

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Apoderado: James Ian Raisbeck Llinas

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Patente de Invención ☒
Vía PCT fase nacional ☒ Cap.I ☒ Cap. II ☐
No. Sol. Internacional PCT/EP2005/055753
Fecha de Presentación Internal. 04/nov/2005

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios: 17 a 788 Como se radicó inicialmente
- 1.2. Reivindicaciones: Folios 817 a 789 Como se radicó inicialmente
- 1.3. Prioridad: Folio 1: US11/010.772, 13/dic/2004

2. Objeto de la invención

Título de la solicitud: INHIBIDORES HETEROCICLICOS DE ASPARTIL
PROTEASA.

El objeto de la solicitud se refiere a 372 compuestos, con estructura química diferente.

- Reivindicación 1: 372 compuestos de estructuras diferentes.
- Reivindicación 2: Composiciones que los contienen.
- Reivindicaciones 3-6, 8-13,15: Procedimiento de tratamiento que consiste en administrar un compuesto a un paciente
- Reivindicación 7,14: Composiciones que contienen los compuestos en mezcla con otros.

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.):

C07D233/88; C07D235/02; C07D239/22; C07D271/07; C07D401/04; C07D401/06; C07D401/10; C07D401/12; C07D401/14; C07D403/04; C07D403/06; C07D403/10; C07D403/12; C07D403/14; C07D405/04; C07D405/06; C07D405/10; C07D405/12; C07D405/14; C07D407/14; C07D409/06; C07D409/10; C07D409/14; C07D413/06; C07D413/12; C07D413/14; C07D417/12; C07D271/06; C07D233/00; C07D235/00; C07D239/00; C07D271/00; C07D401/00; C07D403/00; C07D405/00; C07D407/00; C07D409/00; C07D413/00; C07D417/00; A61K31/4168; A61K31/4178; C07D233/88; C07D239/22; C07D271/06; C07D401/04; C07D401/10; C07D401/12; C07D401/14; C07D403/06; C07D403/10; C07D403/14; C07D405/06; C07D405/14; C07D407/14

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486 de la C.A.N.)

-Las reivindicaciones 7 y 14 no son claras, porque reclaman composiciones que comprenden un compuesto de cualquiera de los que se trata la reivindicación 1 con un inhibidor de colinesterasa o un agonista m_1 muscarinico o un antagonista m_2 o un inhibidor gamma secretasa o un inhibidor de HMG-CoA reductasa o un agente anti-inflamatorio no esteroideal. En primer lugar la reivindicación no está perfectamente delimitada, ya que los segundos principios activos de la mezcla no están referenciados por tan solo una actividad farmacológica deseada, o sea es un resultado por investigar; en segundo lugar no se encuentra el sustento técnico en la descripción, donde se enseñe la actividad real de las mezclas así reclamadas.

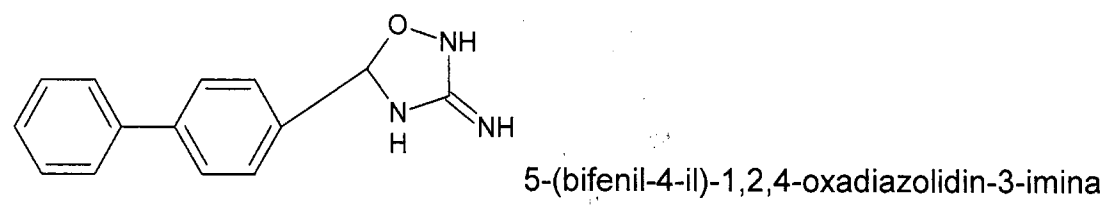
Por demás el Art. 30 D486 de la C.A.N. dispone que las reivindicaciones deberán estar sustentadas enteramente en la memoria descriptiva. Este es un requerimiento sustantivo y no una simple cuestión de consistencia puramente de enunciado. Esto significa que debe existir una base técnica real en

la memoria descriptiva, para el objeto de cada reivindicación y que el ámbito de las mismas no puede ser ampliado más allá de lo realmente justificado por el contenido técnico verdadero de la memoria descriptiva; porque si se trata de extrapolar especulativamente, desde las anterioridades igualmente se puede hacer para destruir la novedad de la materia reivindicada y debe ser igualmente valido.

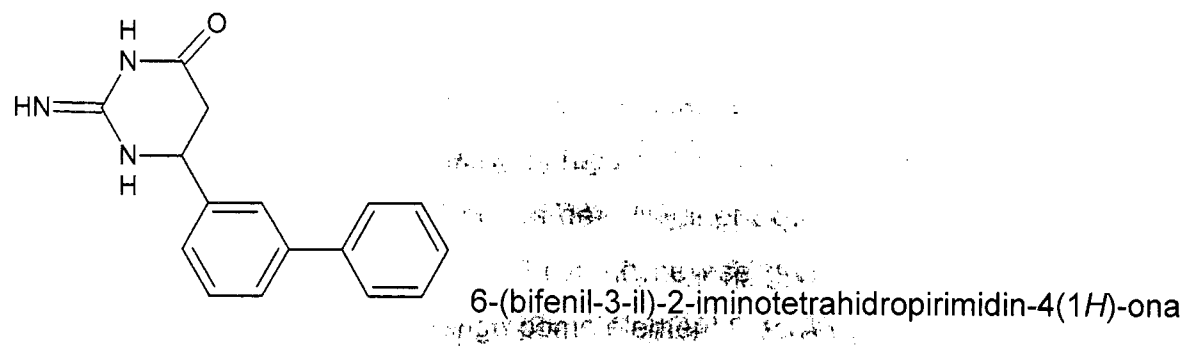
Por lo tanto las reivindicaciones no cumplen con el requisito de claridad, concisión o sustento por la descripción de acuerdo al art. 30 de la Decisión 486.

4. Unidad de invención (artículo 25 D 486 de la C.A.N.)

La solicitud tiene múltiples invenciones ya que las 372 estructuras reclamadas en la reivindicación 1 no tienen elementos técnicos especiales en común, por lo tanto se deben agrupar estructuras de tal manera que cada grupo conserve los elementos técnicos especiales en común de ese grupo, como por ejemplo un grupo podría ser el que contenga como elemento técnico especial la estructura:



Otro grupo podría ser los que contengan la estructura:



y así sucesivamente, hasta que cada grupo quede establecido compartiendo elementos técnicos particulares y comunes.

Por lo tanto la solicitud no cumple con el requisito exigido en el artículo 25 D 486 de la C.A.N.

5. Excepción a la patentabilidad (artículo 20 D486 literal d))

Las reivindicaciones 3-6, 8-13,15, reclaman un método para el tratamiento del cuerpo humano o animal, por lo tanto se encuentran bajo el alcance de lo dispuesto por el artículo 20 D486 literal d) de la C.A.N.

6. Determinación del Estado de la Técnica

Considerando la fecha de prioridad reclamada de la presente solicitud de patente 13/dic/2004, se realizo la búsqueda del estado de la técnica, en bases de datos donde ésta oficina tiene acceso libre, para búsquedas de documentos relacionados con la materia que se reclama como nueva e inventiva en la presente solicitud.

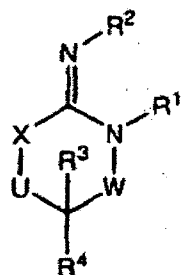
Encontrándose los siguientes documentos relevantes

N°	Documento	Título	Fecha de Presentación*
D1*	WO2005058311	Heterocyclic aspartyl protease inhibitors	15/dic/2003

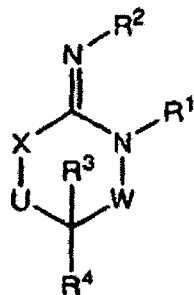
7. Análisis de patentabilidad (artículo 14 D486 de la C.A.N.)

7.1. Novedad (artículo 16 D486 de la C.A.N.)

La solicitud se refiere a 372 compuestos, con estructura química diferente, que originalmente provienen de la fórmula Markush:



-D1[WO2005058311] enseña compuestos de la misma fórmula Markush:



La anterioridad comprende la materia de la solicitud en estudio, toda vez que comparten el mismo contenido técnico en las descripciones, tal como puede verse en las pags. 1, 2-335 de D1, por lo tanto la solicitud en estudio no cumple con el requisito exigido en el artículo 16 D486 de la C.A.N.

8. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO2005058311	1-15	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.

ALIX CARMENZA CESPEDES DE VERGEL

Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha

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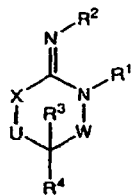
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[Continued on next page]

(54) Title: HETEROCYCLIC ASPARTYL PROTEASE INHIBITORS



(I)

(57) Abstract: Disclosed are compounds of the formula (I) or a stereoisomer, tau-
tomer, or pharmaceutically acceptable salt or solvate thereof. Also disclosed is the
method of inhibiting aspartyl protease, and in particular, the methods of treating car-
diovascular diseases, cognitive and neurodegenerative diseases, and the methods of
inhibiting of Human Immunodeficiency Virus, plasmepsins, cathepsin D and proto-
zoal enzymes. Also disclosed are methods of treating cognitive or neurodegenerative
diseases using the compounds of formula (I) in combination with a cholinesterase in-
hibitor or a muscarinic antagonist.

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HETEROCYCLIC ASPARTYL PROTEASE INHIBITORS**FIELD OF THE INVENTION**

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

BACKGROUND

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

The role of renin-angiotensin system (RAS) in regulation of blood pressure and fluid electrolyte has been well established (Oparril, S, et al. N Engl J Med 1974; 291:381-401/446-57). The octapeptide Angiotensin-II, a potent vasoconstrictor and stimulator for release of adrenal aldosterone, was processed from the precursor decapeptide Angiotensin-I, which in turn was processed from angiotensinogen by the renin enzyme. Angiotensin-II was also found to play roles in vascular smooth muscle cell growth, inflammation, reactive oxygen species generation and thrombosis, influence atherogenesis and vascular damage. Clinically, the benefit of interruption of the generation of angiotensin-II through antagonism of conversion of angiotensin-I has been well known and there are a number of ACE inhibitor drugs on the market. The blockade of the earlier conversion of angiotensinogen to angiotensin-I, i.e. the 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.

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, Alzheimers, disease, connective tissue disease, muscular dystrophy and breast cancer.

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

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

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

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

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

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

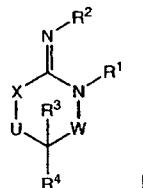
Plasmeprins are essential aspartyl protease enzymes of the malarial parasite. Compounds for the inhibition of aspartyl proteases plasmeprins, particularly I, II, IV and HAP, are in development for the treatment of malaria. Freire, et al. WO 2002074719. Na Byoung-Kuk, et al. Aspartic proteases of Plasmodium 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 plasmeprins (e.g. I, II, IV and HAP), have been used to kill malarial parasites, thus treating patients thus afflicted. Certain compounds also exhibited inhibitory activity against Cathepsin D.

SUMMARY OF THE INVENTION

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The present invention relates to compounds having the structural formula I



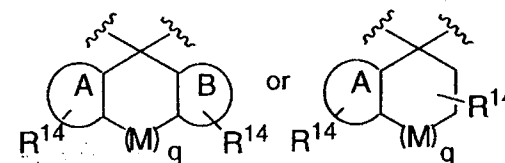
or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, wherein

- 5 W is a bond, -C(=S)-, -S(O)-, -S(O)₂-, -C(=O)-, -O-, -C(R⁶)(R⁷)-, -N(R⁵)- or -C(=N(R⁵))-;
- X is -O-, -N(R⁵)- or -C(R⁶)(R⁷)-; provided that when X is -O-, U is not -O-, -S(O)-, -S(O)₂-, -C(=O)- or -C(=NR⁵)-;
- 10 U is a bond, -S(O)-, -S(O)₂-, -C(O)-, -O-, -P(O)(OR¹⁵)-, -C(=NR⁵)-, -C(R⁶)(R⁷)_b- or -N(R⁵)-; wherein b is 1 or 2; provided that when W is -S(O)-, -S(O)₂-, -O-, or -N(R⁵)-, U is not -S(O)-, -S(O)₂-, -O-, or -N(R⁵)-; provided that when X is -N(R⁵)- and W is -S(O)-, -S(O)₂-, -O-, or -N(R⁵)-, then U is not a bond;
- 15 R¹, R² and R⁵ are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, -OR¹⁵, -CN, -C(O)R⁸, -C(O)OR⁹, -S(O)R¹⁰, -S(O)₂R¹⁰, -C(O)N(R¹¹)(R¹²), -S(O)N(R¹¹)(R¹²), -S(O)₂N(R¹¹)(R¹²), -NO₂, -N=C(R⁸)₂ and -N(R⁸)₂, provided that R¹ and R⁵ are not both selected from -NO₂, -N=C(R⁸)₂ and -N(R⁸)₂;
- 20 R³, R⁴, R⁶ and R⁷ are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CH₂-O-Si(R⁹)(R¹⁰)(R¹⁹), -SH, -CN, -OR⁹, -C(O)R⁸, -C(O)OR⁹, -C(O)N(R¹¹)(R¹²), -SR¹⁹, -S(O)N(R¹¹)(R¹²), -S(O)₂N(R¹¹)(R¹²), -N(R¹¹)(R¹²), -N(R¹¹)C(O)R⁸, -N(R¹¹)S(O)R¹⁰, -N(R¹¹)C(O)N(R¹²)(R¹³), -N(R¹¹)C(O)OR⁹ and -C(=NOH)R⁸; provided that when U is -O- or -N(R⁵)-, then R³, R⁴, R⁶ and R⁷ are not
- 25 halo, -SH, -OR⁹, -SR¹⁹, -S(O)N(R¹¹)(R¹²), -S(O)₂N(R¹¹)(R¹²), -N(R¹¹)(R¹²), -N(R¹¹)C(O)R⁸, -N(R¹¹)S(O)R¹⁰, -N(R¹¹)C(O)N(R¹²)(R¹³), or -N(R¹¹)C(O)OR⁹; provided that when W is -O- or -N(R⁵)-, then R³ and R⁴ are not halo, -SH, -OR⁹, -SR¹⁹, -S(O)N(R¹¹)(R¹²), -S(O)₂N(R¹¹)(R¹²), -N(R¹¹)(R¹²), -N(R¹¹)C(O)R⁸, -N(R¹¹)S(O)R¹⁰, -N(R¹¹)C(O)N(R¹²)(R¹³), or -N(R¹¹)C(O)OR⁹;

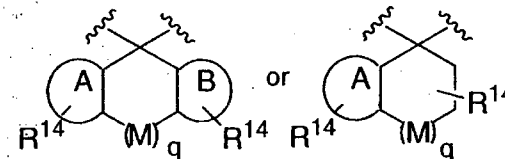
- 5 -

and provided that when X is -N(R⁵)-, W is -C(O)- and U is a bond, R³, R⁴, R⁶ and R⁷ are not halo, -CN, -SH, -OR⁹, -SR¹⁹, -S(O)N(R¹¹)(R¹²) or -S(O)₂N(R¹¹)(R¹²); or R³, R⁴, R⁶ and R⁷, together with the carbon to which they are attached, form a 3-7 membered cycloalkyl group optionally substituted by R¹⁴ or a 3-7 membered cycloalkylether optionally substituted by R¹⁴;

or R³ and R⁴ or R⁶ and R⁷ together with the carbon to which they are attached, are combined to form multicyclic groups such as



- 10 wherein M is -CH₂-, S-, -N(R¹⁹)- or O-, A and B are independently aryl or heteroaryl and q is 0, 1 or 2 provided that when q is 2, one M must be a carbon atom and when q is 2, M is optionally a double bond; and with the proviso that when R³, R⁴, R⁶ and R⁷ form said multicyclic groups



- 15 then adjacent R³ and R⁴ or R⁶ and R⁷ groups cannot be combined to form said multicyclic groups;

R⁸ is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -OR¹⁵, -N(R¹⁵)(R¹⁶), -N(R¹⁵)C(O)R¹⁶, -N(R¹⁵)S(O)R¹⁶, -N(R¹⁵)S(O)₂R¹⁶, -N(R¹⁵)S(O)₂N(R¹⁶)(R¹⁷), -N(R¹⁵)S(O)N(R¹⁶)(R¹⁷), -N(R¹⁵)C(O)N(R¹⁶)(R¹⁷) and -N(R¹⁵)C(O)OR¹⁶;

R⁹ is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;

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

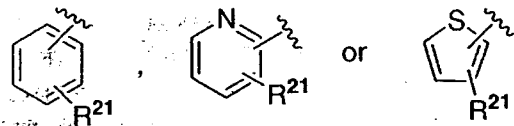
provided that when X is $-N(R^5)-$, U is $-O-$ and W is a bond or $-C(R^6)(R^7)-$, (R^3, R^4) is not (H, -NHC(O)-alkyl-heteroaryl) or (H, alkyl-NHC(O)-alkyl-heteroaryl); and

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

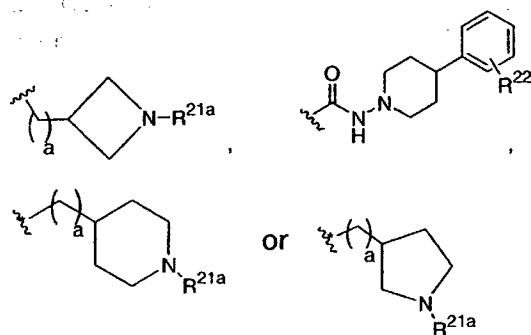
provided that when R^1 is R^{21} -aryl or R^{21} -aryalkyl, wherein R^{21} is $-OCF_3$, $-S(O)CF_3$, $-S(O)_2CF_3$, $-S(O)alkyl$, $-S(O)_2alkyl$, $-S(O)_2CHF_2$, $-S(O)_2CF_2CF_3$, $-OCF_2CHF_2$, $-OCHF_2$, $-OCH_2CF_3$, $-SF_5$ or $-S(O)_2NR^{15}R^{16}$;

10 wherein R^{15} and R^{16} are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, R^{18} -alkyl, R^{18} -cycloalkyl, R^{18} -heterocycloalkyl, R^{18} -aryl and R^{18} -heteroaryl; U is a bond or $-CH_2-$; and X is $-N(R^5)-$; then R^5 is H;

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



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



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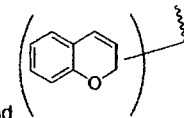
where a is 0 to 6 and R^{22} is alkyl, alkoxy, halo, -CN, -OH, $-NO_2$ or haloalkyl;

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

phenyl,

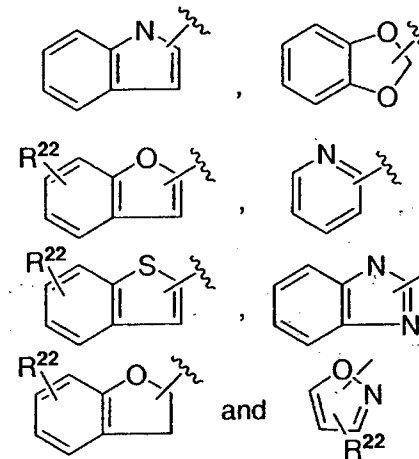
5 phenyl substituted with alkyl,



and

wherein R^{22} is selected from the group consisting of

H, methoxy, nitro, oxo, -OH, halo and alkyl,



10

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

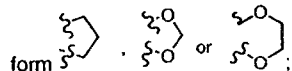
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In another aspect, the invention comprises the method of inhibiting aspartyl protease comprising administering at least one compound of formula I to a patient in need of such treatment.

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

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$-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$,
 $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-N_3$, $=NOR^{15}$, $-NO_2$, $-S(O)R^{15}$ and $-S(O)_2R^{15}$,
 or two R^{21} or two R^{22} moieties on adjacent carbons can be linked together to



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

- R^{23} is 1 to 5 groups independently selected from the group consisting of alkyl,
 alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl,
 15 heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, $-CN$, $-OR^{24}$,
 $-C(O)R^{24}$, $-C(O)OR^{24}$, $-C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$,
 $-C(=NOR^{24})R^{25}$, $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, $-alkyl-N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$,
 $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$,
 $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$,
 20 $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ and
 $-S(O)_2R^{24}$; and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl,
 heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl
 groups in R^{23} are independently unsubstituted or substituted by 1 to 5 R^{27} groups
 25 independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl,
 aryl, heteroaryl, halo, $-CF_3$, $-CN$, $-OR^{24}$, $-C(O)R^{24}$, $-C(O)OR^{24}$, $alkyl-C(O)OR^{24}$,
 $C(O)N(R^{24})(R^{25})$, $-SR^{24}$, $-S(O)N(R^{24})(R^{25})$, $-S(O)_2N(R^{24})(R^{25})$, $-C(=NOR^{24})R^{25}$,
 $-P(O)(OR^{24})(OR^{25})$, $-N(R^{24})(R^{25})$, $-alkyl-N(R^{24})(R^{25})$, $-N(R^{24})C(O)R^{25}$,
 $-CH_2-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-CH_2-N(R^{24})S(O)_2R^{25}$,
 $-N(R^{24})S(O)_2N(R^{25})(R^{26})$, $-N(R^{24})S(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)N(R^{25})(R^{26})$,
 30 $-CH_2-N(R^{24})C(O)N(R^{25})(R^{26})$, $-N(R^{24})C(O)OR^{25}$, $-CH_2-N(R^{24})C(O)OR^{25}$, $-S(O)R^{24}$ and
 $-S(O)_2R^{24}$;

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

- R^{27} is 1-5 substituents independently selected from the group consisting of
 alkyl, aryl, arylalkyl, $-NO_2$, halo, $-CF_3$, $-CN$, $alkyl-CN$, $-C(O)R^{28}$, $-C(O)OH$, $-C(O)OR^{28}$,
 $-C(O)NHR^{29}$, $-C(O)N(alkyl)_2$, $-C(O)N(alkyl)(aryl)$, $-C(O)N(alkyl)(heteroaryl)$, $-SR^{28}$,
 $-S(O)_2R^{29}$, $-S(O)NH_2$, $-S(O)NH(alkyl)$, $-S(O)N(alkyl)(alkyl)$, $-S(O)NH(aryl)$, $-S(O)_2NH_2$,
 10 $-S(O)_2NHR^{28}$, $-S(O)_2NH(aryl)$, $-S(O)_2NH(heterocycloalkyl)$, $-S(O)_2N(alkyl)_2$,
 $-S(O)_2N(alkyl)(aryl)$, $-OH$, $-OR^{29}$, $-O-heterocycloalkyl$, $-O-cycloalkylalkyl$,
 $-O-heterocycloalkylalkyl$, $-NH_2$, $-NHR^{29}$, $-N(alkyl)_2$, $-N(arylalkyl)_2$,
 $-N(arylalkyl)(heteroarylalkyl)$, $-NHC(O)R^{29}$, $-NHC(O)NH_2$, $-NHC(O)NH(alkyl)$,
 $-NHC(O)N(alkyl)(alkyl)$, $-N(alkyl)C(O)NH(alkyl)$, $-N(alkyl)C(O)N(alkyl)(alkyl)$,
 15 $-NHS(O)_2R^{29}$, $-NHS(O)_2NH(alkyl)$, $-NHS(O)_2N(alkyl)(alkyl)$, $-N(alkyl)S(O)_2NH(alkyl)$
 and $-N(alkyl)S(O)_2N(alkyl)(alkyl)$;

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

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

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

- provided that neither R^1 nor R^5 is $-C(O)-alkyl$ -azetidinone or alkyl di-substituted
 with $(-COOR^{15})$ or $-C(O)N(R^{15})(R^{16})$ and $(-N(R^{15})(R^{16}))$, $-N(R^{15})C(O)R^{16}$,
 $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$,
 25 $-N(R^{15})C(O)N(R^{16})(R^{17})$, or $-N(R^{15})C(O)OR^{16}$;

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

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

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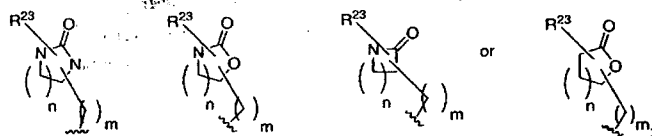
R^{10} is independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and $-N(R^{15})(R^{16})$;

R^{11} , R^{12} and R^{13} are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, $-C(O)R^8$, $-C(O)OR^9$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-C(O)N(R^{15})(R^{16})$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$ and $-CN$;

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

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

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



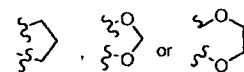
wherein R^{23} numbers 0 to 5 substituents, m is 0 to 6 and n is 1 to 5;

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

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heterocycloalkylalkyl, $-NH_2$, $-NHR^{20}$, $-N(alkyl)_2$, $-N(arylalkyl)_2$, $-N(arylalkyl)$ -(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, cycloalkyl, aryl, arylalkyl or heteroarylalkyl;

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

and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are independently unsubstituted or substituted by 1 to 5 R^{21} groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, $-CN$, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-CH(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, $-alkyl-N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-R^{15}$, $-CH_2N(R^{15})(R^{16})$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$, $-N(R^{15})S(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)N(R^{16})(R^{17})$, $-CH_2-N(R^{15})C(O)N(R^{16})(R^{17})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, $-S(O)R^{15}$, $=NOR^{15}$, $-N_3$, $-NO_2$ and $-S(O)_2R^{15}$; and wherein each of the alkyl, cycloalkenyl, cycloalkyl, cycloalkylalkyl,

heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{21} are independently unsubstituted or substituted by 1 to 5 R^{22} groups independently selected from the group consisting of alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, halo, $-CF_3$, $-CN$, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-alkyl-C(O)OR^{15}$, $C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)N(R^{15})(R^{16})$, $-S(O)_2N(R^{15})(R^{16})$, $-C(=NOR^{15})R^{16}$, $-P(O)(OR^{15})(OR^{16})$, $-N(R^{15})(R^{16})$, $-alkyl-N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{15})S(O)_2N(R^{16})(R^{17})$,

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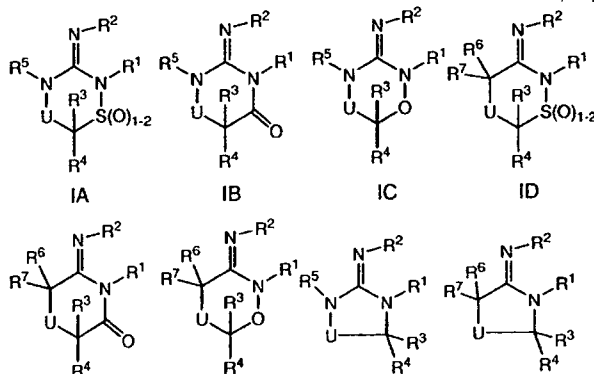
the method of inhibiting plasmepsins I and II for treatment of malaria; the method of inhibiting Cathepsin D for the treatment of Alzheimer's Disease, breast cancer, and ovarian cancer; and the method of inhibiting protozoal enzymes, for example inhibition of plasmodium falciparum, for the treatment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

In another aspect, the invention comprises the method of treating Alzheimer's disease comprising administering to a patient in need of such treatment a combination of at least one compound of formula I and a cholinesterase inhibitor or a muscarinic 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 antagonist in a pharmaceutically acceptable carrier, the combined quantities being an effective amount to treat a cognitive disease or neurodegenerative disease such as Alzheimer's disease.

DETAILED DESCRIPTION:

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



IE IF IG IH

In compounds of formulas IA to IF, U is preferably a bond or -C(R⁶)(R⁷)-. In compounds of formula IG and IH, U is preferably -C(O)-.

It will be understood that since the definition of R¹ is the same as the definition of R⁵, when X is -N(R⁵)-, compounds of formula I wherein W is a bond and U is a bond, -S(O)-, -S(O)₂-, -C(O)-, -O-, -C(R⁶)(R⁷)- or -N(R⁵)- are equivalent to compounds of formula I wherein U is a bond and W is a bond, -S(O)-, -S(O)₂-, -C(O)-, -O-, -C(R⁶)(R⁷)- or -N(R⁵)-.

More preferred compounds of the invention are those of formula IB wherein U is a bond or those of formula IB wherein U is -C(R⁶)(R⁷)-.

Another group of preferred compounds of formula I is that wherein R² is H.

R³, R⁴, R⁶ and R⁷ are preferably selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CH₂-O-Si(R⁹)(R¹⁰)(R¹³), -SH, -CN, -OR⁹, -C(O)R⁸, -C(O)OR⁹, -C(O)N(R¹¹)(R¹²), -SR¹⁰, -S(O)N(R¹¹)(R¹²), -S(O)₂N(R¹¹)(R¹²), -N(R¹¹)(R¹²), -N(R¹¹)C(O)R⁸, -N(R¹¹)S(O)R¹⁰, -N(R¹¹)C(O)N(R¹²)(R¹³), -N(R¹¹)C(O)OR⁹ and -C(=NOH)R⁸.

R³, R⁴, R⁶ and R⁷ are preferably selected from the group consisting of aryl, heteroaryl, heteroarylalkyl, arylalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkyl and cycloalkylalkyl.

In a group of preferred compounds

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

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

X is -N(R⁵)-;

R¹ is H, alkyl, R²¹-alkyl, arylalkyl, R²¹-arylalkyl, cycloalkylalkyl, R²¹-cycloalkylalkyl, heterocycloalkylalkyl or R²¹-heterocycloalkylalkyl,

R² is H;

R³ is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R²¹-alkyl, R²¹-cycloalkylalkyl, R²¹-cycloalkyl, R²¹-aryl or R²¹-arylalkyl;

R⁴ is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R²¹-alkyl, R²¹-cycloalkylalkyl, R²¹-cycloalkyl, R²¹-aryl or R²¹-arylalkyl;

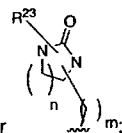
R⁵ is H, alkyl, R²¹-alkyl, arylalkyl, R²¹-arylalkyl, cycloalkylalkyl, R²¹-cycloalkylalkyl, heterocycloalkylalkyl or R²¹-heterocycloalkylalkyl;

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R⁶ is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R²¹-alkyl, R²¹-cycloalkylalkyl, R²¹-cycloalkyl, R²¹-aryl or R²¹-arylalkyl;

R⁷ is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R²¹-alkyl, R²¹-cycloalkylalkyl, R²¹-cycloalkyl, R²¹-aryl or R²¹-arylalkyl;



5 R¹⁵, R¹⁶ and R¹⁷ is H, R¹⁸-alkyl, alkyl or R²¹ is alkyl, aryl, halo, -OR¹⁵, -NO₂, -C(O)R¹⁵, -CH₂-N(R¹⁵)C(O)N(R¹⁶)(R¹⁷) or -CH(R¹⁵)(R¹⁶);

n is 1;

m is 1;

10 R¹⁸ is -OR²⁰;

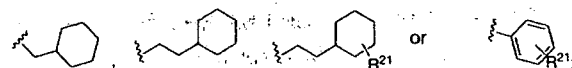
R²⁰ is aryl;

and

R²³ is alkyl.

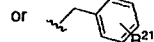
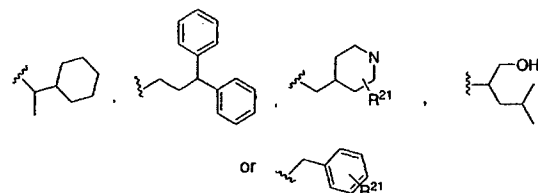
In a group of preferred compounds

15 R³, R⁴, R⁶ and R⁷ are



and

R¹ and R⁵ is H, CH₃,



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In an additional group of preferred compounds;

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

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

X is -N(R⁵)-;

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R¹ is H, alkyl, R²¹-alkyl, arylalkyl, R²¹-arylalkyl, cycloalkylalkyl, R²¹-cycloalkylalkyl, heterocycloalkylalkyl or R²¹-heterocycloalkylalkyl,

R² is H;

R³ is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R²¹-alkyl, R²¹-cycloalkylalkyl, R²¹-cycloalkyl, R²¹-aryl, R²¹-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R²¹-heteroarylalkyl, R²¹-heteroaryl, R²¹-heterocycloalkyl or R²¹-heterocycloalkylalkyl;

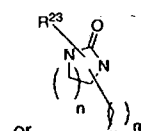
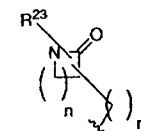
R⁴ is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R²¹-alkyl, R²¹-cycloalkylalkyl, R²¹-cycloalkyl, R²¹-aryl, R²¹-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R²¹-heteroarylalkyl, R²¹-heteroaryl, R²¹-heterocycloalkyl or R²¹-heterocycloalkylalkyl;

R⁵ is H, alkyl, R²¹-alkyl, arylalkyl, R²¹-arylalkyl, cycloalkylalkyl, R²¹-cycloalkylalkyl, heterocycloalkylalkyl or R²¹-heterocycloalkylalkyl;

R⁶ is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R²¹-alkyl, R²¹-cycloalkylalkyl, R²¹-cycloalkyl, R²¹-aryl, R²¹-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R²¹-heteroarylalkyl, R²¹-heteroaryl, R²¹-heterocycloalkyl or R²¹-heterocycloalkylalkyl;

R⁷ is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R²¹-alkyl, R²¹-cycloalkylalkyl, R²¹-cycloalkyl, R²¹-aryl, R²¹-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R²¹-heteroarylalkyl, R²¹-heteroaryl, R²¹-heterocycloalkyl or R²¹-heterocycloalkylalkyl;

R¹⁵, R¹⁶ and R¹⁷ is H, cycloalkyl, cycloalkylalkyl, R¹⁸-alkyl, alkyl, aryl, R¹⁸-aryl,



R¹⁸-arylalkyl, arylalkyl,

n is 1 or 2;

m is 0 or 1;

R¹⁸ is -OR²⁰ or halo;

R²⁰ is aryl or halo substituted aryl;

R²¹ is alkyl, aryl, heteroaryl, R²²-alkyl, R²²-aryl, R²²-heteroaryl, halo, heterocycloalkyl, -N(R¹⁵)(R¹⁶), -OR¹⁵, -NO₂, -C(O)R¹⁵, -N(R¹⁵)C(O)R¹⁶,

25

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

R^{22} is $-OR^{15}$ or halo

and

5 R^{23} is H or alkyl.

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.

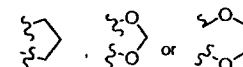
10 "Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. 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^{32} -substituted alkyl groups include fluoromethyl, trifluoromethyl and cyclopropylmethyl.

20 "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.

25 "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-butenyl, 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



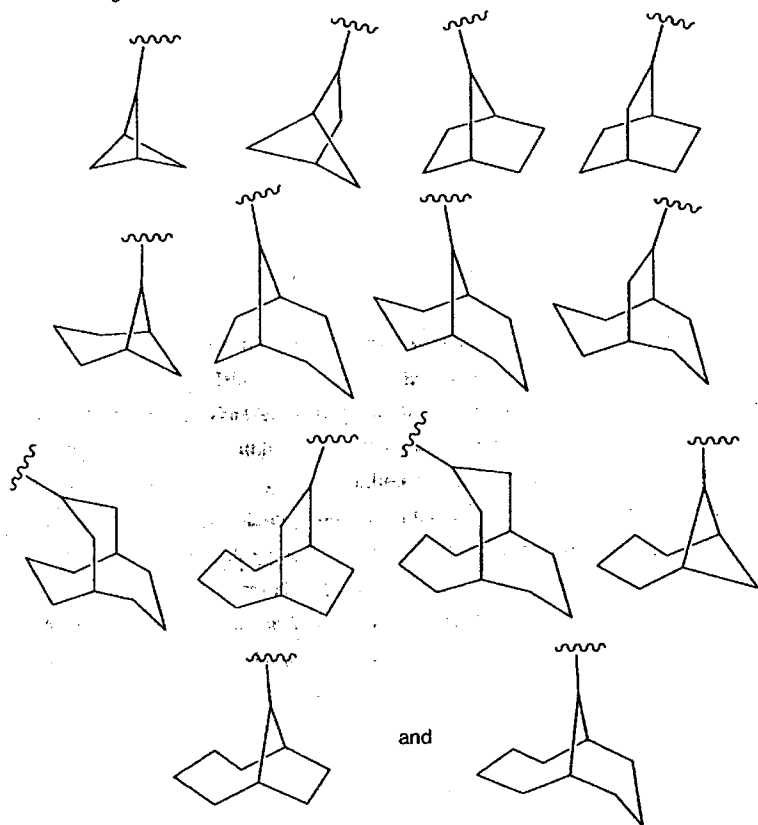
10 Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"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, quinoxalyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidinyl, pyrrolopyridyl, imidazopyridyl, isoquinolyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

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

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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



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

10 "Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. The cycloalkenyl ring

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

5 "Heterocyclenyl" 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-tetrahydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridine, 1,4,5,6-tetrahydropyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolyl, 2-pyrazolyl, and the like. Non-limiting examples of suitable oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, fluorodihydrofuranyl, and the like. Non-limiting example of a suitable multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Non-limiting examples of suitable monocyclic thiaheterocyclenyl rings include dihydrothiophenyl, dihydrothiopyranyl, and the like.

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

30 "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

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