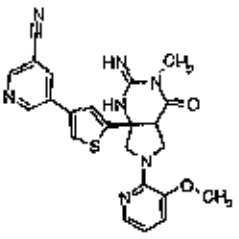


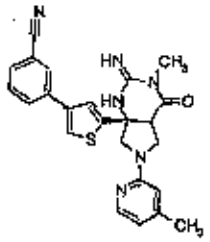
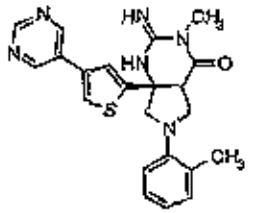
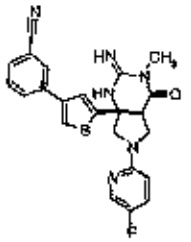
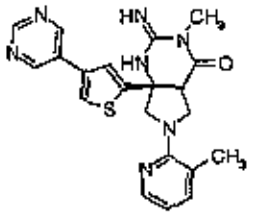
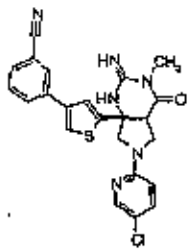
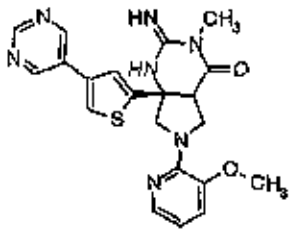
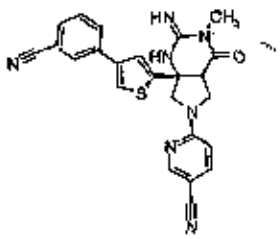
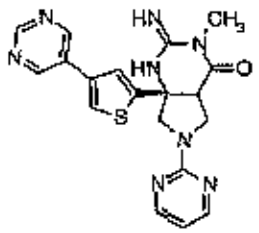
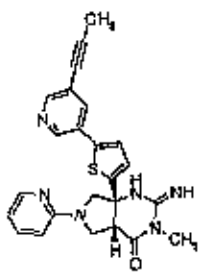










30. A pharmaceutical composition comprising an effective amount of a compound of claim 1 and a pharmaceutically effective carrier.

31. A pharmaceutical composition comprising an effective amount of a compound of claim 29 and a pharmaceutically effective carrier.

32. A method of inhibiting aspartyl protease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1.

33. A method of inhibiting aspartyl protease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 29.

34. A method of treating cardiovascular diseases, cognitive and neurodegenerative diseases, and the methods of inhibiting of Human Immunodeficiency Virus, plasmepins, cathepsin D and protozoal enzymes comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1.

35. The method of claim 34 wherein a cognitive or neurodegenerative disease is treated.

36. The method of claim 35 wherein Alzheimer's Disease is treated.

37. A method of treating cardiovascular diseases, cognitive and neurodegenerative diseases, and the methods of inhibiting of Human Immunodeficiency Virus, plasmepins, cathepsin D and protozoal enzymes comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1.

38. The method of claim 37 wherein a cognitive or neurodegenerative disease is treated.

39. The method of claim 38 wherein Alzheimer's Disease is treated.

40. A pharmaceutical composition comprising an effective amount of a compound of claim 1, and an effective amount of a cholinesterase inhibitor or a muscarinic m_1 agonist or m_2 antagonist in a pharmaceutically effective carrier.

41. A pharmaceutical composition comprising an effective amount of a compound of claim 29, and an effective amount of a cholinesterase inhibitor or a muscarinic m_1 agonist or m_2 antagonist in a pharmaceutically effective carrier.

42. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1 in combination with an effective amount of a cholinesterase inhibitor.

43. The method of claim 42 wherein Alzheimer's Disease is treated.

44. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 29 in combination with an effective amount of a cholinesterase inhibitor.

45. The method of claim 44 wherein Alzheimer's Disease is treated.

46. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1 in combination with an effective amount of a gamma secretase inhibitor, an HMG-CoA reductase inhibitor or non-steroidal anti-inflammatory agent.

47. The method of claim 46 wherein said HMG-CoA reductase inhibitor is atorvastatin, lovastatin, simvastatin, pravastatin, fluvastatin or rosuvastatin.

48. The method of claim 47 wherein Alzheimer's Disease is treated.

49. The method of claim 46 wherein said non-steroidal anti-inflammatory agent is ibuprofen, relafen or naproxen.

50. The method of claim 49 wherein Alzheimer's Disease is treated.

51. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 29 in combination with an effective amount of a gamma secretase inhibitor, an HMG-CoA reductase inhibitor or non-steroidal anti-inflammatory agent.

52. The method of claim 51 wherein said HMG-CoA reductase inhibitor is atorvastatin, lovastatin, simvistatin, pravastatin, fluvastatin or rosuvastatin.

53. The method of claim 52 wherein Alzheimer's Disease is treated.

54. The method of claim 51 wherein said non-steroidal anti-inflammatory agent is ibuprofen, relafen or naproxen.

55. The method of claim 54 wherein Alzheimer's Disease is treated.

56. A pharmaceutical composition comprising an effective amount of a compound of claim 1, and an effective amount of a gamma secretase inhibitor; an HMG-CoA reductase inhibitor or a non-steroidal anti-inflammatory agent.

57. A pharmaceutical composition comprising an effective amount of a compound of claim 29, and an effective amount of a gamma secretase inhibitor; an HMG-CoA reductase inhibitor or a non-steroidal anti-inflammatory agent.

58. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of at least one compound of claim 1 in combination with an effective amount of one or more compounds selected from the group consisting of a cholinesterase inhibitor, muscarinic m_1 agonist or m_2 antagonist, gamma secretase inhibitor, an HMG-CoA reductase inhibitor and non-steroidal anti-inflammatory agent.

59. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of at least one compound of claim 29 in combination with an effective amount of one or more compounds selected from the group consisting of a cholinesterase inhibitor,

INHIBIDORES DE ASPARTIL PROTEASAS

CAMPO DE LA INVENCIÓN

La presente invención se refiere a inhibidores de aspartil proteasas, a composiciones farmacéuticas que comprenden dichos compuestos, a su uso en el tratamiento de enfermedades cardiovasculares, enfermedades cognitivas y neurodegenerativas, y a su uso como inhibidores del Virus de Inmunodeficiencia Humana, plasmepsinas, catepsina D y enzimas de protozoos.

ANTECEDENTES

En la actualidad se conoce una cantidad de proteasas aspárticas, que incluyen la pepsina A y C, renina, BACE, BACE 2, Napsina A, y catepsina D, las cuales se han implicado en afecciones patológicas. La función del sistema renina-angiotensina (SRA) en la regulación de la presión sanguínea y electrolitos de fluidos ha sido bien establecida (Oparil, S, etal. N Engl J Med 1974; 291:381-401/446-57). El octapéptido Angiotensina-II, un potente vasoconstrictor y estimulador para la liberación de la aldosterona adrenal, es procesado a partir del decapéptido precursor Angiotensina-I, el cual a su vez es procesado a partir del angiotensinógeno por la enzima renina. Además se halló que la Angiotensina-II cumple funciones en el desarrollo celular del músculo liso vascular, inflamación, generación de especies con oxígeno reactivo y trombosis y tiene influencia en la aterogénesis y el daño vascular. En materia clínica, se conoce muy bien el beneficio de la interrupción de la generación de la angiotensina-II a través del antagonismo de la conversión de la angiotensina-I y existe una cantidad de fármacos inhibidores de ACE en el mercado. Se espera que el bloqueo de la conversión temprana de la angiotensina en angiotensina-I, es decir la inhibición de la enzima renina, tenga efectos similares aunque no idénticos. Dado que la renina es una aspartil proteasa cuyo único sustrato natural es el angiotensinógeno, se cree que habría menos efectos adversos frecuentes para

controlar la presión sanguínea alta y los síntomas relacionados regulados por la angiotensina-II a través de su inhibición.

Otra proteasa, la Catepsina D, está involucrada en la biogénesis de los lisosomas y la localización de proteínas, y además puede estar involucrada en el procesamiento del antígeno y presentación de los fragmentos del péptido. Se la ha vinculado a numerosas enfermedades que incluyen la enfermedad de Alzheimer, enfermedad del tejido conectivo, distrofia muscular y cáncer de mama.

La enfermedad de Alzheimer (EA) es una enfermedad neurodegenerativa progresiva que finalmente es fatal. El avance de la enfermedad está asociado con la pérdida gradual de la función cognitiva relacionada con la memoria, el razonamiento, la orientación y el juicio. Los cambios en el comportamiento que incluyen confusión, depresión y agresión también se manifiestan a medida que avanza la enfermedad. Se cree que la disfunción cognitiva y psicomotriz surge de la función neuronal alterada y de la pérdida neuronal en el hipocampo y corteza cerebral. Los tratamientos para la EA normalmente disponibles son paliativos, y aunque alivian los trastornos cognitivos y psicomotrices, no evitan el avance de la enfermedad. Por lo tanto, existe una necesidad médica no satisfecha de que los tratamientos de la EA detengan el avance de la enfermedad.

Los sellos distintivos patológicos de la EA son la deposición de placas de β-amiloide extracelular (Aβ) y nudos neurofibrilares intracelulares que contienen la proteína tau fosforilada en forma anormal. Los individuos con EA exhiben depósitos de Aβ característicos, en regiones del cerebro conocidas como importantes para la memoria y la cognición. Se cree que Aβ es el agente causante fundamental de la pérdida y disfunción de las células neuronales que se asocia con la declinación cognitiva y psicomotriz. Las placas amiloides consisten predominantemente en péptidos Aβ compuestos de 40 a 42 residuos de aminoácidos, los cuales derivan del procesamiento de la proteína precursora

amiloide (PPA). La PPA es procesada por múltiples y diferentes actividades de proteasa. Los péptidos Aβ surgen de la escisión de la PPA por la β-secretasa en la posición correspondiente al extremo N-terminal de Aβ, y en el extremo C-terminal por la actividad de γ-secretasa. Además la PPA es escindida por la actividad de α-secretasa que da por resultado el fragmento no-amiloidogénico secretado conocido como PPA soluble.

Una aspartil proteasa conocida como BACE-1 ha sido identificada como la actividad de β-secretasa responsable por la escisión de la PPA en la posición correspondiente al extremo N-terminal de los péptidos Aβ.

La evidencia genética y bioquímica acumulada sostiene un papel central de Aβ en la etiología de la EA. Por ejemplo, se ha demostrado que Aβ es tóxica para las células neuronales in vitro y cuando se inyectan en cerebros de roedores. Más aún, se conocen formas heredadas de EA de aparición temprana en las cuales están presentes mutaciones bien definidas de PPA o las presenilinas. Estas mutaciones intensifican la producción de Aβ y se consideran causales de la EA.

Dado que los péptidos Aβ se forman como resultado de la actividad de β-secretasa, la inhibición de BACE-1 debe inhibir la formación de péptidos Aβ. De este modo, la inhibición de BACE-1 es un enfoque terapéutico al tratamiento de EA y otras enfermedades cognitivas y neurodegenerativas causadas por la deposición de la placa Aβ.

El virus de inmunodeficiencia humana (VIH) es el agente causante del síndrome de inmunodeficiencia adquirida (SIDA). Se ha demostrado clínicamente que los compuestos tales como indinavir, ritonavir y saquinavir, que son inhibidores de la aspartil proteasa del VIH, dan por resultado la disminución de la carga viral. Como tales, los compuestos descriptos en la presente serían útiles para el tratamiento del SIDA. Tradicionalmente, un blanco principal de los

investigadores ha sido la HIV-1 proteasa, una aspartil proteasa relacionada con la renina.

Además, el virus de la leucemia de células T humana tipo I (HTLV-I) es un retrovirus humano que ha sido clínicamente asociado con la leucemia de células T en adultos y otras enfermedades crónicas. Al igual que otros retrovirus, el HTLV-1 requiere una aspartil proteasa para procesar las proteínas precursoras virales, las cuales producen viriones maduros. Esto hace que la proteasa sea un blanco atractivo para el diseño de inhibidores. (Moore, et al. Purification of HTLV-I Protease and Synthesis of Inhibitors for the treatment of HTLV-I Infection 55th Southeast Regional Meeting of the American Chemical Society, Atlanta, GA, US Noviembre 16-19, 2003 (2003), 1073. CODEN; 69EUCH Conference, AN 2004:137641 CAPLUS).

Las plasmepsinas son enzimas aspartil proteasas esenciales del parásito de la malaria. Los compuestos para la inhibición de las aspartil proteasas plasmepsinas, particularmente I, II, IV y HAP, están en desarrollo para el tratamiento de la malaria. (Freire, et al. WO 2002074719. Na Byoung-Kuk, et al., Aspartic proteases of Plasmodium vivax are highly conserved in wild isolates, Korean Journal of Parasitology (Junio 2004), 42(2) 61-6. Journal code: 9435800). Más aún, los compuestos utilizados para apuntar a las aspartil proteasas plasmepsinas (por ej., I, II, IV y HAP), han sido utilizados para matar a los parásitos de la malaria, tratando de este modo a los pacientes así afectados.

Los compuestos que actúan como inhibidores de aspartil proteasas se describen, por ejemplo, en la Solicitud USSN 11/010.772, presentada el 13 de diciembre de 2004, incorporada a la presente como referencia.

El documento WO/9304047, incorporado a la presente como referencia, describe los compuestos que tienen un núcleo de quinazolin-2-(ti)ona. El

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documento argumenta que los compuestos descriptos en el mismo son inhibidores de la transcriptasa inversa del VIH.

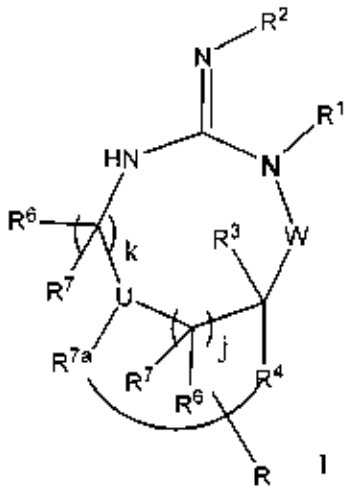
La Publicación Estadounidense No. US 2005/0282826 A1, incorporada a la presente como referencia, describe difenilimidazopirimidin o –imidazol aminas, que se consideran útiles para el tratamiento terapéutico, prevención o alivio de una enfermedad o trastorno caracterizado por los depósitos β-amiloides o niveles β-amiloides elevados en un paciente. Los estados de la enfermedad mencionados en la publicación incluyen la enfermedad de Alzheimer, el desequilibrio cognitivo leve, el síndrome de Down, la hemorragia cerebral hereditaria con amiloidosis de tipo holandés, la angiopatía amiloide cerebral y la demencia degenerativa.

La Publicación Estadounidense No. US 2005/0282825 A1, incorporada a la presente como referencia, describe amino-5,5-difenilimidazolonas, que se consideran útiles para el tratamiento terapéutico, prevención o alivio de una enfermedad o trastorno caracterizado por los depósitos β-amiloides o niveles β-amiloides elevados en un paciente. Los estados de la enfermedad mencionados en la publicación incluyen la enfermedad de Alzheimer, el desequilibrio cognitivo leve, el síndrome de Down, la hemorragia cerebral hereditaria con amiloidosis de tipo holandés, la angiopatía amiloide cerebral y la demencia degenerativa.

Otras publicaciones que revelaron compuestos que son útiles para el tratamiento de la enfermedad de Alzheimer incluyen la WO 2006/044492, la cual revela compuestos de espiropiperidina que son inhibidores de la β-secretasa, y la WO 2006/041404, la cual revela amino compuestos sustituidos que son útiles para el tratamiento o profilaxis de patologías relacionadas con Aβ. Ambas publicaciones se incorporan como referencia.

SÍNTESIS DE LA INVENCIÓN

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



I

o su estereoisómero, tautómero o sal aceptable para uso farmacéutico, donde

j es 0 o 1;

k es 0 o 1, siempre que cuando k es 1, U no puede ser -N-;

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

U es –N- o -$C(R^6)$-;

R es 1 a 5 grupos R^{21};

R^1, R^2 y R^5 se seleccionan independientemente del grupo integrado por H, alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquil-heteroarilo, cicloalquenilheteroarilo, heterocicloalquenilheteroarilo, –OR^{15}, -CN, -$C(=NR^{11})R^8$, -$C(O)R^8$, -$C(O)OR^9$, -$S(O)R^{10}$, -$S(O)_2R^{10}$, -$C(O)N(R^{11})(R^{12})$,

-S(O)N(R^{11})(R^{12}), -$S(O)_2$N(R^{11})(R^{12}), -NO_2, -N=C(R^8)$_2$ y –N(R^{11})(R^{12}), siempre que R^1 y R^5 no sean ambos seleccionados de -NO_2, -N=C(R^8)$_2$ y –N(R^{11})(R^{12});

R^3, R^6 y R^7 se seleccionan independientemente del grupo integrado por H, alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquil-heteroarilo, cicloalquenilheteroarilo, heterocicloalquenilheteroarilo, halo, -CH_2-O-Si(R^9)(R^{10})(R^{19}), -SH, -CN, -OR^9, -C(O)R^8, -C(O)OR^9, -C(O)N(R^{11})(R^{12}), -SR^{19}, -S(O)N(R^{11})(R^{12}), -$S(O)_2$N(R^{11})(R^{12}), -N(R^{11})(R^{12}), -N(R^{11})C(O)R^8, -N(R^{11})S(O)R^{10}, -N(R^{11})$S(O)_2R^{10}$, -N(R^{11})C(O)N(R^{12})(R^{13}), -N(R^{11})C(O)OR^9 y –C(=NOH)R^8;

R^4 y R^{7a} se seleccionan independientemente del grupo integrado por un enlace, alquileno, arilalquileno, heteroarilalquileno, cicloalquilalquileno, heterocicloalquilalquileno, arilcicloalquilalquileno, heteroarilcicloalquilalquileno, arilheterocicloalquilalquileno, heteroarilheterocicloalquilalquileno, cicloalquileno, arilcicloalquileno, heteroarilcicloalquileno, heterocicloalquileno, arilheterociclo-alquileno, heteroarilheterocicloalquileno, alquenileno, arilalquenileno, cicloalquenileno, arilcicloalquenileno, heteroarilcicloalquenileno, heterociclo-alquenileno, arilheterocicloalquenileno, heteroarilheterociclo alquenileno, alquinileno, arilalquinileno, arileno, cicloalquilarileno, heterocicloalquilarileno, cicloalquienilarileno, cicloalquenilarileno, heterocicloalquenilarileno, heteroarileno, cicloalquilheteroarileno, heterocicloalquilheteroarileno, cicloalquenilheteroarileno y

heterocicloalquenilheteroarileno, siempre que ambos R^4 y R^{7a} no sean ambos un enlace;

R^4 y R^{7a} juntos pueden ser una cadena de carbono de C_1 a C_8, donde, opcionalmente, uno, dos o tres carbonos del anillo pueden ser reemplazados por –O-, -C(O)-, -C(S)-, -S-, -S(O)-, $–S(O)_2$- o $–N(R^5)$-, y R^4 y R^{7a} junto con los átomos de carbono a los cuales éstos están unidos, forman un anillo de 3 a 8 miembros, opcionalmente sustituido con R, con las siguientes condiciones:

que cuando al menos uno de los carbonos es reemplazado por –O-, -C(O)-, -C(S)-, -S-, -S(O)- ,$–S(O)_2$-o $–N(R^5)$-, entonces el número de carbonos en la porción R^4 y R^{7a} de la cadena que se une a U es b, donde b es 0 a 5, y el número de carbonos que están en la porción R^4 y R^{7a} de la cadena que se une con el carbono de $–C(R^3)$- es c, donde c es 0 a 5;

que cuando j es 0 o 1, al menos uno de los carbonos del anillo debe estar reemplazado por -O-, -C(O)-, -C(S)-, -S-, -S(O)- ,$–S(O)_2$-o $–N(R^5)$-;

que cuando j es 0 o 1 y sólo un carbono del anillo es reemplazado con –O-, -C(O)-, -C(S)-, -S-, -S(O)- ,$–S(O)_2$-o $–N(R^5)$-, R^4 y R^{7a} no pueden formar un cicloalquiléter;

R^6 se selecciona independientemente del grupo integrado por H, alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquil-heteroarilo, cicloalquenilheteroarilo, heterocicloalquenilheteroarilo, $-OR^{15}$,

$-N(R^{15})(R^{15})$, $-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$ y $-N(R^{15})C(O)OR^{16}$;

R^9 se selecciona independientemente del grupo integrado por H, alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquil-heteroarilo, cicloalquenilheteroarilo y heterocicloalquenilheteroarilo;

R^{10} se selecciona independientemente del grupo integrado por H, alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquil-heteroarilo, cicloalquenilheteroarilo, heterocicloalquenilheteroaril y $-N(R^{15})(R^{16})$;

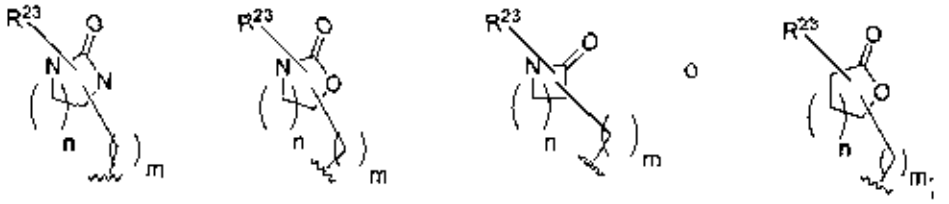
R^{11}, R^{12} y R^{13} se seleccionan independientemente del grupo integrado por H, alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo,

heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquil-heteroarilo, cicloalquenilheteroarilo, heterocicloalquenilheteroarilo, $-C(O)R^8$, $-C(O)OR^9$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-C(O)N(R^{15})(R^{16})$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$ y –CN;

R^{15}, R^{16} y R^{17} se seleccionan independientemente del grupo integrado por H, alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquil-heteroarilo, cicloalquenilheteroarilo, heterocicloalquenilheteroarilo, R^{18}-alquilo, R^{18}-arilalquilo, R^{18}-heteroarilalquilo, R^{18}-cicloalquilalquilo, R^{18}-heterocicloalquilalquilo, R^{18}-arilcicloalquilalquilo, R^{18}-heteroarilcicloalquilalquilo, R^{18}-arilheterocicloalquil-alquilo, R^{18}-heteroarilheterocicloalquilalquilo, R^{18}-cicloalquilo, R^{18}-arilcicloalquilo, R^{18}-heteroarilcicloalquilo, R^{18}-heterocicloalquilo, R^{18}-arilheterocicloalquilo, R^{18}-heteroarilheterocicloalquilo, R^{18}-alquenilo, R^{18}-arilalquenilo, R^{18}-cicloalquenilo, R^{18}-arilcicloalquenilo, R^{18}-heteroarilcicloalquenilo, R^{18}-heterocicloalquenilo, R^{18}-arilheterocicloalquenilo, R^{18}-heteroarilheterocicloalquenilo, R^{18}-alquinilo, R^{18}-arilalquinilo, R^{18}-arilo, R^{18}-cicloalquilarilo, R^{18}-heterocicloalquilarilo, R^{18}-cicloalquenilarilo, R^{18}-heterocicloalquenilarilo, R^{18}-heteroarilo, R^{18}-

cicloalquilheteroarilo, R^{18}-heterocicloalquilheteroarilo, R^{18}-cicloalquenilheteroarilo, y R^{18}-heterocicloalquenilheteroarilo; o

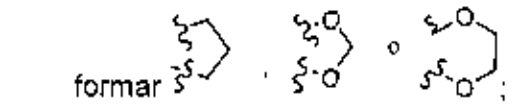
R^{15}, R^{16} y R^{17} son



donde R^{23} representa 0 a 5 sustituyentes, m es 0 a 6 y n es 0 a 5;

R^{18} es 1-5 sustituyentes seleccionados independientemente del grupo integrado por alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquilheteroarilo, cicloalquenil-heteroarilo, heterocicloalquenilheteroarilo, $-NO_2$, halo, HO-alcoxialquilo, $-CF_3$, -CN, alquil-CN, $-C(O)R^{19}$, -C(O)OH, $-C(O)OR^{19}$, $-C(O)NHR^{20}$, $-C(O)NH_2$, $-C(O)NH_2$-$C(O)N(alquilo)_2$, -C(O)N(alquil)(arilo), -C(O)N(alquil)(heteroarilo), $-SR^{19}$, $-S(O)_2R^{20}$, $-S(O)NH_2$, -S(O)NH(alquilo), -S(O)N(alquil)(alquilo), -S(O)NH(arilo), $-S(O)_2NH_2$, $-S(O)_2NHR^{19}$, $-S(O)_2NH$(heterocicloalquilo), $-S(O)_2N(alquilo)_2$, $-S(O)_2N$(alquil)(arilo), $-OCF_3$, -OH, $-OR^{20}$, -O-heterocicloalquilo, -O-cicloalquilalquilo, -O-heterocicloalquilalquilo, $-NH_2$, $-NHR^{20}$, $-N(alquilo)_2$, $-N(arilalquilo)_2$, -N(arilalquil)-(heteroarilalquilo), $-NHC(O)R^{20}$, $-NHC(O)NH_2$, -NHC(O)NH(alquilo), -NHC(O)N(alquil)(alquilo), -N(alquil)C(O)NH(alquilo), -N(alquil)C(O)N(alquil)(alquilo), $-NHS(O)_2R^{20}$, $-NHS(O)_2NH$(alquilo),

-NHS(O)$_2$N(alquil)(alquilo), -N(alquil)S(O)$_2$NH(alquilo) y –N(alquil)S(O)$_2$N(alquil)(alquilo);

o dos restos R^{18} sobre carbonos adyacentes pueden estar unidos para formar  ;

R^{19} es alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterociclo-alquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquilheteroarilo, cicloalquenil-heteroaril o heterocicloalquenilheteroarilo;

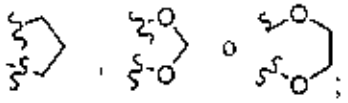
R^{20} es arilo sustituido con halo, alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquil-alquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquilheteroarilo, cicloalquenil-heteroarilo o heterocicloalquenilheteroarilo,

y donde cada uno de los grupos alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquil-

alquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquilheteroarilo, cicloalquenilheteroarilo, heterocicloalquenilheteroarilo, en R, R^1, R^2, R^3, R^4, R^5, R^6, R^7; R^8, R^9, R^{10}, R^{11}, R^{12} y R^{13}

están independientemente no sustituidos o sustituidos con 1 a 5 grupos R^{21} seleccionados independientemente del grupo integrado por alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquilheteroarilo, cicloalquenilheteroarilo, heterocicloalquenilheteroarilo, halo, -CN, $-C(=NR^{11})R^{15}$, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-CH(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, -alquil-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-R^{15}$; $-CH_2N(R^{15})(R^{16})$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-S(O)R^{15}$, $-N_3$, $-NO_2$ y $-S(O)_2R^{15}$;

y donde cada uno de los grupos alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquil-alquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterociclo-alquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquilheteroarilo, cicloalquenil-heteroarilo y heterocicloalquenilheteroarilo en R^{21} están independientemente no sustituidos o sustituidos con 1 a 5 grupos R^{22} seleccionados independientemente del grupo integrado por alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterociclo-alquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquilheteroarilo, cicloalquenil-heteroarilo, heterocicloalquenilheteroarilo, halo, $-CF_3$, -CN, $-C(=NR^{11})R^{15}$, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, -alquil-$C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, -alquil-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-N_3$, $-NO_2$, $-S(O)R^{15}$ y $-S(O)_2R^{15}$;

o dos restos R^{21} o dos R^{22} sobre carbonos adyacentes pueden estar unidos para formar  ;

y cuando R^{21} o R^{22} se seleccionan del grupo integrado por $-C(=NOR^{15})R^{16}$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$ y $-CH_2-N(R^{15})C(O)OR^{16}$, R^{15} y R^{16} juntos pueden ser una cadena de C_2 a C_4 donde, opcionalmente, uno, dos o tres carbonos del anillo pueden ser reemplazados por –C(O)- o –N(H)- y R^{15} y R^{16}, junto con los átomos a los cuales éstos están unidos, forman un anillo de 5 a 7 miembros, opcionalmente sustituido con R^{23};

R^{23} es 1 a 5 grupos seleccionados independientemente del grupo integrado por alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquil-heteroarilo, cicloalquenilheteroarilo, heterocicloalquenilheteroarilo, halo, -CN, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, $-C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, -alquil-$N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$, $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$, $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$, $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$,

-N(R^{24})C(O)OR^{25}, -CH_2-N(R^{24})C(O)OR^{25}, -S(O)R^{24} y -$S(O)_2R^{24}$; y donde cada uno de los grupos alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquilheteroarilo, cicloalquenil-heteroarilo y heterocicloalquenilheteroarilo en R^{23} son independientemente no sustituidos o sustituidos con 1 a 5 grupos R^{27} seleccionados independientemente del grupo integrado por alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquilheteroarilo, cicloalquenil-heteroarilo, heterocicloalquenilheteroarilo, halo, -CF_3, -CN, -OR^{24}, -C(O)R^{24}, -C(O)OR^{24}, alquil-C(O)OR^{24}, -C(O)N(R^{24})(R^{25}), -SR^{24}, -S(O)N(R^{24})(R^{25}), -$S(O)_2$N(R^{24})(R^{25}), –C(=NOR^{24})R^{25}, -P(O)(OR^{24})(OR^{25}), -N(R^{24})(R^{25}), -alquil-N(R^{24})(R^{25}), -N(R^{24})C(O)R^{25}, -CH_2-N(R^{24})C(O)R^{25}, -N(R^{24})S(O)R^{26}, -N(R^{24})$S(O)_2R^{25}$, -CH_2-N(R^{24})$S(O)_2R^{25}$, -N(R^{24})$S(O)_2$N(R^{25})(R^{26}),

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$-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$, $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ y $-S(O)_2R^{24}$;

R^{24}, R^{25} y R^{26} se seleccionan independientemente del grupo integrado por H, alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, *arilcicloalquilalquilo*, *heteroarilcicloalquilalquilo*, *arilheterocicloalquilalquilo*, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquil-heteroarilo, cicloalquenilheteroarilo, heterocicloalquenilheteroarilo, R^{27}-alquilo, R^{27}-arilalquilo, R^{27}-heteroarilalquilo, R^{27}-cicloalquilalquilo, R^{27}-heterocicloalquilalquilo, R^{27}-arilcicloalquilalquilo, R^{27}-heteroarilcicloalquilalquilo, R^{27}-arilheterociclo-alquilalquilo, R^{27}-heteroarilheterocicloalquilalquilo, R^{27}-cicloalquilo, R^{27}-arilcicloalquilo, R^{27}-heteroarilcicloalquilo, R^{27}-heterocicloalquilo, R^{27}-arilheterocicloalquilo, R^{27}-heteroarilheterocicloalquilo, R^{27}-alquenilo, R^{27}-arilalquenilo, R^{27}-cicloalquenilo, R^{27}-arilcicloalquenilo, R^{27}-heteroarilcicloalquenilo, R^{27}-heterocicloalquenilo, R^{27}-arilheterocicloalquenilo, R^{27}-heteroarilheterociclo-alquenilo, R^{27}-alquinilo, R^{27}-arilalquinilo, R^{27}-arilo, R^{27}-cicloalquilarilo, R^{27}-heterocicloalquilarilo, R^{27}-cicloalquenilarilo, R^{27}-heterocicloalquenilarilo, R^{27}-heteroarilo, R^{27}-cicloalquilheteroarilo, R^{27}-heterocicloalquilheteroarilo, R^{27}-cicloalquenilheteroaril y R^{27}-heterocicloalquenilheteroarilo;

R^{27} es 1-5 sustituyentes seleccionados independientemente del grupo integrado por alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo,

arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterociclo-alquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquilheteroarilo, cicloalquenil-heteroarilo, heterocicloalquenilheteroarilo, $-NO_2$, halo, $-CF_3$, -CN, alquil-CN, $-C(O)R^{28}$, -C(O)OH, $-C(O)OR^{28}$, $-C(O)NHR^{29}$, $-C(O)N(alquilo)_2$, -C(O)N(alquil)(arilo), -C(O)N(alquil)(heteroarilo), $-SR^{28}$, $-S(O)_2R^{29}$, $-S(O)NH_2$, -S(O)NH(alquilo), -S(O)N(alquil)(alquilo), -S(O)NH(arilo), $-S(O)_2NH_2$, $-S(O)_2NHR^{28}$, $-S(O)_2NH(arilo)$, $-S(O)_2NH(heterocicloalquilo)$, $-S(O)_2N(alquilo)_2$, $-S(O)_2N(alquil)(arilo)$, -OH, $-OR^{29}$, -O-heterocicloalquilo, -O-cicloalquilalquilo, -O-heterocicloalquilalquilo, $-NH_2$, $-NHR^{29}$, $-N(alquilo)_2$, $-N(arilalquilo)_2$, -N(arilalquil)(heteroarilalquilo), $-NHC(O)R^{29}$, $-NHC(O)NH_2$, -NHC(O)NH(alquilo), -NHC(O)N(alquil)(alquilo), -N(alquil)C(O)NH(alquilo), -N(alquil)C(O)N(alquil)(alquilo), $-NHS(O)_2R^{29}$, $-NHS(O)_2NH(alquilo)$, $-NHS(O)_2N(alquil)(alquilo)$, $-N(alquil)S(O)_2NH(alquilo)$ y $-N(alquil)S(O)_2N(alquil)(alquilo)$;

R^{28} es alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterociclo-alquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo,

heteroarilo, cicloalquilheteroarilo, heterocicloalquilheteroarilo, cicloalquenil-heteroarilo o heterocicloalquenilheteroarilo;

R^{29} es alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquilheteroarilo, cicloalquenil-heteroarilo o heterocicloalquenilheteroarilo;

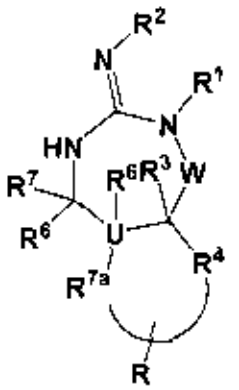
R^{30} es alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo, heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterocicloalquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquilheteroarilo, cicloalquenil-heteroarilo o heterocicloalquenilheteroarilo;

y

R^{31} es alquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilcicloalquilalquilo, heteroarilcicloalquilalquilo, arilheterocicloalquilalquilo, heteroarilheterocicloalquilalquilo, cicloalquilo, arilcicloalquilo, heteroarilcicloalquilo, heterocicloalquilo, arilheterocicloalquilo,

heteroarilheterocicloalquilo, alquenilo, arilalquenilo, cicloalquenilo, arilcicloalquenilo, heteroarilcicloalquenilo, heterocicloalquenilo, arilheterociclo-alquenilo, heteroarilheterocicloalquenilo, alquinilo, arilalquinilo, arilo, cicloalquilarilo, heterocicloalquilarilo, cicloalquenilarilo, heterocicloalquenilarilo, heteroarilo, cicloalquilheteroarilo, heterocicloalquilheteroarilo, cicloalquenil-heteroarilo, heterocicloalquenilheteroarilo;

con la siguiente condición: que cuando U, R^{7a} y R^4 se ciclan para formar la siguiente estructura bicíclica:



W no puede ser un enlace.

En otro aspecto, la invención se refiere a una composición farmacéutica que comprende al menos un compuesto de fórmula I y un vehículo aceptable para uso farmacéutico.

En otro aspecto, la invención comprende el método para inhibir aspartil proteasas que comprende la administración de al menos un compuesto de fórmula I a un paciente que necesita tal tratamiento.

En forma más específica, la invención comprende: el método para tratar una enfermedad cardiovascular tal como hipertensión, insuficiencia renal, insuficiencia cardiaca congestiva u otra enfermedad modulada por la inhibición de la renina; el método para el tratamiento del Virus de Inmunodeficiencia Humana; el método para tratar una enfermedad cognitiva o neurodegenerativa tal como la

enfermedad de Alzheimer; el método para inhibir las plasmepsinas I y II para el tratamiento de la malaria; el método para inhibir la Catepsina D para el tratamiento de la enfermedad de Alzheimer, cáncer de mama y cáncer de ovario; y el método para inhibir enzimas de protozoos, por ejemplo la inhibición del plasmodium falciparum, para el tratamiento de infecciones fúngicas. Dicho método de tratamiento comprende la administración de al menos un compuesto de fórmula I a un paciente que necesita dicho tratamiento. En particular, la invención comprende el método para tratar la enfermedad de Alzheimer que comprende la administración de al menos un compuesto de fórmula I a un paciente que necesita dicho tratamiento.

En otro aspecto, la invención comprende el método para el tratamiento de la enfermedad de Alzheimer que comprende la administración a un paciente que necesita dicho tratamiento de una combinación de al menos un compuesto de fórmula I y un inhibidor de colinesterasa o un agonista m_1 o antagonista m_2 muscarínico.

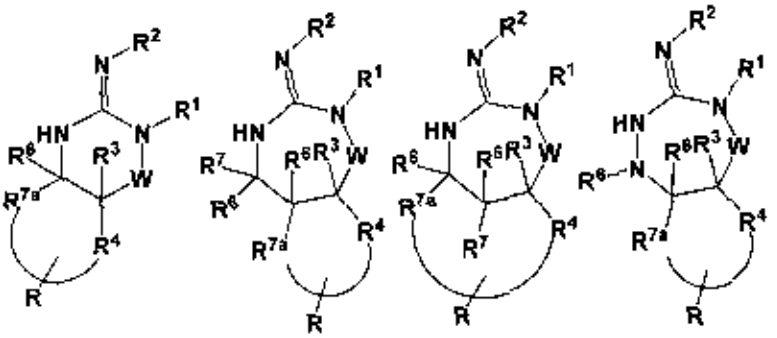
En un aspecto final, la invención se refiere a un kit que comprende en recipientes separados, en un único envase, composiciones farmacéuticas para su uso en combinación, en el cual un recipiente comprende un compuesto de Fórmula I en un vehículo aceptable para uso farmacéutico y un segundo recipiente comprende un inhibidor de colinesterasa o un agonista m_1 o antagonista m_2 muscarínico en un vehículo aceptable para uso farmacéutico, siendo las cantidades combinadas una cantidad eficaz para tratar una enfermedad cognitiva o neurodegenerativa tal como la enfermedad de Alzheimer.

DESCRIPCIÓN DETALLADA:

En general, se entiende que los grupos divalentes deben leerse de izquierda a derecha.

135
15.

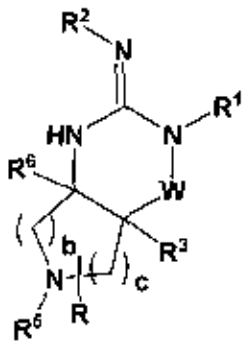
Los compuestos preferidos de fórmula I donde R, R^1, R^2, R^3, R^4, R^6, R^7, R^{7a} y W son según se definieron anteriormente e incluyen las siguientes estructuras:



I II III IV

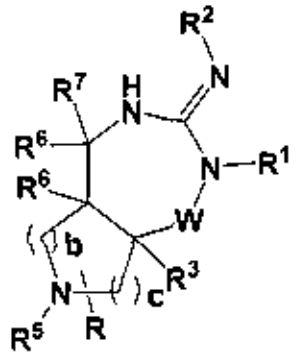
siempre que en la estructura II, W no sea un enlace.

Los compuestos de fórmula I donde R, R^1, R^2, R^3, R^5, R^6, R^7 y W son según se definieron anteriormente también incluyen las siguientes estructuras:



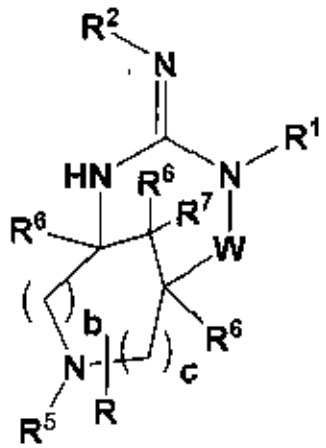
donde b es 1 a 5 y c es 0 a 5.

o



donde R, R^1, R^2, R^3, R^5, R^6, R^7 y W, donde b es 1 a 5 y c es 0 a 5

o

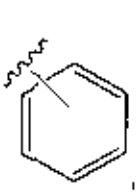
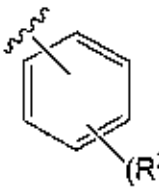
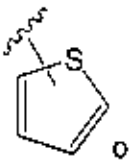
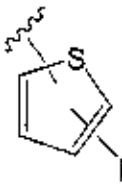


donde R, R^1, R^2, R^3, R^5, R^6, R^7 y W son según se definieron anteriormente, b es 1 a 4 y c es 0 a 4.

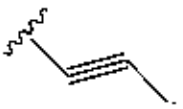
Los compuestos preferidos de fórmula I son aquellos compuestos donde R^1 es alquilo o con mayor preferencia, R^1 es metilo.

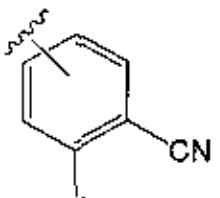
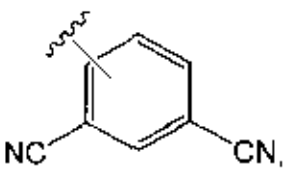
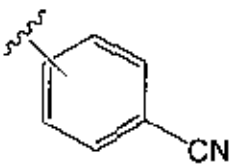
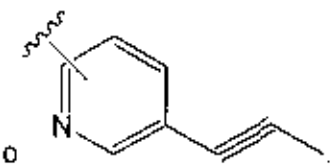
Los compuestos más preferidos de la invención son aquéllos de fórmula I donde R^2 es H.

Otro grupo de compuestos preferidos de fórmula I son aquellos compuestos donde R^6 es arilo, $(R^{21})_{1-5}$-arilo, heteroarilo o $(R^{21})_{1-5}$-heteroarilo

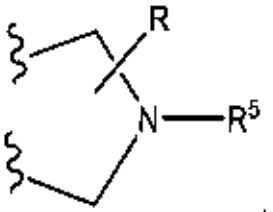
o aún con mayor preferencia, R^6 es  ,  ,  , o  .

Los compuestos preferidos de fórmula I son aquellos compuestos donde R^{21} es –CN, halo, arilo, $(R^{22})_{1-2}$-arilo, heteroarilo o $(R^{22})_{1-2}$-heteroarilo.

Los compuestos preferidos de fórmula I son aquellos compuestos donde R^{22} es –CN, halo o alquino, o con mayor preferencia, R^{22} es F o  .

Los compuestos preferidos de fórmula I son aquellos compuestos donde R^{21} es  ,  ,  , o  .

Los compuestos más preferidos de fórmula I son aquellos compuestos donde W es -C(O)-.

Otro grupo de los compuestos preferidos de fórmula I son aquellos compuestos donde R^4 y R^{7a} forman R^4 y R^{7a} forman  .

Los compuestos preferidos de fórmula I son aquellos compuestos donde R es halo, con mayor preferencia donde R es F.

Los compuestos preferidos de fórmula I son aquellos compuestos donde

R es H o halo;

R^1 es alquilo;

R^2 es H;

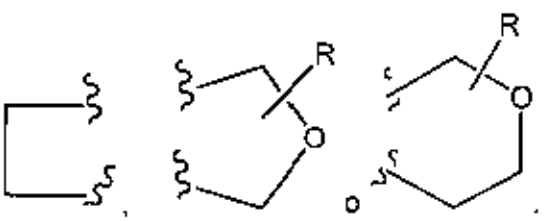
R^6 es R^{21}-arilo;

R^{21} es R^{22}-arilo;

R^{22} es halo o CN;

W es -C(O)-;

y

R^4 y R^{7a} forman 

.

Otro grupo de compuestos preferidos de fórmula I son aquellos compuestos donde

R^1 es alquilo;

R^2 es H;

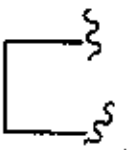
R^6 es R^{21}-arilo;

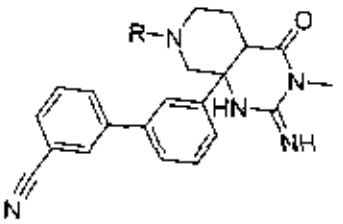
R^{21} es R^{22}-arilo;

R^{22} es halo o CN;

W es -C(O)-;

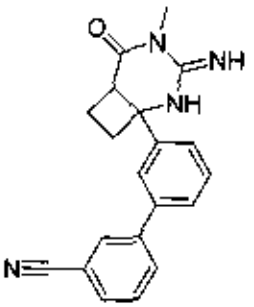
y

R^4 y R^{7a} forman  .

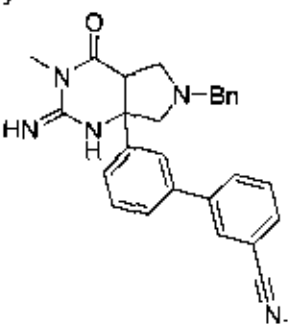


donde R es según define en la presente.

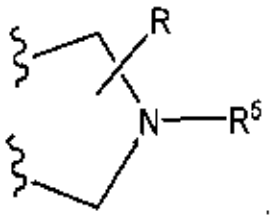
Los siguientes compuestos preferidos de fórmula I tienen las siguientes estructuras;



y

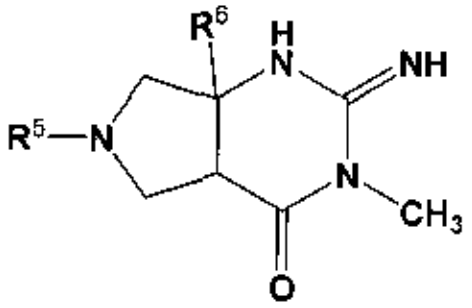


Otro grupo de compuestos preferidos de fórmula I son aquellos compuestos donde R^4 y R^{7a} forman



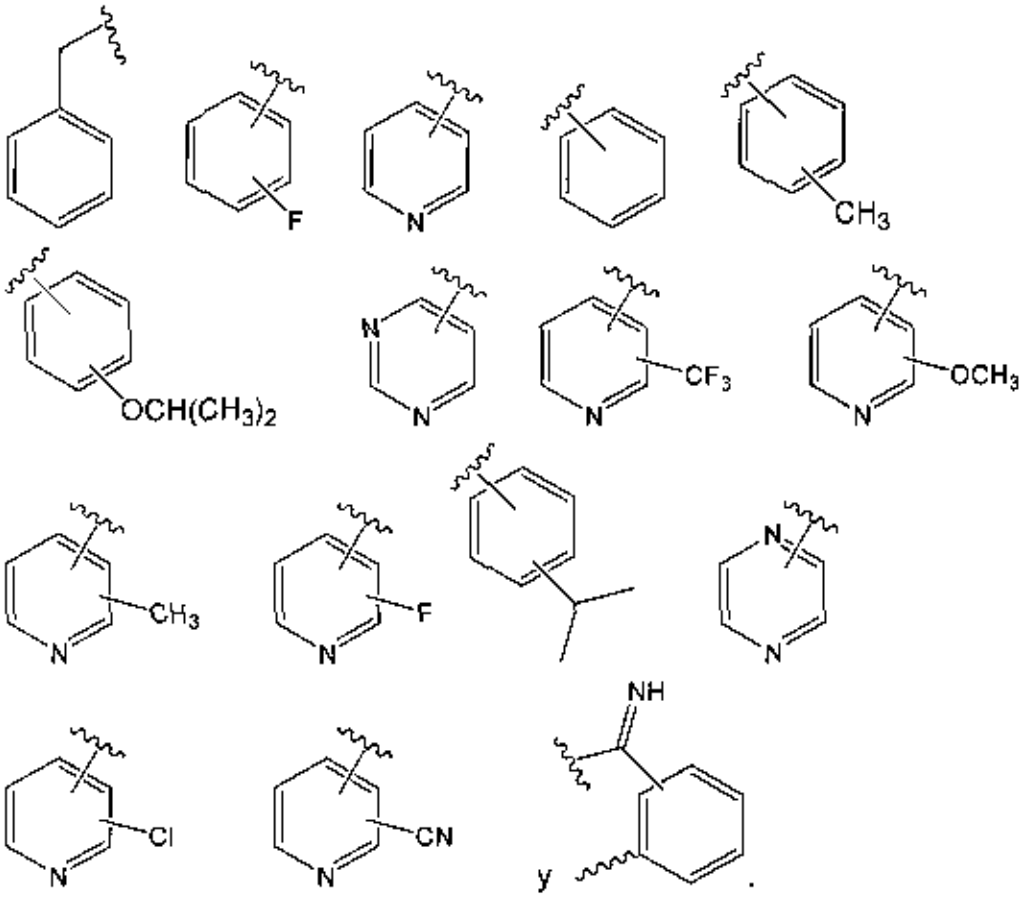
.

Otro grupo de compuestos preferidos de fórmula I son aquellos compuestos que tienen la siguiente estructura:



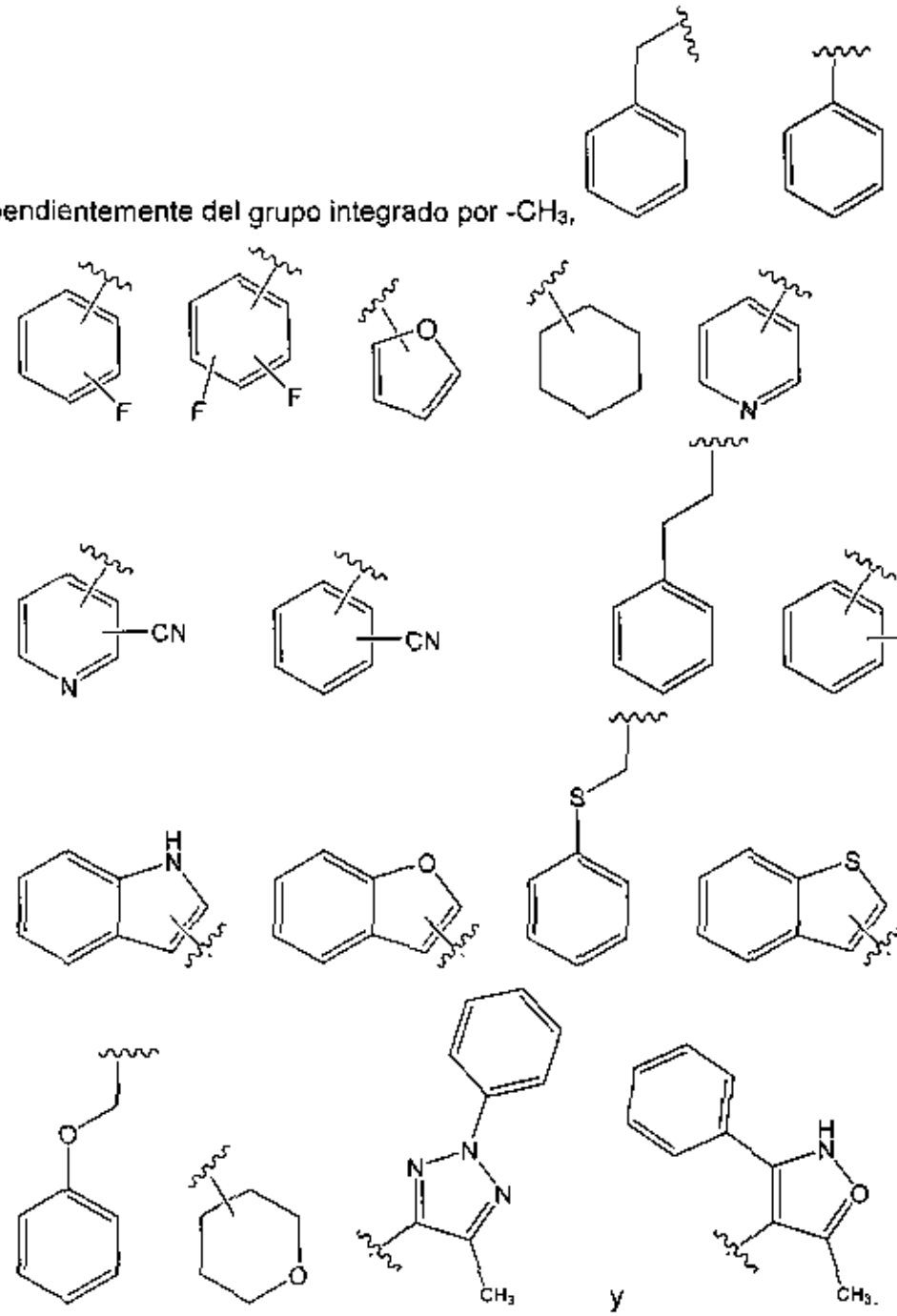
donde R^5 y R^6 son según se definieron anteriormente.

Un grupo de compuestos preferidos de fórmula I son aquellos compuestos donde R^5 se selecciona independientemente del grupo integrado por arilalquilo, arilo, heteroarilo, $-C(=NR^{11})R^8$, $-C(O)R^8$, $-C(O)OR^9$, aril-R^{21} y heteroaril-R^{21}, o con mayor preferencia, R^5 es



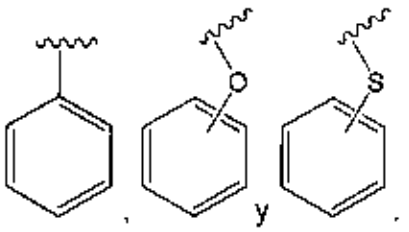
Aún otro grupo de compuestos preferidos de fórmula I son aquellos compuestos donde R^8 o R^9 se selecciona independientemente del grupo integrado

por, alquilo, cicloalquilo, arilo, arilalquilo, heteroarilo, R^{18}-alquilo, R^{18}-arilo, y R^{18}-heteroarilo; o aún con mayor preferencia, R^8 o R^9 se selecciona independientemente del grupo integrado por $-CH_3$,



y

Aún otro grupo de compuestos preferidos de fórmula I son aquellos compuestos donde R^{16} es 1-5 sustituyentes seleccionados independientemente

del grupo integrado por alquilo, halo, $-CF_3$, -CN, $-SR^{19}$ y $-OR^{20}$, o aún con mayor preferencia, R^{18} es 1-5 sustituyentes seleccionados independientemente del grupo integrado por halo, -CN, $-OCH(CH_3)_2$, $-OCH_3$, $-CH_3$, 

y .

Aún otro grupo de compuestos preferidos de fórmula I son aquellos compuestos donde R^{21} es 1-5 sustituyentes seleccionados independientemente del grupo integrado por halo, $-OCH(CH_3)_2$, $-CH_3$, $-CF_3$, $-OCH_3$, $-CH(CH_3)_2$ y –CN.

Debe observarse que los carbonos de fórmula I pueden reemplazarse con 1 a 3 átomos de silicio en la medida que se satisfagan todos los requerimientos de valencia.

Tal como se utilizó anteriormente, y a lo largo de la memoria descriptiva, los siguientes términos, a menos que se indique lo contrario, debe entenderse que tienen los siguientes significados:

"Paciente" incluye ambos seres humanos y animales.

"Mamífero" significa seres humanos y otros animales mamíferos.

"Alquilo" significa un grupo hidrocarbonado alifático el cual puede ser recto o ramificado y que comprende aproximadamente 1 a aproximadamente 20 átomos de carbono en la cadena. Grupos alquilo preferidos contienen aproximadamente 1 a aproximadamente 12 átomos de carbono en la cadena. Grupos alquilo más preferidos contienen aproximadamente 1 a aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos de alquilo inferior tal como metilo, etilo o propilo, se unen a una cadena de alquilo lineal. "Alquilo inferior" significa un grupo que tiene aproximadamente 1 a aproximadamente 6 átomos de carbono en la cadena la cual puede ser recta o ramificada. Ejemplos no limitantes de grupos alquilo adecuados incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, t-butilo, n-pentilo, heptilo, nonilo y decilo.

Grupos alquilo R^{21}-sustituido incluyen fluorometilo, trifluorometilo y ciclopropilmetilo.

"Alquenilo" significa un grupo hidrocarbonado alifático que contiene al menos un enlace doble carbono-carbono y el cual puede ser recto o ramificado y que comprende aproximadamente 2 a aproximadamente 15 átomos de carbono en la cadena. Grupos alquenilo preferidos tienen aproximadamente 2 a aproximadamente 12 átomos de carbono en la cadena; y con mayor preferencia aproximadamente 2 a aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos de alquilo inferior tal como metilo, etilo o propilo, se unen a una cadena alquenilo lineal. " alquenilo inferior" significa aproximadamente 2 a aproximadamente 6 átomos de carbono en la cadena la cual puede ser recta o ramificada. Ejemplos no limitantes de grupos alquenilo adecuados incluyen etenilo, propenilo, n-butenilo, 3-metilbut-2-enilo, n-pentenilo, octenilo y decenilo.

"Alquinilo" significa un grupo hidrocarbonado alifático que contiene al menos un enlace triple carbono-carbono y el cual puede ser recto o ramificado y que comprende aproximadamente 2 a aproximadamente 15 átomos de carbono en la cadena. Los grupos alquinilo grupos preferidos tienen aproximadamente 2 a aproximadamente 12 átomos de carbono en la cadena; y con mayor preferencia aproximadamente 2 a aproximadamente 4 átomos de carbono en la cadena. Ramificado significa que uno o más grupos de alquilo inferior tal como metilo, etilo o propilo, se unen a una cadena alquinilo lineal. "Alquinilo inferior" significa aproximadamente 2 a aproximadamente 6 átomos de carbono en la cadena la cual puede ser recta o ramificada. Ejemplos no limitantes de grupos alquinilo adecuados incluyen etinilo, propinilo, 2-butinilo, 3-metilbutinilo, n-pentinilo, y decinilo.