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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 June 2010 (17.06.2010)

PCT

(10) International Publication Number
WO 2010/066028 A1

(51) **International Patent Classification**:
C07D 401/04 (2006.01) ***A61P 13/12*** (2006.01)
A61K 31/4545 (2006.01) ***A61P 9/00*** (2006.01)

(21) **International Application Number**:
PCT/CA2009/001758

(22) **International Filing Date**:
8 December 2009 (08.12.2009)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/201,367 10 December 2008 (10.12.2008) US

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

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

WO 2010/066028 A1

(54) **Title**: 3,4 - SUBSTITUTED PIPERIDINE DERIVATIVES AS RENIN INHIBITORS

(57) **Abstract**: The present invention relates to 3,4-substituted piperidinyl - based renin inhibitor compounds bearing at 4-position oxopyridine or lsoquinolone and having the formula (I): wherein., S is Formula (IIa) or Formula (IIb). The invention further relates to pharmaceutical compositions containing said compounds, as well as their use in treating cardiovascular events and renal insufficiency.

TITLE OF THE INVENTION

3,4 - SUBSTITUTED PIPERIDINE DERIVATIVES AS RENIN INHIBITORS

JOINT RESEARCH AGREEMENT

The claimed invention was made as a result of activities undertaken within the scope of a joint research agreement between Merck & Co., Inc. and Actelion Pharmaceuticals Ltd. The agreement was executed on December 4, 2003. The field of the invention is described below.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/201,367, filed December 10, 2008.

FIELD OF THE INVENTION

The invention relates to novel renin inhibitors of the general formula (I). The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula (I) and especially their use as renin inhibitors in cardiovascular events and renal insufficiency.

BACKGROUND OF THE INVENTION

In the renin-angiotensin system (RAS) the biologically active angiotensin II (Ang II) is generated by a two-step mechanism. The highly specific enzyme renin cleaves angiotensinogen to angiotensin I (Ang I), which is then further processed to Ang II by the less specific angiotensin-converting enzyme (ACE). Ang II is known to work on at least two receptor subtypes called AT_1 and AT_2. Whereas AT_1 seems to transmit most of the known functions of Ang II, the role of AT_2 is still unknown.

Modulation of the RAS represents a major advance in the treatment of cardiovascular diseases. ACE inhibitors and AT_1 blockers have been accepted to treat hypertension (Waeber B. *et al.*, "The renin-angiotensin system: role in experimental and human hypertension", in Birkenhager W. H., Reid J. L. (eds): *Hypertension*, Amsterdam, Elsevier Science Publishing Co, **1986**, 489-519; Weber M. A., *Am. J. Hypertens.*, **1992**, *5*, 247S). In addition, ACE inhibitors are used for renal protection (Rosenberg M. E. *et al.*, *Kidney International*, **1994**, *45*, 403; Breyer J. A. *et al.*, *Kidney International*, **1994**, *45*, S156), in the prevention of congestive heart failure (Vaughan D. E. *et al.*, *Cardiovasc. Res.*, **1994**, *28*, 159; Fouad-Tarazi F. *et al.*, *Am. J. Med.*, **1988**, *84 (Suppl. 3A)*, 83) and myocardial infarction (Pfeffer M. A. *et al.*, *N. Engl. J. Med.*, **1992**, *327*, 669).

The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The only substrate known for renin is angiotensinogen, which can only be processed (under physiological conditions) by renin. In contrast, ACE can also cleave bradykinin besides Ang I and can be by-passed by chymase, a serine protease (Husain A., *J. Hypertens.*, **1993**, *11*, 1155). In patients, inhibition of ACE thus leads to bradykinin accumulation causing cough (5-20%) and potentially life-threatening angioneurotic edema (0.1-0.2%) (Israili Z. H. *et al.*, *Annals of Internal Medicine*, **1992**, *117*, 234). Chymase is not inhibited by ACE inhibitors. Therefore, the formation of Ang II is still possible in patients treated with ACE inhibitors. Blockade of the AT_1 receptor (e.g. by losartan) on the other hand overexposes other AT-receptor subtypes (e.g. AT_2) to Ang II, whose concentration is significantly increased by the blockade of AT_1 receptors. In summary, renin inhibitors are expected to demonstrate a different pharmaceutical profile than ACE inhibitors and AT_1 blockers with regard to efficacy in blocking the RAS and in safety aspects.

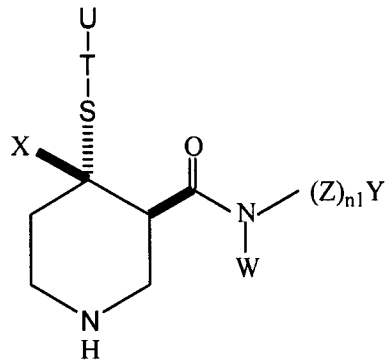
The present invention relates to the identification of renin inhibitors of a non-peptidic nature and of low molecular weight. Described are orally active renin inhibitors of long duration of action which are active in indications beyond blood pressure regulation where the tissular renin-chymase system may be activated leading to pathophysiologically altered local functions such as renal, cardiac and vascular remodeling, atherosclerosis, and possibly restenosis. The compounds described in this invention represent a novel structural class of renin inhibitors.

SUMMARY OF THE INVENTION

The present invention is directed to certain compounds and their use in the inhibition of the renin enzyme, including treatment of conditions known to be associated with the renin system.

The invention in particular is directed to compounds of Formula I:

I

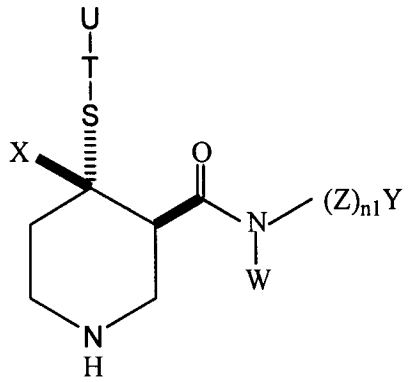


and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, meso-forms, salts, solvates, and morphological forms thereof, wherein constituent members are provided herein.

DETAILED DESCRIPTION OF THE DISCLOSURE

The present invention provides compounds having Formula I:

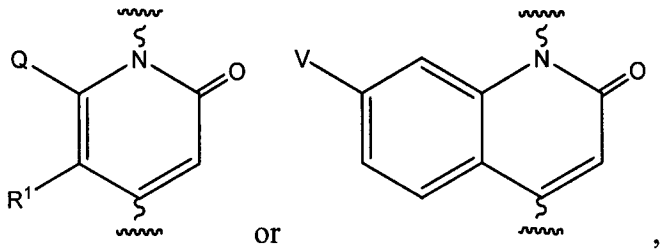
I



or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein:

S is

(IIa) (IIb)



wherein the nitrogen atom in IIa and IIb above is attached to T;

T is a bond; $-(CH_2)_r-$; $-(CH_2)_r-A-(CH_2)_s-$; or $-(CH_2)_r-A-(CH_2)_r-B-$;

A and B are independently selected from the group consisting of -O-. -S-, -S(O)- and $-S(O)_2-$;

r is the integer 2, 3, 4, or 5;

s is the integer 0, 1, or 2;

U is unsubstituted aryl; mono-, di-, tri- or tetra-substituted aryl wherein the substituents are independently selected from the group consisting of halogen, alkyl, alkoxy, cyano and $-CF_3$; or mono-, di-, or tri-substituted heteroaryl wherein the substituents are independently selected from the group consisting of halogen, alkyl, alkoxy, cyano and $-CF_3$;

V is selected from the group consisting of: hydrogen, halogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkenyl, C_2-C_6 alkynyl, cyano and C_1-C_5 alkoxy,

wherein said alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl and alkoxy are optionally substituted with 1-3 substituents, each of which is independently selected from the group consisting of: halogen, C_1-C_5 alkyl, C_2-C_5 alkenyl, cyano and C_1-C_5 alkoxy, wherein

each of the foregoing alkyl, alkenyl and alkoxy substituents is optionally substituted with 1-3 halogens;

Q and R^1 are independently selected from the group consisting of: hydrogen, halogen, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, C_2-C_5 alkenyl, C_3-C_8 cycloalkenyl, C_2-C_5 alkynyl, cyano and C_1-C_5 alkoxy, aryl and heteroaryl;

wherein said aryl and heteroaryl are optionally substituted with 1-4 halogens,

wherein said alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl and alkoxy are optionally substituted with 1-3 substituents, each of which is independently selected from the group consisting of: halogen, C_1-C_5 alkyl, C_2-C_5 alkenyl, cyano and C_1-C_5 alkoxy, wherein each of the foregoing alkyl, alkenyl and alkoxy substituents is optionally substituted with 1-3 halogens;

W is cyclopropyl, unsubstituted or mono-, di-, tri-, tetra- or penta-substituted with halogen, specific embodiments of which the halogen is fluorine;

X is selected from the group consisting of: OR^2, R^2, -(C_1-C_5 alkylene)-$(O)_{0-1}$-aryl and -(C_1-C_5 alkylene)-$(O)_{0-1}$-heteroaryl,

wherein R^2 is selected from the group consisting of: hydrogen, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, C_2-C_5 alkenyl, C_3-C_8 cycloalkenyl, C_2-C_5 alkynyl, C_1-C_5-cyano, -(C_1-C_5 alkylene)-O-R^3, -(C_1-C_5 alkylene)-N(-R^3)-C(=O)-(C_1-C_5 alkyl), -(C_1-C_5 alkylene)-C(=O)-N(-R^3)-(C_1-C_5 alkyl), -(C_1-C_5 alkylene)-N(-R^3)-C(=O)-O-(C_1-C_5 alkyl), -(C_1-C_5 alkylene)-O-C(=O)-N(-R^3)-(C_1-C_5 alkyl);-(C_1-C_5 alkylene)-N(-R^3)-(C_1-C_5 alkyl), -(C_1-C_5 alkylene)-S-(C_1-C_5 alkyl), -(C_1-C_5 alkylene)-S(=O)-(C_1-C_5 alkyl) and -(C_1-C_5 alkylene)-$S(=O)_2$-(C_1-C_5 alkyl),

wherein R^2, except hydrogen, is optionally substituted with 1-3 substituents, independently selected from the group consisting of: halogen, C(=O)OH, C_1-C_5 alkyl, C_2-C_5 alkenyl, and C_1-C_5 alkoxy, wherein each of the alkyl, alkenyl, and alkoxy substituents is optionally substituted with 1-3 halogens,

wherein the heteroaryl of the -(C_1-C_5 alkylene)-$(O)_{0-1}$-heteroaryl contains 1-3 heteroatoms, independently selected from the group consisting of: N, O and S, wherein each N is optionally in the form of an oxide and each S is optionally in the form of an oxide selected from the group consisting of: S(=O) and $S(=O)_2$,

wherein the aryl and heteroaryl of -(C_1-C_5 alkylene)-$(O)_{0-1}$-aryl and -(C_1-C_5 alkylene)-$(O)_{0-1}$-heteroaryl, respectively, are optionally substituted with 1-4 halogens, and

wherein R^3 is selected from the group consisting of: hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkenyl, and C_2-C_6 alkynyl, wherein each of the foregoing alkyl, cycloalkyl, alkenyl, cycloalkenyl and alkynyl substituents is optionally substituted with 1-3 halogens;

Z is C_1-C_2 alkylene optionally substituted with 1-2 substituents, independently selected from the group consisting of: halogen, C_1-C_3 alkyl and C_3 cycloalkyl, wherein the foregoing alkyl and cycloalkyl substituents are optionally substituted with 1-3 halogens;

n1 is 0 or 1;

Y is (i) a five- or six-membered saturated or unsaturated heterocyclic or carbocyclic monocyclic ring ("monocyclic ring") or (ii) a fused ring system which is a five- or six-membered saturated or unsaturated heterocyclic or carbocyclic ring which is fused to a five- or six-membered saturated or unsaturated heterocyclic or carbocyclic ring ("fused ring"),

wherein the heterocyclic ring(s) of (i) or (ii) contain from 1-3 heteroatoms, independently selected from N, O and S, wherein each N is optionally in the form of an oxide and each S is optionally in the form of an oxide selected from the group consisting of: S(=O) and $S(=O)_2$,

wherein the heterocyclic or carbocyclic ring(s) of (i) or (ii) is optionally mono-, di-, tri-, tetra-, penta- or hexa-substituted, each substituent of which is independently selected from the group consisting of:

(1) halogen,
(2) -OH,
(3) -NH(R^4),
(4) oxo,
(5) -C(=O)-R^4,
(6) -O-C(=O)-R^4,
(7) C_1-C_5 alkyl optionally substituted with 1-3 halogens,
(8) C_3-C_8 cycloalkyl optionally substituted with 1-3 halogens,
(9) C_2-C_5 alkenyl optionally substituted with 1-3 halogens,
(10) C_3-C_8 cycloalkenyl optionally substituted with 1-3 halogens,
(11) C_2-C_5 alkynyl optionally substituted with 1-3 halogens,
(12) C_1-C_5 alkoxy optionally substituted with 1-3 halogens,
(13) cyano,
(14) C_1-C_5-cyano optionally substituted with 1-3 halogens,
(15) -OCF_3,
(16) -C(R^5)$_3$,
(17) -(C_1-C_5 alkylene)-OR^6 optionally substituted with 1-3 halogens,
(18) -N(R^4)-(C_1-C_5 alkylene)-OR^6 optionally substituted with 1-3 halogens,
(19) -O-(C_1-C_5 alkylene)-OR^6 optionally substituted with 1-3 halogens,
(20) -S-(C_1-C_5 alkylene)-OR^6 optionally substituted with 1-3 halogens,
(21) -S(=O)-(C_1-C_5 alkylene)-OR^6 optionally substituted with 1-3 halogens,

(22) -S(=O)$_2$-(C_1-C_5 alkylene)-OR^6 optionally substituted with 1-3 halogens,

(23) -(C_1-C_5 alkylene)-N(R^4)-C(=O)-(C_1-C_5 alkylene)-R^6 optionally substituted with 1-3 halogens,

(24) -(C_1-C_5 alkylene)-N(R^4)-C(=O)-OR^6 optionally substituted with 1-3 halogens,

(25) -(C_1-C_5 alkylene)-N(R^4)(R^6) optionally substituted with 1-3 halogens,

(26) -O-(C_1-C_5 alkylene)-C(R^4)$_2$-C(=O)OR^6 optionally substituted with 1-3 halogens,

(27) -(C_1-C_5 alkylene)-C(R^4)$_2$-C(=O)-OR^6 optionally substituted with 1-3 halogens,

(28) -O-(C_1-C_5 alkylene)-morpholine optionally substituted with 1-3 halogens,

(29) -OC(=O)-morpholine,

(30) -SR^6,

(31) -S(=O)-R^6,

(32) -S(=O)$_2$-R^6

(33) -N(R^4)(R^6),

(34) -(C_1-C_5 alkylene)-C(R^4)$_2$-(R^6) optionally substituted with 1-3 halogens,

(35) -(R^7)$_{0-1}$R^8,

(36) C_2-C_5 alkenyl-OR^6 optionally substituted with 1-3 halogens,

(37) C_2-C_5 alkynyl-OR^6 optionally substituted with 1-3 halogens,

(38) -(C_1-C_5 alkylene)-C(=O)-(C_1-C_5 alkylene)-R^6 optionally substituted with 1-3 halogens,

(39) -(C_1-C_5 alkylene)-O-C(=O)-(C_1-C_5 alkylene)-R^6 optionally substituted with 1-3 halogens,

(40) -(C_1-C_5 alkylene)-C(=O)-N(R^4)(R^6) optionally substituted with 1-3 halogens,

(41) -(C_1-C_5 alkylene)-O-C(=O)-N(R^4)(R^6) optionally substituted with 1-3 halogens,

(42) -(C_1-C_5 alkylene)-SR^6 optionally substituted with 1-3 halogens,

(43) -(C_1-C_5 alkylene)-S(=O)-R^6 optionally substituted with 1-3 halogens, and

(44) -(C_1-C_5 alkylene)-S(=O)$_2$-R^6 optionally substituted with 1-3 halogens,

wherein R^4 is selected from the group consisting of: hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkenyl and C_2-C_6 alkynyl, wherein each of the

foregoing alkyl, cycloalkyl, alkenyl, cycloalkenyl and alkynyl substituents is optionally substituted with 1-3 halogens,

wherein R^5 is halogen,

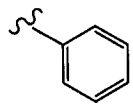
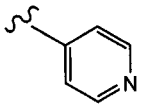
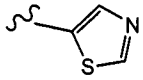
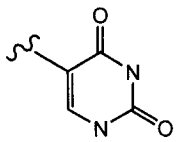
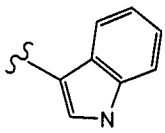
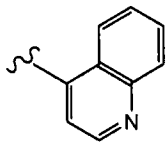
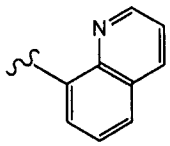
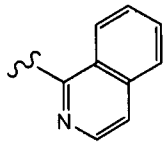
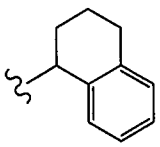
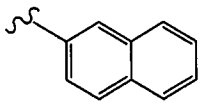
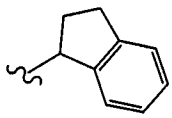
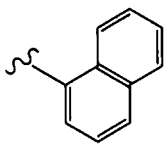
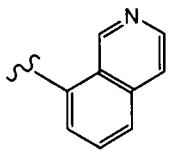
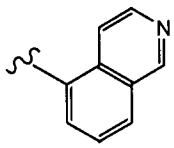
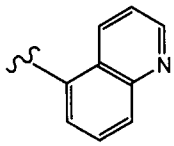
wherein R^6 is selected from the group consisting of: hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkenyl and C_2-C_6 alkynyl, wherein each of the foregoing alkyl, cycloalkyl, alkenyl, cycloalkenyl and alkynl substituents is optionally substituted with 1-3 halogens,

wherein R^7 is selected from the group consisting of: -C(H)(OH)-, -C(=O)-, -OC(=O)-, -C(=O)O-, -O-, -OC(=O)O-, C_1-C_5 alkylene, C_2-C_5 alkenylene, -N(R^4)-, -S-, -S(=O)-, -S(=O)$_2$-, -N(R^4)-C(=O)-, -C(=O)-N(R^4)-, -OC(=O)-N(R^4)-, -N(R^4)-C(=O)O-, -N(R^4)-S(=O)$_2$-, and -S(=O)$_2$-N(R^4)-, wherein each of the foregoing alkylene and alkenylene substituents is optionally substituted with 1-3 halogens, and wherein R^4 is defined above, and

wherein R^8 is a five- or six-membered saturated or unsaturated heterocyclic or carbocyclic ring which is optionally mono-, di-, tri-, tetra- or penta-substituted, wherein each substituent is independently selected from the group consisting of: halogen, -OH, -SR^4, -N(R^4)(R^6), C_1-C_5 alkyl, C_3-C_8 cycloalkyl, C_2-C_5 alkenyl, C_3-C_6 cycloalkenyl, C_2-C_5 alkynyl, C_1-C_5 alkoxy, cyano and C_1-C_5-cyano, wherein said heterocyclic ring contains from 1 to 3 heteroatoms, independently selected from N, O and S, wherein each N is optionally in the form of an oxide and each S is optionally is in the form of an oxide selected from the group consisting of: S(=O)and S(=O)$_2$, and wherein R^4 and R^6 are defined above.

In one embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein the monocyclic or fused ring(s) of Y (i) or (ii), respectively, is selected from the following:

TABLE 3

optionally mono-, di-, tri-, tetra- or penta-substituted as described above for Formula I.

In another embodiment, T is $-CH_2CH_2O-$, or $-CH_2CH_2CH_2O-$, wherein the bivalent radical is linked to the group U of formula (I) via an oxygen atom.

In another embodiment of the invention, U is a mono-, di-, tri- or tetra-substituted aryl. In specific embodiments, U is a mono-, di-, or tri-substituted phenyl wherein the substituents are independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, and $-CF_3$. In specific embodiments, the substituents are independently selected from the group consisting of halogen and C_1-C_6 alkyl. In specific embodiments, U represents 2,6-dichloro-4-methyl-phenyl, and all other variables are as previously defined.

In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein Q and R^1 are independently selected from the group consisting of: H, $-OCH_2OCH_3$ and $-CH_3$.

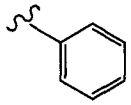
In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein V is hydrogen or halogen. In specific embodiments, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein V is H or Cl.

In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein W is cyclopropyl.

In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein X is H, -OH or $-OCH_3$.

In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein $(Z)_{n1}$ is $-CH_2-$ or a bond.

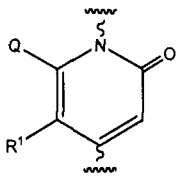
In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein Y is



optionally mono-, di-, tri-, tetra- or penta-substituted as described in Formula I.

In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein:

S is



,

wherein the nitrogen atom in S above is attached to T,

U is a phenyl ring, optionally mono-, di-, tri-, tetra-, or penta-substituted wherein substituents are independently selected from the group consisting of: halogen, alkyl, alkoxy and CF_3,

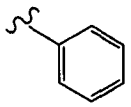
W is cyclopropyl,

X is hydrogen, OH or methoxy,

Z is $-CH_2-$,

n1 is 1,

Y is

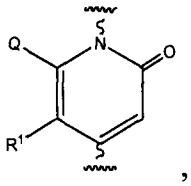


optionally mono-, di-, tri-, tetra- or penta-substituted as described in Formula I.,

wherein all other variables are as described above for Formula I.

In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein:

S is



,

wherein the nitrogen atom in S above is attached to T,

T is $-(CH_2)_r-O-$,

U is a phenyl ring, optionally mono-, di-, tri-, tetra-, or penta-substituted wherein substituents are independently selected from the group consisting of: halogen, alkyl, alkoxy and CF_3,

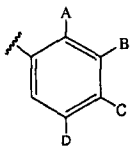
W is cyclopropyl,

X is hydrogen, OH or methoxy,

Z is $-CH_2-$,

n1 is 1,

Y is



wherein:

A is selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) C_1-C_5 alkyl,

(4) C_1-C_5 alkoxy, and

(5) $-S-(CH_2)_{0-3}-CH_3$,

wherein (3) and (4) are optionally substituted with 1-3 halogens,

B is selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) C_1-C_5 alkyl,

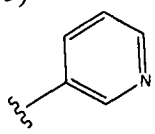
(4) C_1-C_5 alkoxy,

(5) -OH,

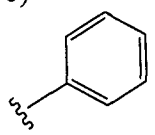
(6) $-CF_3$,

(7) $-C(=O)-CH_3$,

(8) -O-(C_1-C_5 alkylene)-O-cyclopropyl,
(9) -O-(C_1-C_5 alkylene)-O-$(CH_2)_{0-2}$-CH_3,
(10) -(C_1-C_5 alkylene)-O-$(CH_2)_{0-2}$-CH_3,
(11) -OC(=O)-morpholine,
(12) -O-(C_1-C_5 alkylene)-morpholine,
(13) -O-(C_1-C_5 alkylene)-$C(CH_3)_2$-C(=O)OH,
(14) -O-(C_1-C_5 alkylene)-$C(CH_3)_2$-C(=O)OCH_3,
(15)



and
(16)



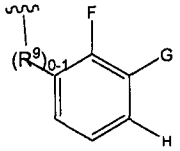
,

wherein (3), (4), (8), (9), (10), (12), (13), (14), (15) and (16) are optionally substituted with 1-3 halogens,

C is selected from the group consisting of:
(1) hydrogen,
(2) halogen,
(3) C_1-C_5 alkyl optionally substituted with 1-3 halogens, and
(4) C_1-C_5 alkoxy optionally substituted with 1-3 halogens, and

D is selected from the group consisting of:
(1) hydrogen,
(2) halogen,
(3) C_1-C_5 alkyl,
(4) C_1-C_5 alkoxy,
(5) C_1-C_5-cyano,
(6) C_2-C_5 alkenylene-O-$(CH_2)_{0-2}$-CH_3,
(7) -(C_1-C_5 alkylene)-N(H)-C(=O)-O-$(CH_2)_{0-2}$-CH_3,
(8) -(C_1-C_5 alkylene)-N(H)-C(=O)-$(CH_2)_{0-2}$-CH_3,
(9) -(C_1-C_5 alkylene)-O-CHF_2,
(10) -(C_1-C_5 alkylene)-O-$(CH_2)_{0-2}$-CH_3,
(11) -O-(C_1-C_5 alkylene)-O-$(CH_2)_{0-2}$-CH_3,
(12) -(C_1-C_5 alkylene)-OH,
(13) -S-(C_1-C_5 alkylene)-OH,
(14) -SCF_3
(15) -N(H)-(C_1-C_5 alkylene)-O-$(CH_2)_{0-2}$-CH_3, and

(16)



wherein F, G and H are independently selected from the group consisting of: hydrogen, halogen and C_1-C_3 alkyl optionally substituted with 1-3 halogens, and

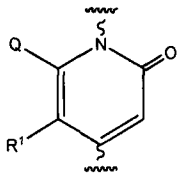
wherein R^9 is selected from the group consisting of: -CH_2-, -C(H)(OH)- and –C(=O)-,

wherein (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13) and (15) are optionally substituted with 1-3 halogens, and

wherein all other variables are as described above for Formula I.

In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein:

S is



wherein the nitrogen atom in S above is attached to T,

T is -$(CH_2)_r$-O-,

U is a phenyl ring, optionally mono-, di-, tri-, tetra-, or penta-substituted wherein substituents are independently selected from the group consisting of: halogen, alkyl, alkoxy and CF_3,

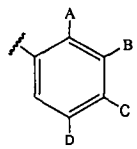
W is cyclopropyl,

X is hydrogen, OH or methoxy,

Z is -CH_2-,

n1 is 1,

Y is



wherein:

A is selected from the group consisting of: hydrogen, halogen, C_1-C_5 alkyl and C_1-C_5 alkoxy,

B is selected from the group consisting of: hydrogen, halogen, C_1-C_5 alkyl, C_1-C_5 alkoxy and -O-(C_1-C_5 alkylene)-O-$(CH_2)_{0-2}$-CH_3,

C is selected from the group consisting of: hydrogen, halogen, C_1-C_5 alkyl and C_1-C_5 alkoxy,

D is selected from the group consisting of: hydrogen, halogen, C_1-C_5 alkyl, C_1-C_5 alkoxy and -(C_1-C_5 alkylene)-O-$(CH_2)_{0-2}$-CH_3,

wherein the alkyl or alkoxy groups of A-D are optionally substituted with 1-3 halogens, and

wherein all other variables are as described above for Formula I.

The compounds of Formula I above, and pharmaceutically acceptable salts thereof, are renin inhibitors. The compounds are useful for inhibiting renin and treating conditions such as hypertension.

Any reference to a compound of formula (I) is to be understood as referring also to optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, meso-forms, as well as salts (especially pharmaceutically acceptable salts) and solvates (including hydrates) of such compounds, and morphological forms, as appropriate and expedient. The present invention encompasses all these forms. Mixtures are separated in a manner known *per se*, e.g. by column chromatography, thin layer chromatography (TLC), high performance liquid chromatography (HPLC), or crystallization. The compounds of the present invention may have chiral centers, e.g. one chiral center (providing for two stereoisomers, (R) and (S)), or two chiral centers (providing for up to four stereoisomers, (R,R), (S,S), (R,S), and (S,R)). This invention includes all of these optical isomers and mixtures thereof. Unless specifically mentioned otherwise, reference to one isomer applies to any of the possible isomers. Whenever the isomeric composition is unspecified, *e.g.*, when bonds to a chiral carbon are depicted as straight lines, it is understood that both (R) and (S) configurations of that chiral carbon and, hence, both enantiomers and mixtures thereof are represented.

In addition, compounds with carbon-carbon double bonds may occur in Z- and E-forms with all isomeric forms of the compounds being included in the present invention.

Compounds of the invention also include nitrosated compounds of formula (I) that have been nitrosated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulfydryl condensation) and/or nitrogen. The nitrosated compounds of the present invention can be prepared using conventional methods known to one skilled in the art. For example, known methods for nitrosating compounds are described in U.S. Pat. Nos. 5,380,758, 5,703,073, 5,994,294, 6,242,432 and 6,218,417; WO 98/19672; and Oae et al., Org. Prep. Proc. Int., 15(3): 165-198 (1983).

Salts are preferably the pharmaceutically acceptable salts of the compounds of Formula (I). The expression "pharmaceutically acceptable salts" encompasses either salts with inorganic acids or organic acids like hydrochloric acid, hydrobromic acid, hydroiodic acid,

sulfuric acid, sulfamic acid, phosphoric acid, nitric acid, phosphorous acid, nitrous acid, citric acid, formic acid, acetic acid, oxalic acid, maleic acid, lactic acid, tartaric acid, fumaric acid, benzoic acid, mandelic acid, cinnamic acid, palmoic acid, stearic acid, glutamic acid, aspartic acid, methanesulfonic acid, ethanesulfonic acid, ethanedisulfonic acid, p-toluenesulfonic acid, salicylic acid, succinic acid, trifluoroacetic acid, and the like that are non toxic to living organisms or, in case the compound of formula (I) is acidic in nature, with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like. For other examples of pharmaceutically acceptable salts, reference can be made notably to "Salt selection for basic drugs", *Int. J. Pharm.* (1986), 33, 201-217.

The invention also includes derivatives of the compound of Formula I, acting as prodrugs. These prodrugs, following administration to the patient, are converted in the body by normal metabolic processes to the compound of Formula 1. Such prodrugs include those that demonstrate enhanced bioavailability (see Table 4 below), tissue specificity, and/or cellular delivery, to improve drug absorption of the compound of Formula I. The effect of such prodrugs may result from modification of physicochemical properties such as lipophilicity, molecular weight, charge, and other physicochemical properties that determine the permeation properties of the drug.

The general terms used hereinbefore in Formula I and hereinafter preferably have, within this disclosure, the following meanings, unless otherwise indicated. Where the plural form is used for compounds, salts, pharmaceutical compositions, diseases and the like, this is intended to mean also a single compound, salt, or the like.

The term "alkyl", alone or in combination with other groups, unless indicated otherwise, means saturated, straight and branched chain groups with one to six carbon atoms (which may be represented by "C_{1-6} alkyl" or "C_1-C_6 alkyl"). When the intended meaning is other than this, for example, when the number of carbon atoms is in the range of one to four carbon atoms, this meaning is represented in like fashion as "C_{1-4} alkyl" or "C_1-C_4 alkyl". Examples of alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl. The methyl, ethyl and isopropyl groups are preferred.

Structural depictions of compounds may show a terminal methyl group as "-CH_3", "CH_3", "-Me", "Me"or "" (*i.e.*, these have equivalent meanings). A terminal ethyl group may be depicted as "-CH_2CH_3", "CH_2CH_3", "-Et", " Et "or "" (*i.e.*, these have equivalent meanings).

The term "alkylene" refers to any divalent linear or branched chain aliphatic hydrocarbon radical having a number of carbon atoms in the specified range. Thus, for example, "-C_1-C_6 alkylene-" refers to any of the C_1 to C_6 linear or branched alkylenes, and "-C_1-C_4 alkylene-" refers to any of the C_1 to C_4 linear or branched alkylenes. A class of alkylenes of particular interest with respect to the invention is -$(CH_2)_{1-6}$-, and sub-classes of particular

interest include -$(CH_2)_{1-4}$-, -$(CH_2)_{1-3}$-, -$(CH_2)_{1-2}$-, and -CH_2-. Another sub-class of interest is an alkylene selected from the group consisting of -CH_2-, -$CH(CH_3)$-, and -$C(CH_3)_2$-. Expressions such as "C_1-C_4 alkylene-phenyl" and "C_1-C_4 alkyl substituted with phenyl" have the same meaning and are used interchangeably.

The term "alkenyl", alone or in combination with other groups, unless indicated otherwise, means unsaturated (i.e., having at least one double bond) straight and branched chain groups with two to six carbon atoms (which may be represented by "C_{2-6} alkenyl" or "C_2-C_6 alkenyl"). When the intended meaning is other than this, for example, when the number of carbon atoms is in the range of two to four carbon atoms, this meaning is represented in like fashion as "C_{2-4} alkenyl" or "C_2-C_4 alkenyl".

The term "alkenylene" refers to any divalent linear or branched chain aliphatic mono-unsaturated hydrocarbon radical having a number of carbon atoms in the specified range.

The term "alkynyl", alone or in combination with other groups, unless indicated otherwise, means unsaturated (i.e., having at least one triple bond) straight and branched chain groups with two to six carbon atoms (which may be represented by "C_{2-6} alkynyl" or "C_2-C_6 alkynyl"). When the intended meaning is other than this, for example, when the number of carbon atoms is in the range of two to four carbon atoms, this meaning is represented in like fashion as "C_{2-4} alkynyl" or "C_2-C_4 alkynyl".

The term "alkoxy", alone or in combination with other groups, refers to an R-O- group, wherein R is an alkyl group. Examples of alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, iso-butoxy, sec-butoxy and tert-butoxy.

The term "hydroxy-alkyl", alone or in combination with other groups, refers to an HO-R- group, wherein R is an alkyl group. Examples of hydroxy-alkyl groups are HO-CH_2-, HO-CH_2CH_2-, HO-$CH_2CH_2CH_2$- and $CH_3CH(OH)$-.

The term "halogen" means fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, especially fluorine or chlorine.

The term "cycloalkyl", alone or in combination with other groups, unless indicated otherwise, means a saturated cyclic hydrocarbon ring system with 3 to 8 carbon atoms, e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. This may be represented by "C_{3-8} cycloalkyl" or "C_3-C_8 cycloalkyl"). When the intended meaning is other than this, for example, when the number of carbon atoms is in the range of three to six carbon atoms, this meaning is represented in like fashion as "C_{3-6} cycloalkyl" or "C_3-C_6 cycloalkyl".

The term "carbocycle" (and variations thereof such as "carbocyclic" or "carbocyclyl") as used herein, unless otherwise indicated, refers to a C_3 to C_8 monocyclic saturated or unsaturated ring. The carbocycle may be attached to the rest of the molecule at any carbon atom which results in a stable compound. Saturated carbocyclic rings are also referred to as cycloalkyl rings, *e.g.,* cyclopropyl, cyclobutyl, *etc.*

The term "heterocycle" (and variations thereof such as "heterocyclic" or "heterocyclyl") broadly refers to a stable 4- to 8-membered, saturated or unsaturated monocyclic ring which contains one or more heteroatoms (e.g., from 1 to 6 heteroatoms, or from 1 to 4 heteroatoms) selected from N, O and S and a balance of carbon atoms (typically at least one carbon atom); wherein any one or more of the nitrogen and sulfur heteroatoms is optionally oxidized, and any one or more of the nitrogen heteroatoms is optionally quaternized. Unless otherwise specified, the heterocyclic ring may be attached at any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. Unless otherwise specified, when the heterocyclic ring has substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results.

The term "aryl", alone or in combination, relates to a phenyl, naphthyl or indanyl group, preferably a phenyl group. The abbreviation "Ph" represents phenyl.

The term "heteroaryl", alone or in combination, means six-membered aromatic rings containing one to four nitrogen atoms; benzofused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; benzofused five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; five-membered aromatic rings containing two heteroatoms independently selected from oxygen, nitrogen and sulfur and benzofused derivatives of such rings; five-membered aromatic rings containing three nitrogen atoms and benzofused derivatives thereof; a tetrazolyl ring; a thiazinyl ring; or coumarinyl. Examples of such ring systems are furanyl, thienyl, pyrrolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazolyl, isothiazolyl, pyridazinyl, pyrazolyl, oxazolyl, isoxazolyl, benzothienyl, quinazolinyl and quinoxalinyl.

Specific examples of compounds of formula I, and pharmaceutically acceptable salts thereof, include those listed below:

trans-*N*-Cyclopropyl-4-{1-[2-(2,6-dichloro-4-methylphenoxy)ethyl]-2-oxo-1,2-dihydro-4-pyridinyl}-4-hydroxy-*N*-[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]-3-piperidinecarboxamide

trans-*N*-Cyclopropyl-4-{1-[2-(2,6-dichloro-4-methylphenoxy)ethyl]-2-oxo-1,2-dihydro-4-pyridinyl)-4-methoxy-*N*-[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]-3-piperidinecarboxamide

trans-*N*-Cyclopropyl-4-{1-[3-(2,6-dichloro-4-methylphenoxy)propyl]-2-oxo-1,2-dihydro-4-pyridinyl}-4-hydroxy-*N*-[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]-3-piperidinecarboxamide

trans-*N*-Cyclopropyl-4-{1-[3-(2,6-dichloro-4-methylphenoxy)propyl]-2-oxo-1,2-dihydro-4-pyridinyl)-4-methoxy-*N*-[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]-3-piperidinecarboxamide

trans-*N*-[2-Chloro-5-(2-methoxyethyl)benzyl]-*N*-cyclopropyl-4-{1-[3-(2,6-dichloro-4-methylphenoxy)propyl]-2-oxo-1,2-dihydro-4-pyridinyl)-4-hydroxy-3-piperidinecarboxamide

The present invention also encompasses a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and the compound of Formula I or a pharmaceutically acceptable crystal form or hydrate thereof. A preferred embodiment is a pharmaceutical composition of the compound of Formula I, comprising, in addition, a second agent.

List of abbreviations:

BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BOC	*t*-butyloxycarbonyl
BSA	bovine serum albumin
COD	1,5-cyclooctadiene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBAl-H	diisobutylaluminum hydride
DMAP	4-dimethylamino pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DPPB	1,4-bis(diphenylphosphino)butane
DPPF	1,1'-bis(diphenylphosphino)ferrocene
EDTA	ethylenediaminetetraacetic acid
EIA	enzyme immunoassay
Et_2O	diethylether
EtOAc	ethyl acetate
HATU	O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
Hex	hexanes

KHMDS	potassium hexamethyldisilazide
*m*CPBA	*meta*-chloroperbenzoic acid
MeOH	methanol
NBS	*N*-bromo succinimide
NMO	*N*-methylmorpholine-*N*-oxide
n-PrOH	*n*-propanol
PBS	phosphate-buffered saline
PG	protecting group
PPh3	triphenylphosphine
RT	room temperature
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
Tol	toluene

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, an alkyl group described as C_1 - C_6 alkyl means the alkyl group can contain 1, 2, 3, 4, 5 or 6 carbon atoms.

When a given range includes 0 (*e.g.*, $(CH_2)_{0-3}$), 0 implies a direct covalent bond.

When any variable occurs more than one time in any constituent or in any formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence.

Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "substituted" (e.g., as in "aryl which is optionally substituted with one or more substituents ...") includes mono- and poly-substitution by a named substituent to the extent such single and multiple substitution (including multiple substitution at the same site) is chemically allowed and results in a stable compound.

A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (*e.g.*, therapeutic or prophylactic administration to a subject).

In compounds of the invention having pyridyl N-oxide moieties, the pyridyl-N-oxide portion is structurally depicted using conventional representations such as



which have equivalent meanings.

The invention relates to a method for the treatment and/or prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary hypertension, systolic hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases known to be related to the renin-angiotensin system, which method comprises administrating a compound as defined above to a human being or animal.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases, which are associated with a dysregulation of the renin-angiotensin system as well as for the treatment of the above-mentioned diseases.

The invention also relates to the use of compounds of formula (I) for the preparation of a medicament for the treatment and/or prophylaxis of the above-mentioned diseases.

Compounds of formula (I) or the above–mentioned pharmaceutical compositions are also of use in combination with other pharmacologically active compounds comprising ACE-inhibitors, neutral endopeptidase inhibitors, angiotensin II receptor antagonists, endothelin receptors antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, sympatholitics, beta-adrenergic antagonists, alpha-adrenergic antagonists or with other drugs beneficial for the prevention or the treatment of the above-mentioned diseases.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of Formula I mean providing the compound or a prodrug of the compound to the individual in need of treatment or prophylaxis. When a compound of the invention or a prodrug thereof is provided in combination with one or more other active agents (e.g., an agent such as anangiotensin II receptor antagonist, ACE inhibitor, or other active agent which is known to reduce blood pressure), "administration" and its variants are each understood to include provision of the compound or prodrug and other agents at the same time or at different

times. When the agents of a combination are administered at the same time, they can be administered together in a single composition or they can be administered separately.

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

By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

The term "subject" as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. In one embodiment, the effective amount is a "therapeutically effective amount" for the alleviation of the symptoms of the disease or condition being treated. In another embodiment, the effective amount is a "prophylactically effective amount" for prophylaxis of the symptoms of the disease or condition being prevented. The term also includes herein the amount of active compound sufficient to inhibit renin and thereby elicit the response being sought (i.e., an "inhibition effective amount"). When the active compound (i.e., active ingredient) is administered as the salt, references to the amount of active ingredient are to the free form (i.e., the non-salt form) of the compound.

In a preferred embodiment, this amount is comprised between 1 mg and 1000 mg per day. In a particularly preferred embodiment, this amount is comprised between 1 mg and 500 mg per day. In a more particularly preferred embodiment, this amount is comprised between 1 mg and 200 mg per day.

In the method of the present invention (i.e., inhibiting renin), the compounds of Formula I, optionally in the form of a salt, can be administered by any means that produces contact of the active agent with the agent's site of action. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The compounds of the invention can, for example, be administered orally, mucosally (including sublingual, buccal, rectal, nasal or vaginal administrations), parenterally (including subcutaneous injection, bolus injection, intraarterial, intravenous, intramuscular, intrasternal injection or infusion administrations techniques), by inhalation spray, transdermal, such as passive or iontophoretic delivery, or topical administration, in the form of a unit dosage of a pharmaceutical composition containing an

effective amount of the compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (*e.g.,* nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (*e.g.,* aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (*e.g.,* crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient. Liquid preparations suitable for oral administration (e.g., suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water, glycols, oils, alcohols and the like. Solid preparations suitable for oral administration (e.g., powders, pills, capsules and tablets) can be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other ingredients, such as a solubility aid. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions for use in the present invention and of ingredients suitable for use in said compositions is provided in Remington's Pharmaceutical Sciences, 18th edition, edited by A. R. Gennaro, Mack Publishing Co., 1990.

Methods of Synthesis

Compounds of the present invention can be made by a variety of methods depicted in the illustrative synthetic reaction schemes shown and described below. The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis; Wiley & Sons: New York, Volumes 1-21; R. C. LaRock, Comprehensive Organic Transformations, 2.sup.nd edition Wiley-VCH, New York 1999; Comprehensive Organic Synthesis, B. Trost and I. Fleming (Eds.) vol. 1-9 Pergamon, Oxford, 1991; Comprehensive Heterocyclic Chemistry, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1984, vol. 1-9; Comprehensive Heterocyclic Chemistry II, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1996, vol. 1-11; and Organic Reactions, Wiley & Sons: New York, 1991, Volumes 1-40. The following synthetic reaction schemes and examples are merely

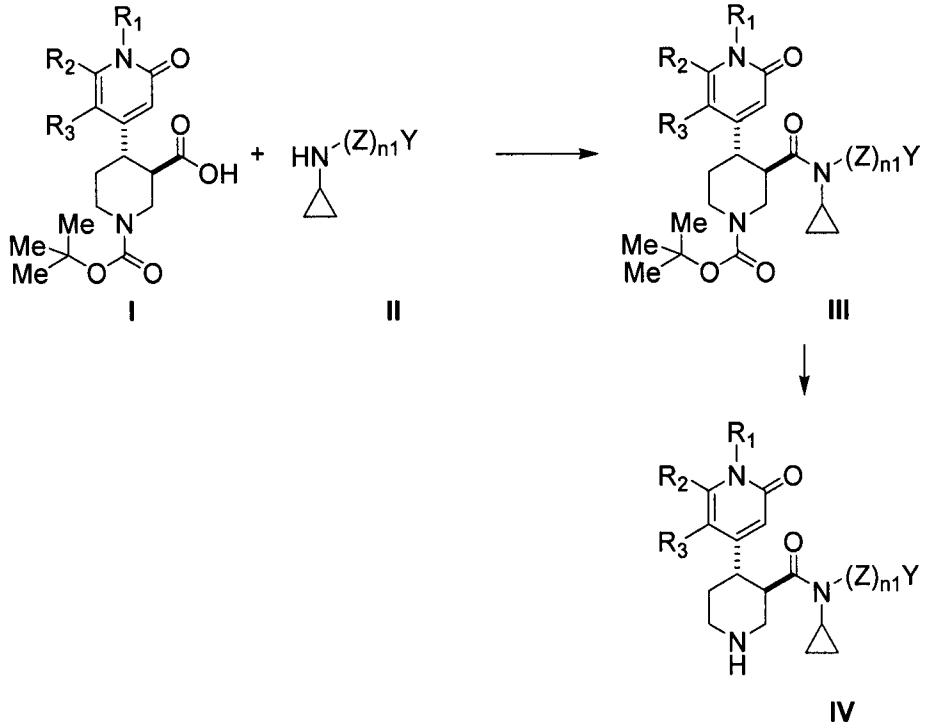
illustrative of some methods by which the compounds of the present invention can be synthesized, and various modifications to these synthetic reaction schemes can be made and will be suggested to one skilled in the art having referred to the disclosure contained in this application.

The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm Hg) with a bath temperature of up to 60 ^{o}C. Reactions are typically run under nitrogen atmosphere at ambient temperature if not otherwise mentioned. Anhydrous solvent such as THF, DMF, Et_2O, DME and Toluene are commercial grade. Reagents are commercial grade and were used without further purification. Flash chromatography is run on silica gel (230-400 mesh). The course of the reaction was followed by either thin layer chromatography (TLC) or nuclear magnetic resonance (NMR) spectrometry and reaction times given are for illustration only. The structure and purity of all final products were ascertained by TLC, mass spectrometry, ^{1}H NMR and high-pressure liquid chromatography (HPLC). Chemical symbols have their usual meanings. The following abbreviations have also been used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliter(s)), g (gram(s)), mg (milligram(s)), mol (mole(s)), mmol (millimole(s)), eq. (equivalent(s)). Unless otherwise specified, all variables mentioned below have the meanings as provided above.

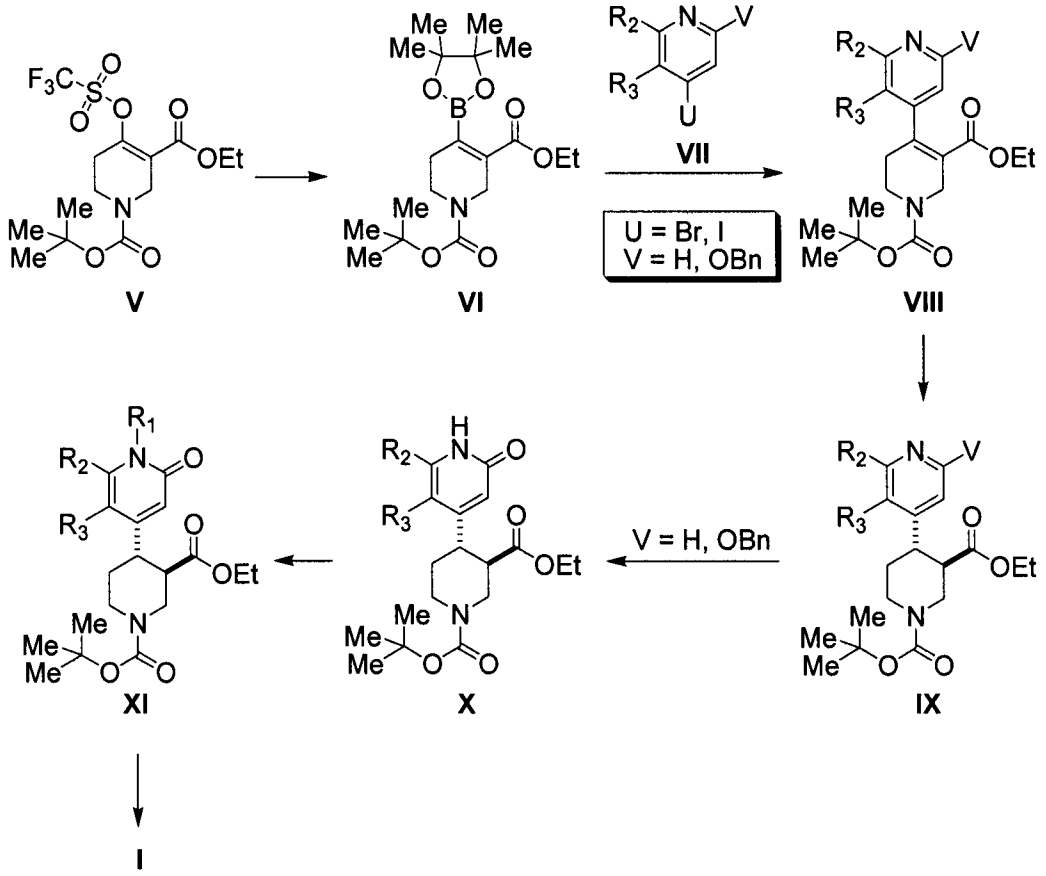
Generally, compounds of the present invention can be prepared via the coupling of an appropriately substituted pyridone **I** with an appropriately functionalized amine **II**, followed by the removal of the BOC-protecting group from amide **III** (**Scheme 1**).

Scheme 1



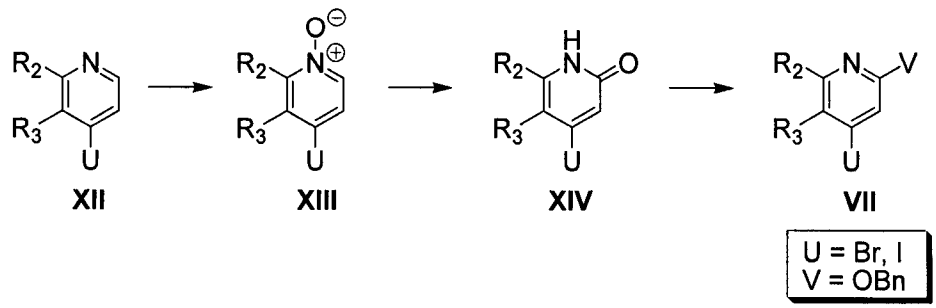
Synthesis of the requisite pyridone **I** can, for example, be performed as exemplified in **Scheme 2**. Typically, metal-catalyzed Suzuki coupling of boronate **VI**, prepared from known triflate **V**, with halide **VII**, can provide α,β-unsaturated ester **VIII**. Reduction of the double bond; most conveniently accomplished using either magnesium or samarium iodide, and subsequent base-mediated equilibration, would then afford saturated ester **IX** as a single diastereomer. Its conversion to the corresponding pyridone **X** can be realized in two steps via the initial treatment of ester **IX** with *m*CPBA; or an equivalent oxidant, followed by the reaction of the resulting pyridine *N*-oxide with TFAA in triethylamine; or an equivalent rearrangement promoter. Alternatively, for cases where the V group of ester **IX** is OBn, a simple hydrogenation under typical conditions would directly furnish pyridone **X**. Indeed, one can also access **XI** via *N*-alkylation of pyridone **X** with an appropriate reagent. Finally, saponification of pyridone **XI** would furnish pyridone **I**.

Scheme 2



For halides **VII** used in the preparation of **I** where V is OBn, their synthesis can most readily be accomplished from the corresponding pyridone **XIV** using, for example, benzyl halide in the presence of silver carbonate (**Scheme 3**). For cases where pyridone **XIV** was neither commercially available nor known in the literature, the requisite compound could be prepared from its corresponding pyridine **XII** via the intermediacy of pyridine *N*-oxide **XIII**.

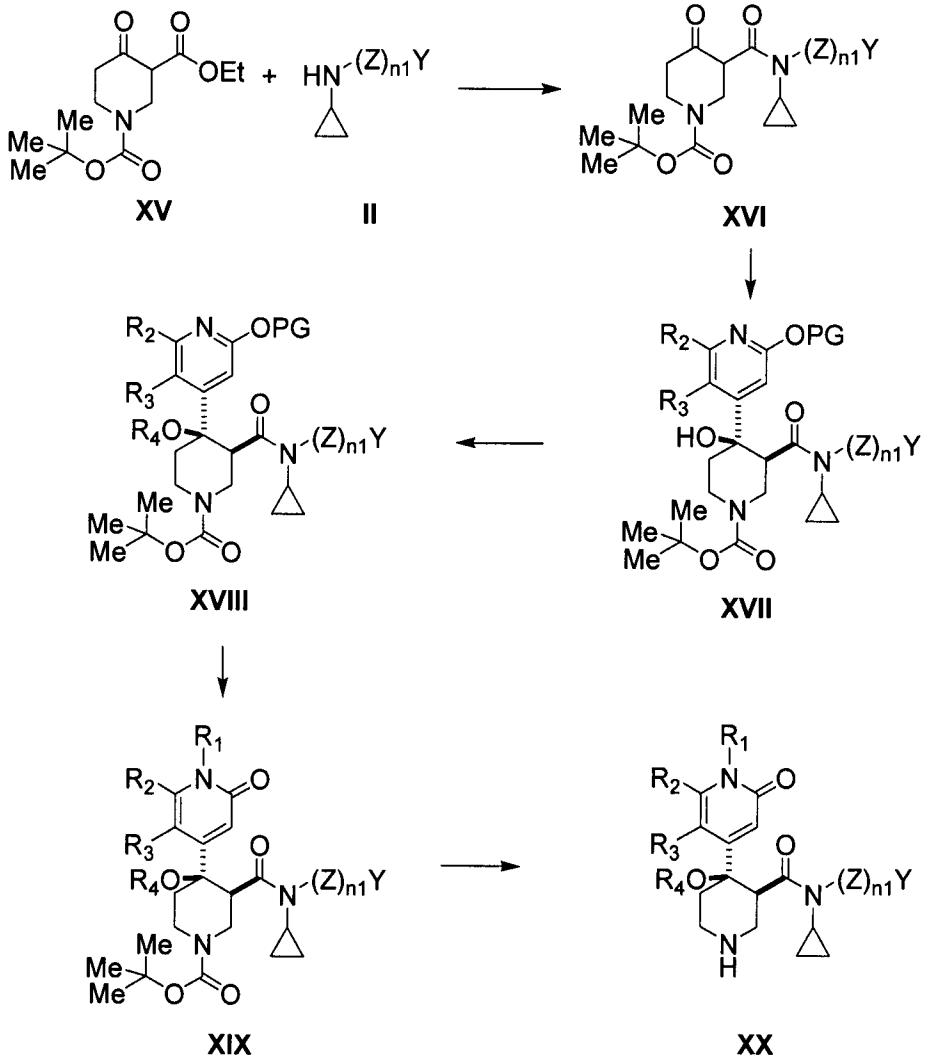
Scheme 3



For compounds of the present invention bearing an alkoxy group at position 4 of the piperidine ring, they are most conveniently accessed via an initial amide formation between amine **II** and β-ketoester **XV**, followed by the addition of Gignard reagent derived from a suitably-protected and appropriately substituted hydroxypyridine. Functionalization of the

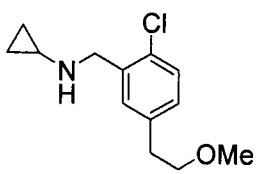
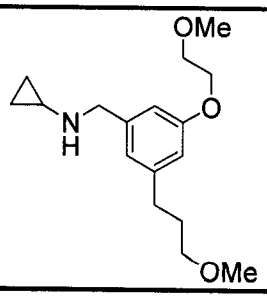
resulting alcohol **XVII**, if necessary, would precede the conversion of the protected hydroxypyridine **XXVIII** into the desired pyridone **XIX** using chemistry described earlier. Finally, BOC removal can be accomplished under typical conditions (**Scheme 4**).

Scheme 4



Representative cyclopropylamine building blocks are shown in **Table 1**.

Table 1

Compound	Structure
Amine 1	
Amine 2	

Amine 1

N-({2-Chloro-5-[2-(methyloxy)ethyl]phenyl}methyl)cyclopropanamine

Amine 1 was prepared according to the procedure described in **WO 2007/009250 A1** patent.

Amine 2

N-({3-{[2-(Methyloxy)ethyl]oxy}-5-[3-(methyloxy)propyl]phenyl}methyl)cyclopropanamine

Step 1: 3-Bomo-5-hydroxybenzaldehyde

To a toluene solution (1.6 M) of *n*-butyl lithium (2.5 M in hexane, 2.1 eq.) was added at -10 °C *n*-butyl magnesium chloride (2.0 M in THF, 0.6 eq.). The reaction mixture was stirred at -10 °C for 30 min before a toluene solution (0.7 M) of 3,5-dibromophenol (1 eq.) was added dropwise at -10 °C over a period of 35 min. After stirring at -10°C for a further 30 min, the reaction mixture was cooled to -40 °C before DMF (20 eq.) was added dropwise over 20 min. The reaction mixture was then slowly warmed to RT and allowed to stir at RT for 1 h. The reaction was carefully quenched at 0°C with 1 N aq. HCl and extracted with ether. The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and filtered. Concentration of the filtrate *in vacuo* afforded a yellow solid. Recystallization of the crude product thus obtained from ether – hexane afforded the title compound as a beige powder.

Step 2: 3-Hydroxy-5-[(1*E*)-3-(methyloxy)-1-propen-1-yl]benzaldehyde

3-Bomo-5-hydroxybenzaldehyde (1 eq.) from the previous step and 2-[(1*E*)-3-methoxyprop-1-en-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1 eq.) were combined in DMF (0.05 M). To this solution was then added palladium acetate (0.1 eq.), triphenylphosphine (0.2 eq.) and 2 M aq. sodium carbonate (4 eq.). The resulting suspension was heated at 80 °C for 16 h. The reaction mixture was quenched with 1 N aq. HCl and extracted with ether. The combined organic extracts were washed with water, sat. aq. $NaHCO_3$ and brine. Drying over $MgSO_4$, filtration and concentration of the filtrate *in vacuo* afforded the crude product as a brown tar. Further purification by way of flash chromatography (SiO_2, 4:1 (v/v) Hex : EtOAc → 2:1 (v/v) Hex : EtOAc) afforded the title compound as a yellow oil.

Step 3: 3-{[2-(Methyloxy)ethyl]oxy}-5-[(1*E*)-3-(methyloxy)-1-prop-1-en-1-yl]benzaldehyde

3-Hydroxy-5-[(1*E*)-3-(methyloxy)-1-propen-1-yl]benzaldehyde (1 eq.) from the previous step and 2-bromoethyl methyl ether (2.2 eq.) were combined in DMF. To this solution was then added cesium carbonate (2 eq.) and the reaction suspension was heated at 100 °C for 16 h. The resulting reaction mixture was quenched with water and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over $MgSO_4$, filtered and the filtrate concentrated *in vacuo*. Further purification of the crude product thus obtained by

way of flash chromatography (SiO_2, 19:1 (v/v) Hex : EtOAc → 1:1 (v/v) Hex : EtOAc) afforded the title compound as a yellow oil.

Step 4: *N*-({3-{[2-(Methyloxy)ethyl]oxy}-5-[(1*E*)-3-(methyloxy)-1-propen-1-yl]phenyl}methyl)cyclopropanamine

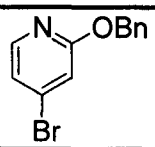
To a solution of 3-{[2-(methyloxy)ethyl]oxy}-5-[(1*E*)-3-(methyloxy)-1-prop-1-en-1-yl]benzaldehyde (1 eq.) from the previous step (1 eq.) in dichloromethane (0.5 M) was added cyclopropylamine (2 eq.) and magnesium sulfate (1.5 eq.). The resulting suspension was stirred at RT for 12 h. The insolubles were removed via filtration. Concentration of the filtrate *in vacuo* afforded the crude imine as a yellow oil. This was then taken up in methanol (0.3 M) and then added at 0 °C sodium borohydride (1.5 eq.) portionwise over 5 min. The reaction mixture was slowly warmed to RT over 1 h and then stirred at RT for 2 h. After carefully quenching with sat. aq. $NaHCO_3$, the resulting mixture was extracted with ether. The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and filtered. Concentration of the filtrate *in vacuo* afforded the title compound as a golden, yellow oil.

Step 5: **Amine 2**

To a solution of *N*-({3-{[2-(methyloxy)ethyl]oxy}-5-[(1*E*)-3-(methyloxy)-1-propen-1-yl]phenyl}methyl)cyclopropanamine (1 eq.) from the previous step in EtOAc (0.04 M) was added palladium (10% w/w over activated carbon, 0.1 eq). The vessel was evacuated and back filled with hydrogen. The reaction suspension was then stirred under a balloon atmosphere of hydrogen for 1.5 h. The reaction was quenched with dichloromethane and filtered through a bed of celite. The insolubles were washed further with EtOAc and methanol. Concentration of the filtrate *in vacuo* afforded the title compound as a colorless oil.

The arene building blocks in **Table 2** were synthesized as follows.

Table 2

Compound	Structure
Arene 1	

Arene 1

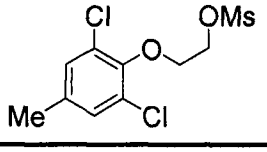
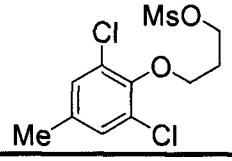
2-(Benzyloxy)-4-bromopyridine

To a solution of 4-bromo-2-fluoropyridine (1 eq.), benzyl alcohol (1.2 eq.) and dibenzo-18-crown-6 (0.05 eq.) in toluene (0.4 M) was added potassium hydroxide (2 eq.). A Dean-Stark apparatus was then attached and the reaction suspension was heated at reflux for 3 h. After cooling to RT, the reaction mixture was diluted with hexanes and then filtered through a pad of celite. Concentration of the filtrate *in vacuo* afforded a yellow oil. Purification of the

crude product thus obtained by way of column chromatography (SiO_2, 97:3 (v/v) Hex : Et_2O) afforded the title compound as a colorless oil.

Representative alkylation building blocks are shown in **Table 3**.

Table 3

Compound	Structure
Mesylate 1	
Mesylate 2	

Mesylate 1

2-(2,6-Dichloro-4-methylphenoxy)ethyl methanesulfonate

Step 1: 2-(2,6-Dichloro-4-methylphenoxy)ethanol

2,6-Dichloro-4-methylphenol (1 eq.), ethylene carbonate (1 eq.) and imidazole (0.5% loading) were combined and heated at 150°C for 4 h to afford the title compound as a brown oil.

Step 2: **Mesylate 1**

To a dichloromethane solution (0.18 M) solution of 2-(2,6-dichloro-4-methylphenoxy)ethanol (1 eq.) from the previous step was added at -40°C methanesulfonyl chloride (1.5 eq.) and triethylamine (3 eq.). The resulting mixture was then slowly warmed to 5°C over 1.5 h. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with dichloromethane. The combined organic extracts were washed with water and brine. Drying over $MgSO_4$, filtration and concentration of the filtrate *in vacuo* afforded the crude product that could be further purified by way of flash chromatography (SiO_2, 4:1 (v/v) Hex: EtOAc → 2:1 (v/v) Hex: EtOAc). The title compound was obtained as a pale yellow oil.

Mesylate 2

3-(2,6-Dichloro-4-methylphenoxy)propyl methanesulfonate

Step 1: *tert*-Butyl[3-(2,6-dichloro-4-methylphenoxy)propoxy]dimethylsilane

To a THF solution (0.23 M) of 2,6-dichloro-4-methylphenol (1 eq.), 3-{[*tert*-butyl(dimethyl)silyl]oxy}-1-propanol (1 eq.) and di-*tert*-butyl azodicarboxylate (1.3 eq.) was added tri-*n*-butylphosphine (1.5 eq.). The resulting suspension was stirred at RT for 16 h. The reaction mixture was the diluted with ether and washed sequentially with 10% aq. HCl, 1 N aq. NaOH, water and brine. Drying over $MgSO_4$, filtration and concentration of the filtrate *in vacuo* afforded the crude product that could be further purified by way of flash chromatography (SiO_2, 99:1 (v/v) Hex: Et_2O → 97:3 (v/v) Hex: Et_2O). The title compound was obtained as a colourless oil.

Step 2: 3-(2,6-Dichloro-4-methylphenoxy)-1-propanol

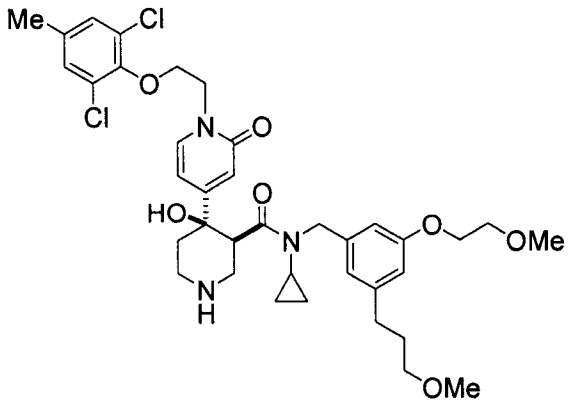
To a THF solution (0.25 M) solution of *tert*-butyl[3-(2,6-dichloro-4-methylphenoxy)propoxy]dimethylsilane (1 eq.) from the previous step was added tetrabutylammonium fluoride (1.0 M THF solution, 1.1 eq.). The resulting mixture was stirred at RT for 4 h. The reaction mixture was then quenched with sat. aq. NH_4Cl and extracted with ether. The combined organic extracts were washed with water and brine. Drying over $MgSO_4$, filtration and concentration of the filtrate *in vacuo* afforded the crude product that could be further purified by way of flash chromatography (SiO_2, 4:1 (v/v) Hex : EtOAc → 2:1 (v/v) Hex : EtOAc) afforded the title compound as a colourless oil.

Step 3: **Mesylate 2**

To a dichloromethane solution (0.15 M) solution of 3-(2,6-dichloro-4-methylphenoxy)-1-propanol (1 eq.) from the previous step was added at -40°C methanesulfonyl chloride (1.5 eq.) and triethylamine (3 eq.). The resulting mixture was then slowly warmed to 5°C over 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with dichloromethane. The combined organic extracts were washed with water and brine. Drying over $MgSO_4$, filtration and concentration of the filtrate *in vacuo* afforded the crude product that could be further purified by way of flash chromatography (SiO_2, 4:1 (v/v) Hex: EtOAc → 2:1 (v/v) Hex: EtOAc). The title compound was obtained as a pale yellow oil.

Example 1

trans-*N*-Cyclopropyl-4-{1-[2-(2,6-dichloro-4-methylphenoxy)ethyl]-2-oxo-1,2-dihydro-4-pyridinyl}-4-hydroxy-*N*-[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]-3-piperidinecarboxamide



Step 1: *tert*-Butyl 3-({cyclopropyl[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]amino}carbonyl)-4-oxo-1-piperidinecarboxylate

1-*tert*-Butyl 3-ethyl 4-oxo-1,3-piperidinedicaroboxylate (1 eq.), **Amine 2** (1 eq.) and DMAP (0.2 eq.) were heated at 140°C for 5 h. Purification of the crude product thus obtained by way of column chromatography (SiO_2, 95:5 → 3:7 (v/v) Hex: EtOAc) followed by swishing in 9:1 (v/v) Hex: Et_2O afforded the title compound as a white solid.

Step 2: *tert*-Butyl *trans*-4-[2-(benzyloxy)-4-pyridinyl]-3-({cyclopropyl[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]amino}carbonyl)-4-hydroxy-1-piperidinecarboxylate

To a THF solution (0.08 M) of **Arene 1** was added at -78°C *n*-butyl lithium (2.5 M solution in hexanes, 2.1 eq.). After stirring at -78°C for 30 min, solid magnesium bromide (2.5 eq.) was added in one rapid portion and the resulting mixture was stirred at -78°C for 20 min. The reaction mixture was then slowly warmed to 0°C over 30 min and *tert*-butyl 3-({cyclopropyl[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]amino}carbonyl)-4-oxo-1-piperidinecarboxylate (1 eq.) from the previous step was added as a THF solution. The reaction mixture was then stirred at 0°C for 1 h and at RT for 30 min. The reaction was then quenched with the addition of sat. aq. NH_4Cl and ether. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with brine, dried over $MgSO_4$, filtered and the filtrate concentrated *in vacuo*. Purification of the crude product thus obtained by way of column chromatography (SiO_2, 96:4 → 93:7 (v/v) acetone: toluene) afforded the title compound.

Step 3: *tert*-Butyl *trans*-3-({cyclopropyl[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]amino}carbonyl)-4-hydroxy-4-(2-oxo-1,2-dihydro-4-pyridinyl)-1-piperidinecarboxylate

To a solution of *tert*-butyl *trans*-4-[2-(benzyloxy)-4-pyridinyl]-3-({cyclopropyl[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]amino}carbonyl)-4-hydroxy-1-piperidinecarboxylate

(1 eq.) from the previous step in EtOAc (0.1 M) was added palladium (10% w/w on carbon, 0.5 eq.) and acetic acid (1.1 eq.). The resulting suspension was stirred under a balloon atmosphere of hydrogen for 4 h. The reaction was quenched with dichloromethane and the insolubles were removed *via* filtration through a pad of celite. Concentration of the filtrate thus obtained afforded the title compound.

Step 4: *tert*-Butyl *trans*-3-({cyclopropyl[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]amino}carbonyl)-4-{1-[2-(2,6-dichloro-4-methylphenoxy)ethyl]-2-oxo-1,2-dihydro-4-pyridinyl}4-hydroxy-1-piperidinecarboxylate

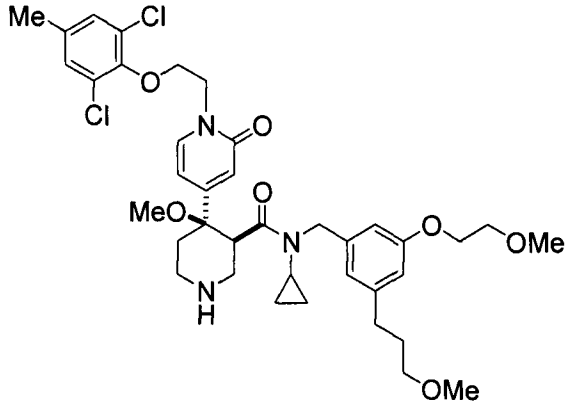
To a methanol solution (0.07 M) of *tert*-butyl *trans*-3-({cyclopropyl[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]amino}carbonyl)-4-hydroxy-4-(2-oxo-1,2-dihydro-4-pyridinyl)-1-piperidinecarboxylate (1 eq.) from the previous step was added NaOH (2 N aq. solution, 3 eq.) and **Mesylate 1** (3 eq.). The resulting mixture was then stirred at 60°C for 16 h. The volatiles were then removed *in vacuo* and the residue thus obtained was directly subjected to purification by way of preparatory HPLC-MS (C-18 reverse phase column, 15 mL/min, 70:30 (v/v) H_2O : CH_3CN → 5:95 (v/v) H_2O : CH_3CN).

Step 5: *trans*-*N*-Cyclopropyl-4-{1-[2-(2,6-dichloro-4-methylphenoxy)ethyl]-2-oxo-1,2-dihydro-4-pyridinyl}-4-hydroxy-*N*-[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]-3-piperidinecarboxamide

To a CH_2Cl_2 solution (0.05 M) of *tert*-butyl *trans*-3-({cyclopropyl[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]amino}carbonyl)-4-{1-[2-(2,6-dichloro-4-methylphenoxy)ethyl]-2-oxo-1,2-dihydro-4-pyridinyl}4-hydroxy-1-piperidinecarboxylate (1 eq.) from the previous step was added HCl (4.0 M dioxane solution, 30 eq.). The resulting solution was stirred at RT for 3 h. Following the removal of the volatiles *in vacuo*, the resulting residue was directly loaded onto a SiO_2 column packed with 94:6 (v/v) CH_2Cl_2: 2.0 M NH_3 in MeOH. Elution with the same solvent system furnished the title compound. MS (ESI+, M+H): 716. ^{1}H NMR (acetone-d_6): δ (ppm) 0.75-1.04 (*m*, 4H), 1.74-1.83 (*m*, 3H), 2.29 (*s*, 3H), 2.57 (*t*, *d* = 7.5 Hz, 2H), 2.66-2.73 (*m*, 1H), 2.85-2.87 (*br m*, 2H), 3.13-3.18 (*br m*, 3H), 3.28 (*s*, 3H), 3.32-3.36 (*br m*, 3H), 3.39 (*s*, 3H), 3.69 (*t*, *d* = 6.8 Hz, 2H), 3.84-3.90 (*m*, 1H), 4.08 (*t*, *d* = 6.8 Hz, 2H), 4.22-4.34 (*m*, 4H), 4.34 (*d*, *J* = 13.4 Hz, 1H), 4.56 (*d*, *J* = 13.4 Hz, 1H), 6.37-6.39 (*br m*, 2H), 6.51-6.58 (*m*, 3H), 6.63 (*s*, 1H), 7.22 (*s*, 2H), 7.58 (*d*, *J* = 7.0 Hz, 1H).

Example 2

trans-*N*-Cyclopropyl-4-{1-[2-(2,6-dichloro-4-methylphenoxy)ethyl]-2-oxo-1,2-dihydro-4-pyridinyl)-4-methoxy-*N*-[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]-3-piperidinecarboxamide



Step 1: *tert*-Butyl *trans*-4-[2-(benzyloxy)-4-pyridinyl]-3-({cyclopropyl[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]amino}carbonyl)-4-methoxy-1-1-piperidinecarboxylate

To a DMF solution (0.15 M) of *tert*-butyl *trans*-4-[2-(benzyloxy)-4-pyridinyl]-3-({cyclopropyl[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]amino}carbonyl)-4-hydroxy-1-piperidinecarboxylate (1 eq., **Example 1, Step 2**) was added sodium hydride (1.2 eq.) and iodomethane (1.2 eq.). The reaction mixture was stirred at RT for 30 min before it was diluted with ether and water. The organic layer was separated and washed further with water and brine, dried over $MgSO_4$, filtered and the filtrate concentrated *in vacuo*. Purification of the crude

product thus obtained by way of column chromatography (SiO_2, 3:2 (v/v) Hex: EtOAc → EtOAc) afforded the title compound.

Step 2: *tert*-Butyl *trans*-3-({cyclopropyl[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]amino}carbonyl)-4-methoxy-4-(2-oxo-1,2-dihydro-4-pyridinyl)-1-piperidinecarboxylate

To a solution of *tert*-butyl *trans*-4-[2-(benzyloxy)-4-pyridinyl]-3-({cyclopropyl[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]amino}carbonyl)-4-methoxy-1-1-piperidinecarboxylate

(1 eq.) from the previous step in EtOAc (0.08 M) was added palladium (10% w/w on carbon, 0.5 eq.) and acetic acid (1.1 eq.). The resulting suspension was stirred under a balloon atmosphere of hydrogen for 4 h. The reaction was quenched with dichloromethane and the insolubles were removed *via* filtration through a pad of celite. Concentration of the filtrate thus obtained afforded the title compound.

Step 3: *tert*-Butyl *trans*-3-({cyclopropyl[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]amino}carbonyl)-4-{1-[2-(2,6-dichloro-4-methylphenoxy)ethyl]-2-oxo-1,2-dihydro-4-pyridinyl}4-methoxy-1-piperidinecarboxylate

To a methanol solution (0.1 M) of *tert*-butyl *trans*-3-({cyclopropyl[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]amino}carbonyl)-4-methoxy-4-(2-oxo-1,2-dihydro-4-pyridinyl)-1-piperidinecarboxylate (1 eq.) from the previous step was added NaOH (2 N aq. solution, 3 eq.) and **Mesylate 1** (3 eq.). The resulting mixture was then stirred at 60°C for 16 h. The volatiles were then removed *in vacuo* and the residue thus obtained was directly subjected to purification by way of preparatory HPLC-MS (C-18 reverse phase column, 15 mL/min, 70:30 (v/v) H_2O : CH_3CN → 5:95 (v/v) H_2O : CH_3CN).

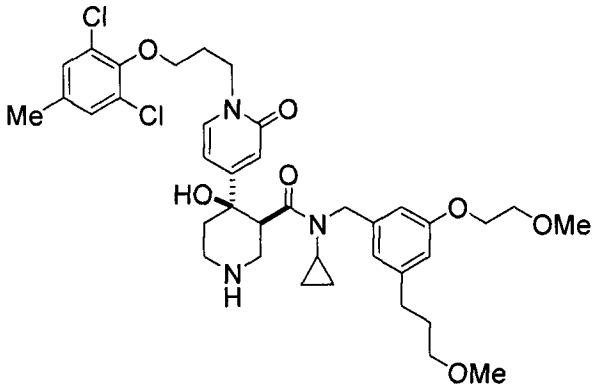
Step 4: *trans*-*N*-Cyclopropyl-4-{1-[2-(2,6-dichloro-4-methylphenoxy)ethyl]-2-oxo-1,2-dihydro-4-pyridinyl}-4-methoxy-*N*-[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]-3-piperidinecarboxamide

To a CH_2Cl_2 solution (0.06 M) of *tert*-butyl *trans*-3-({cyclopropyl[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]amino}carbonyl)-4-{1-[2-(2,6-dichloro-4-methylphenoxy)ethyl]-2-oxo-1,2-dihydro-4-pyridinyl}4-methoxy-1-piperidinecarboxylate (1 eq.) from the previous step was added HCl (4.0 M dioxane solution, 30 eq.). The resulting solution was stirred at RT for 3 h. Following the removal of the volatiles *in vacuo*, the resulting residue was directly loaded onto a SiO_2 column packed with 94:6 (v/v) CH_2Cl_2: 2.0 M NH_3 in MeOH. Elution with the same solvent system furnished the title compound. MS (ESI+, M+H): 730. ^1H NMR (acetone-d_6): δ (ppm) 0.75-1.03 (*m*, 4H), 1.78-1.84 (*m*, 2H), 2.26-2.47 (*m*, 5H), 2.52-2.64 (*m*, 3H), 2.72 (*br s*, 1H), 3.02 (*s*, 3H), 3.11-3.23 (*br m*, 4H), 3.26 (*s*, 3H), 3.33-3.35 (*m*, 5H), 3.68 (*t*, d = 6.9 Hz, 2H), 3.92 (*br s*, 1H), 4.13 (*t*, d = 6.9 Hz, 2H), 4.19-4.39 (*m*, 5H), 4.93 (*br d*, J =

13.0 Hz, 1H), 6.39 (*d*, *J* = 6.8 Hz, 1H), 6.53 (*s*, 1H), 6.69 (*s*, 1H), 6.74 (*s*, 1H), 6.76 (*s*, 1H), 7.22 (*s*, 2H), 7.59 (*d*, *J* = 6.8 Hz, 1H).

Example 3

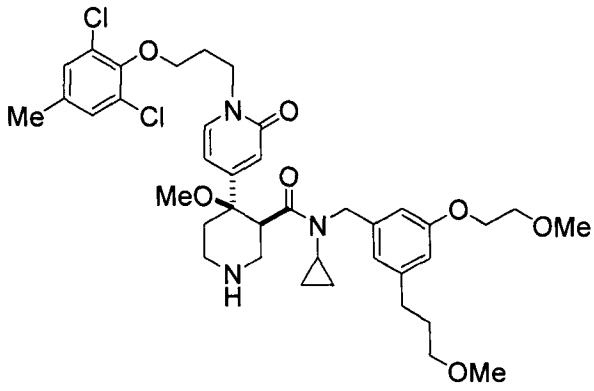
trans-*N*-Cyclopropyl-4-{1-[3-(2,6-dichloro-4-methylphenoxy)propyl]-2-oxo-1,2-dihydro-4-pyridinyl}-4-hydroxy-*N*-[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]-3-piperidinecarboxamide



Prepared according to the procedure described in **Example 1** but using instead **Mesylate 2** as alkylation reagent in **Step 4**. MS (ESI+, M+H): 730.

Example 4

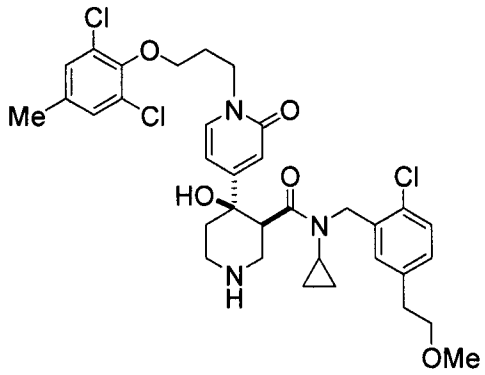
trans-*N*-Cyclopropyl-4-{1-[3-(2,6-dichloro-4-methylphenoxy)propyl]-2-oxo-1,2-dihydro-4-pyridinyl)-4-methoxy-*N*-[3-(2-methoxyethoxy)-5-(3-methoxypropyl)benzyl]-3-piperidinecarboxamide



Prepared according to the procedure described in **Example 2** but using instead **Mesylate 2** as alkylation reagent in **Step 3**. MS (ESI+, M+H): 744.

Example 5

trans-*N*-[2-Chloro-5-(2-methoxyethyl)benzyl]-*N*-cyclopropyl-4-{1-[3-(2,6-dichloro-4-methylphenoxy)propyl]-2-oxo-1,2-dihydro-4-pyridinyl)-4-hydroxy-3-piperidinecarboxamide

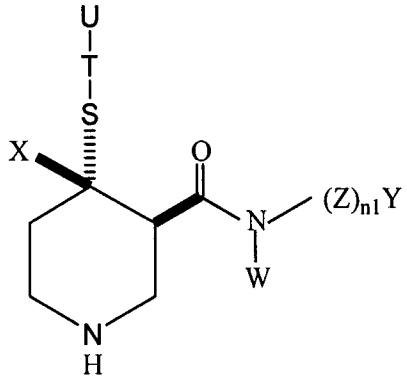


Prepared according to the procedure described in **Example 1** but using instead **Amine 2** as starting material in **Step 1** and **Mesylate 2** as alkylation reagent in **Step 4**. MS (ESI+, M+H): 676. ^{1}H NMR (acetone-d_6): δ (ppm) 0.75-1.02 (*m*, 4H), 1.48-1.52 (*br m*, 1 H), 1.79-1.84 (*m*, 1H), 2.23-2.28 (*m*, 3H), 2.31 (*s*, 3H), 2.72 (*t*, *d* = 7.3 Hz, 2H), 2.75-2.90 (*m*, 5H), 3.14-3.28 (*m*, 7H), 3.51 (*t*, *d* = 7.3 Hz, 2H), 3.92-4.28 (*m*, 5H), 4.49 (*d*, *J* = 13.1 Hz, 1H), 4.55 (*d*, *J* = 13.1 Hz, 1H), 6.42 (*d*, *J* = 6.8 Hz, 1H), 6.53 (*s*, 1H), 6.72 (*s*, 1H), 7.11 (*d*, *J* = 6.8 Hz, 1H), 7.25-7.27 (*m*, 3H), 7.58 (*d*, *J* = 7.0 Hz, 1H).

WHAT IS CLAIMED IS:

1. A compound of formula I, or a pharmaceutically acceptable salt thereof having formula (I)

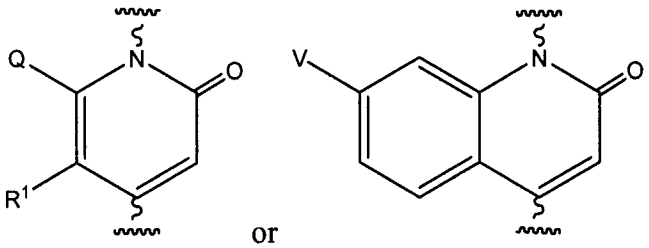
I



wherein:

S is

(IIa) (IIb)



wherein the nitrogen atom in IIa and IIb above is attached to T;

T is a bond; $-(CH_2)_r-$; $-(CH_2)_r-A-(CH_2)_s-$; or $-(CH_2)_r-A-(CH_2)_r-B-$;

A and B are independently selected from the group consisting of -O-. -S-, -S(O)- and $-S(O)_2-$;

r is the integer 2, 3, 4, or 5;

s is the integer 0, 1, or 2;

U is unsubstituted aryl; mono-, di-, tri- or tetra-substituted aryl wherein the substituents are independently selected from the group consisting of halogen, alkyl, alkoxy, cyano and $-CF_3$; or mono-, di-, or tri-substituted heteroaryl wherein the substituents are independently selected from the group consisting of halogen, alkyl, alkoxy, cyano and $-CF_3$;

V is selected from the group consisting of: hydrogen, halogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkenyl, C_2-C_6 alkynyl, cyano and C_1-C_5 alkoxy,

wherein said alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl and alkoxy are optionally substituted with 1-3 substituents, each of which is independently selected from the

group consisting of: halogen, C_1-C_5 alkyl, C_2-C_5 alkenyl, cyano and C_1-C_5 alkoxy, wherein each of the foregoing alkyl, alkenyl and alkoxy substituents is optionally substituted with 1-3 halogens;

Q and R^1 are independently selected from the group consisting of: hydrogen, halogen, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, C_2-C_5 alkenyl, C_3-C_8 cycloalkenyl, C_2-C_5 alkynyl, cyano and C_1-C_5 alkoxy, aryl and heteroaryl;

wherein said aryl and heteroaryl are optionally substituted with 1-4 halogens,

wherein said alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl and alkoxy are optionally substituted with 1-3 substituents, each of which is independently selected from the group consisting of: halogen, C_1-C_5 alkyl, C_2-C_5 alkenyl, cyano and C_1-C_5 alkoxy, wherein each of the foregoing alkyl, alkenyl and alkoxy substituents is optionally substituted with 1-3 halogens;

W is cyclopropyl, unsubstituted or mono-, di-, tri-, tetra- or penta-substituted with halogen;

X is selected from the group consisting of: OR^2, R^2, -(C_1-C_5 alkylene)-$(O)_{0-1}$-aryl and -(C_1-C_5 alkylene)-$(O)_{0-1}$-heteroaryl,

wherein R^2 is selected from the group consisting of: hydrogen, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, C_2-C_5 alkenyl, C_3-C_8 cycloalkenyl, C_2-C_5 alkynyl, C_1-C_5-cyano, -(C_1-C_5 alkylene)-O-R^3, -(C_1-C_5 alkylene)-N(-R^3)-C(=O)-(C_1-C_5 alkyl), -(C_1-C_5 alkylene)-C(=O)-N(-R^3)-(C_1-C_5 alkyl), -(C_1-C_5 alkylene)-N(-R^3)-C(=O)-O-(C_1-C_5 alkyl), -(C_1-C_5 alkylene)-O-C(=O)-N(-R^3)-(C_1-C_5 alkyl), -(C_1-C_5 alkylene)-N(-R^3)-(C_1-C_5 alkyl), -(C_1-C_5 alkylene)-S-(C_1-C_5 alkyl), -(C_1-C_5 alkylene)-S(=O)-(C_1-C_5 alkyl) and -(C_1-C_5 alkylene)-$S(=O)_2$-(C_1-C_5 alkyl),

wherein R^2, except hydrogen, is optionally substituted with 1-3 substituents, independently selected from the group consisting of: halogen, C(=O)OH, C_1-C_5 alkyl, C_2-C_5 alkenyl, and C_1-C_5 alkoxy, wherein each of the alkyl, alkenyl, and alkoxy substituents is optionally substituted with 1-3 halogens,

wherein the heteroaryl of the -(C_1-C_5 alkylene)-$(O)_{0-1}$-heteroaryl contains 1-3 heteroatoms, independently selected from the group consisting of: N, O and S, wherein each N is optionally in the form of an oxide and each S is optionally in the form of an oxide selected from the group consisting of: S(=O) and $S(=O)_2$,

wherein the aryl and heteroaryl of -(C_1-C_5 alkylene)-$(O)_{0-1}$-aryl and -(C_1-C_5 alkylene)-$(O)_{0-1}$-heteroaryl, respectively, are optionally substituted with 1-4 halogens, and

wherein R^3 is selected from the group consisting of: hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkenyl, and C_2-C_6 alkynyl, wherein each of the foregoing alkyl, cycloalkyl, alkenyl, cycloalkenyl and alkynyl substituents is optionally substituted with 1-3 halogens;

Z is C_1-C_2 alkylene optionally substituted with 1-2 substituents, independently selected from the group consisting of: halogen, C_1-C_3 alkyl and C_3 cycloalkyl, wherein the foregoing alkyl and cycloalkyl substituents are optionally substituted with 1-3 halogens;

n1 is 0 or 1;

Y is (i) a five- or six-membered saturated or unsaturated heterocyclic or carbocyclic monocyclic ring ("monocyclic ring") or (ii) a fused ring system which is a five- or six-membered saturated or unsaturated heterocyclic or carbocyclic ring which is fused to a five- or six-membered saturated or unsaturated heterocyclic or carbocyclic ring ("fused ring"),

wherein the heterocyclic ring(s) of (i) or (ii) contain from 1-3 heteroatoms, independently selected from N, O and S, wherein each N is optionally in the form of an oxide and each S is optionally in the form of an oxide selected from the group consisting of: S(=O) and $S(=O)_2$,

wherein the heterocyclic or carbocyclic ring(s) of (i) or (ii) is optionally mono-, di-, tri-, tetra-, penta- or hexa-substituted, each substituent of which is independently selected from the group consisting of:

(1) halogen,
(2) -OH,
(3) $-NH(R^4)$,
(4) oxo,
(5) $-C(=O)-R^4$,
(6) $-O-C(=O)-R^4$,
(7) C_1-C_5 alkyl optionally substituted with 1-3 halogens,
(8) C_3-C_8 cycloalkyl optionally substituted with 1-3 halogens,
(9) C_2-C_5 alkenyl optionally substituted with 1-3 halogens,
(10) C_3-C_8 cycloalkenyl optionally substituted with 1-3 halogens,
(11) C_2-C_5 alkynyl optionally substituted with 1-3 halogens,
(12) C_1-C_5 alkoxy optionally substituted with 1-3 halogens,
(13) cyano,
(14) C_1-C_5-cyano optionally substituted with 1-3 halogens,
(15) $-OCF_3$,
(16) $-C(R^5)_3$,
(17) -(C_1-C_5 alkylene)-OR^6 optionally substituted with 1-3 halogens,
(18) $-N(R^4)$-(C_1-C_5 alkylene)-OR^6 optionally substituted with 1-3 halogens,
(19) -O-(C_1-C_5 alkylene)-OR^6 optionally substituted with 1-3 halogens,
(20) -S-(C_1-C_5 alkylene)-OR^6 optionally substituted with 1-3 halogens,
(21) -S(=O)-(C_1-C_5 alkylene)-OR^6 optionally substituted with 1-3 halogens,

(22) -S(=O)$_2$-(C_1-C_5 alkylene)-OR^6 optionally substituted with 1-3 halogens,

(23) -(C_1-C_5 alkylene)-N(R^4)-C(=O)-(C_1-C_5 alkylene)-R^6 optionally substituted with 1-3 halogens,

(24) -(C_1-C_5 alkylene)-N(R^4)-C(=O)-OR^6 optionally substituted with 1-3 halogens,

(25) -(C_1-C_5 alkylene)-N(R^4)(R^6) optionally substituted with 1-3 halogens,

(26) -O-(C_1-C_5 alkylene)-C(R^4)$_2$-C(=O)OR^6 optionally substituted with 1-3 halogens,

(27) -(C_1-C_5 alkylene)-C(R^4)$_2$-C(=O)-OR^6 optionally substituted with 1-3 halogens,

(28) -O-(C_1-C_5 alkylene)-morpholine optionally substituted with 1-3 halogens,

(29) -OC(=O)-morpholine,

(30) -SR^6,

(31) -S(=O)-R^6,

(32) -S(=O)$_2$-R^6

(33) -N(R^4)(R^6),

(34) -(C_1-C_5 alkylene)-C(R^4)$_2$-(R^6) optionally substituted with 1-3 halogens,

(35) -(R^7)$_{0-1}$R^8,

(36) C_2-C_5 alkenyl-OR^6 optionally substituted with 1-3 halogens,

(37) C_2-C_5 alkynyl-OR^6 optionally substituted with 1-3 halogens,

(38) -(C_1-C_5 alkylene)-C(=O)-(C_1-C_5 alkylene)-R^6 optionally substituted with 1-3 halogens,

(39) -(C_1-C_5 alkylene)-O-C(=O)-(C_1-C_5 alkylene)-R^6 optionally substituted with 1-3 halogens,

(40) -(C_1-C_5 alkylene)-C(=O)-N(R^4)(R^6) optionally substituted with 1-3 halogens,

(41) -(C_1-C_5 alkylene)-O-C(=O)-N(R^4)(R^6) optionally substituted with 1-3 halogens,

(42) -(C_1-C_5 alkylene)-SR^6 optionally substituted with 1-3 halogens,

(43) -(C_1-C_5 alkylene)-S(=O)-R^6 optionally substituted with 1-3 halogens, and

(44) -(C_1-C_5 alkylene)-S(=O)$_2$-R^6 optionally substituted with 1-3 halogens,

wherein R^4 is selected from the group consisting of: hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, C_3-C_8 cycloakenyl and C_2-C_6 alkynyl, wherein each of the

foregoing alkyl, cycloalkyl, alkenyl, cycloalkenyl and alkynyl substituents is optionally substituted with 1-3 halogens,

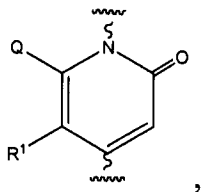
wherein R^5 is halogen,

wherein R^6 is selected from the group consisting of: hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkenyl and C_2-C_6 alkynyl, wherein each of the foregoing alkyl, cycloalkyl, alkenyl, cycloalkenyl and alkynl substituents is optionally substituted with 1-3 halogens,

wherein R^7 is selected from the group consisting of: -C(H)(OH)-, -C(=O)-, -OC(=O)-, -C(=O)O-, -O-, -OC(=O)O-, C_1-C_5 alkylene, C_2-C_5 alkenylene, -N(R^4)-, -S-, -S(=O)-, -S(=O)$_2$-, -N(R^4)-C(=O)-, -C(=O)-N(R^4)-, -OC(=O)-N(R^4)-, -N(R^4)-C(=O)O-, -N(R^4)-S(=O)$_2$-, and -S(=O)$_2$-N(R^4)-, wherein each of the foregoing alkylene and alkenylene substituents is optionally substituted with 1-3 halogens, and wherein R^4 is defined above, and

wherein R^8 is a five- or six-membered saturated or unsaturated heterocyclic or carbocyclic ring which is optionally mono-, di-, tri-, tetra- or penta-substituted, wherein each substituent is independently selected from the group consisting of: halogen, -OH, -SR^4, -N(R^4)(R^6), C_1-C_5 alkyl, C_3-C_8 cycloalkyl, C_2-C_5 alkenyl, C_3-C_6 cycloalkenyl, C_2-C_5 alkynyl, C_1-C_5 alkoxy, cyano and C_1-C_5-cyano, wherein said heterocyclic ring contains from 1 to 3 heteroatoms, independently selected from N, O and S, wherein each N is optionally in the form of an oxide and each S is optionally is in the form of an oxide selected from the group consisting of: S(=O)and S(=O)$_2$, and wherein R^4 and R^6 are defined above.

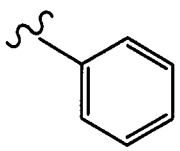
2. The compound of Claim 1 wherein S is:



,

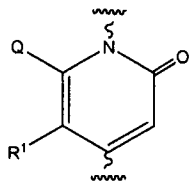
wherein the nitrogen atom in S above is attached to T; and
wherein Q and R1 are defined in claim 1.

3. The compound of Claim 1 wherein Y is:

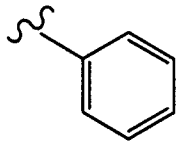


optionally mono-, di-, tri-, tetra- or penta-substituted as described in Claim 1.

4. The compound of Claim 1 wherein S is:



wherein the nitrogen atom in S above is attached to T;
wherein Q and R1 are as defined in claim 1, and
wherein Y is:



optionally mono-, di-, tri-, tetra- or penta-substituted as described in Claim 1.

5. The compound of Claim 1 wherein T is $-CH_2-CH_2-O-$ or $-CH_2-CH_2-CH_2-O-$.

6. The compound of Claim 1 wherein U is a mono, di-, tri-or tetra-substituted aryl.

7. The compound of Claim 1 wherein U is a mono, di-, tri-or tetra-substituted phenyl wherein the substituents are independently selected from the group consisting of: halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano and $-CF_3$.

8. The compound of Claim 1 wherein U is 2, 6-dichloro-4methyl-phenyl.

9. The compound of Claim 1 wherein Q and R^1 are independently selected from the group consisting of: H, $-OCH_2OCH_3-$ and $-CH_3$.

10. The compound of Claim 1 wherein V is hydrogen or halogen.

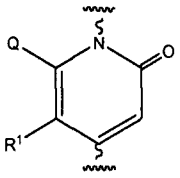
11. The compound of Claim 1 wherein W is unsubstituted cyclopropyl.

12. The compound of Claim 1 wherein X is -H, -OH, or $-OCH_3$.

13. The compound of Claim 1 wherein $(Z)_{n1}$ is $-CH_2-$.

14. The compound of Claim 1 wherein:

S is



;

wherein the nitrogen atom in S above is attached to T,

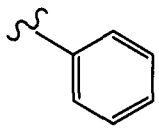
U is an optionally mono-, di-, tri-, or tetra-substituted phenyl ring, wherein substituents are independently selected from the group consisting of: halogen, alkyl, alkoxy, cyano and $-CF_3$,

W is cyclopropyl, unsubstituted or mono-, di-, tri-, tetra- or penta-substituted with halogen;

X is hydrogen, OH or methoxy,

$(Z)_{n1}$ is $-CH_2-$,

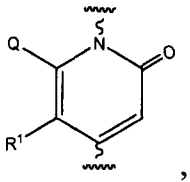
Y is



optionally mono-, di-, tri-, tetra- or penta-substituted as described in Claim 1.

15. The compound of Claim 1 wherein:

S is



,

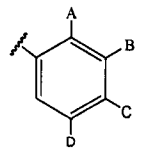
wherein the nitrogen atom in S above is attached to T,

T is $-(CH_2)_r-O-$,

U is an optionally mono-, di-, tri-, or tetra-substituted phenyl ring, wherein substituents are independently selected from the group consisting of: halogen, alkyl, alkoxy, cyano and $-CF_3$,

W is cyclopropyl, unsubstituted or mono-, di-, tri-, tetra- or penta-substituted with halogen;

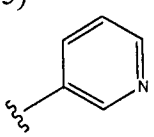
X is hydrogen, OH or methoxy,
$(Z)_{n1}$ is $-CH_2-$,
Y is



wherein:

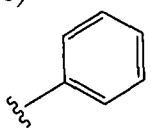
A is selected from the group consisting of:
(1) hydrogen,
(2) halogen,
(3) C_1-C_5 alkyl,
(4) C_1-C_5 alkoxy, and
(5) $-S-(CH_2)_{0-3}-CH_3$,
wherein (3) and (4) are optionally substituted with 1-3 halogens,

B is selected from the group consisting of:
(1) hydrogen,
(2) halogen,
(3) C_1-C_5 alkyl,
(4) C_1-C_5 alkoxy,
(5) -OH,
(6) $-CF_3$,
(7) $-C(=O)-CH_3$,
(8) -O-(C_1-C_5 alkylene)-O-cyclopropyl,
(9) -O-(C_1-C_5 alkylene)-O-$(CH_2)_{0-2}-CH_3$,
(10) -(C_1-C_5 alkylene)-O-$(CH_2)_{0-2}-CH_3$,
(11) -OC(=O)-morpholine,
(12) -O-(C_1-C_5 alkylene)-morpholine,
(13) -O-(C_1-C_5 alkylene)-$C(CH_3)_2$-C(=O)OH,
(14) -O-(C_1-C_5 alkylene)-$C(CH_3)_2$-$C(=O)OCH_3$,
(15)



and

(16)



,

wherein (3), (4), (8), (9), (10), (12), (13), (14), (15) and (16) are optionally substituted with 1-3 halogens,

C is selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) C_1-C_5 alkyl optionally substituted with 1-3 halogens, and

(4) C_1-C_5 alkoxy optionally substituted with 1-3 halogens, and

D is selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) C_1-C_5 alkyl,

(4) C_1-C_5 alkoxy,

(5) C_1-C_5-cyano,

(6) C_2-C_5 alkenylene-O-$(CH_2)_{0-2}$-CH_3,

(7) -(C_1-C_5 alkylene)-N(H)-C(=O)-O-$(CH_2)_{0-2}$-CH_3,

(8) -(C_1-C_5 alkylene)-N(H)-C(=O)-$(CH_2)_{0-2}$-CH_3,

(9) -(C_1-C_5 alkylene)-O-CHF_2,

(10) -(C_1-C_5 alkylene)-O-$(CH_2)_{0-2}$-CH_3,

(11) -O-(C_1-C_5 alkylene)-O-$(CH_2)_{0-2}$-CH_3,

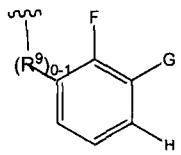
(12) -(C_1-C_5 alkylene)-OH,

(13) -S-(C_1-C_5 alkylene)-OH,

(14) -SCF_3

(15) -N(H)-(C_1-C_5 alkylene)-O-$(CH_2)_{0-2}$-CH_3, and

(16)



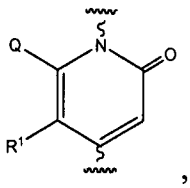
wherein F, G and H are independently selected from the group consisting of: hydrogen, halogen and C_1-C_3 alkyl optionally substituted with 1-3 halogens, and

wherein R^9 is selected from the group consisting of: -CH_2-, -C(H)(OH)- and –C(=O)-,

wherein (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13) and (15) are optionally substituted with 1-3 halogens.

16. The compound of Claim 1 wherein:

S is



,

wherein the nitrogen atom in S above is attached to T,

T is $-CH_2-CH_2-O-$ or $-CH_2-CH_2-CH_2-O-$,

U is 2, 6-dichloro-4methyl-phenyl,

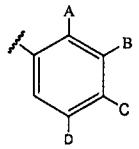
Q and R^1 are independently selected from the group consisting of: -H, $-OCH_2OCH_3-$ and $-CH_3$,

W is unsubstituted cyclopropyl,

X is hydrogen, OH or methoxy,

$(Z)_{n1}$ is $-CH_2-$,

Y is



wherein:

A is selected from the group consisting of: hydrogen, halogen, C_1-C_5 alkyl and C_1-C_5 alkoxy,

B is selected from the group consisting of: hydrogen, halogen, C_1-C_5 alkyl, C_1-C_5 alkoxy and -O-(C_1-C_5 alkylene)-O-$(CH_2)_{0-2}$-CH_3,

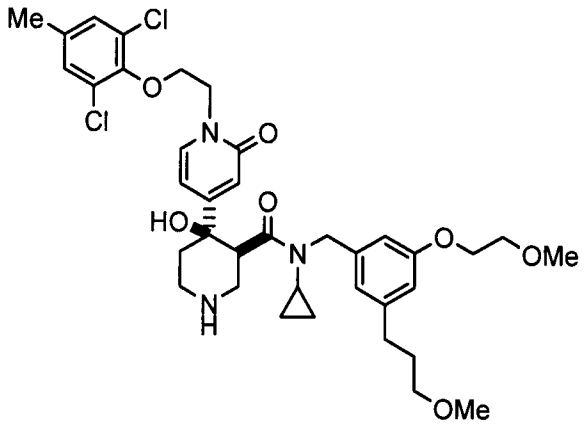
C is selected from the group consisting of: hydrogen, halogen, C_1-C_5 alkyl and C_1-C_5 alkoxy,

D is selected from the group consisting of: hydrogen, halogen, C_1-C_5 alkyl, C_1-C_5 alkoxy and -(C_1-C_5 alkylene)-O-$(CH_2)_{0-2}$-CH_3,

wherein the alkyl or alkoxy groups of A-D are optionally substituted with 1-3 halogens.

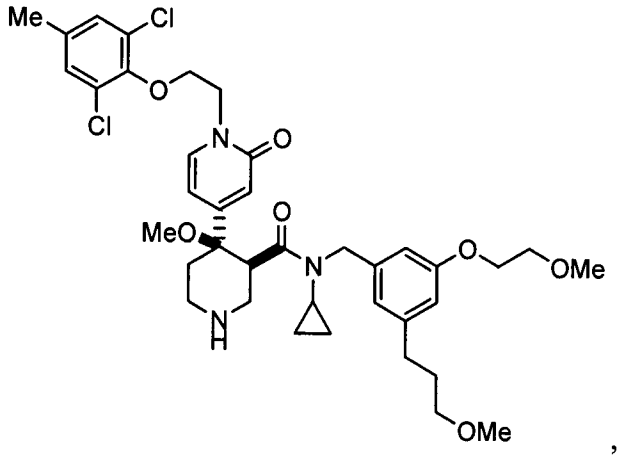
17. The compound of Claim 1 which is selected from the group consisting of:

Ex. 1



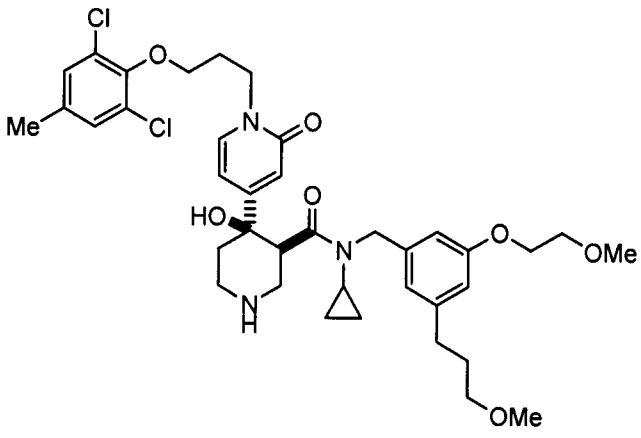
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Ex. 2



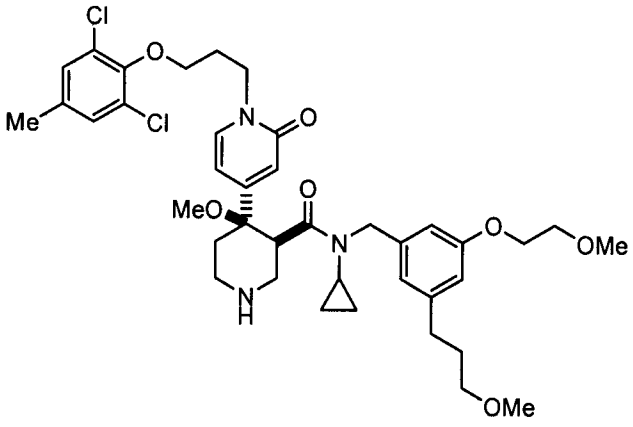
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Ex. 3

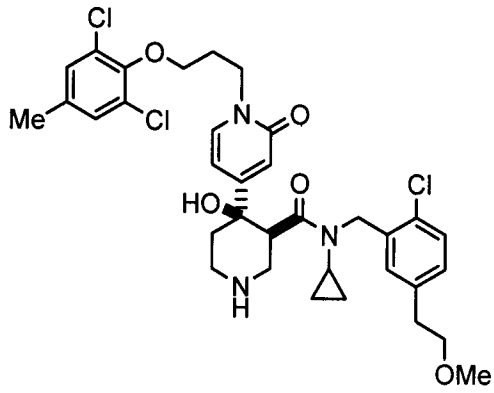


,

Ex. 4



Ex. 5



, and

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable salt of the stereoisomer thereof.

18. A pharmaceutical composition comprising an effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

19. Use of a compound according to Claim 1 for the manufacture of a medicament for the treatment or prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases known to be related to the renin-angiotensin system.

20. A method for the treatment or prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other

diseases known to be related to the renin-angiotensin system, comprising the administration to a patient of a pharmaceutically active amount of a compound according to Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2009/001758

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***C07D 401/04*** (2006.01) , ***A61K 31/4545*** (2006.01) , ***A61P 13/12*** (2006.01) , ***A61P 9/00*** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[8]: C07D 401/04, A61K 31/4545

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

STN (chemical structure search) and Canadian Patent Database with keywords: piperidin* and renin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2587348 (Breitenstein et al.) 6 July 2006 (06-07-2006) entire document	1-20
X	CA 2608685 (Ehara et al.) 30 November 2006 (30-11-2006) entire document	1-20

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 February 2010 (02-02-2010)	1 March 2010 (01-03-2010)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Irena Wisniewska (819) 953-8589

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. : 20

because they relate to subject matter not required to be searched by this Authority, namely :

Claim 20 is directed to a method for treatment of the human or animal body which the International Search Authority is not required to search. However, this Authority has carried out a search based on the alleged effect or purpose/use of the product defined in claim 20.

2. [X] Claim Nos. : 1-16 and 18-20 (in part)

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

The claims relate to an extremely large number of possible compounds. Therefore, the search has been carried out for compounds of formula I representing a generalization of examples 1-5 given in the description.

3. [ ] Claim Nos. :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA2587348A1	06-07-2006	AR052446A1	21-03-2007
		AT448217T	15-11-2009
		AU2005321475A1	06-07-2006
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		CA2587348A1	06-07-2006
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		DE602005017665D1	24-12-2009
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		EP1833816B1	11-11-2009
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		JP2008542221T	27-11-2008
		KR20080013933A	13-02-2008
		RU2007147591A	10-07-2009
		US2009137566A1	28-05-2009
		WO2006125621A1	30-11-2006
		WO2006125621A8	27-03-2008