

Señores
DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y
Bogotá, D.C.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-047111- -00003-0000

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Expediente No. 07-47.111
Fase Nacional de Solicitud
de Patente PCT
GLENMARK
PHARMACEUTICALS S.A.

En relación con el Expediente de la referencia por medio del presente escrito muy respetuosamente me permito solicitarles se sirvan proceder a efectuar el **EXAMEN DE PATENTABILIDAD** de la solicitud aquí contenida.

Para tal efecto acompaño el comprobante de pago por valor de \$ 420.000.00,
recibo No. 33,635

De Ustedes Atentamente,

LUIS FELIPE CASTILLO GIBSONE
T.P. # 68.995 del C.S.J.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Dep. 2020 NOCLERACIONE
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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VAL. PAGO
CASTILLO GRAU Y ASOCIADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	0977520	25/04/2008	523,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
		TOTAL :	\$ 420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-47111

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **589** DE

FECHA **29 DE FEBRERO DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **03 DE JUNIO DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

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Europäisches Patentamt
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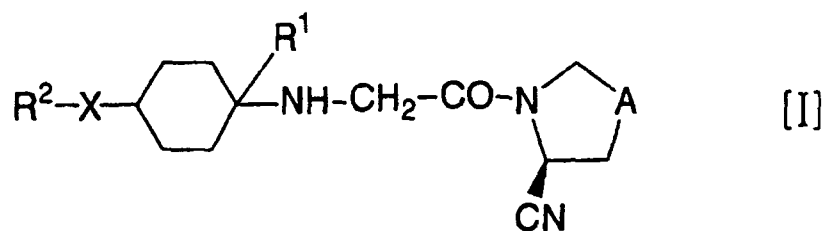
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(54) ALIPHATIC NITROGENOUS FIVE-MEMBERED RING COMPOUNDS

(57) The present invention is to provide an aliphatic nitrogen-containing 5-membered ring compound represented by the formula [I]:



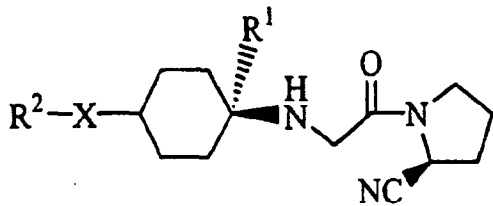
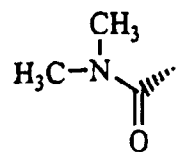
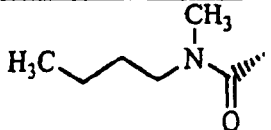
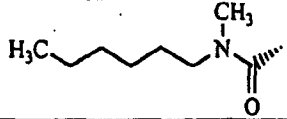
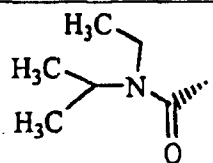
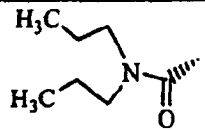
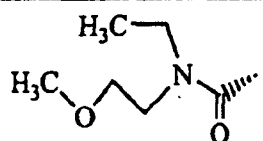
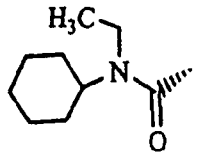
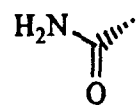
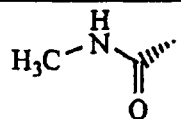
wherein A represents -CH₂- or -S-,

R¹ represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group,

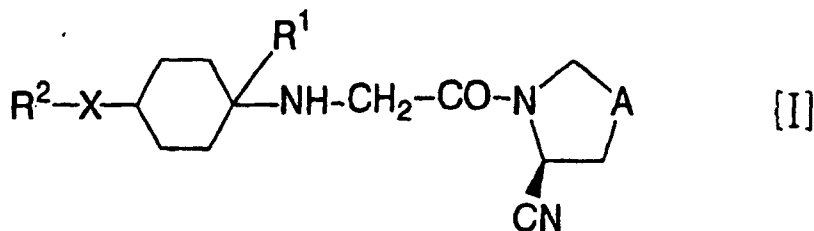
X represents -N(R³)-, -O- or -CO-, where R³ represents hydrogen atom or a lower alkyl group, and R² represents (1) a cyclic group which may be substituted, or (2) an amino group which may be substituted, or a pharmaceutically acceptable salt thereof, a method for preparing the above-mentioned compound and a pharmaceutical composition comprising the above-mentioned compound as an effective ingredient.

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Table 1c (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1c-10		H	HCl	Colorless crystal Melting point: 211°C (decomposed) MS·APCI (m/z): 307 [M+H]
1c-11		H	HCl	Purified powder MS·APCI (m/z): 349
1c-12		H	HCl	Colorless powder MS·APCI (m/z): 377 [M+H] ⁺
1c-13		H	HCl	Purified powder MS·APCI (m/z): 349
1c-14		H	HCl	Colorless powder MS·APCI (m/z): 363 [M+H] ⁺
1c-15		H	HCl	Purified powder MS·APCI (m/z): 365
1c-16		H	HCl	Colorless powder MS·APCI (m/z): 389 [M+H] ⁺
1c-17		H	HCl	Pale brownish purified resin state MS·APCI (m/z): 279 [M+H] ⁺
1c-18		H	HCl	Purified powder MS·APCI (m/z): 293 [M+H] ⁺

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10 wherein A represents -CH₂- or -S-,

R¹ represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group,

X represents -N(R³)-, -O- or -CO-, where R³ represents hydrogen atom or a lower alkyl group, and

15 R² represents (1) a cyclic group which may be substituted, where the cyclic group portion is

(i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or

(ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or

20 (2) an amino group which may be substituted,
or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1, wherein R² is

25 (1) a cyclic group which may have 1 to 3 substituents which are the same or different and selected from the substituents of Group A mentioned below, where the cyclic group portion is (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or

(2) an amino group which may have 1 or 2 substituents which are the same or different and selected from the substituents of Group B mentioned below.

30 Substituents of Group A:

a halogen atom; cyano group; nitro group; oxo group; hydroxy group; carboxy group; oxidyl group; amino group; carbamoyl group; aminosulfonyl group; a lower alkyl group;

35 a lower alkoxy group; a lower alkanoyl group; a lower alkoxycarbonyl group; a lower alkoxy-substituted lower alkanoyl group;

a lower alkoxycarbonyl-substituted lower alkoxy group;

a lower alkoxycarbonyl-substituted lower alkoxycarbonyl group;

a lower alkylthio group;

40 a lower alkylsulfonyl group;

a di-lower alkylamino-substituted lower alkoxy group;

a di-lower alkylaminocarboxy group;

a lower alkyl group substituted by a group selected from amino group, carbamoyl group, a halogen atom, hydroxy group, carboxy group, a lower alkoxy group and mono- or di-substituted amino group;

45 a mono- or di-substituted amino group;

a mono- or di-substituted carbamoyl group;

a substituted or unsubstituted lower cycloalkyl group;

a substituted or unsubstituted lower cycloalkyl-CO-;

a substituted or unsubstituted lower cycloalkyl-lower alkyl group;

50 a substituted or unsubstituted phenyl group;

a substituted or unsubstituted phenyl-O-;

a substituted or unsubstituted phenyl-CO-;

a substituted or unsubstituted phenyl-lower alkyl group;

a substituted or unsubstituted phenyl-O-lower alkyl group;

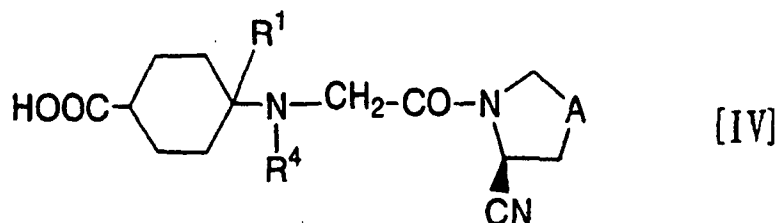
55 a substituted or unsubstituted phenylsulfonyl group;

a substituted or unsubstituted phenyl-lower alkoxy group;

a substituted or unsubstituted phenyl-lower alkoxycarbonyl group;

a substituted or unsubstituted lower cycloalkenyl group;

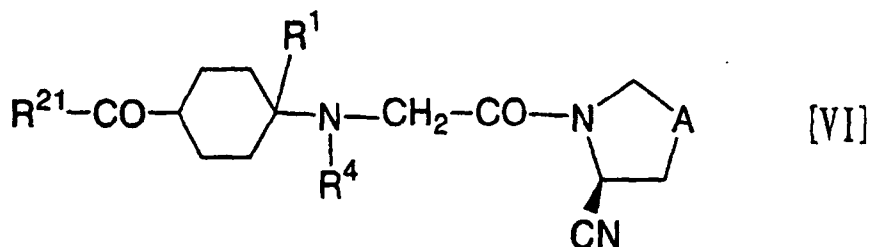
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10 wherein A and R¹ have the same meanings as defined above and R⁴ represents a protective group for an amino group,
or a salt thereof with the compound represented by the formula [V] :



20 wherein R²¹ has the same meaning as defined above, or a salt thereof to obtain a compound represented by the formula [VI] :



30 wherein R¹, R⁴, R²¹ and A have the same meanings as defined above,
or a salt thereof, and subsequently removing the protective group for an amino group R⁴, and optionally making
the product into a pharmaceutically acceptable salt thereof.

35 20. A method for inhibiting dipeptidylpeptidase IV activity by using the compound according to any one of Claims 1 to 17.

21. A method for treatment or prophylaxis of a disease, which comprises administering to a patient an effective dose
of the compound according to any one of Claims 1 to 17.

40 22. The method for treatment or prophylaxis of a disease according to Claim 21, wherein the disease is expected to
be alleviated by inhibiting dipeptidylpeptidase IV activity.

23. The method for treatment or prophylaxis of a disease according to Claim 21, wherein the disease is diabetes.

45 24. The method for treatment or prophylaxis of a disease according to Claim 21, wherein the disease is type 2 diabetes.

25. Use of the compound according to any one of Claims 1 to 17 as an inhibitor of dipeptidylpeptidase IV.

26. Use of the compound according to any one of Claims 1 to 17 as a pharmaceutically effective ingredient of a med-
icine.

50 27. Use of the compound according to any one of Claims 1 to 17 for the preparation of a medicine.

28. The use according to Claim 26 or 27, wherein the medicine is for the treatment or prophylaxis of a disease that is
expected to be improved by inhibiting dipeptidylpeptidase IV activity.

55 29. The use according to Claim 26 or 27, wherein the medicine is for the treatment or prophylaxis of diabetes.

(19)



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Patent- und Rechtsanwälte

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(54) **DIPEPTIDYL PEPTIDASE IV INHIBITOR**

(57) A compound represented by general formula

(I):

A-B-D

<wherein

A represents a substituted or unsubstituted 1-pyr-

rolidiny group, a substituted or unsubstituted 3-thi-
azolidiny group, a substituted or unsubstituted
1-oxo-3-thiazolidiny group, or the like;

B represents a) a group represented by $-(C(R^1)(R^2))_kCO-$ (wherein k represents an integer of from
1 to 6, R^1 and R^2 may be the same or different and
each represents a hydrogen atom, a hydroxyl
group, a halogen atom, or the like) or the like;

D represents -U-V [wherein U represents a substi-

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A represents a substituted or unsubstituted 1-pyrrolidinyl group, a substituted or unsubstituted 3-thiazolidinyl group, a substituted or unsubstituted 1-oxo-3-thiazolidinyl group, a substituted or unsubstituted 1,1-dioxo-3-thiazolidinyl group, a substituted or unsubstituted 3-oxazolidinyl group, a substituted or unsubstituted 2,5-dihydro-1-pyrrolyl group, a substituted or unsubstituted 1-pyrrolyl group, a substituted or unsubstituted piperidino group, a substituted or unsubstituted 1-indolinyl group, a substituted or unsubstituted 1-indolyl group, a substituted or unsubstituted 1-octahydroindolyl group, a substituted or unsubstituted 1-tetrahydroquinolyl group, or a substituted or unsubstituted 1-decahydroquinolyl group;

B represents

a) a group represented by $-(C(R^1)(R^2))_kCO-$ (wherein k represents an integer of 1 to 6, R^1 and R^2 may be the same or different and each represents a hydrogen atom, a hydroxyl group, a halogen atom, a cyano group, a nitro group, a substituted or unsubstituted alkyl group, a substituted or unsubstituted alicyclic alkyl group, a substituted or unsubstituted alicyclic heterocyclic group, a substituted or unsubstituted alkenyl group, a substituted or unsubstituted alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted heteroaryl group, or a substituted or unsubstituted heteroarylalkyl group, or R^1 and R^2 , which attach to the same carbon atom, together with said carbon atom, or two R^1 's, which attach to adjacent carbon atoms, respectively, together with the two carbon atoms when k is two or more, may combine to form a substituted or unsubstituted alicyclic alkyl group or a substituted or unsubstituted alicyclic heterocyclic group),

b) a group represented by $-CO(C(R^3)(R^4))_m-$ (wherein R^3 and R^4 may be the same or different and each has the same meaning as that defined above for R^1 and R^2 , respectively, and m represents an integer of 1 to 6),

c) a group represented by $-(C(R^5)(R^6))_n-$ (wherein R^5 and R^6 may be the same or different and each has the same meaning as that defined above for R^1 and R^2 , respectively, and n represents an integer of 2 to 7)

d) $-CO-$, or

e) $-SO_2$,

D represents

a group represented by $-U-V$ [wherein U represents a substituted or unsubstituted piperazinediyl group or a homopiperazinediyl group; V represents $-E-R^7$ (wherein E represents a single bond, $-CO-$, $-C(=O)O-$, or $-SO_2-$; R^7 represents a hydrogen atom, a substituted or unsubstituted alkyl group, a substituted or unsubstituted alicyclic alkyl group, a substituted or unsubstituted alicyclic heterocyclic group, a substituted or unsubstituted alkenyl group, a substituted or unsubstituted alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted heteroaryl group, or a substituted or unsubstituted heteroarylalkyl group)]

or

a group represented by $-W^A-X^A-Y^A-Z^A$ [wherein

1) W^A and Y^A may be the same or different and each represents an oxygen atom, a sulfur atom, $-SO-$, $-SO_2-$, or $-N(R^{8A})-$ (wherein R^{8A} has the same meaning as that defined above for R^7); X^A represents a substituted or unsubstituted alicyclic alkylene group, a group formed by eliminating one hydrogen atom from a substituted or unsubstituted alicyclic heterocyclic group, a substituted or unsubstituted arylene group, a substituted or unsubstituted aralkylene group, a substituted or unsubstituted heteroarylene group, a substituted or unsubstituted heteroarylalkylene group, or $-(C(R^9)(R^{10}))_q-$ [wherein q represents an integer of 1 to 6, R^9 and R^{10} may be the same or different and each represents a hydrogen atom, a substituted or unsubstituted alkyl group, a substituted or unsubstituted alicyclic alkyl group, a substituted or unsubstituted alicyclic heterocyclic group, a substituted or unsubstituted alkenyl group, a substituted or unsubstituted alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted heteroaryl group, or a substituted or unsubstituted heteroarylalkyl group, or R^9 and R^{10} , which attach to the same carbon atom, may combine together with said carbon atom to form a substituted or unsubstituted alicyclic alkyl group (provided that not all of the substituents R^9 and R^{10} in the chain consisting of $-(C(R^9)(R^{10}))_q-$ are hydrogen atoms)], or X^A may combine together with one $-N(R^{8A})-$ represented by W^A or Y^A to form a substituted or unsubstituted pyrrolidinediyl group, a substituted or unsubstituted piperidinediyl group, or a substituted or unsubstituted homopiperidinediyl group; Z^A has the same meaning as that defined above for V (when X^A combines with one $-N(R^{8A})-$ represented by W^A or Y^A to form a substituted or unsubstituted pyrrolidinediyl group or a substituted or unsubstituted piperidinediyl group,

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V is not a hydrogen atom or an aralkyl group); or

2) W^A and Y^A may be the same or different and each represents an oxygen atom, a sulfur atom, $-SO-$, $-SO_2-$, or $N(R^{8B})-$ (wherein R^{8B} has the same meaning as that defined above for R^7); X^A represents $-(CH_2)_r-$ (wherein r represents an integer of 1 to 6); Z^A represents a substituted or unsubstituted alicyclic alkyl group, a substituted or unsubstituted alicyclic heterocyclic group, a substituted or unsubstituted alkenyl group, a substituted or unsubstituted alkynyl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted heteroarylalkyl group, a pyridyl group substituted with $-SO_2-N(R^{15})(R^{16})$ [wherein R^{15} and R^{16} may be the same or different and each represents a hydrogen atom, a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted heteroaryl group, or a substituted or unsubstituted heteroarylalkyl group, or R^{15} and R^{16} , together with the adjacent nitrogen atom, may form a substituted or unsubstituted alicyclic heterocyclic group (said alicyclic heterocyclic group is selected from a pyrrolidinyl group, an oxazolidinyl group, a thiazolidinyl group, a piperidino group, a homopiperidino group, a piperazinyl group, a morpholino group, and a thiomorpholino group)], or a group selected from a trifluoromethylphenyl group, a methanesulfonylphenyl group, a nitrophenyl group, a cyanophenyl group, a naphthyl group, a pyrazinyl group, a pyridazinyl group, a triazinyl group, a thienyl group, a furyl group, a pyrrolyl group, an imidazolyl group, a pyrazolyl group, a triazolyl group, a tetrazolyl group, an oxazolyl group, a thiazolyl group, an isoxazolyl group, an isothiazolyl group, an oxadiazolyl group, a thiadiazolyl group, and a condensed heteroaryl group, each of which may be substituted or unsubstituted, or G^A-R^{17} (wherein G^A represents $-CO-$, $-C(=O)O-$, or $-SO_2-$, R^{17} has the same meaning as that defined above for R^7) (wherein when W^A represents an oxygen atom, Z^A may represent a pyridyl group substituted with a cyano group; when B represents $-CO-$ or $-CH_2CO-$, Z^A may represent a pyridyl group substituted with a nitro group or a cyano group)> or a pharmacologically acceptable salt thereof.

2. The compound according to claim 1, wherein D represents $-W^A-X^A-Y^A-Z^A$, or a pharmacologically acceptable salt thereof.
3. The compound according to claim 1 or claim 2, wherein B represents $CO(C(R^3)(R^4))_m$ (wherein R^3 , R^4 , and m have the same meanings as those defined above, respectively), or a pharmacologically acceptable salt thereof.
4. The compound according to claim 2, wherein A represents a substituted or unsubstituted 1-pyrrolidinyl group or a substituted or unsubstituted 3-thiazolidinyl group;

B represents $-CO(C(R^3)(R^4))_m$ (wherein R^3 , R^4 , and m have the same meanings as those defined above, respectively);

D represents $-W^C-X^C-Y^C-Z^C$ (wherein W^C and Y^C represent $-N(R^{8C})-$ (wherein R^{8C} has the same meaning as that defined above for R^7); X^C represents a substituted or unsubstituted alicyclic alkylene group, a group formed by eliminating one hydrogen atom from a substituted or unsubstituted alicyclic heterocyclic group, a substituted or unsubstituted arylene group, a substituted or unsubstituted aralkylene group, a substituted or unsubstituted heteroarylene group, a substituted or unsubstituted heteroarylalkylene group, or $-(C(R^9)(R^{10}))_q$ [wherein q represents an integer of 1 to 6, R^9 and R^{10} may be the same or different and each represents a hydrogen atom, a substituted or unsubstituted alkyl group, a substituted or unsubstituted alicyclic alkyl group, a substituted or unsubstituted alicyclic heterocyclic group, a substituted or unsubstituted alkenyl group, a substituted or unsubstituted alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted heteroaryl group, or a substituted or unsubstituted heteroarylalkyl group, or R^9 and R^{10} , which attach to the same carbon atom, may combine together with said carbon atom to form a substituted or unsubstituted alicyclic alkyl group (provided that not all of the substituents R^9 and R^{10} in the chain consisting of $(C(R^9)(R^{10}))_q$ are hydrogen atoms)], or X^C combines with one $-N(R^{8C})-$ represented by W^C or Y^C to form a substituted or unsubstituted pyrrolidinediyl group, a substituted or unsubstituted piperidinediyl group, or a substituted or unsubstituted homopiperidinediyl group; and Z^C has the same meaning as that defined above for V), or a pharmacologically acceptable salt thereof.

5. The compound according to claim 2, wherein A represents a substituted or unsubstituted 1-pyrrolidinyl group or a substituted or unsubstituted 3-thiazolidinyl group;

B represents $-CO(C(R^3)(R^4))_m$ (wherein R^3 , R^4 , and m have the same meanings as those defined above, respectively);

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PCT

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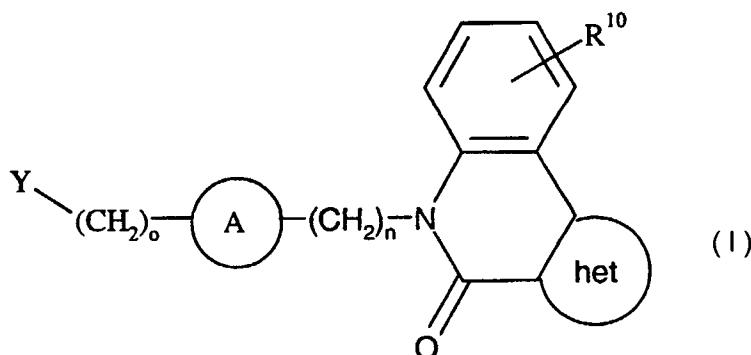
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LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
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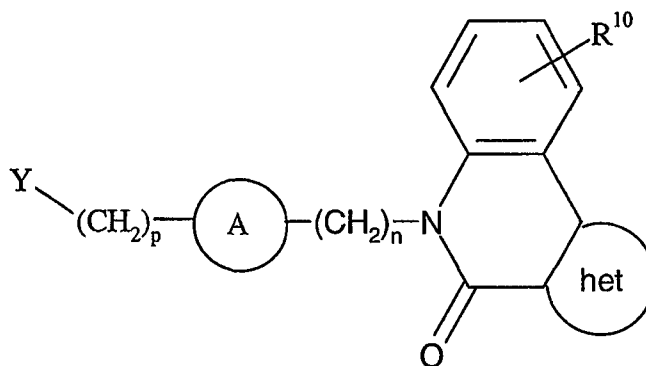
[Continued on next page]

(54) Title: METHODS AND COMPOUNDS FOR INHIBITING MRP1

(57) Abstract: The present invention
further relates to a method of inhibiting
MRP1 in a mammal which comprises
administering to a mammal in need
thereof an effective amount of a
compound of formula (I).

We Claim:

1. A compound of formula I:



I

where:

A is a C₃-C₈ cycloalkyl, optionally substituted 1-3 times with a C₁-C₄ alkyl;

het is a five (5) membered heterocyclic ring comprising N and a second heteroatom selected from N, O, or S;

wherein the non-fused carbon atom of the heteroaryl ring may be optionally substituted with R^b: C₁-C₆ alkyl, optionally substituted aryl, optionally substituted heterocycle, an amino acid ester, CH₂OH, CH₂O-heterocycle, halo, CH₂N₃, CH₂SR¹, CH₂NR⁴R⁶, OR¹, SR¹³, S(CH₂)_k-phenyl, or NR⁴R⁶; provided that when het is pyrazole or imidazole, the saturated nitrogen of the het ring may be optionally substituted with R^a: C₁-C₄ alkyl;

k is 0, 1, 2, 3, or 4;

n is 0, 1, or 2;

p is 0 or 1;

q is 0, 1, or 2;

r is 0, 1, or 2;

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Preparation 12

2-(3-{[3-(2-Chloro-6-fluorophenyl)-5-methylisoxazol-4-yl]carbonylamino}cyclopentyl)-
N-(3,4,5-trimethoxyphenyl)acetamide

5 A solution of 0.123 g (0.42 mmol) of a compound from preparation 10, 0.03 g
(0.46 mmol) of 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyl chloride, and
0.07 mL (0.5 mmol) of triethylamine in dichloromethane (10 mL) was stirred for 12 h.
The solvent was removed *in vacuo* and replaced with ethyl acetate. The organic layer was
washed with 1N HCl, then aq. NaHCO₃, followed by brine and dried. The solvent was
10 removed *in vacuo* to yield 0.255 g of the title compound. MS(ES+) m/z=545.8. *cis*
(racemic)

Preparation 13

15 2-(3-{[3-(2-Chloro-6-fluorophenyl)-5-methylisoxazol-4-yl]carbonylamino}cyclopentyl)-
N-(3,4,5-trimethoxyphenyl)acetamide

In the same manner as preparation 12, 0.2 g (0.65 mmol) of a compound from
preparation 11 was converted to 0.324 g of the title compound. MS(ES+)m/z=545.8.
Racemic

20

Preparation 14

N-((1S,3R)-3-Cyanomethylcyclopentyl)(*t*-butoxy)carboxamide

To a solution of 8.2 g (0.0222 mol) of N-[*t*-butoxycarbonyl]-2-(*p*-
25 toluenesulfonyloxymethyl)cyclopentylamine in DMF (250 mL) was added 3.3 g (0.067
mmol) of NaCN and the suspension was heated at 80 °C for 4 h. The solvent was
removed *in vacuo* at 40 °C and the residue was slurried in brine. The aqueous layer was
extracted with ethyl acetate, dried and the solvent was removed *in vacuo* to yield 5.7 g of
the title compound. MS(ES+)m/z=225. (one enantiomer)

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Preparation 152-{(3S,1R)-3-[(*t*-Butoxy)carbonylamino]cyclopentyl}acetic acid

5 A suspension of 2.0 g (8.9 mmol) of a compound from preparation 14 in 3N KOH (32 mL) and EtOH (12 mL) was heated at reflux for 6 h (solution). The alcohol was removed *in vacuo* and the reaction was cooled and neutralized with 3N HCl. The product was separated by filtration, rinsed with water and dried *in vacuo* at 40 °C to yield 1.33 g of the title compound.

MS(ES+)m/z=244.

10

Preparation 162-{(3S,1R)-3-[(*t*-Butoxy)carbonylamino]cyclopentyl-N-(3,4,5-trimethoxyphenyl)acetamide

15 To a solution of 0.1 g (0.4 mmol) of a compound from preparation 15 in THF/DMF 1:1 (5 mL) was added 0.061 g (0.44 mmol) of 1-hydroxy-7-azabenzotriazole and 0.086 g (0.44 mmol) of EDCI. After 40 min, 0.083 g (0.44 mmol) of 3,4,5-trimethoxyaniline was added. After 3.25 h, the solvent was removed *in vacuo* and replaced with ethyl acetate. The organic layer was rinsed with 1N HCl, aq. NaHCO₃, then
20 3X with water. The organic layer was dried and the solvent was removed *in vacuo* to yield 0.144 g of the title compound. MS(ES+)m/z=409.

Preparation 17

2-((3S,1R)-3-Aminocyclopentyl)-N-(3,4,5-trimethoxyphenyl)acetamide

25

A solution of 0.48 g (0.362 mmol) of a compound from preparation 16 in TFA (10 mL) was stirred for 1 h, after which the TFA was removed *in vacuo* and replaced with ethyl acetate. The organic layer was rinsed with 1N NaOH followed by brine and dried. The organic layer was removed *in vacuo* to yield 0.3 g of the title compound.

30 MS(ES+)m/z=309.

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cooling was removed. After 3 additional min, 1N HCl was added and the mixture was extracted with ethyl acetate. The organic layer was rinsed with water, dried and concentrated to a foam *in vacuo* which was chromatographed on silica gel with hexane/ethyl acetate 3:1 to yield 0.057 g of the title compound. MS(ES+)m/z=432.

5

Preparation 25

2-(3-Aminocyclopentyl)ethanenitrile

In the same manner as preparation 17, 0.3 g (4.5 mmol) of a compound from preparation 14 was deprotected with TFA to yield 0.087 g of the title compound. MS(ES+)m/z=125.

10

Preparation 26

N-[(1R,3S)-3-(cyanomethyl)cyclopentyl][3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl]carboxamide

15

In the same manner as preparation 18, 0.08 g (0.65 mmol) of a compound from preparation 26 was acylated with 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyl chloride to yield a residue which after chromatography on silica gel with hexane/ethyl acetate 1:1 yielded 0.177 g of the title compound. MS(ES+)m/z=362.

20

Preparation 27

2-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl)cyclopentyl]ethanenitrile

25

In the same manner as preparation 24, 0.166 g (0.46 mmol) of a compound from preparation 27 was cyclized to a residue which upon chromatography on silica gel with hexane/ethyl acetate 2:1 yielded 0.099 g of the title compound. MS(ES+)m/z=342.

519	N-[3-(9-Chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl)-cyclopentylmethyl]-2-(3,4,5-trimethoxyphenyl)acetamide	prep 207	ESMS: 540 (M+1)+, 574 (M+35)-, 598 (M+59)-	
520	N-[3-(9-Chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-ylmethyl)-cyclopentyl]carbamic acid <i>t</i> -butyl ester	prep 208	ESMS: 432 (M+1)+	
521	[3-(9-Chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-ylmethyl)-cyclopentyl]carbamic acid <i>t</i> -butyl ester	prep 209	ESMS: 432 (M+1)+	
522	<i>trans</i> -[1-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]-quinolin-5-yl)-3-[[[(1,1-dimethylethyloxy)carbonyl]amino]]-cyclohexane	prep 22	ESIMS <i>m/e</i> 432 ³⁵ Cl (M ⁺ +1); 434 ³⁷ Cl (M ⁺ +1)	
523	N-[3-(9-Cyano-3-methyl-4-oxo-5H-isoxazole[4,3-c]quinolin-5-yl)-cyclohexylmethyl]-benzamide	prep 267	MS(ES+) (m/z) 441.2 [M+1]	
524	[3-(9-Cyano-3-methyl-4-oxo-5H-isoxazole[4,3-c]quinolin-5-yl)-cyclohexylmethyl]-carbamic acid benzyl ester	prep 269	MS(ES+) (m/z) 471.2 [M+1]	
525	[3-(9-Chloro-3-methyl-4-oxo-5H-isoxazole[4,3-c]quinolin-5-ylmethyl)-cyclohexyl]-carbamic acid <i>tert</i> -butyl ester	prep 278	MS(ES+) (m/z) 346.1 [M-BOC].	
526	N-[3-(9-Chloro-3-diethylamino-4-oxo-5H-isoxazole[4,3-c]quinolin-5-yl)-cyclohexylmethyl]-benzamide	prep 280	MS(ES+) (m/z) 507.2 [M+1]	
527	N-[3-(9-Chloro-4-oxo-3-pyrroldin-1-yl-5H-isoxazole[4,3-c]quinolin-5-yl)-cyclohexylmethyl]-benzamide	prep 281	MS(ES+) (m/z) 505.1 [M+1]	
528	N-[3-(9-Chloro-3-ethylamino-4-oxo-5H-isoxazole[4,3-c]quinolin-5-yl)-cyclohexylmethyl]-benzamide	prep 280	MS(ES+) (m/z) 479.1 [M+1]	

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with ammonia solution in methanol (1M, 20 mL) and evaporated to obtain the title compound (150 mg, 90%). ESMS: 332 (M+1)⁺.

Example 620

5 5-(((1R,3S)-3-Aminocyclopentyl)methyl)-9-chloro-3-methyl-5*H*-isoxazolo[4,3-
c]quinolin-4-one

N-[(1S,3R)-3-[(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl)methyl]cyclopentyl}(tert-butoxy)carboxamide was converted to the amine by TFA in DCM at rt. for three hours. ESMS: 332 (M+1)+.

Example 621

5-(((1S,3R)-3-Aminocyclopentyl)methyl)-9-chloro-3-methyl-5*H*-isoxazolo[4,3-
c]quinolin-4-one

15 N-{(1R,3S)-3-[(9-chloro-3-methyl-4-oxo-5H-isoxazolo-[4,3-c]quinolin-5-yl)methyl]cyclopentyl}(tert-butoxy)carboxamide was converted to the amine as described in Example 620 . ESMS: 332 (M+1)+.

20 Example 622

cis-1-(9-Chloro-3-methyl-4-oxo-5*H*-isoxazolo[4,3-*c*]quinolin-5-yl)-3-(3-phenyluriedo)-cyclohexane

To the suspension of *cis*-1-(9-chloro-3-methyl-4-oxo-5*H*-isoxazolo[4,3-
c]quinolin-5-yl)-3-amino-cyclohexane (0.0446 g, 0.121 mmol) in 1 mL anhydrous
THF at RT was added 2N NaOH (0.60 mL, 0.121 mmol). After 5 min. the
phenylisocyanate (0.013 mL, 0.121 mmol). After 20 min. the reaction was diluted
with EtOAc, washed with water and concentrated to near dryness. After sonication
and filtration a white solid (0.0412, 75%) was obtained. ESIMS *m/e* 451 ³⁵Cl (M⁺+1)
and 453 ³⁷Cl (M⁺+1).

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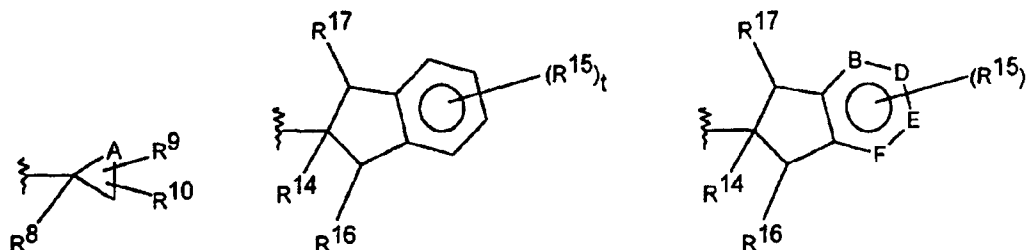
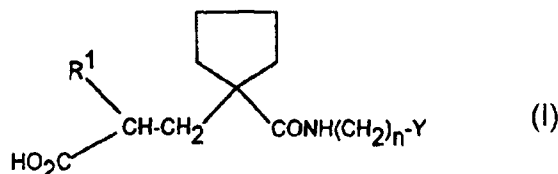
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LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
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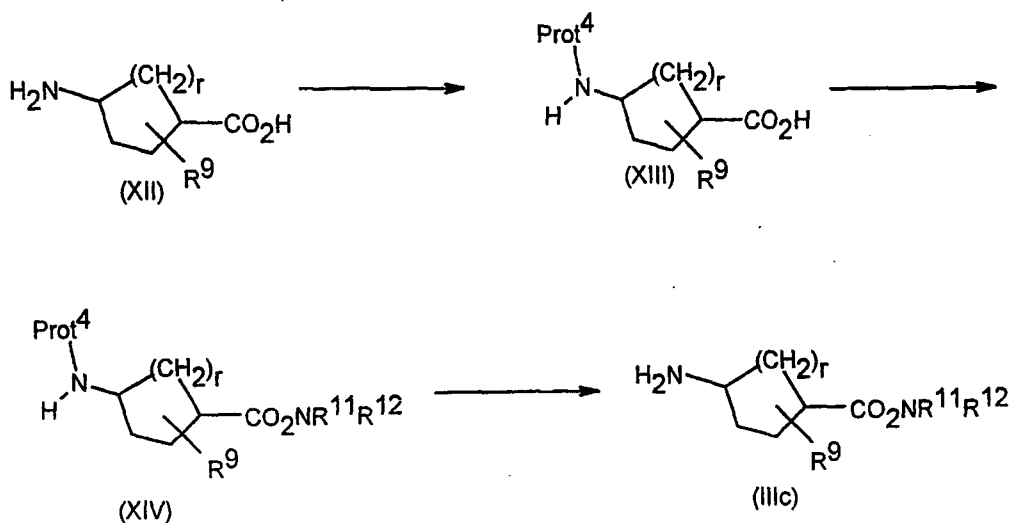
(54) Title: CYCLOPENTYL-SUBSTITUTED GLUTARAMIDE DERIVATIVES AS INHIBITORS OF NEUTRAL ENDOPEP-
TIDASE(57) Abstract: The invention provides compounds of formula I wherein R¹ is optionally substituted C₁₋₆alkyl, optionally substituted C₃₋₇ cycloalkyl, optionally substituted aryl or optionally substituted heterocyclyl; n is 0, 1 or 2; and Y is -NR¹⁸S(O)_uR¹⁹ or a group shown below.

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Scheme 5

Typical reaction conditions for introducing the *tert*-butoxycarbonyl protecting group comprise treating compounds of formula XII with (*tert*-butoxycarbonyl)₂O in dioxan and 2N sodium hydroxide at room temperature for 18 hrs.

Typical acid/amine coupling conditions comprise treating compounds of formula XIII and $\text{NHR}^{11}\text{R}^{12}$ with benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PYBOP), 1-hydroxybenzotrazole hydrate (HOBT), Hünigs base, an amine (eg triethylamine), in dimethylformamide at room temperature for 2hrs. Alternatively, compounds of formula XIII and $\text{NHR}^{11}\text{R}^{12}$ may be treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBT, N-methyl morpholine (NMM), in dimethylformamide at room temperature for 18 hrs.

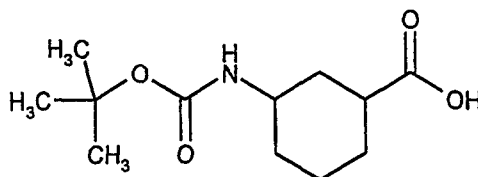
Typical reaction conditions for deprotection when Prot^4 is *tert*-butoxycarbonyl comprise reacting XIV with hydrochloric acid or trifluoroacetic acid in dichloromethane at room temperature for 2 to 4 hrs

Compounds of formula IIIc may be prepared according to reaction scheme 6. The protecting group is preferably *tert*-butoxycarbonyl, which may be removed under standard conditions, as previously described.

1.58-2.06 (m, 5H), 2.21 (m, 1H), 2.84 (m, 1H), 4.01 (m, 1H), 4.84 (m, 1H); LRMS: m/z 228 (M-H)⁺.

Preparation 9

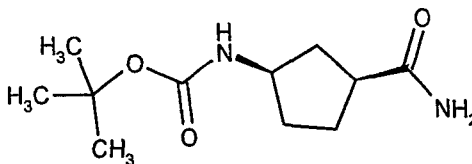
3-[(*tert*-Butoxycarbonyl)amino]cyclohexanecarboxylic acid



The title compound was obtained as a white solid in 81% yield, from 3-aminocyclohexanecarboxylic acid, following the procedure described in preparation 8; ¹H NMR (CDCl₃, 400MHz) δ: 1.04 (m, 1H), 1.19-1.50 (m, 13H), 1.83 (m, 1H), 1.97 (m, 2H), 2.24 (m, 1H), 2.40 (m, 1H), 3.44 (bs, 1H), 4.42 (bs, 1H).

Preparation 10

tert-Butyl (1*R*,3*S*)-3-(aminocarbonyl)cyclopentylcarbamate



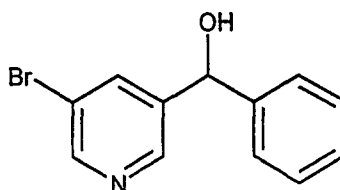
Benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (3.4g, 6.54mmol), 1-hydroxybenzotriazole hydrate (883mg, 6.54mmol), ammonium chloride (467mg, 8.72mmol) and *N*-ethyldiisopropylamine (3.04ml, 17.5mmol) were added sequentially to a solution of the acid from preparation 8 (1.0g, 4.37mmol) in *N,N*-dimethylformamide (16ml), and the reaction stirred at room temperature for 2 hours. The mixture was diluted with ethyl acetate (100ml), washed with water (3x), and brine, then dried (MgSO₄) and evaporated under reduced pressure. The residual gum was purified by chromatography on silica gel using a Biotage® column, and an elution gradient of dichloromethane:methanol (98:2 to 95:5). The product was triturated with ether to afford the title compound as a white solid, 438mg, 44%; ¹H NMR (DMSO-d₆, 400MHz) δ: 1.34 (s, 9H), 1.40 (m, 2H), 1.64 (m, 3H), 1.90 (m, 1H), 2.55 (m, 1H), 3.70 (m, 1H), 6.70 (bs, 1H), 6.80 (d, 1H), 7.22 (bs, 1H).

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300MHz) δ : 1.30 (s, 9H), 2.77 (m, 1H), 2.97 (m, 1H), 3.84 (m, 1H), 5.95 (bs, 1H), 6.96 (m, 2H), 7.08 (m, 3H), 7.42 (m, 1H), 8.05 (d, 1H), 8.60 (d, 1H), 8.84 (m, 1H); $[\alpha]_D = -10^\circ$ (0.1% solution in methanol).

Preparation 19

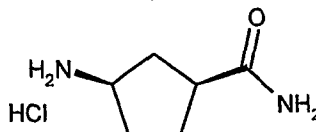
(5-Bromo-3-pyridinyl)(phenyl)methanol



n-Butyl lithium (17ml, 2.5M in hexanes, 42.5mmol) was added dropwise to cooled (-78°C) solution of 3,5-dibromopyridine (10g, 42.2mmol) in ether (200ml), so as to maintain an internal temperature $<-70^\circ\text{C}$. The mixture was then stirred for 15 minutes and a solution of benzaldehyde (4.5g, 42.5mmol) in ether (20ml) was added dropwise, again maintaining the temperature $<-70^\circ\text{C}$. The mixture was stirred for 15 minutes, then allowed to warm to room temperature over an hour. The reaction was quenched by the addition of 0.9M ammonium chloride solution (200ml), the layers separated, and the aqueous phase extracted with ether. The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure. The residual yellow oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane:ether (95:5 to 80:20) to give the title compound as a yellow oil, 7.6g, 68%; ^1H NMR (D_2O , 300MHz) δ : 5.80 (s, 1H), 7.37 (m, 5H), 7.90 (s, 1H), 8.40 (s, 1H), 8.44 (s, 1H).

Preparation 20

(1S,3R)-3-Aminocyclopentanecarboxamide hydrochloride



Hydrogen chloride gas was bubbled through an ice-cooled solution of the amide from preparation 10 (438mg, 1.92mmol) in dichloromethane (50ml) for 10 minutes, and the resulting suspension stirred at room temperature for 2 hours. The mixture was purged with nitrogen, then evaporated under reduced pressure. The residue was triturated with ether, to afford the title compound as a solid; ^1H NMR (D_2O , 400MHz) δ : 1.63-1.82 (m, 3H), 1.92-2.07 (m, 2H), 2.19 (m, 1H), 2.82 (m, 1H), 3.62 (m, 1H).



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(21) International Application Number: PCT/US98/26704 (22) International Filing Date: 15 December 1998 (15.12.98) (30) Priority Data: 60/080,042 31 March 1998 (31.03.98) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DUDLEY, Danette, Andrea [US/US]; 290 Village Green Boulevard #201, Ann Arbor, MI 48105 (US). EDMUNDS, Jeremy, John [GB/US]; 3957 Beech Drive, Ypsilanti, MI 48197 (US). (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al. (81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.		
(54) Title: QUINOXALINONES AS SERINE PROTEASE INHIBITORS SUCH AS FACTOR XA AND THROMBIN (57) Abstract This invention discloses quinoxalinones according to Formula (I) or stereoisomers or pharmaceutically acceptable salts, esters, amides or prodrugs thereof, which display inhibitory effects on serine proteases such as factor Xa, thrombin, and/or factor VIIa. The invention also discloses pharmaceutically acceptable salts and prodrugs of the compounds, pharmaceutically acceptable compositions comprising the compounds, their salts or prodrugs, and methods of using them as therapeutic agents for treating or preventing disease states in mammals characterized by abnormal thrombosis.		
(I)		

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3-(3-Aminocyclopentyl)-1-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2(1*H*)-quinoxalinone;

3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2-quinoxaliny)cyclopentanecarboximidamide;

5 3-[(3-Aminocyclopentyl)methyl]-1-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2(1*H*)-quinoxalinone;

3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2-quinoxaliny)methyl]cyclopentanecarboximidamide;

10 3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]butyl-3-oxo-3,4-dihydro-2-quinoxaliny)benzenecarboximidamide;

3-(4-6-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]hexyl-3-oxo-3,4-dihydro-2-quinoxaliny)benzenecarboximidamide;

2-[3-3-[Amino(imino)methyl]phenyl-2-oxo-1(2*H*)-quinoxaliny]-*N*-2-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]ethylacetamide;

15 3-[3-3-[Amino(imino)methyl]phenyl-2-oxo-1(2*H*)-quinoxaliny]-*N*-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]methylpropanamide;

3-4-[2-(2-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]ethylamino)ethyl]-3-oxo-3,4-dihydro-2-quinoxalinybenzenecarboximidamide;

20 3-[4-(2-2-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]ethoxyethyl)-3-oxo-3,4-dihydro-2-quinoxaliny]benzenecarboximidamide;

3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]phenyl-3-oxo-3,4-dihydro-2-quinoxaliny)benzenecarboximidamide;

25 3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]benzyl-3-oxo-3,4-dihydro-2-quinoxaliny)benzenecarboximidamide;

3-[4-(4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]methylphenyl)-3-oxo-3,4-dihydro-2-quinoxaliny]benzenecarboximidamide;

3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]cyclohexyl-3-oxo-3,4-dihydro-2-quinoxaliny)benzenecarboximidamide;

30 3-[4-(4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]cyclohexylmethyl)-3-oxo-3,4-dihydro-2-quinoxaliny]benzenecarboximidamide;



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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 265/36, 279/16, A61K 31/535, 31/54		A1	(11) International Publication Number: WO 99/50257 (43) International Publication Date: 7 October 1999 (07.10.99)
(21) International Application Number: PCT/US98/26708 (22) International Filing Date: 15 December 1998 (15.12.98) (30) Priority Data: 60/080,142 31 March 1998 (31.03.98) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BERRYMAN, Kent, Alan [US/US]; P.O. Box 2494, Silverthorne, CO 80498 (US). DOWNING, Dennis, Michael [US/US]; 3737 Burbank, Ann Arbor, MI 48105 (US). DUDLEY, Danette, Andrea [US/US]; 290 Village Green Boulevard #201, Ann Arbor, MI 48105 (US). EDMUNDS, Jeremy, John [GB/US]; 3957 Beech Drive, Ypsilanti, MI 48197 (US). NARASIMHAN, Lakshmi, Sourirajan [IN/US]; 45680 Larchmont Drive, Canton, MI 48197 (US). RAPUNDALO, Stephen, Taras [CA/US]; 3106 Bluett Road, Ann Arbor, MI 48105 (US). (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.			(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: BENZOXAZINONES/BENZOTHIAZINONES AS SERINE PROTEASE INHIBITORS			
(57) Abstract This invention discloses benzoxazinone and benzothiazinone compounds which display inhibitory effects on serine proteases such as factor Xa, thrombin, and/or factor VIIa. The invention also discloses pharmaceutically acceptable salts of the compounds, pharmaceutically acceptable compositions comprising the compounds or their salts, and methods of using them as therapeutic agents for treating or preventing disease states in mammals characterized by abnormal thrombosis.			

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2-[(6-Amino-2-pyridinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;

4-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-2-pyrimidinecarboximidamide;

5 2-[(2-Amino-4-pyrimidinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;

2-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-4-pyrimidinecarboximidamide;

10 2-[(4-Amino-2-pyrimidinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;

6-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]-2-pyrazinecarboximidamide;

2-[(6-Amino-2-pyrazinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;

15 2-(3-Aminocyclohexyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;

3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)cyclohexanecarboximidamide;

20 2-[(3-Aminocyclohexyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;

3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]cyclohexanecarboximidamide;

2-(3-Aminocyclopentyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;

25 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)cyclopentanecarboximidamide;

2-[(3-Aminocyclopentyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzothiazin-3(4*H*)-one;

30 3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)methyl]cyclopentanecarboximidamide;

3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]butyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)benzenecarboximidamide;

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- 2-[(6-Amino-2-pyridinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 4-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]-2-pyrimidinecarboximidamide;
- 5 2-[(2-Amino-4-pyrimidinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 2-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]-4-pyrimidinecarboximidamide;
- 2-[(4-Amino-2-pyrimidinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 10 6-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]-2-pyrazinecarboximidamide;
- 2-[(6-Amino-2-pyrazinyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 15 2-(3-Aminocyclohexyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)cyclohexanecarboximidamide;
- 2-[(3-Aminocyclohexyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 20 3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]cyclohexanecarboximidamide;
- 2-(3-Aminocyclopentyl)-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 25 3-(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)cyclopentanecarboximidamide;
- 2-[(3-Aminocyclopentyl)methyl]-4-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2*H*-1,4-benzoxazin-3(4*H*)-one;
- 3-[(4-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)methyl]cyclopentanecarboximidamide;
- 30 3-(4-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]butyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)benzenecarboximidamide;



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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 401/06, 401/14, 409/14, 407/14, 413/14, 403/06, A61K 31/44, 31/47	A1	(11) International Publication Number: WO 99/50263 (43) International Publication Date: 7 October 1999 (07.10.99)
(21) International Application Number: PCT/US98/26709 (22) International Filing Date: 15 December 1998 (15.12.98) (30) Priority Data: 60/080,090 31 March 1998 (31.03.98) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DUDLEY, Danette, Andrea [US/US]; 290 Village Green Boulevard #201, Ann Arbor, MI 48105 (US). EDMUNDS, Jeremy, John [GB/US]; 3957 Beech Drive, Ypsilanti, MI 48197 (US). (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: QUINOLONES AS SERINE PROTEASE INHIBITORS (57) Abstract This invention discloses quinolinones which display inhibitory effects on serine proteases such as factor Xa, thrombin and/or factor VIIa. The invention also discloses pharmaceutically acceptable salts and prodrugs of the compounds, pharmaceutically acceptable compositions comprising the compounds, their salts or prodrugs, and methods of using them as therapeutic agents for treating or preventing disease states in mammals characterized by abnormal thrombosis.		

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3-(3-Aminocyclohexyl)-1-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2(1*H*)-quinolinone;

3-(1-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-oxo-1,2-dihydro-3-quinolinyl)cyclohexanecarboximidamide;

5 3-[(3-Aminocyclohexyl)methyl]-1-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2(1*H*)-quinolinone;

3-[(1-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-oxo-1,2-dihydro-3-quinolinyl)methyl]cyclohexanecarboximidamide;

10 3-(3-Aminocyclopentyl)-1-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2(1*H*)-quinolinone;

3-(1-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-oxo-1,2-dihydro-3-quinolinyl)cyclopentanecarboximidamide;

3-[(3-Aminocyclopentyl)methyl]-1-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2(1*H*)-quinolinone;

15 3-[(1-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-oxo-1,2-dihydro-3-quinolinyl)methyl]cyclopentanecarboximidamide;

3-(1-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]butyl-2-oxo-1,2-dihydro-3-quinolinyl)benzenecarboximidamide;

20 3-(1-6-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]hexyl-2-oxo-1,2-dihydro-3-quinolinyl)benzenecarboximidamide;

2-[3-3-[Amino(imino)methyl]phenyl-2-oxo-1(2*H*)-quinolinyl]-N-2-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]ethylacetamide;

3-[3-3-[Amino(imino)methyl]phenyl-2-oxo-1(2*H*)-quinolinyl]-N-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]methylpropanamide;

25 3-1-[2-(2-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]ethylamino)ethyl]-2-oxo-1,2-dihydro-3-quinolinylbenzenecarboximidamide;

3-[1-(2-2-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]ethoxyethyl)-2-oxo-1,2-dihydro-3-quinolinyl]benzenecarboximidamide;

30 3-(1-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]phenyl-2-oxo-1,2-dihydro-3-quinolinyl)benzenecarboximidamide;

3-(1-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]benzyl-2-oxo-1,2-dihydro-3-quinolinyl)benzenecarboximidamide;

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- 4-[(1-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-oxo-1,2,3,4-tetrahydro-3-quinolinyl)methyl]-2-pyrimidinecarboximidamide;
- 3-[(2-Amino-4-pyrimidinyl)methyl]-1-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3,4-dihydro-2(1*H*)-quinolinone;
- 5 2-[(1-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-oxo-1,2,3,4-tetrahydro-3-quinolinyl)methyl]-4-pyrimidinecarboximidamide;
- 3-[(4-Amino-2-pyrimidinyl)methyl]-1-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3,4-dihydro-2(1*H*)-quinolinone;
- 10 6-[(1-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-oxo-1,2,3,4-tetrahydro-3-quinolinyl)methyl]-2-pyrazinecarboximidamide;
- 3-[(6-Amino-2-pyrazinyl)methyl]-1-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3,4-dihydro-2(1*H*)-quinolinone;
- 3-(3-Aminocyclohexyl)-1-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3,4-dihydro-2(1*H*)-quinolinone;
- 15 3-(1-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-oxo-1,2,3,4-tetrahydro-3-quinolinyl)cyclohexanecarboximidamide;
- 3-[(3-Aminocyclohexyl)methyl]-1-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3,4-dihydro-2(1*H*)-quinolinone;
- 20 3-[(1-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-oxo-1,2,3,4-tetrahydro-3-quinolinyl)methyl]cyclohexanecarboximidamide;
- 3-(3-Aminocyclopentyl)-1-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3,4-dihydro-2(1*H*)-quinolinone;
- 3-(1-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-oxo-1,2,3,4-tetrahydro-3-quinolinyl)cyclopentanecarboximidamide;
- 25 3-[(3-Aminocyclopentyl)methyl]-1-5-[(2*R*,6*S*)-2,6-dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-3,4-dihydro-2(1*H*)-quinolinone;
- 3-[(1-5-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]pentyl-2-oxo-1,2,3,4-tetrahydro-3-quinolinyl)methyl]cyclopentanecarboximidamide;
- 30 3-(1-4-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]butyl-2-oxo-1,2,3,4-tetrahydro-3-quinolinyl)benzenecarboximidamide;
- 3-(1-6-[(2*R*,6*S*)-2,6-Dimethyltetrahydro-1(2*H*)-pyridinyl]hexyl-2-oxo-1,2,3,4-tetrahydro-3-quinolinyl)benzenecarboximidamide;



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(21) International Application Number: PCT/SE99/01145 (22) International Filing Date: 23 June 1999 (23.06.99) (30) Priority Data: 9802538-0 13 July 1998 (13.07.98) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): KARABELAS, Kostas [SE/SE]; Astra Draco AB, P.O. Box 34, S-221 00 Lund (SE). LEPISTÖ, Matti [SE/SE]; Astra Draco AB, P.O. Box 34, S-221 00 Lund (SE). SJÖ, Peter [SE/SE]; Astra Draco AB, P.O. Box 34, S-221 00 Lund (SE). (74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>

(54) Title: NEW PHARMACEUTICALLY ACTIVE COMPOUNDS



(1)

(57) Abstract

The present invention relates to compounds of formula (I) wherein: Ar₁ or Ar₂ is an optionally substituted indole, and the other group is an optionally substituted aromatic or heteroaromatic group, preferably an optionally substituted indole, X is O or S, and R₂ is H, hydroxy, amino, C₁-alkyl, hydroxyC₁-alkyl or aminoC₁-alkyl, and salts and solvates thereof and solvates of such salts, and the use of such compounds in medical therapies.

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APCI-MS m/z: 605 [MH+].

EXAMPLE 55

5 **5-{1-[(1*S*,3*R*)-1-(3-Amino)cyclopentylmethyl]-3-indolyl}-4-cyano-1-(1-methyl-3-indolyl)-2,3-dihydroimidazol-2-one trifluoroacetic acid salt**

a) 5-{1-[(1*S*,3*R*)-1-(3-*tert*-Butoxycarbonyl-amino)cyclopentylmethyl]-3-indolyl}-4-cyano-3-(2,4-dimethoxybenzyl)-1-(1-methyl-3-indolyl)-2,3-dihydroimidazol-2-one

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A portion of 150 mg of the crude from Example 54 c) was dissolved in 0.5 ml of dry THF and stirred with 9.6 mg (0.4 mmol) of sodium hydride for 0.5 hours. 44 mg (0.2 mmol) of (BOC)₂O and 2.4 mg (0.02 mmol) of dimethyl aminopyridine were added, and the reaction was stirred for 1.5 hours at room temperature. The reaction was evaporated. The crude
15 dissolved in ethyl acetate and saturated NH₄Cl(aq). The organic layer was separated, washed twice with a saturated NH₄Cl(aq), once with brine and dried over Na₂SO₄. The solvent was evaporated and the crude dissolved in methanol (2.5 ml). Magnesium powder was added and the reaction vessel was sonicated for 2.5 hours. Ethyl acetate and saturated NH₄Cl(aq) were added. The organic layer collected, washed with saturated NH₄Cl(aq) and
20 brine and dried over Na₂SO₄. The crude product was used without further purification.

APCI-MS m/z: 701 [MH+].

The crude from step a) dissolved in 5 ml of acetonitrile was treated with 1.1 ml of
25 trifluoromethane sulfonic acid and 60 µl of tioanisole at 70 °C for 4 hours. Sodium acetate was added followed by purification by preparative HPLC to give 3 mg of the title product.

¹H-NMR (400MHz, CDCl₃): 1.19-1.04 (3H, m), 1.56-1.46 (1H, m), 2.00-1.82 (2H, m), 2.18-2.06 (1H, m), 3.47-3.39 (1H, m), 3.93 (1H, dd, J 14 Hz, 8 Hz), 4.12 (1H, ddt, J 14Hz, 6.8 Hz), 6.96 (1H, t, J 7.6 Hz), 7.06 (1H, t, J 7.6 Hz), 7.10 (1H,s), 7.20-7.14 (3H, m), 7.35
30 (1H, s), 7.38 (1H, d, J 8.4 Hz), 7.38 (1H, d, J 8.8 Hz), 7.53 (1H, d, J 8.0 Hz).